Causes, mechanisms, and mitigation of socially-induced nocebo effects

Cosette Emilie Saunders

School of Psychology

Faculty of Science

The University of Sydney

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Statement of Originality

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*co-first authors

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I designed the study, analysed the data, and wrote the drafts of the manuscript. Chapter 3 reproduces the published article in full. The article reports three studies. Study 1 was originally submitted as part of my Honours thesis and does not form part of the PhD

research contribution. Only Studies 2 and 3 and the pooled analysis contribute to the doctoral research presented in this thesis.

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Signature:

Supervisor's Name: Ben Colagiuri

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Abstract

The nocebo effect refers to adverse symptoms that arise in response to a treatment but cannot be explained by its active pharmacological properties. Nocebo effects remain relatively understudied despite their substantial clinical, societal, and economic impact. Social learning, the process of acquiring information through observing or interacting with others, has been identified as a particularly potent pathway through which nocebo effects may develop. In contemporary healthcare environments, where treatment experiences are frequently shared face-to-face and via mainstream and social media, understanding socially-acquired nocebo effects is of increasing importance. The overarching aim of this thesis was to investigate the causes, mechanisms, spread, and potential mitigation of socially-induced nocebo effects. Chapter 1 introduces the nocebo effect, discussing known methods of induction and key mechanisms. Chapter 2 presents a systematic review and meta-analysis synthesising existing research on socially-induced nocebo effects. The findings demonstrate that observing another person experience adverse symptoms produces nocebo effects with a medium-large effect compared to no treatment and that the effect of social learning was similar in magnitude to classical conditioning and greater than explicit instruction. Importantly, all existing research examined social learning only where the model and observer undergo identical experiences. Chapters 3 and 4 extended this work by testing whether socially-acquired nocebo effects can still arise when the model's experience differs from the observer's. Using a virtual reality model of cybersickness and a simulated clinical paradigm, these studies demonstrated that socially-induced nocebo effects can extend to similar, but not identical, treatments and contexts. These findings suggest that socially transmitted expectations are not confined to the originally modelled intervention, expanding the potential scope of nocebo-related harm in real world settings. Given the substantial harm associated with nocebo effects, Chapters 3 and 5 examined strategies to attenuate socially-induced nocebo effects. Chapter 3 tested whether

providing participants with choice over their VR environment could reduce socially elicited cybersickness; however, choice did not mitigate symptoms. Chapter 5 evaluated a novel intervention in which standard side effect warnings were paired with a social model who communicated an absence of side effects, termed positive social modelling. Results indicated that positive social modelling reduced nocebo symptom severity, providing preliminary support for leveraging social learning mechanisms to counteract the formation of nocebo effects. Collectively, this thesis advances theoretical understanding of socially-induced nocebo effects, demonstrates their capacity to generalise across contexts, confirms expectancy and anxiety as central mechanisms, and provides novel evidence for an intervention grounded in positive social modelling. Continued research to develop and rigorously evaluate strategies to mitigate nocebo effects is essential for reducing the substantial burden nocebo effects impose on individuals and the wider community.

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List of Abbreviations

Abbreviation	Definition
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
CARM	New Zealand Centre for Adverse Reactions Monitoring
COVID-19	Coronavirus Disease 2019
EDA	Electrodermal Activity
EEG	Electroencephalography
EMF	Electromagnetic Field
fMRI	Functional Magnetic Resonance Imaging
GASE	General Assessment of Side Effects
HREC	Human Research Ethics Committee
HRV	Heart Rate Variability
IRI	Interpersonal Reactivity Index
MPI	Mass Psychogenic Illness
NHS	National Health Service
PASS	Pain Anxiety Symptoms Scale
RVIP	Rapid Visual Information Processing
RoB 2	Risk of Bias 2
SAM	Self-Assessment Manikin
SEM	Standard Error of the Mean
SSQ	Simulator Sickness Questionnaire
STAI-6	State-Trait Anxiety Inventory – Short Form
VAS	Visual Analogue Scale
VR	Virtual Reality

Chapter 1: Introduction

In 1998, a Tennessee high school teacher arrived at work and noticed a “gasoline-like smell”. She soon developed a range of symptoms, including headache, dizziness, shortness of breath, and nausea (Jones et al., 2000). Soon after, nearly 100 students and staff were taken to the emergency room, with 38 requiring overnight admission due to severe symptoms. Investigators, however, could not find any environmental or medical cause to explain what happened. How could so many people experience such symptoms in the absence of any toxic agent? A number of case studies have reported similar phenomena in which groups of people experience severe symptoms requiring medical intervention despite no apparent causal agent (e.g., Fisher et al., 1995; Müller-Vahl et al., 2021; Reeves et al., 2007).

These examples can be explained by the nocebo effect, the negative counterpart of the placebo effect. The nocebo effect is a psychobiological phenomenon whereby negative expectancies can increase symptom reporting beyond any active properties of an intervention (Faasse, 2019). With respect to the Tennessee high school, the staff and students believed they had been exposed to a dangerous chemical and thus expected to experience symptoms. These negative expectancies caused them to experience symptoms even though they had never actually been exposed to a dangerous chemical. In this case, the symptoms were not spread by a pathogen, but rather through communication with and observation of peers. Investigators found that reporting symptoms was associated with knowing of or seeing another ill person. This suggests that social learning, the process of learning from observing or interacting with others, played a role in the spread of these symptoms. This incident is just one of many examples of how social learning can trigger and intensify physical experiences through the nocebo effect. Beyond the individual level, when this phenomenon is scaled across communities, it can generate substantial societal and economic harm, with the nocebo effect implicated in community-level concerns such as wind turbine syndrome, electromagnetic sensitivity, and vaccine hesitancy (Bräscher et al., 2017; Chapman &

Crichton, 2017; Eltiti et al., 2018; Hoffman et al., 2022). The present thesis investigates how social learning can contribute to the experience of nocebo effects, exploring underlying mechanisms and ways in which we may reduce its occurrence and impact.

Placebo and Nocebo Effects

The placebo phenomenon was first documented by Dr. Henry Beecher during World War II, when shortages of morphine forced him to substitute saline injections to maintain soldier morale. Although this saline contained no active pain-relieving agent, approximately a third of the soldiers reported a reduction in their pain levels (Beecher, 1955; Benedetti, 2022). In a subsequent meta-analysis Beecher showed the placebo effect was not limited to pain; it also extended to a variety of symptoms, including seasickness, cough, mood, and anxiety. The placebo effect is now understood as the beneficial psychological and physiological effects of a substance or procedure that cannot be attributed to its inherent powers (Stewart-Williams & Podd, 2004).

Importantly, improvements observed after placebo administration include many non-specific influences such as natural symptom fluctuation, regression to the mean, patient and clinician biases, demand characteristics, and behavioural changes due to being observed (Benedetti & Shaibani, 2026; Colagiuri & Lovibond, 2013). Together, the influence of these factors constitutes the placebo response. In contrast, the placebo effect refers specifically to the psychobiological change caused by the treatment context itself (Benedetti & Shaibani, 2026). Because these non-specific factors are present in most clinical and health settings (Price et al., 2008), isolating the placebo effect requires experimental control (Benedetti & Shaibani, 2026; Colloca & Miller, 2011b). This is typically achieved by including a no-treatment comparison group: changes observed in that group are assumed to reflect non-specific influences, whereas additional improvement in the placebo group is attributed to the placebo effect.

The term ‘nocebo’ was first used by Kennedy (1961) to describe the negative counterpart to the placebo, the *negative* psychological and physiological effects unattributable to the inherent powers of an intervention. Nocebo effects are widely understood to be driven by negative expectations and anxiety, with the underlying mechanisms discussed later in this chapter. As with placebo phenomena, it is important to distinguish between the nocebo response and the nocebo effect. The nocebo effect refers specifically to harm driven by negative psychosocial expectations surrounding the treatment context and their neurobiological bases, and can only be estimated using a no-treatment control, whereas the nocebo response encompasses all adverse changes, including non-specific biases that influence symptom reporting (Benedetti & Shaibani, 2026; Colloca & Miller, 2011b). In clinical trials, Kennedy noted that subjects exhibited adverse reactions despite not taking anything with an active pharmacological component. This nocebo response is now well documented. An analysis of 231 clinical trials including over half a million participants revealed that almost three quarters of subjects assigned to the placebo arm reported experiencing adverse events, and adverse events reported in placebo arms were highly correlated (r = .91) with adverse events reported in the treatment groups (Mahr et al., 2017).

Both placebo and nocebo effects can exert a significant influence on clinical outcomes. For example, Bingel et al. (2011) showed that treatment expectations can dramatically alter the efficacy of the potent opioid remifentanil. Healthy volunteers were exposed to identical heat-pain stimuli while they received an infusion of remifentanil. Compared to when participants were unaware the opioid was being delivered, awareness of the opioid infusion doubled reported analgesia. Conversely, informing participants that the infusion had been stopped, and that this interruption may worsen pain, eliminated the drug’s benefit; pain ratings were then equivalent to those recorded when no active treatment was given. Furthermore, fMRI confirmed that these shifts in subjective pain were mirrored by

corresponding changes in neural activity within regions of the brain involved with pain processing. These examples are testament to the prevalence and strength with which the nocebo effect can influence clinical outcomes, and therefore understanding the nocebo effect is of significant clinical concern.

The nocebo effect extends beyond adverse reactions to medical treatments and has been documented in a broad range of non-clinical contexts. For instance, electromagnetic fields (EMF) emitted by Wi-Fi or mobile phones have been implicated in mass psychogenic episodes such as "electromagnetic hypersensitivity" wherein people attribute nonspecific symptoms like headaches or fatigue to EMF exposure despite limited objective evidence (Eltiti et al., 2018). When people are blinded to whether or not they were exposed, the reported detrimental effects of EMF technology seemingly disappear (Eltiti et al., 2018). Furthermore, negative media coverage can magnify these perceived symptoms. For example, research indicates that participants who watched a film about the adverse health effects of Wi-Fi subsequently reported more severe symptoms under a sham exposure condition (Witthöft & Rubin, 2013). Similarly, "wind turbine syndrome"—where individuals report symptoms supposedly induced by nearby wind farms—has been hypothesised to arise largely from the nocebo effect. Anxiety and negative expectations concerning the proximity of wind turbines supposedly play key roles in shaping and amplifying somatic complaints (Crichton & Petrie, 2015; Rubin et al., 2014). Chapman and Crichton (2017) have gone as far as terming the syndrome a "communicated disease" underscoring how the disease is likely not spread by properties of the technology itself rather by negative communication within communities and from mainstream media. Nocebo effects have also been documented in response to Virtual Reality (VR) exposure, where studies have shown that warning participants about the possibility of cybersickness can exacerbate nausea-like symptoms (Mao et al., 2021; Tan et al., 2023). These examples of nocebo effects in non-clinical settings

can have significant consequences. They can impede technology adoption, shape public policy, provoke business push-back, and, most importantly, cause real distress while fostering suspicion toward innovations that are generally considered safe. Therefore, understanding the nocebo effect is of significant societal concern.

Despite the clear clinical and non-clinical impacts of the nocebo effect, it remains markedly understudied relative to the placebo effect. As of June 2025, a PubMed search returns approximately 8,100 papers on the placebo effect but fewer than 900 on the nocebo effect—a disparity of about nine to one. This knowledge gap is striking given that the nocebo effect can intensify unpleasant symptoms, decrease treatment adherence, and increase healthcare costs. Therefore, it is important that research addresses this gap in knowledge through focused investigation into the nocebo effect's causes, underlying mechanisms, and potential strategies for mitigation.

Implications of Nocebo Effects

Physiological effects. Historically, placebo effects, and by extension nocebo effects, were assumed to influence only subjective complaints without affecting underlying biology (Colloca, 2019). Growing evidence, however, reveals that placebo and nocebo effects can also exert influence on physiological responses like neurobiological, immune, and endocrine markers (See Ortega et al., 2022 for a review). For instance, research on placebo analgesia demonstrates that not only does reported pain diminish, but this occurs alongside measurable physiological changes. Specifically, endogenous opioid release is triggered alongside a reduction in activity of pain-processing neural pathways (Colloca, 2019). Conditioning studies show that immune responses can be modified. In Goebel et al. (2008), patients with allergic rhinitis took an antihistamine while drinking a novel-flavoured beverage for five consecutive days. When subsequently presented with the drink alone their subjective symptoms, skin-prick-test reactivity, and basophil activation all declined, mirroring the

effects previously produced by the antihistamine itself. Another study investigated kidney transplant patients who had been prescribed immunosuppressant drugs. After the immunosuppressive drugs were repeatedly paired with a novel taste, exposure to the gustatory stimulus alone significantly reduced T-cell proliferative capacity (Kirchhof et al., 2018). Moreover, endocrine modulation has been documented, with conditioning procedures producing increases in salivary oxytocin and insulin (Skvortsova et al., 2020; Stockhorst et al., 1999), and nocebo-induced stress responses elevating cortisol levels (Sabbioni et al., 1997). While placebo and nocebo phenomena generally appear more robust when measured using self-reported rather than physiological measures, objective impacts have nevertheless been reported across various domains, including changes in gastric motility (Meissner et al., 2020), sleep patterns (Labarca et al., 2023; Muench et al., 2023), postural stability (Russell et al., 2022) and inflammatory markers in rheumatoid arthritis (Vollert et al., 2020). These findings collectively underscore that the nocebo effect can not only influence perceived experiences but also induce genuine and concerning, physiological changes.

Prevalence and clinical significance. In a clinical context, nocebo responses are widespread: Mahr et al. (2017) estimate that up to 97% of all side effects reported in clinical trials can be attributed to the nocebo response. Another study investigating the prevalence of side effects associated with statins found that relative to no treatment, the nocebo effect accounted for 89% of reported symptoms with the drug itself only accounting for 11% (Howard et al., 2021). The experience of side effects can pose a significant burden to the individual, decreasing quality of life, and is associated with poorer adherence to medical regimens across numerous chronic conditions (Dunbar-Jacob & Mortimer-Stephens, 2001). For example, one study of individuals with schizophrenia who experienced treatment-related side effects were between 21-43% less likely to follow their prescribed regimen, depending on the specific side effect experienced (DiBonaventura et al., 2012). Comparable findings

have emerged in multiple sclerosis (Mohr et al., 1998), HIV (Ammassari et al., 2001), adjuvant hormonal therapy for breast cancer (Cahir et al., 2015; Pan et al., 2018) and statin therapy aimed at reducing cardiovascular risk (Wei et al., 2013). Moreover, side effects can precipitate complete discontinuation of treatment, which can be detrimental to one's health (Barsky et al., 2002). In fact, discontinuation has been documented in placebo arms of clinical trials at rates comparable to the active treatment arm (Preston et al., 2000). These examples are testimony to the significant burden the nocebo effect poses to the individual.

In addition to the consequences to the individual, the management of side effects poses a significant burden to the healthcare system and comes at great expense. In 2008, managing medically-unexplained symptoms was estimated to cost the NHS £3 billion a year, approximately 10% of its primary-care budget (Bermingham et al., 2010). In the United States, downstream non-adherence that follows unpleasant side effects adds a further US $100–300 billion annually in avoidable hospitalisations and emergency care (Iuga & McGuire, 2014). Thus, even if only a small proportion of side-effects are attributable to the nocebo effect this would still represent an immense cost to the public. As outlined above, emerging evidence suggests the proportion of side effects attributable to the nocebo effect is likely substantially higher. Taken together, the burden imposed by the nocebo effect and side effects more broadly is substantial for both individuals and society, underscoring the need to understand how nocebo effects arise and how they can be mitigated.

Modes of Induction

Classical Conditioning

Classical conditioning describes the learning process in which repeated pairings of a neutral cue and a salient outcome can lead the cue to elicit a response on its own. This was illustrated in Pavlov's classical experiments, where dogs learned to associate a sound with food and subsequently began to salivate upon hearing the sound, even in the absence of food

(Pavlov, 1927). Classical conditioning can elicit nocebo effects when a previously neutral cue becomes associated with an aversive experience, such that the cue alone eventually triggers a conditioned negative response. For instance, Bąbel et al. (2017) paired two different coloured lights with the experience of moderate and high-intensity electrical shocks respectively. In a subsequent test phase, even though all electrical stimuli administered were equivalent, participants reported increased pain in response to the colour that was previously paired with higher pain. Classical conditioning has been shown to elicit placebo and nocebo effects within a variety of domains including itch (Blythe et al., 2021), shortness of breath (Van Den Bergh et al., 1995), nausea (Klosterhalfen et al., 2000), and cognitive performance (Turi et al., 2018). See Rooney, Sharpe, Todd, Tang, et al. (2024) and Wolters et al. (2019) for reviews of classically conditioned nocebo effects. Classical conditioning can also occur through the association between outcome and context. For example, Kamen et al. (2014) have reported contextual conditioning in cancer patients receiving chemotherapy. In this case, the treatment environment such as the nurses, infusion room, and medical equipment become associated with chemotherapy's nauseating effects, such that the mere presence of the context can elicit anticipatory nausea.

Explicit Instruction

Nocebo effects can be elicited in the absence of prior direct experience by the written or verbal information disseminated about a treatment. This is termed explicit instruction or verbal suggestion. For example, patients in labour receiving epidural analgesia told "You are going to feel a big bee sting, this is the worst part of the procedure" reported significantly more pain from the epidural than patients briefed with more neutral instruction (Varelmann et al., 2010). Nocebo effects induced by instruction have been shown to be specific to the side effects warned. For example, Neukirch and Colagiuri (2015) gave participants an inert pill described as an insomnia treatment and told half that it would increase appetite, while the

other half were told it would decrease appetite. After taking the placebo pill, participants' reported appetite changed in the direction of the warning they had received. Similarly, van Laarhoven et al. (2011) demonstrated this pattern of results with respect to pain and itch, where participants reported increased levels of the symptom they were warned of in response to an ambiguous somatosensory stimulus. As with classical conditioning, explicit instruction has been documented to influence a broad range of nocebo symptoms including pain, headache, cybersickness, insomnia, sexual dysfunction and itch (Mao et al., 2021; Mondaini et al., 2007; Schweiger & Parducci, 1981; Silvestri et al., 2003; van Laarhoven et al., 2011).

In clinical settings, adverse outcomes sometimes occur simply because patients have been informed of the potential for unpleasant effects (Wells & Kaptchuk, 2012). In one investigation by Silvestri et al. (2003), adults taking beta-blockers were either warned that the medication "may cause erectile dysfunction", not warned, or unaware of the treatment they had received. In the group that was warned about the side effect, the incidence of erectile dysfunction (31.2%) was approximately double that of the group that was not warned (15.6%) and was approximately ten times larger than the group that was not aware of the medication they had taken (3.1%). These outcomes underscore the dilemma for clinicians, who must disclose relevant risks under informed consent, yet risk amplifying such risks via the nocebo effect (Colloca & Miller, 2011a). In an attempt to strike a balance between these concerns, a proposed strategy is "contextualised informed consent" (Faasse, 2019; Wells & Kaptchuk, 2012). This strategy involves tailoring risk disclosure to the specifics of the individual's circumstances, considering the underlying condition, the types of side effects, and the patient's risk of developing nocebo effects. However, this strategy has yet to be investigated empirically and may still undermine informed consent (Faasse, 2019). Ultimately, instruction-based nocebo effects highlight how disclosures about side effects

required to maintain informed consent can unintentionally heighten patients' perception and experience of adverse effects.

Social Learning

In addition to our past experiences and what we are told, nocebo effects can be elicited by what we learn from others, termed social learning. The literature also refers to this phenomenon as observational learning or social modelling, with the terms often used interchangeably. This chapter will provide a brief overview of how social learning can contribute to the nocebo effect, with a more extensive review of the literature provided in Chapter 2. A growing body of work shows that witnessing someone experience adverse treatment-related outcomes can elicit negative expectations in the observer and produce the same adverse outcomes in the observer once they receive the same inert exposure. Social learning was first hypothesised to contribute to placebo effects by Colloca and Benedetti (2009) in which they investigated placebo analgesia induced through social observation. Participants observed a demonstrator show an analgesic effect when the painful stimuli were paired with a green light. They found that placebo analgesia in groups that underwent conditioning themselves was comparable to those who merely observed a peer experience conditioning, and these effects were both larger than that of explicit instruction. This finding was then replicated in a nocebo design, showing that seeing a confederate communicate increased pain to a certain stimulus can increase the observers' own pain scores and skin conductance responses despite being presented with identical thermal or electrical stimuli (Świder & Bąbel, 2013; Vögtle et al., 2013). The effect of social learning is not limited to pain, and has been documented in a diverse array of symptoms (Rooney, Sharpe, Todd, Tang, et al., 2024) with a capacity to sustain over several days (Zhang et al., 2017).

Despite research indicating that social learning is one of the strongest predictors of the nocebo effect (Webster et al., 2016), social learning remains the least explored of the three

nocebo routes (Bajcar & Bąbel, 2018). In an era when therapies are routinely discussed; in support groups, social circles, and virtually across social media, patients constantly encounter social information that has the potential to influence their expectations (Benedetti, 2013). It is therefore relevant both clinically and to society more broadly that we understand the mechanisms of social learning.

Socially-Acquired Placebo and Nocebo Effects

What Counts as Social Information?

Social learning can occur via any communication, both verbal and non-verbal, from a peer concerning a treatment or intervention. The richest version is live, face-to-face modelling: observing a peer discuss or display adverse reactions from a treatment. For example, Faasse et al. (2015) investigated the effects of a sham beta-blocker with participants seated beside a confederate (model) in the waiting room for 15 minutes who had purportedly taken the same beta-blocker. When the experimenter asked the model how they were feeling, they complained citing headache, dizziness, drowsiness, and dry mouth. Participants who observed the model describe symptoms reported twice the number of symptoms compared to participants who viewed the model describe the absence of symptoms. Instead of a confederate, other paradigms have participants observe the model genuinely experiencing the symptoms they report. For example, in a study by Mostafa et al. (2024), observers viewed naive participants undergo classical conditioning in which higher pain was paired with a specific cue (a coloured light). Those who observed the responses of the naive participants subsequently reported increased pain to the same cue despite receiving identical thermal stimuli. Video footage, streamed live or pre-recorded, can also convey this social information (Quinn et al., 2023; Tan et al., 2023; Vögtle et al., 2013; 2016; 2019). However, it has been hypothesised that the magnitude of the nocebo is smaller in these formats in comparison to face-to-face due to factors like camera angle, resolution and the absence of shared context

which can degrade emotional contagion and empathy. Social information can also be communicated via written information. Yoshida et al. (2013) presented participants with pain scores ostensibly provided by eight previous volunteers. They found a relationship between the displayed scores and the observers' own pain reports, demonstrating that social learning can occur without a physical representation of the model.

Mainstream Media. Social information can also be communicated via mainstream media, when news reports include the details of the lived experiences of other individuals with a particular treatment or intervention. This information has been shown to subsequently influence what viewers experience and report. For instance, Bräscher et al. (2017) showed six minutes of a sensational TV segment on the "dangers" of Wi-Fi which was sufficient to increase anxiety and more than double participant reported intensity of innocuous electrical pulses subsequently delivered. Case studies have documented similar effects in the real world, illustrating how the same mechanisms scale outside the lab. In 2008, the manufacturer of 'Eltroxin', a thyroxine medication used in New Zealand, introduced a minor formulation change that testing confirmed was bioequivalent to the original. Despite this, the change was followed by a dramatic increase in reports of adverse reactions to the New Zealand Centre for Adverse Reactions Monitoring (CARM). The first prime-time bulletin to cover the formulation change was followed by a 40-fold jump in daily adverse-event reports, with spikes concentrated in the exact symptoms named on air (Faasse et al., 2012). A similar pattern emerged when negative television stories about a compulsory switch from the branded antidepressant 'Venlafaxine' to the generic 'Enlafax XR' aired in 2018. Reports submitted to CARM rose more than 200%, and again the rise was driven by the side-effects highlighted in the broadcasts, whereas earlier newspaper articles had produced only a modest uptick (MacKrill et al., 2019). More recently, analysis of 64,000 COVID-19-vaccine reports showed that weeks of coverage linking the Pfizer vaccine to myocarditis preceded a 190%

surge in chest-symptom complaints submitted to the CARM accompanied by a rise in vaccine-related anxiety (MacKrill, 2023). Media effects are not confined to symptom reporting: a study found that the UK debate about statin safety was followed by a statistically significant, though temporary, increase in drug cessation among existing users, a behavioural nocebo effect that could translate into thousands of avoidable cardiac events (Matthews et al., 2016). Together, these findings demonstrate that modern mass media can act as potent transmitters of social information resulting in real symptoms, and clinically meaningful changes in health behaviour.

Social Media. Social media contains a wealth of social information that could potentially influence one's expectation and subsequent treatment experience. A prospective survey during the COVID-19 rollout showed that the number of side-effect posts people reported encountering on social media predicted stronger expectancies for vaccine-related side effects and, in turn, more intense post-vaccination symptoms even after controlling for demographic and pharmacological factors (Clemens et al., 2023). A cross-sectional study replicated this finding and identified who is most vulnerable: viewers who already worry about side-effects, rate social media as more credible than mainstream outlets, or had negative emotional states (Tan, Colagiuri, et al., 2022). To date, however, no controlled experiment has systematically investigated the influence of social media on nocebo effects and associated factors like platform algorithms, valence of content, or exposure frequency to establish causal pathways. Thus, the influence of these factors remains empirically unverified and presents an avenue for future nocebo research in the digital age.

Mechanisms and Moderators of Socially-Acquired Nocebo Effects

Expectancy

Expectancy is generally accepted as the primary mechanism through which nocebo effects develop across the three modes of induction (Bajcar & Bąbel, 2018; Benedetti et al.,

2007; Blasini et al., 2017; Faasse, 2019). Across all three pathways, nocebo symptom production is hypothesised to be driven by 'response expectancy' (Kirsch, 1985). Response expectancy refers to one's expectation of a response to an event or stimulus, which Kirsch argued, and subsequent experimental work confirms, is enough to elicit or exacerbate a physiological response. Because the experience of the symptom then confirms the prior expectancy, response expectancies can be self-perpetuating and thus more resistant to extinction (Kirsch, 2018). Therefore, whether aversive expectations are conditioned, suggested, or witnessed in others, it is the same expectancy-driven feedback loop that drives nocebo effects. A recent meta-analysis investigating expectancy and nocebo effects reported that nocebo manipulations increased negative expectancy with a large effect size, and the changes in expectancy due to the nocebo manipulation were in turn associated with larger nocebo effects (Rooney et al., 2022). This relationship between expectancy and experience has also been demonstrated in clinical settings. Meta-analyses of patient expectancies for side effects arising from chemotherapy reveal expectancies for side effects are predictive of side effect experiences above and beyond cancer and treatment related factors (Colagiuri & Zachariae, 2010; Devlin et al., 2017).

While almost all theoretical models of placebo and nocebo effects include expectancy as a central mechanism, there is a paucity of empirical evidence in the context of social learning. The aforementioned meta-analysis by Rooney et al. (2022) of expectancy and the nocebo effect included 28 studies that met specific inclusion criteria, none of which investigated social learning. The evidence that does exist within the social learning literature has limitations. For instance, Vögtle et al. (2019) investigated nocebo hyperalgesia elicited by observation of a social model experiencing heightened pain after the application of an inert cream. They found no relationship between participants expectancies for pain and nocebo response; however, expectancies were measured retrospectively after the pain had occurred

which may have influenced accuracy. Both Koban and Wager (2016) and Tan, Pickup, et al. (2022) report expectancy does mediate socially-acquired nocebo effects, providing the first empirical evidence to support the notion that expectations do play a fundamental role in the development of socially-acquired nocebo effects. Tentative evidence suggests the relationship between expectancy and experience may depend on gender. Quinn et al. (2023) used video-based modelling of medication side-effects and demonstrated that watching others report symptoms heightened side-effect expectations and subsequent nocebo symptoms in female participants only and negative expectancies mediated the modelling-symptom link for women. Given existing evidence is sparse and findings sometimes inconsistent, there is a need for further research to replicate these findings across the broad range of experimental designs to elucidate the precise role expectancy plays in the formation of socially-acquired nocebo effects.

Anxiety

The second central tenet of the nocebo effect is theorised to be anxiety, whereby expectations of a negative outcome causes anxiety which can in turn exacerbate nocebo effects (Faasse, 2019). Theoretically, anxiety has two distinct facets: First, trait anxiety referring to an individual's general propensity towards anxiety. Second, state anxiety referring to context-specific anxiety that may be aroused by receiving treatment in a study involving pain. State anxiety is also sometimes referred to interchangeably as "anticipatory anxiety" or "pre-treatment anxiety" although some consider this to be a third distinct facet referring to specific anxiety in anticipation of an imminent noxious stimulus (Colagiuri & Quinn, 2018; Faasse, 2019; Geers et al., 2021).

State anxiety is theorised to mediate the relationship between expectancy and the nocebo effect. Woo (2015) examined this relationship in patients with chronic wounds who received a change in wound dressing measuring expectation of pain, state anxiety (as

measured by the 'STAI-6', Marteau & Bekker, 1992) and pain intensity. They found that the relationship between pain expectancy and pain perception was mediated via state anxiety. Similarly, another clinical sample consisting of patients receiving chemotherapy, found a significant association between state anxiety and expectation of nausea (Meissner et al., 2019). To the best of our knowledge, only one study has empirically investigated the link between expectancy and anxiety within the nocebo effect. In a combined instruction-and-conditioning experiment, Rooney, Sharpe, Todd, Livesey, et al. (2024) showed that stronger negative expectancies significantly heightened anticipatory anxiety, and path analyses confirmed that nocebo hyperalgesia was mediated by expectancy though anticipatory anxiety. These studies provide preliminary evidence for the relationship between expectancy and anxiety however empirical research is yet to systematically elucidate the link between expectancy, anxiety and the nocebo effect.

A meta-analysis of 21 studies showed nocebo manipulations increased state anxiety with a large effect size and this anxiety was also associated with a larger nocebo effect, however no effect of trait anxiety was found (Rooney et al., 2022). As with expectancy, however, experimental evidence concerning anxiety and socially-acquired nocebo effects is very limited, with only two social learning studies included in the meta-analysis measuring state anxiety and five measuring trait anxiety.

With respect to social learning, the limited empirical evidence concerning state anxiety is mixed. For example, Vögtle et al. (2013) found no significant relationship between pain specific anxiety (as measured by the 'PASS', McCracken et al., 1992) and the magnitude of socially-induced nocebo hyperalgesia. Similarly, Faasse et al. (2015) found that observing a confederate complain of beta-blocker side-effects increased symptom reporting but this modelling did not affect state anxiety. In contrast, Tan, Pickup, et al. (2022) found that participants who viewed a model experience VR cybersickness had increased state anxiety

(STAI-6, Marteau & Bekker, 1992), reported more cybersickness themselves, and that the effect of observation on cybersickness was mediated by state anxiety. Furthermore, Witthöft and Rubin (2013) found that participants with high state anxiety (STAI-6, Marteau & Bekker, 1992) who watched a television segment linking Wi-Fi to health problems later reported more symptoms during a sham Wi-Fi exposure than those who were less anxious. Taken together, the evidence regarding the role of state anxiety in socially-induced nocebo effects is mixed, presenting a need for research to investigate precisely what role state anxiety plays in these effects.

Empathy

The ability to perceive, understand, and feel the negative experiences of others may be necessary to social transmission of symptoms, thus empathy has been hypothesised as a key mechanism for specifically socially learned nocebo effects. Empathy is defined as the capacity to share and understand another person's internal state which can allow observers to translate what they see in others into predictions about their own experience. Contemporary models distinguish affective empathy, referring to one's capacity to share another's emotions, from cognitive empathy, their ability to infer another's thoughts and emotions (Cuff et al., 2016). When an observer watches a model experience symptoms, affective empathy may amplify vicarious distress, heightening salience of the model's symptoms and strengthening negative expectancies about one's own outcome; cognitive empathy may refine those expectancies by allowing the observer to map the model's context onto the self ("that could happen to me"). Without an understanding of the model's experience and emotions perhaps one cannot translate and apply the models' experience to their own.

In an observational experiment investigating the incidence of adverse reactions after donating blood, Mennitto et al. (2021) found a significant effect of social modelling; donors who observed another experiencing an adverse reaction were more likely to report symptoms

themselves and to be treated for a reaction. Donors with higher affective empathy reported more symptoms, exhibited hyperventilation, and were more likely to be treated than those with lower affective empathy. Interestingly, donors with higher cognitive empathy were less likely to require treatment if they witnessed a reaction. A meta-analysis of placebo analgesia and nocebo hyperalgesia induced by observational learning by Meeuwis et al. (2023) found that observational learning was greatest in individuals with the most empathic concern – a subscale of Interpersonal Reactivity Index reflecting the affective component of empathy (IRI, Davis, 1983).

Preliminary evidence suggests the effect of empathy on socially-acquired effects may depend on the medium of consumption, face-to-face or via video. This is supported by tentative evidence borrowed from the placebo literature that found empathy correlated with placebo analgesic effects from in-person modelling, but not pre-recorded video modelling (Hunter et al., 2014). The authors hypothesise that while the pre-recorded videos may have been sufficient to communicate information to influence expectation of pain, more subtle non-verbal cues may have been more difficult to perceive and comprehend via video. This effect has not yet been tested in a nocebo paradigm, but the available evidence points the same way: empathy moderated nocebo responses are present in two studies that used face-to-face modelling (Faasse, Yeom, et al., 2018; Świder & Bąbel, 2013) whereas four video-based studies detected no such influence (Tan et al., 2023; Vögtle et al., 2013; 2016; 2019). Pinpointing when, and through which channels, empathy magnifies or dampens socially-acquired nocebo effects is therefore a key task for future research.

Model and Observer Gender

Model and observer characteristics like gender have been hypothesised to influence the formation of socially-induced nocebo effects (Faasse, 2019). Epidemiological observations of mass psychogenic illness (MPI) have long suggested a sex bias: outbreaks

typically disproportionately affect women or girls (Bartholomew & Wessely, 2002; Bartholomew et al., 2012; Faasse et al., 2012; Jones et al., 2000). The pattern is generally attributed to a combination of greater interoceptive focus, higher baseline anxiety, and gendered social roles. A recent exception was the predominance of men reporting adverse events after extensive media coverage of COVID-19 vaccines, however, this appears attributable to sex-specific messaging that emphasised risk for males (MacKrill, 2023).

Interestingly, the recent outbreak of "Tourette-like" symptoms purportedly driven by social media exposure illustrates how the model's gender can also play a role (Müller-Vahl et al., 2021). In Germany, where the most prominent influencer displaying functional tic behaviours was the male YouTuber Jan Zimmermann, approximately half of the newly affected adolescents presenting to specialty clinics were boys. In contrast, Canadian centres reported approximately 90% of affected adolescents were female which aligned with the gender of the prominent English-language influencer, the TikTok creator Evie Meg. The authors contend that identification with a same-sex role model on social media may have facilitated symptom adoption, an interpretation that aligns with Bandura and Walters (1977)'s hypothesis that social learning is amplified by similarity between model and observer. While such case studies suggest increased susceptibility in women, controlled experiments are needed to disentangle the influence of observer gender, model gender, and their interaction.

Several laboratory studies have shown that female observers are more vulnerable to socially-acquired symptoms than males. In Lorber et al. (2007) participants inhaled an inert substance presented as a potential environmental toxin. After watching a female confederate complain of symptoms, only female observers reported significant increases in symptoms communicated by the model. Similarly, Faasse et al. (2015) found that watching a female model report side-effects increased symptom reporting in women but not men, a pattern Quinn et al. (2023) replicated even when two confederates, a male and female were present.

Świder and Bąbel (2013) attempted to disentangle the effects of model and observer gender by comparing nocebo hyperalgesia following observation of male versus female models in both male and female participants. They found no effect of observer gender in nocebo hyperalgesia produced by electrical stimuli. Interestingly, the *model*'s gender was found to play a significant role. They found male models produced significantly larger nocebo hyperalgesia than female models regardless of observer gender. The authors hypothesise that the male demonstrator may simply be judged a more credible source about a nociceptive stimulus: observers of either sex tend to believe that men under-report pain (Robinson et al., 2001), so complaints from males may be interpreted more seriously. Taken together, these studies suggest that male models may elicit nocebo effects in both male and female observers, however, female models are only effective for female observers.

Yet perhaps it is not the model or observers' gender but a *match* that facilitates nocebo effects. In Faasse, Yeom, et al. (2018) participants self-administered a placebo nasal spray and sat beside either a male or a female confederate who did, or did not, report headache and dizziness. Observation of symptoms increased those same symptoms in all observers, but in contrast to the studies previously discussed, this effect was independent of both observer and model gender. Regardless of whether the participant observed the model display symptoms or an explicit lack thereof, females paired with a female confederate revealed elevated levels of symptoms. This concurs with Mazzoni et al. (2010) who found that the match between confederate and observer gender facilitated increased symptom reporting. As with Faasse, Yeom, et al. (2018) this effect was independent of modelling condition such that the mere presence of a same sex confederate increased symptom reporting even if the confederate did not model symptoms. Given the diversity in the design of these experiments and outcome symptoms it is therefore difficult to understand these inconsistent results and synthesise a cohesive theoretical account of the effect of gender within socially-induced nocebo effects.

Other Model and Observer Characteristics

The theory of social learning proposes that social learning is facilitated by model observer similarity such as shared gender, age, ethnicity, or even values and that social status may also play a role (Bandura & Walters, 1977). Empirical tests of these moderators in the nocebo domain are scarce, but preliminary insights can be drawn from placebo analgesia research. Bieniek and Bąbel (2022) showed healthy volunteers a video of either a high-status "professor" or a low-status "janitor" rating colour-coded pain stimuli. Both groups later exhibited socially-induced placebo analgesia, and this effect did not differ by the model's assigned status. However, participants' own perceptions of the model's prestige predicted the magnitude of their analgesic response, suggesting that subjective status appraisals, not nominal role labels, modulate social-learning effects. Beyond gender and status, no studies have yet manipulated model–observer characteristics to investigate the role of similarity in the formation of socially-induced nocebo effects. Systematic tests of these variables are needed to clarify what characteristics of models and observers amplify or attenuate symptom transmission.

Generalisation and Spread of Nocebo Effects

Peer-to-peer spread. Recent evidence suggests that nocebo effects are not restricted to the individual in whom they originate; instead, they can be socially transmitted, producing "symptom chains". Tan et al. (2023) provided the first experimental demonstration of such propagation using a three-generation design delivered via video conferencing software Zoom. Participants in the "First generation" observed a model communicate the experience of cybersickness after a VR experience. This observation elevated the observers' state anxiety, negative expectations, and subsequent cybersickness when they themselves experienced VR. Participants in the "second generation" observed participants in the "first generation" undergo the VR experience, and the "third generation" observed the experience of the second.

Whether cybersickness propagated further along the "social chain" depended on what the participants in the first and second generation then verbally communicated: if the first-generation (or second) participant voiced strong symptoms, the second-generation (or third) observer also felt sicker; if they verbally reported no ill-effects, transmission ceased. Mostafa et al. (2024) replicated and extended these findings with a thermal-pain paradigm. Naïve "first-generation" demonstrators underwent classical conditioning in which one of the two visual cues was paired with higher heat pain. "Second-generation" observers then watched these demonstrators, whereas "third-generation" observers watched the second generation receive identical heat stimuli for both cues. Despite the absence of differential thermal stimuli beyond the first generation, robust nocebo hyperalgesia emerged in both later generations. Its magnitude was predicted by the extent to which each observer's electrodermal activity and expected pain correlated with the demonstrator's responses, indicating that interpersonal physiological and psychological synchrony acted as a conduit for social transmission. Collectively, these studies show that nocebo effects can propagate through social networks, whether interactions occur face-to-face or online, and that this contagion is fuelled by heightened anxiety, negative expectancies, and synchrony between observers and demonstrators.

Spread to non-modelled symptoms. In contexts where more than one symptom can be elicited by a treatment or intervention a distinction emerges between modelled and non-modelled symptoms. Modelled symptoms refer to the symptoms explicitly communicated via the confederate, and non-modelled symptoms referring those symptoms not expressly communicated by the confederate. Interestingly, social modelling has been shown to influence both. Faasse, Yeom, et al. (2018) investigated the effect on participant reported symptoms who viewed a model reporting the experience of headaches and dizziness in response modafinil (actually a placebo) compared to observation of a model who described

the absence of such side effects. After one hour, they found a significant increase in modelled symptoms (i.e., headaches and dizziness specifically) in participants who viewed the model report symptoms, but no increase in general symptoms (remaining general symptoms as measured by a modified version of the GASE). Interestingly, when measured the following day (24 hours), they found the effect of social modelling generalised with increased incidence of both modelled *and* non-modelled symptoms. Tan et al. (2023) also documented an increase in modelled and non-modelled symptoms after social modelling compared to a no social modelling control. These cases appear to demonstrate the propensity for nocebo effects to spread beyond information communicated by the model, which is of significant concern and warrants further investigation.

Generalisation to similar stimuli and contexts. Generalisation refers to the adaptive tendency for learning acquired in one situation to transfer to novel but related stimuli or contexts (See Ghirlanda & Enquist, 2003 for a review). For example, rats trained to learn that a specific tone leads to shock will display a defence response to that specific tone and other similar tones (Armory et al., 1997). Evidence suggests that placebo and nocebo effects exhibit similar generalisation gradients. In a heat pain paradigm, Kampermann et al. (2021) demonstrated that placebo analgesia generalised according to similarity of treatment cues. Likewise, learned pain modulation generalises across perceptually similar stimuli, with Koban et al. (2018) showing that pain responses to novel visual cues followed a graded pattern predicted by similarity to previously conditioned high- and low-pain cues, driven by expectancy. Generalisation has also been documented across treatment features and contexts, with conditioned placebo and nocebo effects transferring to differently branded treatments (Kessner et al., 2014), alternate administration routes (Zunhammer et al., 2017), and new environmental settings (Quinn et al., 2015). In socially-acquired contexts, generalisation may occur when an observer applies another person's treatment experience to their own. However,

research to date has exclusively examined social learning under conditions where the model and observer receive identical interventions. In real-world settings, social information concerning side effects is unlikely to remain confined to like-for-like experiences and social transmission of side effects may occur across related treatments, substantially expanding the opportunity for social information to shape symptom perception. Investigating whether socially-acquired nocebo effects generalise in this way is therefore essential.

Interventions to Reduce Nocebo Effects

Socially transmitted nocebo effects can amplify symptoms, undermine adherence, and impose a substantial burden on patients and healthcare systems, thus identifying strategies to attenuate these responses is a clinical priority. Several promising approaches have emerged, although the evidence specific to social learning remains preliminary and sometimes inconsistent.

Positive Side-effect Framing

One proposed technique involves presenting statistical risk information in a positive way, instead of warning that "three in ten patients *will* experience headaches", emphasise that "seven in ten patients *will not* experience headaches" (Barnes et al., 2019). Although Faasse, Huynh, et al. (2018) found that positively framed information decreased nocebo side-effects during a one-hour session, this benefit was not present at a 24-hour follow-up, suggesting that framing alone may deliver only temporary protection. Another study revealed positive framing of adverse-event statistics for COVID-19 boosters increased vaccine intentions in Australian adults, showing translational potential for public-health messaging (Barnes et al., 2023). However, other research has failed to detect any framing benefit (Caplandies et al., 2017; Devlin et al., 2019), indicating that framing effects may be small or depend on factors like the mode of warning delivery and statistical presentation of the side effects. To our

knowledge, only one unpublished honours thesis has investigated the framing in the context of socially elicited nocebo effects which found no effect, tentatively undermining the utility of this method in mitigating socially elicited nocebo effects (Pickup, 2020).

Nocebo Education

Educating people about the nocebo effect may be a promising avenue for future research. The logic is that, once patients understand that some adverse reactions are driven by expectations rather than by the drug itself, they may reinterpret benign sensations and report fewer side-effects. Early evidence in the context of instructed nocebo effects supports this idea, with education delivered via leaflet, video or counselling session each resulting in a reduction of symptoms in response to infrasound exposure, chemotherapy and a placebo pill respectively (Crichton & Petrie, 2015; Michnevich et al., 2022; Pan et al., 2019). MacKrill et al. (2021) compared nocebo education with a negative media clip about a supposed cognitive enhancer (actually a placebo); education yielded fewer reported side-effects than the negative media, although the study did not test whether education can actively offset media-induced nocebo responses. With respect to the utility of education in the prevention of socially elicited nocebo effects empirical research is limited and in some cases education may actually have negative consequences. Boland (2022) used a VR model of socially elicited cybersickness where half of participants were randomised to receive education or no education prior to observing a model experience cybersickness. Nocebo education paradoxically increased both expectancies and state anxiety and failed to reduce socially elicited symptoms. There are a few potential causes of this unusual result. Firstly, the education included an account of how the nocebo effect could contribute to cybersickness which may have unintentionally emphasised the possibility of cybersickness. A similar backfire effect was observed in a study that designed an educational video intended to boost confidence in generic analgesics, which paradoxically increased symptom reporting and reduced analgesic benefit (Colgan et al.,

2016). Colgan et al. also hypothesize that the intervention may have unintentionally drawn attention to value of branded medications. A complication with educational interventions more generally is the necessity to repeat misinformation, or in the case of nocebo effects, side effect information, to provide an alternative explanation which can place unintended emphasis on the wrong information (Swire-Thompson et al., 2020). Secondly, delivering the education to model and observer simultaneously at the beginning of the session may have undermined its credibility. The confederate's visible distress could have suggested to the observer that either the education was ineffective or that the VR headset genuinely caused illness, thereby failing to mitigate nocebo responses. Thus, nocebo education may be ineffective in situations where nocebo education is delivered prior to social modelling. Overall, nocebo education is inexpensive and easy to deliver, but its impact is variable depending on careful attention to message content, framing, and possibly route of nocebo induction.

Choice

Choice is inherently desirable, and conversely, the restriction of choice can be stressful (Leotti & Delgado, 2011), thus choice has been proposed as a low cost, ethical intervention to enhance placebo effects and reduce nocebo effects. A recent meta-analysis showed that allowing patients to choose their treatment enhances the placebo effect (Tang et al., 2022). The literature concerning the effect of choice in the context of the nocebo effect is limited and the evidence mixed. Bartley et al. (2016) gave volunteers either a choice of (placebo) beta-blockers or an assigned pill after an explicit side-effect warning. Participants granted choice reported fewer adverse effects and lower state anxiety than assigned counterparts. In a similar experimental paradigm, Faasse et al. (2023) conducted two laboratory studies examining whether treatment choice influences nocebo side effects following sham medications. In Study 1 (sham beta-blocker) and Study 2 (sham

benzodiazepine), participants were assigned to either no choice, choice between two treatments, or a no-treatment control. Across both studies, participants given no choice showed significant nocebo effects, reporting more warned side effects than the control group. In contrast, participants offered a choice between two options did not show a significant nocebo effect. Study 2 further demonstrated that excessive choice can undermine this benefit: when participants chose between ten options, side effect reporting increased to levels comparable with the no-choice condition. These findings suggest that some choice may reduce the nocebo effect, but too many options may negate this protective effect. Interestingly, recent experimental work suggests that choice can backfire in the context of conditioned pain. Tang et al. (2024) examined conditioned nocebo hyperalgesia using a sham device and found that participants given instrumental control over treatment administration showed greater nocebo hyperalgesia than those without choice. That is, allowing participants to choose when to activate the (sham) device amplified pain rather than providing a protective effect. A follow-up study demonstrated that providing positive information about the benefits of control did not attenuate this effect. Given these mixed findings, it remains uncertain the precise effect choice has on the nocebo effect. Furthermore, whether choice can offset nocebo effects acquired through observing others remains untested, but the theoretical mechanism—restoring/maintaining a sense of agency—may be particularly relevant when negative expectations originate in external social cues.

Framing, nocebo education and choice represent only a fraction of the available approaches; a comprehensive overview is provided by Faasse (2019). Crucially, no study we are aware of has successfully identified an intervention that can dampen nocebo effects that arise through social modelling. Since the mechanisms and moderators of social learning differ to that of instruction and conditioning, it cannot be assumed that methods effective for instruction or conditioning-based nocebo effects will generalise. Empirical investigation is

therefore necessary to develop and refine strategies that address socially transmitted nocebo responses. Given the considerable clinical and economic burden of nocebo-induced symptoms, designing and implementing such evidence-based interventions should be a high research priority.

The Current Project

The overarching aim of the present thesis was to explore socially-acquired nocebo effects by elucidating the mechanisms, identifying moderating factors and investigating interventions to prevent its occurrence. As an introduction to the literature, Chapter 2 presents a systematic review and meta-analysis of socially-acquired nocebo effects, published in *Health Psychology* (Saunders et al., 2024). This chapter estimates the size of socially-acquired nocebo effects relative to control and relative to other forms of induction, while also exploring moderators of these effects. Chapter 2 therefore provides insights into the current understanding of socially-induced nocebo effects.

Given the propensity for socially-acquired nocebo effects to spread, propagating through chains of peers and from modelled to non-modelled symptoms, Chapters 3 and 4 explore a novel kind of spread: between similar treatments. Previous research has focused exclusively on instances where the model and observer undergo identical treatments/ interventions. Considering the wealth of (primarily negative) treatment related information on social media, it is likely one could come across information that relates to one's specific treatment, as well as other similar treatments that may contribute to expectations. Chapter 3 is published in *Annals of Behavioral Medicine* exploring this question using a VR model of cybersickness, where participants either observe a model undergo the same VR experience as them or a similar, but different experience (Saunders et al., 2023). Chapter 4 investigates this same question within a simulated clinical setting, where participants either observe a model experience side-effects as a result of the same treatment they received, or a similar, but

different treatment. Chapter 4 is published in *Scientific Reports* (Saunders, Tan, Barnes, et al., 2025). Together, these studies investigate whether socially-acquired nocebo effects can generalise to novel contexts and treatments.

As discussed, investigating strategies to reduce socially elicited nocebo effects is of utmost importance. To address this gap in the literature Chapters 3 and 5 investigate two methods with which to reduce socially-acquired nocebo effects. Chapter 3 investigates whether giving participants choice in the VR environment can mitigate the effect of observation and is the first study to examine choice as an intervention in a social learning context. Chapter 5 designs and explores a novel intervention, utilising social modelling itself, investigating whether the pairing of positive social information with side effects warnings can reduce the subsequent impact of side effect modelling. Chapter 5 is published in *Annals of Behavioral Medicine* (Saunders, Tan, Ng, et al., 2025).

In line with the thesis' aim to investigate mechanisms and moderators of the nocebo effect, Chapters 3, 4 and 5 all include measures of expectancy and anxiety to elucidate their role in socially-acquired nocebo effects.

Finally, Chapter 6 synthesises and discusses the collective findings of the present project, including theoretical and practical implications, limitations, and future avenues of research.

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Chapter 2: The effect of social learning on the nocebo effect: a systematic review and meta-analysis with recommendations for the future

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*co-first authors

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Introduction

The nocebo effect is a psychobiological phenomenon in which an individual experiences an increase in the severity, or even the genesis, of adverse health outcomes (e.g., pain, nausea, side effects) that cannot be otherwise explained by a treatment or intervention's active components. As many as 76% of systemic adverse events experienced in the active arms of COVID-19 vaccination trials also occurred in the placebo arms, suggesting a strong role of nocebo effects in ubiquitous experiences such as COVID-19 vaccine side effects (Haas et al., 2022). Beyond the experience of these undesirable symptoms, nocebo effects can lead to perceptions of poorer treatment outcomes (Corsi et al., 2016) and cause non-adherence to otherwise effective treatments (Barsky et al., 2002). As such, it is paramount that we identify the mechanisms driving nocebo effects so that interventions to combat them can be devised. Social learning is a potentially key factor in the formation of these nocebo effects.

Social learning occurs when individuals modify their beliefs and behaviours after observing the behaviour of others (Bandura & Walters, 1977). It can play a considerable role in shaping an individual's expectations and experiences, particularly within health contexts. As social learning can occur independent of direct experience, it enables individuals to receive additional, albeit often anecdotal, information about treatments and medications. This information may extend beyond the health information typically disseminated by health professionals. For example, while a doctor may provide written descriptions and verbal suggestions about a treatment's side effects, individuals can also learn by observing another person's treatment experience or receiving experiential information through social channels such as conversations with friends and the use of social media. Consequently, individuals may develop negative expectancies concerning the likelihood or severity of side effects by observing others independently of the information communicated to them by their physicians.

A growing body of literature has demonstrated that social learning can modulate the experience of a variety of health outcomes – e.g., pain (Vögtle et al., 2013; 2016; 2019), medication side effects such as headache and dizziness (Faasse et al., 2015; Faasse et al., 2018), and nausea (Tan et al., 2023). Furthermore, social learning has been proposed to play a central role in community-level nocebo effects including idiopathic environmental intolerance attributed to electromagnetic fields (Witthöft & Rubin, 2013) and wind turbine syndrome (Rubin et al., 2014). Experiential information communicated through social media has also been implicated in the experience of COVID-19 vaccination side effects (Clemens et al., 2023; Tan et al., 2022). Information about the experience of others thus appears to be pivotal in the construction of our own perceptions and experiences of treatments and health-related interventions.

However, it is important to emphasise that what is modelled by an individual can differ in valence. Social modelling can be negative, positive, or neutral in nature. Negative modelling occurs when an individual demonstrates worsened health outcomes following a treatment or intervention (e.g., increased pain). Positive modelling occurs when a model emphasises the alleviation of negative symptoms or an increase in a desired effect (e.g., decreased pain). Last, neutral modelling occurs when the model presents no difference in outcomes before, during, or after exposure to the intervention (e.g., no change in pain). The valence of the social information presented by the model can also be multifaceted, in that an intervention or treatment could lead to positive effects in some domains (e.g., improved cognitive performance) at the same time as negative effects in others (e.g., adverse side effects). This is important because existing studies on socially-induced nocebo effects vary in the types of comparison groups they employ (e.g., negative versus neutral modelling). This may subsequently influence the effect size observed.

In addition to social learning, nocebo effects are known to be induced via other processes such as conditioning and explicit instruction (Blasini et al., 2017). Conditioned nocebo effects arise when a neutral conditioned cue is repeatedly paired with an active unconditioned stimulus such that the conditioned cue elicits adverse outcomes when presented alone (Stewart-Williams & Podd, 2004). For example, elements of the chemotherapy treatment context (e.g., the catheter) can become associated with the chemotherapy-induced nausea such that the appearance of treatment (e.g., connection of the catheter) elicits anticipatory nausea and vomiting prior to the administration of the chemotherapy itself (Kamen et al., 2014). On the other hand, nocebo effects induced by explicit instruction occur when physicians inform patients that they may experience enhanced pain, increased symptom severity, or adverse side effects (Colloca & Miller, 2011). In one instance, when verbally informed that a local anaesthetic injection would "feel like a big bee sting; this is the worst part of the procedure", participants experienced significantly greater pain relative to those who were told that "the local anaesthetic injection will numb the area and you will be comfortable during the procedure" (Varelmann et al., 2010). While classical conditioning and explicit instruction have been shown to be highly influential in placebo and nocebo contexts, social learning has received less theoretical and empirical attention despite its potential relevance to both individual and community-level nocebo effects.

To date, there has not been a comprehensive appraisal of socially-induced nocebo effects. A recent systematic review included social learning as part of a wider exploration of contributing factors to nocebo effects, highlighting that social learning could be one of the strongest forms of nocebo induction (Webster et al., 2016). However, in this systematic review, only three nocebo studies with a social learning manipulation were identified. Recent interest in social learning as a mechanism of nocebo effects means that more studies are currently available, which will allow a meta-analysis of studies. This was not attempted in the

Webster et al. (2016) review. A subsequent meta-analysis of 17 studies focused on placebo and nocebo effects arising from social learning specifically for pain (Meeuwis et al., 2023). While interesting for understanding pain itself, the review's focus on pain limits the ability to determine the extent to which social learning can influence other symptom domains often experienced in clinical settings (e.g., headache, dizziness, and nausea). The present meta-analysis therefore aimed to quantify the effect of social learning across a variety of nocebo-related health outcomes. Most recently, a large-scale meta-analysis estimated the nocebo effect size in 130 studies across any induction type and condition, but it only briefly compared social learning to other forms of induction at an omnibus level and did so including indirect cross-study comparisons that do not control for key factors, such as type of sample and target condition (Rooney et al., in press). Accurately estimating the effect size of socially-induced nocebo effects is essential for developing interventions to minimise their occurrence in clinical and community settings.

In terms of mediators and moderators, negative expectations and state anxiety are two constructs thought to drive the formation of nocebo effects (Faasse, 2019). A meta-analysis of 59 studies found that increased negative expectations for adverse outcomes and higher state anxiety were both associated with larger nocebo effects (Rooney et al., 2022). However, the specific association between these factors and socially-induced nocebo effects has yet to be explored. Individual characteristics such as trait empathy have also been suggested as a contributing factor, with some indication that the affective component of empathy is critical across pain-based (Meeuwis et al., 2023) and side effect-based (Mennitto et al., 2021) symptom domains. Moreover, while there is some indication that females may be more susceptible to the social modelling of nocebo effects (Faasse, 2019), there has yet to be a systematic evaluation of the role of gender. Beyond these factors, there are several other features, particularly those relevant to the content of the modelling itself, that could moderate

socially-induced nocebo effects. For example, the mode of delivery (e.g., whether the modelling occurs in a face-to-face setting or through video observation) could be pivotal, given that the complexity of available social cues is likely to vary. Relatedly, it might be intuitive to assume that longer exposure to negative modelling would be positively associated with greater nocebo effects, yet this has not been examined.

In summary, despite increasing research in the area, we currently do not know the effect size of social learning on nocebo effects across multiple symptom domains and relative to other forms of nocebo induction, nor which factors moderate the effect. The present meta-analysis thus aimed to synthesise the current understanding of socially-induced nocebo effects by addressing three key research questions: (1) does social learning elicit nocebo effects?; (2) what is the relative influence of social learning compared to classical conditioning and explicit instruction?; and (3) what are the moderating factors that underpin socially-induced nocebo effects?

Methods

The present meta-analysis protocol was pre-registered on the PROSPERO register (registration ID: CRD42022383720).

Search Strategy

Studies were identified by searching the following databases: Embase, CINAHL, PubMed, Scopus, PsycINFO, and Web of Science. A subsequent citation search was conducted by manually searching the reference lists of included studies (backward search) and reviewing studies that had cited included studies (forward search). The search strategy can be found in section 1 of the Supplementary Material.

Selection Criteria

Included studies had to report original data where there was at least one social learning manipulation. This manipulation required the observation of another's behaviours, attitudes, or emotional expressions regarding side effects or unwanted effects experienced as a result of a treatment or procedure described to participants as being active.

In addition, included studies required at least one of the following comparator conditions:

a) No treatment control. A condition in which the participant does not receive any social information and/or does not receive treatment.

b) Neutral social modelling control. A condition in which the participants receive modelling of either an absence of negative effects (e.g., not feeling side effects) or no difference between nocebo stimulus and control (e.g., the same reaction to a nocebo cream and control cream).

c) Explicit Instruction. This condition consists of verbal or written information communicated to individuals regarding the supposed effects of a treatment/an intervention that is not social in nature.

d) Classical Conditioning. This condition consists of direct experience with the supposed effects of a treatment/intervention.

In addition, all included studies had to report symptom intensity and/or frequency outcomes (e.g., pain or side effects) or related data (e.g., unpleasantness). Between and within-subject designs were included. In all cases, studies had to fully or quasi-randomise participants, either in terms of group allocation (between-subjects designs) or counterbalancing the order in which participants undergo each condition (within-subjects designs) to be eligible. The review intended to include data from healthy and clinical populations.

Study Selection

Two researchers (W.T. and C.S.) conducted an initial search and compiled the retrieved titles and abstracts into Covidence, from which duplicates were removed. The same two researchers then independently performed a title and abstract screening. If any conflicts in the decisions between the researchers existed, the two researchers resolved this conflict via discussion. Following this initial screening, the texts of all potentially relevant studies were independently reviewed in full by the two researchers to determine the final included studies. Conflicts in decisions were reviewed by a third researcher (K.B.), who discussed their own opinion with the first two researchers until consensus was reached.

Data Extraction

Data from the included studies were extracted using a Covidence data extraction template designed by the researchers. Extracted information included relevant study characteristics such as: publication year, country of origin, sample size, study population (i.e., healthy or clinical), gender (% female), and mean age. The following information was also extracted: experimental design, medium of social learning, type of nocebo intervention (i.e., primary or secondary), model gender (% female), number of models, type of nocebo exposure (i.e., inert or active nocebo stimulus), modelled symptoms, type of treatment/manipulation, and duration of modelling procedure. Where available, data regarding measures of trait empathy, expectancy, and anxiety were also extracted. Correlations were extracted between individual empathy scores and symptom intensity scores for between-subjects designs (or the social learning stimulus intensity minus the control stimulus intensity if within-subjects or mixed) across social learning conditions. This correlation reflects the relationship between empathy and social learning. In cases where data was not available and authors did not respond to requests for data (k = 4; 20%), the R

package ‘metaDigitise’ was used to extract primary outcome, expectancy, and anxiety data from figures with sufficient resolution (Pick et al., 2018).

Independence of Results

If a study measured more than one primary outcome (Barbiani et al., 2018), the outcome that most closely aligned with the symptoms that were modelled was chosen. If more than one time point was measured (Lorber et al., 2007; Zhang et al., 2017), measurement closest in time after the nocebo manipulation was extracted. If a study had multiple eligible groups/conditions for analysis within the same research question and thus “shared” a group in the calculation of each effect size (i.e., Quinn et al., 2023, investigates the effect of both neutral modelling and no treatment), the sample of the shared group (i.e., the negative modelling group) was halved to generate two effect sizes (Higgins et al., 2011). Therefore, all comparisons included can be considered independent. The random effects model implemented accounted for the effect of study in the case that there were multiple independent effects reported from the same study (Harrer et al., 2021).

Outcome Data

The meta-analysis was conducted using R 4.2.2 (R Core Team, 2022) using the package ‘metafor’ (Viechtbauer, 2010). The included studies utilised different designs in different populations, therefore a random-effects model was implemented to take into account the within-study error and the between-study variance. Between-study heterogeneity (τ^2) was estimated using a restricted maximum likelihood procedure recommended by Viechtbauer (2005). Hedges’ *g* values of 0.2, 0.5 and 0.8 were respectively interpreted as small, medium, and large effect sizes (Cohen, 1988).

Heterogeneity and Publication Bias

To assess the presence of between study heterogeneity, Cochrane's Q was examined and I^2 was calculated to quantify the percentage of between study heterogeneity. In accordance with Cochrane recommendation, I^2 was interpreted using the following thresholds: <40% - not important; 40-60% - moderate heterogeneity; 50-90% substantial heterogeneity, and 75-100% - considerable heterogeneity (Deeks et al., 2022). To test for publication bias, graphical funnel plots were created, and the Egger test subsequently used to assess asymmetry (Egger et al., 1997).

Moderators

Moderator analysis was conducted using sub-groups analysis for categorical moderators and meta-regression for continuous moderators. This analysis was only conducted when sufficient data existed. For categorical variables the minimum number of studies per group was three, and for continuous variables a minimum of nine was required (Fu et al., 2010).

Risk of Bias Assessment

All included studies were assessed using the Risk of Bias 2 (RoB 2) tool provided by the Cochrane Collaboration (Sterne et al., 2019), as highlighted in the PRISMA 2020 Statement (Page et al., 2021). This assessment was conducted by two researchers (W.T. and C.S.), and disagreements were adjudicated by a third independent assessor (B.C.). Risk of bias for each study was assessed in five domains: randomisation, deviation from intended interventions, missing outcome data, measurement of the outcome, and reporting bias. Within the context of nocebo research, any form of verbal suggestion prevents participants from being blinded to the intervention. Furthermore, the key intervention assessed in the present meta-analysis is social learning, rather than the effects of the specific treatment or

intervention. Therefore, deviation from intended intervention bias was assessed based on participant blinding to the social learning manipulation rather than to the treatment/manipulation itself. Reporting bias was weighted less heavily in calculation of overall risk of bias as all included studies were experimental and the pre-registration of studies was not common practice for these studies when most were originally conducted.

Deviations from the Registered Protocol

Over the course of the literature review and study search, it became apparent that a significant portion of the social learning literature compared the social modelling of negative outcomes to the social modelling of the *absence* of negative outcomes. That is, in the latter scenario, the model experiences the treatment but communicates a lack of negative response. In one example, after taking a supposed beta blocker, the model reported feeling fine, with no experience of side effects (Faasse et al., 2015). Thus, in the interest of accurately reflecting the state of the literature, the first pre-registered research question was expanded to answer: "Does social learning elicit a nocebo effect in comparison to a control?" and "Does the type of control group implemented (no treatment vs neutral modelling) affect the size of the nocebo effect elicited?".

Results

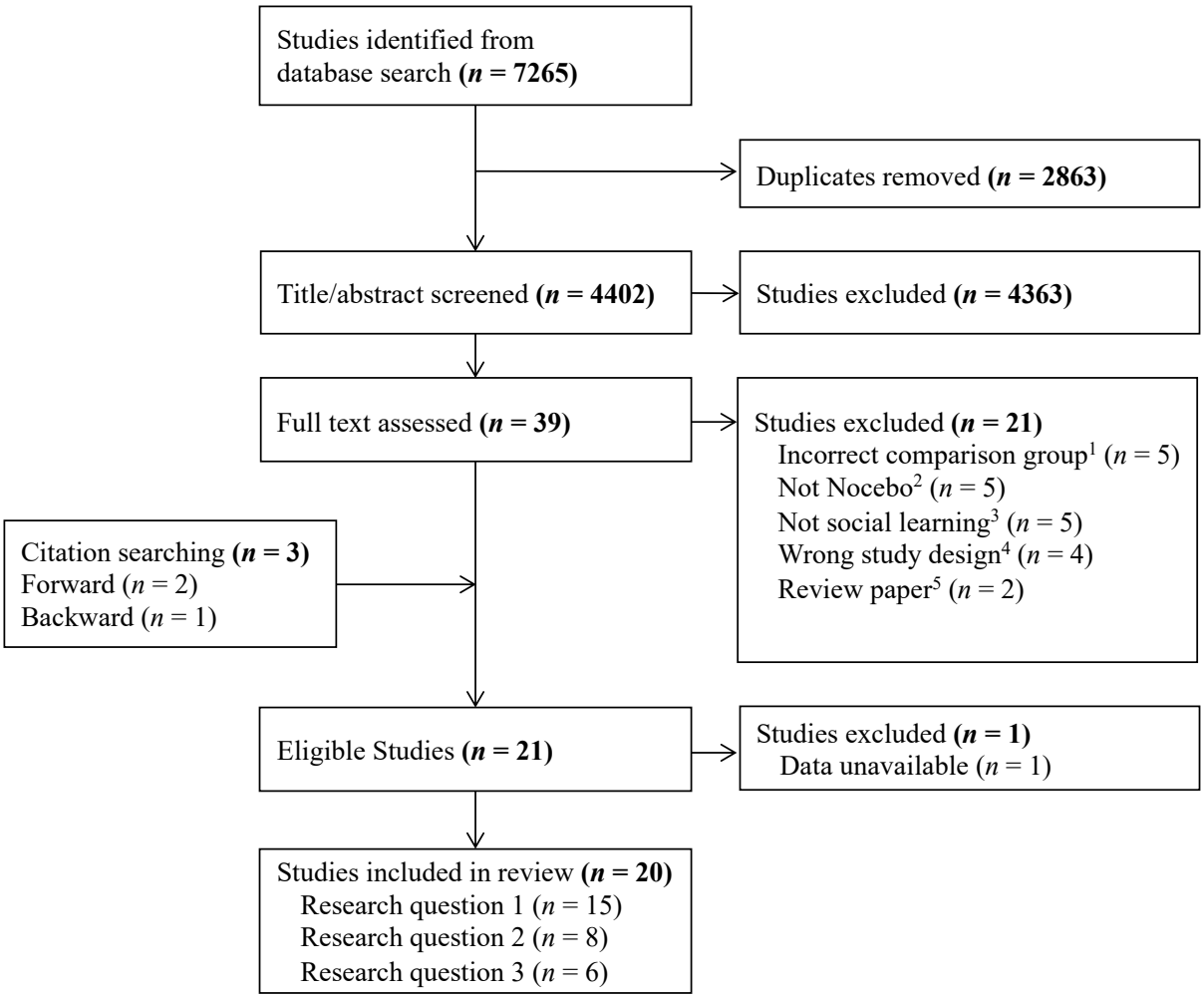
Study Selection

A total of 7,264 articles were identified through an initial database search, with 4,402 remaining following the removal of duplicates. Title and abstract screening resulted in the exclusion of a further 4,363 studies. Full text review was conducted on the remaining 39 studies, with 21 identified as ineligible. Of the 18 studies determined eligible, citation searching resulted in the inclusion of an additional 3 studies. Data was unavailable for only

one eligible study. Therefore, 20 total studies were included. Refer to section 2 of the Supplementary Materials for the references of included studies.

Figure 1.

PRISMA flow diagram.



Note. [1]Did not have a comparison group that satisfied any of the prespecified criteria. [2]Only assessed placebo effect. [3]No social information communicated, e.g., media reports without explicit social information. [4]Study was not fully or quasi-randomised. [5]Review paper, no original data.

Study Characteristics

A summary of the study characteristics is provided in Table 1. The 20 included studies had an average included sample size of 66 participants, ranging from 20 (Egorova et al., 2015) to 147 (Witthöft & Rubin, 2013) participants. The mean participant age across included studies ranged from 19 to 43, with the exception of one study conducted with children (Van Lierde et al., 2020). All included studies had a minimum of 50% female participants (overall mean 68%). Most studies originated from Europe (k = 11, consisting of studies originating from Germany, UK, Poland, Italy, Netherlands, Belgium, and Turkey) or the United States *(k* = 4). All included studies were based on samples of healthy participants. Nine studies used a mixed design, three used a within-subjects design, and eight used a between-subjects design. There were several types of nocebo stimuli, with placebo treatments including creams (k = 4), pills (k = 3), and nasal sprays (k = 3), and manipulations such as electrical and heat manipulations (k = 4), virtual reality, EEG caps, high altitude, metal rings, cold pressor tasks, and electromagnetic field (EMF) exposure (each k = 1). Fourteen studies investigated primary nocebo effects (e.g., where negative health outcomes were the primary or main focus of treatment) and five investigated secondary nocebo effects (e.g., where negative health outcomes existed as a corollary to positive outcomes). The majority of nocebo interventions were inert (k = 14), while a minority of studies assessed active nocebo interventions (k = 6). Eight studies communicated social information face-to-face, while 12 utilised video observation. Of these 12 video modelling studies, one study utilised live modelling via Zoom (as opposed to pre-recorded videos) (Tan et al., 2023) and Witthöft and Rubin (2013) utilised a pre-recorded media report that contained excerpts of a “genuine” sufferer of EMF exposure describing their symptoms. Most studies only had one social model deliver the social learning manipulation to participants (k = 17), however three studies investigated social learning with two models. The duration of the social learning manipulation ranged from 1 minute (Faasse

et al., 2015; Faasse et al., 2018) to 12 hours (Barbiani et al., 2018), however with the exception of Barbiani et al. (2018), all other studies had social learning interventions of less than 1 hour. A variety of symptom domains were explored, with pain as the most frequently studied (k = 10). Other symptoms studied included itch, headache, nausea, and dizziness with many studies assessing more than one symptom. Seven studies measured empathy and reported a correlation between empathy and the nocebo response within the social learning condition. Of the studies that measured empathy, six employed the full form Interpersonal Reactivity Index (IRI; Davis, 1983) and one the brief version of the IRI (Ingoglia et al., 2016), therefore the analysis of the third research question was conducted on total IRI score.

Table 1.

Summary of Characteristics for all Included Studies

Experiment	Country	*N*	Age (*M*)	% Female	Design	Nocebo stimulus	Type of nocebo intervention	Type of nocebo exposure	Medium	Model gender (% female)	Model (*N*)	Modelled symptoms	Duration of modelling (minutes)
Barbiani et al., 2018	Italy	36	29	50	mixed	Manipulation: high altitude	primary	active	face-to-face	50	2	headache; insomnia	720
Blythe et al., 2021	Netherlands	58	22	100	between	Treatment: cream/gel/ointment	primary	inert	video	100	1	itch	Not Reported
Broderick et al., 2011	US	39	42	58	between	Treatment: pill	secondary	inert	face-to-face	50	2	headache; dizziness; nausea	Not Reported
Buglewicz-Przewoźnik et al., 2022	Poland	44	24	50	mixed	Manipulation: electrical stimulation	primary	inert	face-to-face	0	1	pain	5
Egorova et al., 2015	US	20	23	60	within	Manipulation: heat stimulation	primary	active	video	50	1	pain	Not Reported
Faasse et al., 2015	NZ	82	21	50	between	Treatment: pill	secondary	inert	face-to-face	100	1	headache; dizziness; drowsiness; dry mouth	1
Faasse et al., 2018	NZ	96	21	50	mixed	Treatment: nasal spray/inhaler	secondary	inert	face-to-face	50	1	headache; dizziness	1
Lorber et al., 2007	US	43	Not Reported	59	between	Treatment: nasal spray/inhaler	primary	inert	face-to-face	100	1	headache; drowsiness; itch; nausea	50
Mazzoni et al., 2010	UK	120	21	50	between	Treatment: nasal spray/inhaler	primary	inert	face-to-face	50	1	headache; drowsiness; itch; nausea	50
Quinn et al., 2023	Australia	107	19	61	mixed	Treatment: pill	secondary	inert	video	50	2	headache; dizziness; nausea; tiredness	Not Reported
Świder & Bąbel, 2013	Poland	84	23	50	between	Manipulation: electrical stimulation	primary	active	face-to-face	50	1	pain	5

Table 1.

Continued

Experiment	Country	*N*	Age (*M*)	% Female	Design	Nocebo stimulus	Type of nocebo intervention	Type of nocebo exposure	Medium	Model gender (% female)	Model (*N*)	Modelled symptoms	Duration of modelling (minutes)
Tan et al., 2023	Australia	97	26	61	mixed	Manipulation: virtual reality	primary	active	video	0	1	nausea; sweating, general discomfort	5
Tu et al., 2019	US	21	25	57	within	Manipulation: heat stimulation	primary	active	video	50	1	pain	22
Türkarslan & Çinarbaş, 2020	Turkey	50	22	78	between	Manipulation: EEG cap	secondary	inert	video	Not Reported	1	pain	Not Reported
Van Lierde et al., 2020	Belgium	44	10	61	within-subjects	Manipulation: cold pressor task	primary	active	video	100	1	pain	2
Vögtle et al., 2013	Germany	80	23	100	mixed	Treatment: cream/gel/ointment	primary	inert	video	100	1	pain	10
Vögtle et al., 2016	Germany	97	43	100	mixed	Treatment: cream/gel/ointment	primary	inert	video	100	1	pain	10
Vögtle et al., 2019	Germany	80	22	100	between	Treatment: cream/gel/ointment	primary	inert	video	100	1	pain	Not Reported
Witthöft & Rubin, 2013	UK	147	30	67	mixed	Manipulation: EMF exposure	primary	inert	video	100	1	headache; nausea; burning skin	9
Zhang et al., 2017	China	43	21	100	mixed	Manipulation: metal ring	primary	inert	video	0	1	pain	20

Notes. [1]*N* refers to the number of participants analysed in the meta-analysis, and potentially excludes participants in conditions not included in the meta-analysis.

[2]Design refers to the design used to calculate the effect size for the meta-analysis, e.g., if the design was originally between-groups pre-post (mixed) but only post scores were able to be extracted, the design was recorded as between subjects.

Risk of Bias

The risk of bias assessment is summarised in Table 2. Overall, seven studies were considered low risk of bias. Eleven were judged to have some concerns, primarily based on no specified pre-registration of a data analysis plan (reporting bias). Two were judged to have a high risk of bias. Very few studies showed any risk of bias for deviation from intended intervention (n = 0) or outcome measurement (n = 1).

Table 2.

Risk of bias assessment (by category and overall) for each study.

	Randomisation	Deviation from intended intervention	Missing outcome data	Measurement	Reporting	Overall
Barbiani et al., 2018	Some	Low	Low	Low	Some	Some
Blythe et al., 2021	Low	Low	Low	Low	Low	Low
Broderick et al., 2011	Some	Low	Low	Some	High	High
Buglewicz-Przewoźnik et al., 2022	Some	Low	Low	Low	Some	Some
Egorova et al., 2015	Low	Low	Low	Low	Some	Low
Faasse et al., 2015	Low	Low	Low	Low	Some	Low
Faasse et al., 2018	Low	Low	Low	Low	Some	Low
Lorber et al., 2007	Some	Low	Low	Low	Some	Some
Mazzoni et al., 2010	Some	Low	Low	Low	Some	Some
Quinn et al., 2023	Low	Low	Low	Some	Some	Some
Świder & Bąbel, 2013	Some	Low	Low	Low	Some	Some
Tan et al., 2023	Low	Low	Low	Low	Low	Low
Tu et al., 2019	Low	Low	Some	Low	Some	Some
Türkarslan & Çinarbaş, 2020	High	Low	Low	Low	Some	High
Van Lierde et al., 2020	Some	Low	Low	Low	Some	Some
Vögtle et al., 2013	Some	Low	Low	Low	Some	Some
Vögtle et al., 2016	Low	Low	Low	Low	Some	Low
Vögtle et al., 2019	Low	Low	Low	Low	Some	Low
Witthöft & Rubin, 2013	Some	Low	Low	Low	Some	Some
Zhang et al., 2017	Some	Low	Low	Low	Some	Some

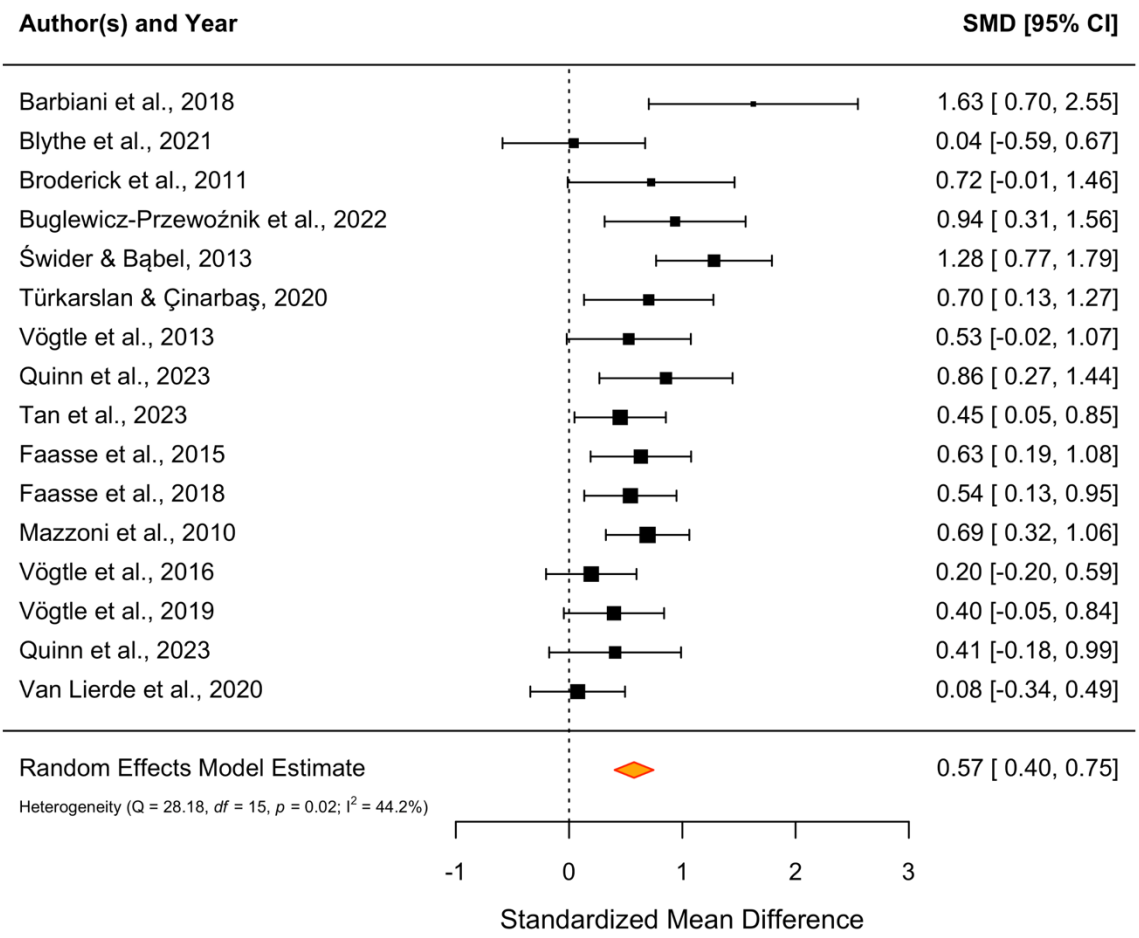
Research Question 1: Effect size of social learning compared to control condition

Fifteen unique studies were included, with a total of 560 participants in social learning conditions, 223 participants in no treatment conditions (k = 9) and 317 in neutral modelling conditions (k = 7). Figure 2 presents a forest plot of individual study and overall effect sizes. The overall pooled effect size for the nocebo effect elicited social learning was medium (g = 0.57; 95%CI [0.40, 0.75]; p < .001). Relative to a control condition, social learning significantly increased the nocebo outcome. Visual inspection of the funnel plot and the Egger test indicated potential publication bias (p = .04; see section 3 of the Supplementary Material). Duval and Tweedie's trim and fill method suggested there were three missing studies, and produced an adjusted effect size g = 0.47, 95%CI [0.27, 0.67]; p<.001[1].

[1] Due to the random effect of study included in the original model, the trim and fill method was not able to be applied. Therefore, the trim and fill method was applied to a reduced model without this random effect to generate an approximate adjusted effect size.

Figure 2.

Forest plots displaying Hedges' g (+/- 95%CI) for each included study and an overall effect size (+/- 95%CI) for the effect of social learning.



Note. Larger values of Hedges' *g* indicate larger effects of social learning relative to the control condition.

Moderator analysis. Table 3 presents the results of moderator analysis. Meta-regression revealed that the size of the social learning effect did differ significantly between studies that employed a no treatment compared to a neutral modelling control condition (Q_M = 4.09, *df* = 1, *p* = .04). Relative to studies that employed no treatment control conditions, when a neutral modelling condition was employed the effect size for social learning was smaller (*b* = -0.32, 95%CI [-0.63, -0.01]; *p* = .04). The effect size of social learning was inversely associated with the proportion of females in the sample (*b* = -0.01, 95%CI [-0.02,

<-0.01]; p = .02) and the proportion of models that were female (b < -0.01, 95%CI [-0.01, <-0.01]; p = .04). Furthermore, the medium through which the modelling was delivered significantly moderated the size of the social learning effect (Q_M = 9.73, df = 1 , p = .002). That is, relative to modelling delivered face-to-face, video modelling was associated with a significantly smaller social learning effect (b = -0.43, 95%CI [-0.70, -0.16], p = .002). The social learning effect size was also positively associated with the duration of the modelling intervention, (b = 0.09, 95%CI [<0.01, 0.18]; p = .05). No other moderator reached statistical significance, including other social learning related factors (i.e., type of nocebo intervention, number of models, type of nocebo exposure), study/sample characteristics (i.e., mean age, design, year of publication, risk of bias). There were insufficient data to conduct pre-registered moderator analyses of country, type of participant (i.e., healthy, clinical), symptoms modelled, expectancy, and anxiety.

Table 3.

RQ1: Moderator analysis of the effect of social learning

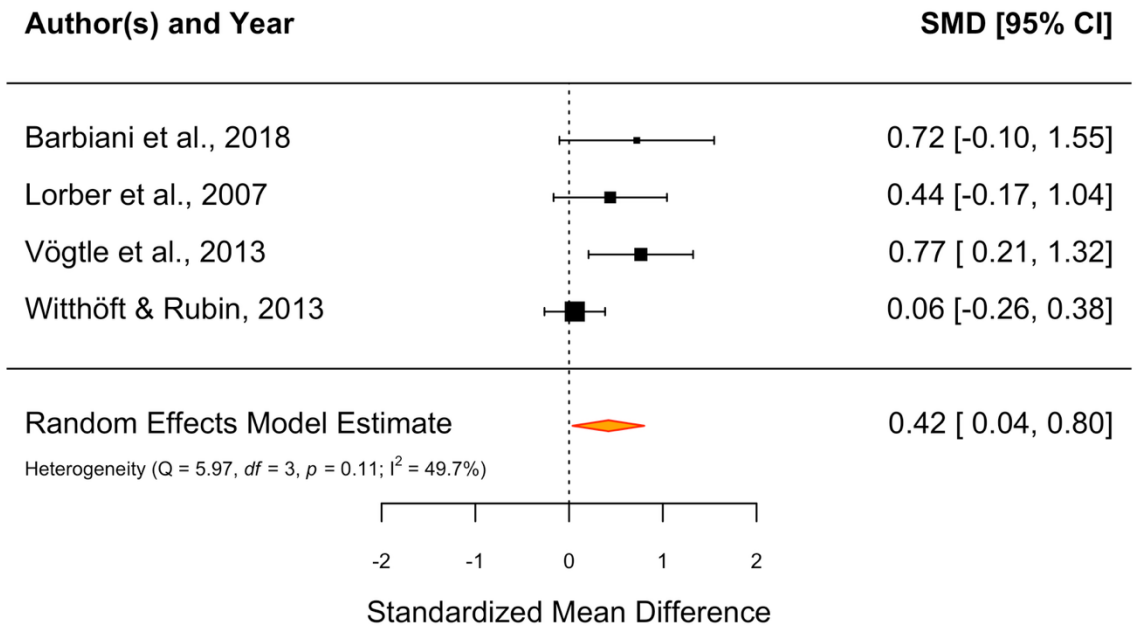
Moderator	K	Subgroup Differences	*b*	95%CI	*p*
Type of control (ref = No treatment)	9	Q_M = 4.09, *df* = 1, *p* = .04	0.74	(0.51, 0.98)	<.001
Neutral Modelling	7		-0.32	(-0.64, -0.01)	.043
Year of publication	16		-0.02	(-0.06, 0.02)	.264
Mean age of sample	16		<0.01	(-0.02, 0.02)	.847
Gender (% Female)	16		-0.01	(-0.02, <-0.01)	.015
Model Gender (% Female)	15		<-0.01	(-0.01, <-0.01)	.043
SM Medium (ref = Face-to-Face)	7	Q_M = 9.73, *df* = 1, *p* = .002	0.80	(0.60, 1.01)	<.001
Video	9		-0.43	(-0.70, -0.16)	.002
Duration of modelling	10		0.09	(<0.01, 0.18)	.049
Design (ref = Between Subjects)	7	Q_M = 0.65, *df* = 1, *p* = .42	0.65	(0.40, 0.90)	<.001
Mixed/Within	9		-0.14	(-0.48, 0.20)	.420
Type of nocebo intervention (ref = Primary)	10	Q_M = 0.20, *df* = 1, *p* = .65	0.55	(0.33, 0.76)	<.001
Secondary	6		0.09	(-0.29, 0.46)	.652
Number of models (ref = One)	12	Q_M = 1.65, *df* = 1, *p* = .20	0.53	(0.34, 0.72)	<.001
Two	4		0.32	(-0.17, 0.81)	.200
Type of nocebo exposure (ref = Active)	4	Q_M = 0.47, *df* = 1, *p* = .49	0.69	(0.33, 1.05)	<.001
Inert	12		-0.15	(-0.56, 0.27)	.492
ROB overall (ref = Low)	6	Q_M = 3.56, *df* = 1, *p* = .06	0.40	(0.15, 0.64)	.001
Some Concerns & High	10		0.32	(-0.01, 0.64)	.059

Research Question 2: Effect size of social learning compared to explicit instruction

There were 4 unique studies, with a total of 135.5 participants in social learning conditions compared to 131.5 participants in explicit instruction conditions[2]. Figure 3 presents a forest plot of overall and individual study effect sizes. The overall pooled effect size for the nocebo effect of social learning relative to explicit instruction was significant, meaning that the size of nocebo effect generated was larger when elicited via social learning than explicit instruction (g = 0.42; 95%CI [0.04, 0.80]; p = .03). Visual inspection of the funnel plot, the Egger test and moderator analysis could not be performed due to insufficient number of studies (Page et al., 2023).

Figure 3.

Forest plots displaying Hedges' g (+/- 95%CI) for each included study and an overall effect size (+/- 95%CI) for the effect of social learning in comparison to explicit instruction



Note. Larger values of Hedges' g indicate larger effects of social learning relative to the other modes of nocebo induction.

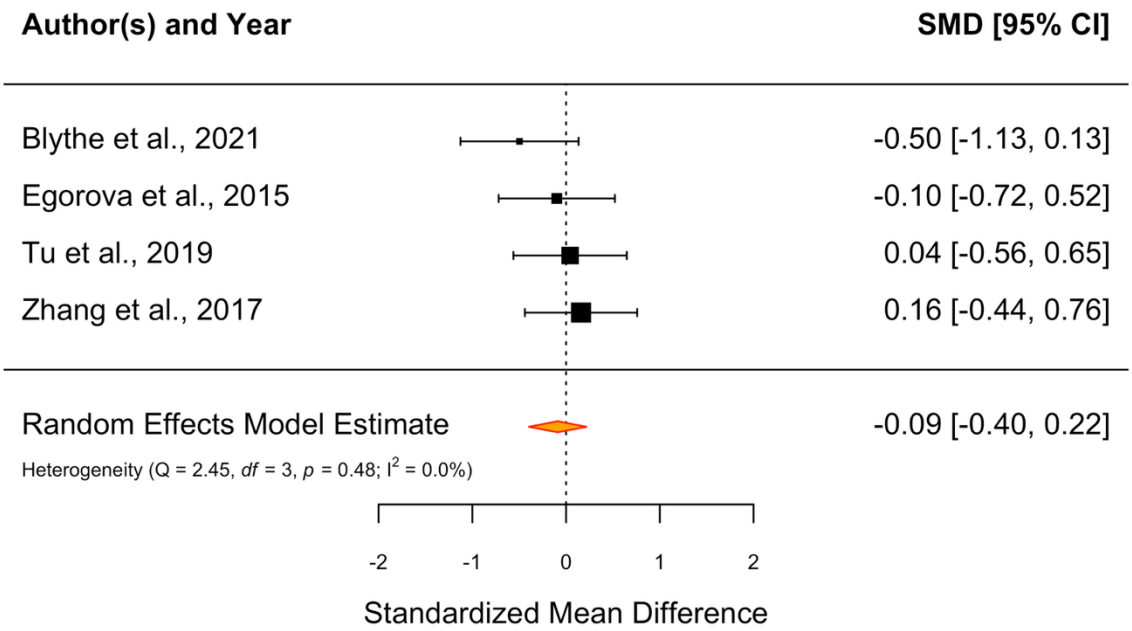
[2] In one case (Lorber et al., 2007), an estimate of 21-22 participants per group was reported. A request for clarification of group sample sizes was not responded to, and as such, the midpoint of 21.5 participants was used for each group.

Research Question 2: Effect size of social learning compared to classical conditioning

Data from 4 unique studies, with a total of 83 participants in social learning conditions, 82 participants in explicit instruction conditions were included. Figure 4 presents a forest plot of overall and individual study effect sizes. The overall pooled effect size for the nocebo effect of social learning relative to classical conditioning was not significant (g = -0.09; 95%CI [-0.40, 0.22]; p = .56).

Figure 4.

Forest plots displaying Hedges' g (+/- 95%CI) for each included study and an overall effect size (+/- 95%CI) for the effect of social learning in comparison to classical conditioning



Note. Larger values of Hedges' g indicate larger effects of social learning relative to the other modes of nocebo induction.

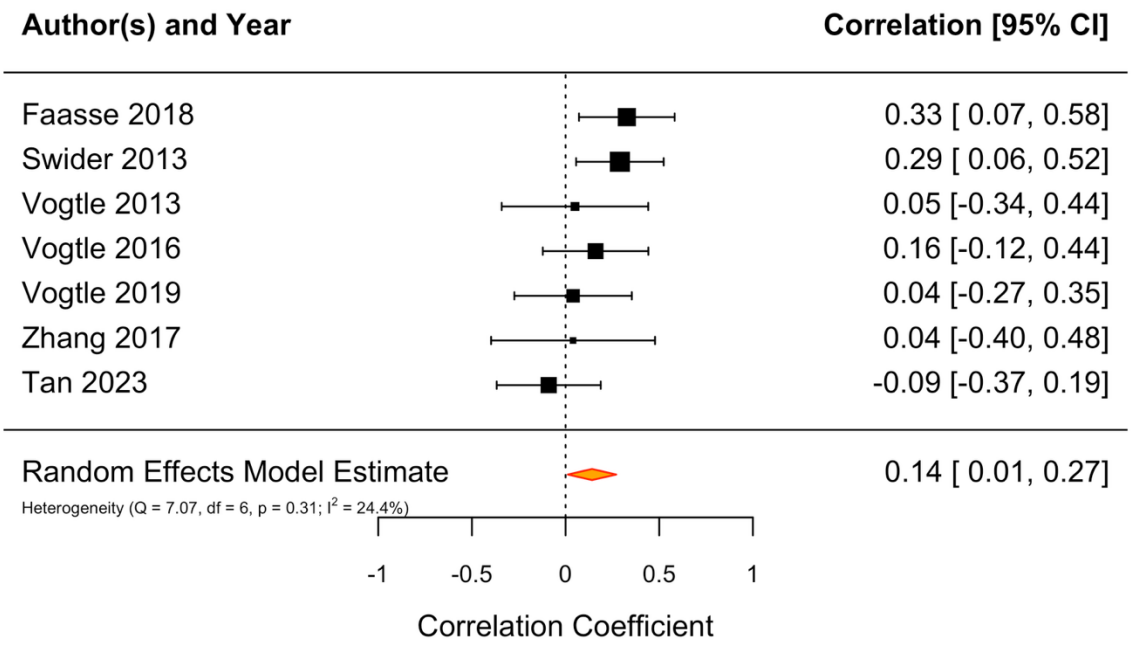
Research Question 3: Effect size of empathy within social learning condition

Seven studies reported correlations between empathy and social learning resulting in a total sample of 292 participants. The overall pooled effect size for the correlation between the

nocebo effect elicited via social learning and empathy was statistically significant, but small (r = 0.14; 95%CI [0.01, 0.27]; p = .03). Additional analysis at the subscale level (i.e., perspective taking, personal distress, fantasy, and empathic concern) is reported in section 4 of the Supplementary Material.

Figure 5.

Forest plots displaying Correlation (+/- 95%CI) for each included study and an overall effect size (+/- 95%CI) for the effect of empathy on social learning.



Note. Larger values of r indicate larger correlations between empathy and nocebo response.

Discussion

The present systematic review and meta-analysis had three primary aims. First, to identify the influence of social learning in the formation of the nocebo effect across multiple symptom types. Here, evidence suggests that there was a medium-sized effect of social learning. The second aim was to investigate the magnitude of socially-induced nocebo effects relative to those induced from classical conditioning and explicit instruction. Analyses demonstrated that social learning had a comparable effect size to classical conditioning.

Relative to explicit instruction, on the other hand, there was a small-medium increase in the effect size of nocebo outcomes induced by social learning. The third aim was to identify situational and dispositional factors that modulate socially-induced nocebo effects. Several factors, including face-to-face modelling and greater empathy, facilitated stronger effects. These outcomes have important theoretical, methodological, and practical implications.

The finding that socially-induced nocebo effects manifest beyond pain to a multitude of other symptomatic contexts including headache, nausea, and drowsiness is important. If social learning can produce the nocebo effect with a medium effect, clinicians need to understand that their patients will be influenced by social information across a variety of domains, such as medication side effects, and not just pain. Critically, previous research has often overlooked distinctions between types of control conditions. The present outcomes elucidate that the type of control implemented leads to distinct social learning effect sizes. When compared to a no treatment control, social learning produced a medium to large-sized effect. On the other hand, when compared to a neutral modelling control, this effect was small-medium. This is contrary to prior suggestions that exposure to neutral modelling could be protective, whereby observers are informed that the intervention does not lead to the experience of unwanted or negative health outcomes (Tan et al., 2023). This is an interesting finding in that intuitively it would make sense that modelling the absence of side effects would reduce them, but the results suggest the opposite. One explanation is that modelling the absence of symptoms may highlight the *possibility* of symptoms to the observer, whereas no observation provides no expectation of symptoms at all. This is important because it suggests that in real life scenarios the discussion of either the presence or absence of side effects might both increase the likelihood of side effects. With regards to research, it is crucial to note that the type of control condition studies employ is an important methodological detail to consider.

Though prior research has demonstrated that classical conditioning and explicit instruction have differing effects on the formation of the nocebo effect (Bąbel et al., 2017; Bajcar et al., 2019; Bartels et al., 2014; Colloca, 2014), there has yet to be a comprehensive analysis including social learning comparisons. The present meta-analysis thus employed head-to-head comparisons between social learning and these two other nocebo induction methods. Results indicated that the effect of social learning in inducing nocebo effects was similar in magnitude to classical conditioning and larger than explicit instruction. This implies observing another person's experience can be as influential to health outcomes as our own prior experiences. Moreover, this social learning has a greater influence than explicit instruction. This is of great concern as it suggests the potential for social anecdotal evidence to override information communicated to patients by their health care professionals. Given that it is not feasible to prevent individuals from consuming this social information, further research needs to investigate if the impact of this social information can be minimised in clinical settings. Exposure to experiential information is therefore an important factor that must be considered in healthcare settings.

Moderator analyses highlighted that several individual characteristics and contextual factors modulate the influence of social learning. First, the medium through which a social model is observed is important, with face-to-face modelling producing larger effects than modelling through video. This difference could be attributed to the difficulty in the processing of social cues and non-verbal behaviours (e.g., eye contact) associated with video-based observations (Bohannon et al., 2013; Hietanen et al., 2020). This result is also consistent with the finding that face-to-face and live video interactions prompt stronger social mimicry than pre-recorded video-based observations (Diana et al., 2023), the latter of which was used in seven of the eight included studies utilising video modelling manipulations. As face-to-face modelling elicited greater effects, one might argue that the experiences we

observe in real world settings are more influential than those observed through video. However, that is not to say that video-based observations are not of importance. The prevalence of the internet and ubiquity of video-based platforms have allowed for interindividual communication and observation to occur on a mass scale, bolstering the ease at which individuals can be socially influenced. For instance, the propagation of tic-like behaviour through video-based modelling has been observed within TikTok communities (Olvera et al., 2021). As such, the large quantity of anecdotal information accessible online may rival the salience of single individual in face-to-face interactions, particularly given that longer exposure leads to stronger nocebo outcomes, though this remains to be investigated.

Surprisingly, studies with higher proportions of female participants and studies in which only female social models could be observed both demonstrated weaker nocebo effects. While unexpected, it is hard to disentangle whether the presence of female observers, the presence of female demonstrators, a match in female gender, or other experimental factors unrelated to gender drove these results. Two studies included in the analysis have reported that a match between female observers and demonstrators increased symptom reporting (relative to other observer/demonstrator configurations) irrespective of whether social modelling occurred (Faasse et al., 2018; Mazzoni et al., 2010). This inflated effect in the no modelling conditions would therefore decrease the effect size associated with modelling itself for female participants. This pattern of results, however, is complicated by other studies that have reported larger social modelling effects in female participants (Quinn et al., 2023). Further, four studies that only included female participant samples also only employed female social models (Blythe et al., 2021; Vögtle et al., 2013; 2016; 2019). These studies had some of the lowest effect sizes, but also shared a common methodology, being conducted within the same laboratory, using a similar design. This complicates interpretation of what is already a varied pattern of results. This ambiguity, however, highlights the need for further

systematic investigation into the roles of both observer and model gender. It also appeared that longer modelling manipulations were associated with stronger nocebo outcomes, though this effect was small and should be interpreted with caution as there was a single study with a large effect in which modelling occurred over a twelve-hour period.

Individual differences in empathy may determine whether one understands and applies the experiences of others to their own. There was a small but significant positive association between empathy and nocebo outcomes, indicating that more empathic individuals were more strongly influenced by social modelling. Although there were insufficient studies to investigate moderators of this effect, visual inspection of the Forest plot suggests that the finding was driven primarily by the two studies that employed face-to-face modelling. This is consistent with research indicating that empathy is relevant for face-to-face modelling but not video modelling in placebo paradigms (Hunter et al., 2014) and may explain the finding that face-to-face modelling led to stronger nocebo outcomes than video-based modelling. However, the application of the IRI across the included studies raises questions as its use has not been well-validated, there is no consensus on the factorial structure of empathy (Lima & Osório, 2021), and the personal distress subscale may be more strongly related to negative emotionality than empathy (Murphy et al., 2020). Use of alternative measures such as the Affective and Cognitive Measure of Empathy (ACME;Vachon & Lynam, 2016), which has been used in an existing observational social learning study (Mennitto et al., 2021), should therefore be considered. As such, although the present outcomes suggest that trait empathy plays a small role in socially-induced nocebo effects, the components of trait empathy that contribute to this phenomenon need to be better understood before stronger conclusions can be made. Altogether, the present evidence suggests that the medium and length of social modelling manipulations, the gender of the model and observer, and individual trait empathy moderate the strength of social learning.

Despite several important findings, a number of limitations of the existing literature were also clear. Given the effects of negative expectancies and state anxiety in eliciting the nocebo effect within conditioning and explicit instruction paradigms (Rooney et al., 2022), it has been theorised that these constructs could also drive socially-induced nocebo effects (Benedetti et al., 2020; Faasse, 2019). Yet, across the literature, only three studies assessed expectancies after social learning and only four measured anxiety. To move beyond theoretical postulations, it is pivotal that measures of expectancies and state anxiety continue to be implemented in future studies, ideally before and after social learning manipulations. Continued implementation of these variables may also elucidate whether their inhibition could be an effective strategy to reduce the occurrence of socially-induced nocebo effects.

Across the included studies, only three designs had participants observe more than one model, with the maximum being two. Whether an individual's expectations and experiences differ based on the number of models observed is an important consideration, particularly given the ease at which anecdotal information spreads through the internet. For example, the exploration of multiple models may help to explain the occurrence of community-level nocebo effects, such as those involving episodes of mass psychogenic illnesses. Mass psychogenic illnesses describe situations in which a population experience physical symptoms that cannot be explained by an observable or medical cause, and are thought to be partially driven by social influence (Bartholomew et al., 2012). Relatedly, whether an individual is influenced by a social model may depend on the interpersonal dynamics between the model and observer. While preliminary research has been conducted on factors such as observers' perceptions of model social status and self-confidence in placebo paradigms (Bajcar et al., 2020; Bieniek & Bąbel, 2022; Brączyk & Bąbel, 2021), these and similar factors, such as warmth and competence, which has attenuated nocebo

outcomes in a clinician-patient paradigm (Barnes et al., 2023), have not been investigated in nocebo social modelling contexts.

Regarding social modelling manipulations, it is apparent that some include a form of explicit instruction, making it difficult to isolate the effect of social learning. In one instance, before the observation of a social model, participants were informed that the stimulus was associated with multiple symptoms (Lorber et al., 2007). On the other hand, the provision of risk warnings associated with treatment, such as the potential for side effects, is a cornerstone of individual autonomy in the informed consent process (Gelfand, 2020). As such, these scenarios may in fact better represent clinical settings and thereby demonstrate greater ecological validity. Relatedly, however, no studies with clinical samples were eligible for review, making it difficult to determine if these outcomes do in fact translate to clinical settings.

As mentioned, future research should carefully consider the type of control implemented and how that influences the interpretations that can be drawn regarding the effects of social learning. We posit that comparisons between negative social modelling and no modelling conditions indicate whether social modelling can elicit a nocebo effect. On the other hand, comparisons with neutral modelling may be instead asking how the valence of social modelling affects nocebo outcomes. Neutral modelling therefore highlights to the observer that there is a potential for symptoms to occur but that the model did not experience symptoms themselves. In turn, the observer recognises that there is potential for them to experience symptoms even if the model did not. As such, both types of control conditions have theoretical significance, but researchers need to be explicitly aware of this distinction. It is also clear from the included studies that social modelling in nocebo contexts has only been investigated dichotomously (i.e., negative versus none, or negative versus neutral). If we extend this dichotomy to re-conceptualise that the severity of social modelling may exist on a

continuum, the severity of symptoms communicated could correspond with the strength of the nocebo effect elicited. Furthermore, this relationship may not be linear, whereby extremely severe experiences have a disproportionate effect on observers.

Unfortunately, the level of detail provided on social learning manipulations in the existing literature has been relatively inconsistent and vague. As a result, conclusions that could be made with respect to further moderating factors are limited. For instance, two studies may report that their respective social models verbally stated the experience of dizziness and headache to observing participants. However, the tone, duration, and severity of such modelling, and the characteristics of the models themselves, may be substantially different. Furthermore, this raises questions regarding the "visibility" of the model's symptom severity. Intuitively, more visible physical symptoms (e.g., pain) could be more susceptible to socially-induced nocebo effects. While the present study lacked the data to explore this question, it would be prudent for future research to investigate. It would therefore be beneficial for future studies to provide thorough and transparent descriptions of their social modelling manipulations or added these to open repositories that could be analysed. Beyond assisting in the determination of social learning elements that most actively contribute to nocebo effects, it would aid in the replication of experimental outcomes. We recommend that design elements are outlined explicitly in text, and ideally, accompanied by a video or transcript of the social interaction on an open data repository such as Open Science Framework. This recommended list of factors is as follows:

(1) the characteristics of the social model including their gender, age, ethnicity, and perceived status (e.g., whether the model is presented as another student, a stranger, or as someone known to the experimenter);

(2) details regarding the interaction with participants (e.g., duration of the contact between participant/model which could influence rapport, and duration of the symptom modelling itself); and

(3) information regarding how the content of the modelling is presented (e.g., whether participants learn through a model's verbal reports, observable behaviours, or other means).

The requested provisions would enable researchers to understand whether there are verbal and behavioural intricacies otherwise missed when only a brief description of the modelling is provided. In addition, studies should pre-register their designs and data analysis plans, as most of the included studies did not, thereby increasing the risk of bias.

The present systematic review and meta-analysis elucidates the key role social learning plays in the development of nocebo effects. The first novel finding demonstrates that social learning has a medium-sized effect on inducing nocebo effects across multiple health outcomes. To best of our knowledge, it is also the first to directly compare the influence of social learning to the other modes of nocebo induction. Results suggest that social learning has substantial influence in the formation of nocebo effects, with the magnitude of such effects being comparable to classical conditioning and larger than explicit instruction. Analysis of contextual factors showed that face-to-face modelling and longer modelling manipulations elicited stronger nocebo effects, and that individual characteristics, such as the gender of observers and models, as well as the observer's trait empathy, modulate social learning. However, awareness of how design elements, such as the type of control condition implemented, need to be carefully considered by future studies. It is argued that implementations of neutral modelling conditions, where the control is allocated to observe a model experiencing an absence of symptoms, explore the effect of social modelling valence, whereas comparisons with no observation controls indicate whether the nocebo effect can be socially-induced. As such, these questions may have differing theoretical and practical

implications. Continued measurement and reporting of psychosocial variables, particularly in relation to negative expectations and anxiety, is also critical to understand the underlying mechanisms driving socially-induced nocebo effects. Given the reliable effect of social learning on nocebo effects and the availability of models, particularly online, a key priority for future research is to identify ways to mitigate these effects to reduce the substantial personal and societal harm nocebo effects cause.

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Chapter 3: Socially-acquired nocebo effects generalize but are not attenuated by choice

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Pre-Registration: AsPredicted #68104 & AsPredicted #103304

Supplementary Materials: Appendix B

Open Science Framework: https://osf.io/w2xcp/overview

Introduction

Our prior beliefs and experiences are known to modulate our perception of the world, including the experience of symptoms and side-effects (Faasse, 2019). A primary route through which these symptom-related expectancies are formed concerns the observation of others (Webster et al., 2016). For example, witnessing another individual experience side-effects to a treatment can increase side-effect reporting in the observer when the same treatment is subsequently encountered (Benedetti, 2013; Faasse et al., 2015; Faasse et al., 2018). These socially-acquired nocebo effects have been documented across a diverse range of symptoms, including pain, headache, and nausea (Bajcar & Bąbel, 2018; Faasse et al., 2015; Faasse et al., 2018; Świder & Bąbel, 2013; Vögtle et al., 2013; 2019; 2016; Yoshida et al., 2013). Further, they have significant clinical and societal ramifications given that socially propagated symptoms of this type have been demonstrated to spread at the community-level (Chapman et al., 2013).

Somewhat surprisingly, however, studies have yet to investigate: 1) how social information regarding symptoms generalise across similar contexts and interventions, and; 2) how nocebo effects generated through social modelling (i.e., observing another individual) can be attenuated or blocked. These factors are of importance. As discussed below, not only do they provide novel information about the way socially modelled symptoms are transmitted, but also potential routes to mitigate the burden of nocebo effects.

At present, we know that the social-acquisition of negative health outcomes can occur with identical interventions and treatments (e.g. Faasse et al., 2015; Faasse et al., 2018; Zhang et al., 2017). Of even greater concern, is that socially modelled symptoms may generalise (i.e., spread) to other treatments. That is, observing a person experience a negative outcome to a specific treatment, may not only cause the observer to experience nocebo effects with that specific treatment, but also other similar treatments. Hypothesising that

socially-acquired nocebo effects might generalise in this manner is not unfounded. While not concerned with socially modelled symptoms, nocebo effects induced via direct classical conditioning have been demonstrated to generalise across contexts. For example, participants conditioned to expect nausea from active Galvanic Vestibular Stimulation (GVS), experienced similar levels of nocebo nausea at test, irrespective of whether sham-GVS was delivered in the same or a different context (Quinn et al., 2015). Given the mechanisms underlying the nocebo effect have been suggested to be similar across modes of induction (i.e., conditioning, social modelling, and explicit instruction) (Blasini et al., 2017), it is of interest to determine whether socially modelled symptoms can generalise beyond identical interventions, as well as confirm the underlying mediators of any such effect.

Further, given the documented strength of socially modelled nocebo effects (Webster et al., 2016), it is important to find interventions that can reduce these maladaptive health outcomes. One potential candidate is the perception of choice over treatment, although research in this area has yet to be applied to social modelling. Choice is inherently desirable (Leotti & Delgado, 2011; Leotti et al., 2010), and thus presents a low cost, non-deceptive, and ethical intervention (Bartley et al., 2016; Geers et al., 2013), previously shown to facilitate the placebo effect with respect to pain, discomfort, and sleep (Geers et al., 2013; Rose et al., 2012; Tang et al., 2022; Totman, 1976). To date, however, only one published study has investigated choice with respect to the nocebo effect (Bartley et al., 2016). Here, participants who were given choice between two supposed betablockers (actually placebos) reported lower anxiety and fewer side-effects than those assigned to one of the supposed betablockers without any choice. As such, choice provides a potential but untested route through which to diminish socially modelled symptoms.

In order to bridge these two gaps in the literature, across three experiments, the present study investigated the effects of generalisation and choice on socially-acquired

symptoms, using a novel VR model of cybersickness; a constellation of nausea-related symptoms (Chang et al., 2020) previously reported to be susceptible to social modelling (Tan et al., 2022). To explore generalisation, participants witnessed a confederate experience cybersickness resulting from a VR activity that was either the same (i.e., Social Modelling Consistent) or different (i.e., Social Modelling Inconsistent) to the one that they subsequently experienced. The perception of choice was manipulated by allowing half of the participants to select a VR environment and yoking the remaining participants to their choices. Finally, expectancy, anxiety, control, and affect were measured throughout the experimental session, allowing for an exploration of potential underlying mechanisms of social modelling and choice.

Past research has repeatedly shown an effect of social observation on the nocebo effect for identical treatments (Bajcar & Bąbel, 2018; Faasse et al., 2015; Faasse et al., 2018; Świder & Bąbel, 2013; Tan et al., 2022; Yoshida et al., 2013). Therefore, it was hypothesised that participants assigned to the social modelling groups would report higher levels of cybersickness when compared to those that received no social modelling, occurring even when participants believe they are viewing a model experience symptoms in a VR environment different to their own. The latter case being a novel assessment of generalisation. We anticipated that participants given choice over their VR environment would report lower levels of cybersickness across all social modelling conditions (Bartley et al., 2016). Evidence for the influence of psychological factors that mediate socially-acquired nocebo effects is inconclusive (Faasse, 2019; Koban & Wager, 2016; Tan et al., 2022; Vögtle et al., 2013; Vogtle et al., 2019). As such, state anxiety, expectancy, control, and affect were explored as mediators of the social modelling and choice effects. We present details regarding the primary outcome of each of the three experiments in the text (with secondary analyses in

Supplementary Materials) and then a pooled analysis of the combined data across the three experiments.

Experiment 1

Methods

Experimental design and analyses were pre-registered (AsPredicted #68104). Ethical approval was granted by the University of Sydney Human Research Ethics Committee (Protocol 2021/301). The recruitment process for all experiments is depicted in Electronic Supplementary Material 1. Data collection occurred between June 30th – August 20th 2021.

Participants

Participants (*N*=134) were recruited Australia-wide via Facebook advertisements. The sample comprised of 68 males and 66 females, 18-58 years of age (*M*=32.20, *SD*=7.06). Information regarding sample race and SES were not collected. In keeping with our previous research (Barnes, Yu, et al., 2019; Mao et al., 2021; Tan et al., 2022), participants were ineligible if they had experienced VR>10 times, had a medical condition increasing postural instability or risk of nausea, were pregnant, had epilepsy, a pacemaker, or pre-existing binocular visual abnormalities. Access to a smartphone with diagonal screen size of 4.7-6.4 inches and able to run the latest YouTube application was necessary for participation. All participants were provided with a VR headset which they kept as compensation for their time.

Design

The current study was presented to participants as an investigation regarding online learning in VR. However, the true purpose was to examine the role of choice and generalisation with respect to socially-acquired nocebo nausea using a VR-based cybersickness model. Testing took place via the video-conferencing application Zoom, with all participants experiencing a VR rollercoaster ride. A 3(Social Modelling: No Social

Modelling, Consistent, Inconsistent) x 2(Choice: No Choice, Choice) between-subjects design was employed. Participants were randomly assigned (via random number generator) to experimental condition and type of VR environment using a gender-stratified yoking procedure based on their order of participation. Full details are provided in Electronic Supplementary Material 2. The primary outcome was the severity of symptoms previously modelled by the confederate (general discomfort, nausea and stomach awareness). State measures of anticipatory anxiety and expectancy were measured as potential mediators of virtually transmitted cybersickness.

Social Modelling Manipulation. Those randomly assigned to the social modelling groups watched an actor (who they believed was a real participant) experience VR and report symptoms of cybersickness before they experienced VR themselves. In line with previous social modelling research (Faasse et al., 2015; Faasse et al., 2018; Zhang et al., 2017) those in the 'Consistent' condition observed the actor describe the same VR activity that they chose/were assigned to (i.e., a rollercoaster ride). Importantly, those in the 'Inconsistent' condition watched a description of a different environment and activity from their own (i.e., VR Aerobatics). Evidence of increased symptom reporting in the Inconsistent group, relative to control, is therefore indicative of the generalisation of a socially modelled nocebo effect across VR environments. The control group did not witness any social modelling prior to their VR experience. The two VR environments were selected from pilot data (N=28), where five VR activities were paired with four environmental conditions. Preference for the snowy vs. sunny environment, and rollercoasters vs. aerobatics did not differ (both ps>.05).

Choice. Participants assigned to the Choice condition chose which of two VR videos they preferred to watch. To control for differences in cybersickness that could be induced by substantial differences in the content of the VR video (e.g., a rollercoaster vs. aerobatics), participants chose their VR video based on peripheral environmental features (i.e., the

weather; a snowy or sunny day). Unbeknownst to participants, the primary property of the VR that may provoke cybersickness (i.e., the rollercoaster ride) was constrained, while they were led to believe that they had chosen this (i.e., "you chose the snowy environment, which is a rollercoaster"). This isolated the manipulation to the perception of choice alone and controlled for the endogenous features of the VR. A manipulation of this type is similar to existing choice studies regarding the placebo effect that typically administer identical sham-treatments with peripheral perceptual differences (Geers et al., 2013; Tang et al., 2022). Manipulation of these peripheral environmental features (e.g. brightness/contrast associated with the different environments) should not modulate the induction of cybersickness (Shahal et al., 2016).

Materials and Measures

Social Model. Social modelling took place virtually with live video interactions occurring via webcam on Zoom. While the participant believed the social model to be another participant (referred to as 'Julian') who was present in the Zoom session, interactions with the model were actually a series of pre-recorded videos of a male confederate. Open Broadcasting Software was used to pipe the pre-recorded film of the social model into Zoom. This ensured that all participants within each experimental condition were presented with identical social information. The scripts delivered by the confederate were indistinguishable between conditions except for a single reminder concerning the environment (i.e., sunny or snowy), and two reminders of the activity (i.e. rollercoaster or aerobatics). The videos contained subtle cues (e.g., the model looking to the left) that allowed the experimenter to 'talk' to the confederate, creating the illusion that he was participating in real time. Only one participant (0.7% of the sample) reported being aware that the model was not real in a post-experiment manipulation check. During the actor's modelling phase, they verbalised and gestured three distinct symptoms of cybersickness (nausea, general discomfort, and stomach

awareness). See https://youtu.be/AcTfjDa4AjY for an excerpt of an experimental session, containing the script the confederate delivered as he modelled symptoms.

VR Headsets and Environments. Participants experienced VR using a Shinecon VR G034A head-mounted display. All participants watched one of two VR videos that depicted the same rollercoaster on either a sunny day (see: https://youtu.be/19tjefId4oE) or a snowy day (see: https://youtu.be/M9Vc-AT-TeM) which served as the 'cybersickness-inducing' stimulus. In reality, the short rollercoaster ride served as a plausible activity to experience cybersickness while minimising the occurrence of cybersickness due to the VR video alone. The videos were created using the custom rollercoaster simulator software NoLimits2(Lange, 2014) which allowed for the generation of identical videos in length and content while only manipulating the environmental features that participants experienced. Screenshots are presented in Electronic Supplementary Material 3.

Primary Outcome:

Cybersickness. Cybersickness was measured using the 16-item Simulator Sickness Questionnaire (SSQ) (Kennedy et al., 1993). Symptoms were rated on an eleven-point scale: 0 (*not at all*) to 10 (*severely*). A baseline measure was taken at the beginning of each session, with the active measure taken immediately after VR. The difference score (active minus baseline) was used to measure cybersickness. Given three symptoms of the SSQ were specifically modelled to participants (general discomfort, nausea and stomach awareness), cybersickness severity based on these items (referred to hereafter as 'Modelled-SSQ') formed the primary outcome, with the full sum-scored SSQ pre-registered as a secondary outcome ('Full-SSQ').

Secondary Outcomes:

Analysis of secondary outcomes are presented as Supplementary Materials.

Expectancy. Expectancy was assessed with the single-item: "How much do you expect to experience feelings of cybersickness (e.g., nausea, general discomfort, stomach awareness) during the VR video?", with an eleven-point scale: 0(*not at all*) to 10(*severely*).

State Anxiety. The short-form State-Trait Anxiety Inventory (STAI-6) (Marteau & Bekker, 1992) was employed with a four-point rating scale: 1(*not at all*) to 4(*very much*). The overall STAI-6 sum score was calculated as the outcome.

VR Anxiety. VR-specific state anxiety was measured via the single-item: "How anxious do you feel about experiencing the Virtual Reality video?", with the same scale as expectancy.

Baseline measures of secondary outcomes were recorded at the beginning of the study session, and active measures immediately prior to the rollercoaster experience (i.e., following the observation of the social model in the Social Modelling groups). Higher scores indicated greater baseline adjusted expectancy, state anxiety, and VR anxiety.

Control and Affective State. Control and Affect were measured via the Self-Assessment Manikin (SAM) (Bradley & Lang, 1994), with a nine-point pictorial scale (Soleymani et al., 2014). The SAM included the dimensions of valence (unhappy/happy), arousal (calm/agitated) and dominance (controlled/in control). Measurement occurred immediately after participants chose/were assigned their environment. Higher scores indicated a more positive valence, greater arousal, and more perceived control.

Manipulation Check. A manipulation check was implemented at the end of each experimental session. Participants were asked to provide an open response to the question "Briefly describe (1-2 sentences) what you thought the purpose of this experiment was:"

Procedure

Participants were first screened for eligibility via Qualtrics. Ineligible participants were directed out of the signup process and eligible participants proceeded to the Participant

Information Statement and Consent form. Upon consent, participants completed a short demographic survey.

Participants attended the experiment via Zoom, with the same female experimenter and male social model (actually pre-recorded footage). Participants received study information and completed baseline measures via Qualtrics. To maintain the cover story and avoid suspicion concerning repetition of questions regarding their well-being, participants were informed that monitoring their wellbeing throughout the experiment was an ethical requirement of the study. Then, all participants viewed information regarding the two VR environments (location – i.e., sunny environment presented on the right or left of the screen - was counterbalanced across participants). Those in the Choice conditions chose their preferred environment, while those in the No Choice conditions were told to click on their assigned environment (controlling for differences in the experience of agency).

All participants then completed the SAM to measure their sense of control and affect after VR selection. Participants in the No Social Modelling condition also completed a five-minute distractor task consisting of spatial reasoning questions (Raven's progressive matrices, Raven & Court, 1938) aligning the timing of the VR experience between Social Modelling and No Social Modelling groups. This ensured that there was no confounding effect of time on anxiety and expectancy ratings, which may be stronger towards the beginning of the experimental session (Tan et al., 2022). Those in the social modelling groups were told the confederate would experience VR first. Depending on the participant's chosen or assigned environment, those in the Social Modelling Consistent condition were told: "both you and Julian [the confederate] chose/were assigned to experience the 'sunny day' environment, which contains a rollercoaster ride", while those in the Social Modelling Inconsistent group were told "You chose/were assigned to experience the 'sunny day' environment which contains a rollercoaster ride, while Julian, you chose/were assigned to

experience the ‘snowy day’ environment which contains ‘aerobatics’”. These two groups subsequently witnessed the confederate describe the VR environment including the experience of general discomfort, nausea, and stomach awareness (i.e., modelled symptoms). The experimenter then asked the confederate: 1) Could you describe your experience of that VR video?; and 2) Can you tell me how you feel (physically) at the moment? The confederate responded with the modelled symptoms. After observing the confederate, participants in the social modelling groups completed the active expectancy and anxiety measures. They then underwent the VR experience themselves, with the confederate ‘watching’. Those in the ‘No Social Modelling’ group undertook the same procedure but in reverse. Participants answered the same two questions regarding their VR experience as the confederate (i.e., description and symptoms) and completed the active SSQ measure, several bogus memory questions to uphold the cover story, and the manipulation check. Upon completion participants were thanked for their time and informed they would receive a debriefing statement via email once data collection was complete.

Power & Data Analysis

Sample size was determined *a priori*. A minimum of 22 participants per-group were required to achieve 80% power (α=.05) with an effect size of η_p^2=.07 (based on the effect size of choice reported by Bartley et al. (2016), the hypothesised smaller effect of the two manipulations).

Participants with extreme baseline cybersickness (pre-specified as 3*SD* above the mean, *N*=3) were excluded from analysis. Participants that failed the manipulation check (by explicitly noting that the social model was not a real participant) were also excluded from the analysis (*N*=1). Participants were also excluded due to technical difficulties, not following instructions, or withdrawal (*N*=7).

The primary analysis was a two-way ANCOVA with the between-subjects factors of social modelling (Social Modelling Consistent, Social Modelling Inconsistent, and No Social Modelling) and choice (Choice and No Choice) as the independent variables and baseline-adjusted Modelled-SSQ score as the dependent variable (active measure minus baseline). Gender was entered as a covariate, as it has previously been shown to moderate socially-acquired nocebo effects (Świder & Bąbel, 2013). Two planned orthogonal contrasts were conducted: 1) social modelling groups (Social Modelling Consistent and Inconsistent, combined) vs. control (No Social Modelling); 2) Social Modelling Consistent vs. Social Modelling Inconsistent. Those in the groups that were given choice were compared to those without choice. Unless otherwise specified, all statistical analyses were performed using R version 4.0.3 (R Core Team, 2020). The significance value for all tests was set at an alpha rate of .05.

Results

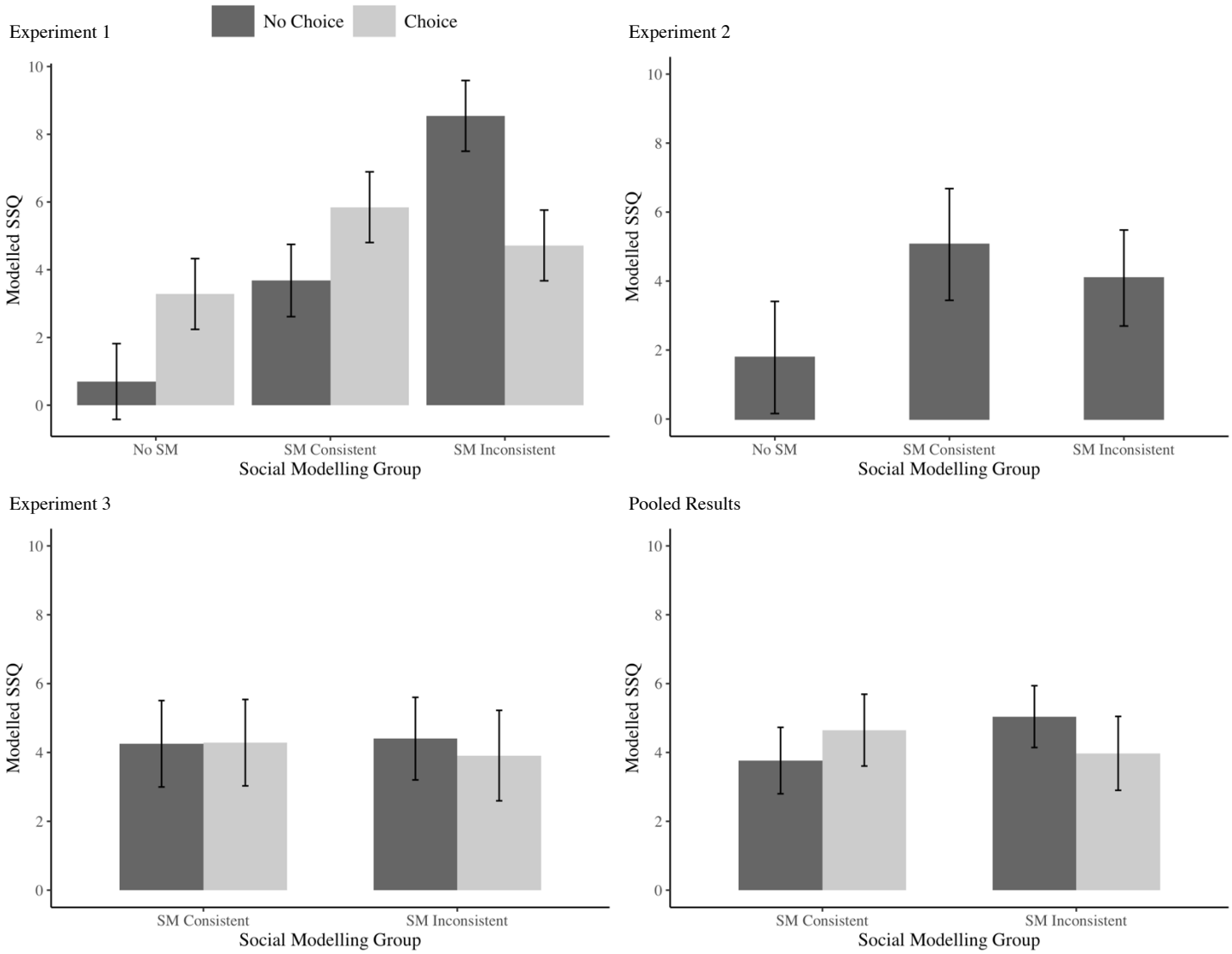
There were no significant between-group differences in age, baseline measures (SSQ, state anxiety, VR anxiety, and expectancy), gender, or prior VR experience (all *ps*>.05), See Electronic Supplementary Material 4.

Figure 1 depicts the group means for the primary outcome. The ANCOVA model revealed that there was no main effect of the covariate, gender $F(1,127)=1.44$, $p=.23$, $\eta_p^2=.01$, nor was there a main effect of choice $F(1,127)=0.12$, $p=.72$, $\eta_p^2<.01$. However, a significant main effect of social modelling $F(2,127)=9.60$, $p<.001$, $\eta_p^2=.13$ and a social modelling*choice interaction $F(2,127)=5.79$, $p=.004$, $\eta_p^2=.08$ were observed. Planned orthogonal contrasts revealed that Modelled-SSQ scores were elevated in the Social Modelling, relative to No Social Modelling, conditions $F(1,127)=15.94$, $p<.001$, $\eta_p^2=.11$. However, there was no significant difference in Modelled-SSQ scores between the Consistent

and Inconsistent groups, $F(1,127)=3.16$, $p=.08$, $\eta_p^2=.02$. There was also no significant difference in the effect of Choice on Modelled-SSQ scores for groups that received Social Modelling relative to the No Social Modelling groups, $F(1,127)=3.38$, $p=.07$, $\eta_p^2=.03$. However, the effect of Choice on Modelled-SSQ scores differed significantly between the Social Modelling Consistent and Inconsistent conditions, with the lack of choice seemingly exacerbating Modelled-SSQ scores in the Inconsistent condition. $F(1,127)=8.14$, $p<.001$, $\eta_p^2=.06$.

Figure 1

Mean baseline adjusted Modelled-SSQ score by group for Experiments 1, 2 and 3



Note. All error bars are ± 1 SEM and account for the covariate (gender)

Summary

As hypothesised, an effect of social modelling was found, with no overall difference between the Consistent and Inconsistent conditions. The present study therefore extended previous research by demonstrating for the first time that social information does not have to be specific to the individual's imminent experience to elicit socially-acquired nocebo cybersickness. Importantly, choice reduced nocebo cybersickness when the social model undertook a different VR activity but had no effect on the other conditions. Unexpectedly, in the conditions without the intervention (i.e., No Choice), watching the confederate undertake a different VR activity exacerbated cybersickness relative to the Social Modelling Consistent condition (with significant differences confirmed in exploratory analysis; see Electronic Supplementary Materials 4). This contradicted expectations, as generalisation to a new context (independent of choice) is typically similar, if not weaker. Therefore, this unanticipated finding warranted further investigation.

Experiment 2

Given the unanticipated pattern of exploratory results concerning the generalisation of social modelling found in Experiment 1 with respect to the No Choice condition, a second study was conducted in an attempt to replicate Experiment 1 results (Simmons et al., 2016). Experiment 2 is therefore a direct replication of the Social Modelling conditions excluding choice.

Methods

Data collection occurred between April 7th – July 13th 2022.

Participants

The sample (N=78) comprised of 30 males, 46 females, and 2 of other gender identities ranging from 17-50 years of age (M=31.09, SD=7.96).

Design and Procedure

A one way (Social Modelling: Consistent, Inconsistent, No Social Modelling) between-subjects design was employed. All participants underwent the No Choice procedure as described in Experiment 1.

Materials and Measures

All methods and materials are consistent with Experiment 1

Power & Data Analysis

A minimum of 26 participants per-group were required to achieve 80% power (α=.05) with an effect size of η_p^2=.13 (based on the main effect of social modelling found in Experiment 1). Exclusions were extreme baseline cybersickness (*N*=2), technical difficulties (*N*=1), not following instructions (*N*=6), withdrawal (*N*=1) or failure of the manipulation check (*N*=1).

Results

Figure 1 depicts the group means of the primary outcome. The main ANCOVA model revealed that there was no main effect of the covariate, gender $F(2,73)=0.48$, $p=.62$, $\eta_p^2=.01$. There was no significant main effect of social modelling $F(2,73)=2.79$, $p=.07$, $\eta_p^2=.07$. However, planned orthogonal contrasts revealed that Modelled-SSQ scores were elevated in social modelling groups, compared to the No Social Modelling group $F(1,73)=5.00$, $p=.03$, $\eta_p^2=.06$. However, there was no significant difference in Modelled-SSQ scores between the Consistent and Inconsistent group, $F(1,73)=0.44$, $p=.51$, $\eta_p^2=.006$.

Summary

In contrast to Experiment 1, those in the Inconsistent (No Choice) group did not experience exacerbated levels of cybersickness relative to the Consistent (No Choice) group (see Figure 1). Instead, their SSQ scores were comparable to the Social Modelling Consistent group. Combined, both sets of results provide novel evidence of generalisation of socially-acquired nocebo effects, whereby the model and observer do not need to undertake identical interventions to induce a socially-acquired nocebo effect relative to control. However, in Experiment 1, choice was found to reduce cybersickness in the Inconsistent group. It is unclear whether this difference was driven specifically by the exacerbated scores observed among those in the No Choice/Social Modelling Inconsistent condition in Experiment 1, or were associated with the Inconsistent environment more generally (i.e., would have still been observed in Experiment 2 had Choice been tested).

Experiment 3

The discrepancy in results between Experiment 1 and 2 (i.e., whether the Inconsistent condition exacerbates symptoms) calls into question the effect of choice found in the Inconsistent group in Experiment 1. A final experiment was therefore conducted to assess the presence of a differential effect of choice between Social Modelling Consistent and Inconsistent groups, and to confirm that cybersickness elicited in the Inconsistent group is at least similar, if not greater, than the Social Modelling Consistent group. As the control (No Social Modelling) groups in both Experiment 1 and 2 revealed consistently low levels of cybersickness compared to the Social Modelling groups – establishing a robust effect of social modelling consistent with the literature (Faasse et al., 2015; Faasse et al., 2018; Tan et al., 2022; Zhang et al., 2017), Experiment 3 omitted this condition.

Methods

Small adjustments to refine the method and analyses were pre-registered (AsPredicted #103304). Data collection occurred between July 26th – October 9th 2022.

Participants

The sample (*N*=124) comprised of 60 males, 60 females, and 4 of other gender identities ranging from 18-54 years of age (*M*=31.91, *SD*=6.60).

Design and Procedure

A 2(Social Modelling: Consistent, Inconsistent) x 2(Choice: No Choice, Choice) between-subjects design was employed. All participants underwent the Social Modelling procedure as described in Experiment 1

Secondary Outcomes: Materials and Measures

Given that no effect of choice on control was observed in Experiment 1 (see Supplementary Materials 4), the measure was adapted to a single item with greater face validity: "How in control do you feel right now?" rated on a VAS from 0 (Not at all), 50 (Moderately) to 100 (Very much). Extra memory questions were included to reinforce the cover story, and participants were asked to rate how positive an experience they perceived the social model to have had during the VR, and to what extent they perceived the social model to have experienced cybersickness.

Power & Data Analysis

A total of 31 participants per group (124 total) were recruited, powered to detect an effect of η_p^2=.06, with α=.05 with 80% power. The effect size is derived from the interaction effect of choice and social modelling observed in Experiment 1. Exclusions were: extreme baseline cybersickness (pre-registered as ≥40 sum score baseline SSQ or any single item ≥8,

N=9), technical difficulties (*N*=6), not following instructions (*N*=1), withdrawal (*N*=1), or failure of the manipulation check (*N*=1).

Results

Figure 1 depicts the group means for the primary outcome. The ANCOVA model revealed that there was a main effect of the covariate gender, $F(2,118)=5.45$, $p=.005$, $\eta_p^2=.08$. However, there was no significant main effect of choice $F(1,118)=0.06$, $p=.81$, $\eta_p^2<.001$ or social modelling (Consistent vs Inconsistent) $F(1,118)=0.01$, $p=.91$, $\eta_p^2<.001$ and no significant social modelling*choice interaction $F(1,118) = 0.08$, $p=.78$, $\eta_p^2<.001$ on Modelled-SSQ scores.

Correlations were run between Modelled-SSQ scores and whether the confederate: 1) was perceived as experiencing cybersickness, and 2) was perceived as having a positive experience. Neither correlation was statistically significant (both *p*s>.05).

Summary

Contrary to the results of Experiment 1, no interaction between choice and social modelling was observed. This suggests that the difference reported in Experiment 1 was driven specifically by the exacerbated scores observed among those in the No Choice/Social Modelling Inconsistent condition, which was not replicated in Experiment 2, rather than via choice itself. Consistent with the results of Experiment 2 was the lack of difference in cybersickness elicited between the two Social Modelling groups. This suggests that at a minimum, the Inconsistent group experienced similar levels of cybersickness due to social modelling as the Consistent group, thereby providing consistent novel evidence across the three experiments that socially-acquired nocebo effects do generalise.

Pooled Analysis

Results from all experiments were combined for a pooled analysis. Table 1 summarises the number of pooled participants in each experimental condition. To explore the main effects of Social Modelling and Choice, and their interaction, the analysis was conducted as a 2(Modelling Type: Consistent, Inconsistent) x 2(Choice: No Choice, Choice) + 1(No Social Modelling: both Choice and No Choice groups) ANCOVA controlling for gender as a covariate. There were no significant differences between experiments in the demographics (gender, age, and VR experience) of participants - see Electronic Supplementary Materials 4.

Table 1

Count of participants in each condition across experiments

Social Modelling Condition	Choice Condition	Experiment 1	Experiment 2	Experiment 3	Total
No Social Modelling	No Choice	20	26	0	46
	Choice	23	0	0	23
Social Modelling Consistent	No Choice	22	26	31	79
	Choice	23	0	31	54
Social Modelling Inconsistent	No Choice	23	26	31	80
	Choice	23	0	31	54
Total (*N*)		134	78	124	336

Primary Outcome: Modelled SSQ

Controlling for gender, $F(2,332)=5.21$, $p=.005$, $\eta_p^2=.04$, participants assigned to the experimental conditions (Modelling type: Consistent Choice, Consistent No Choice, Inconsistent Choice, Inconsistent No Choice) combined had significantly higher Modelled-

SSQ scores (*M*=4.50, *SE*=.74) relative to those in the control group (No Social Modelling Choice and No Social Modelling No Choice; *M*=1.11, *SE*=.99) $F(1,332)=23.21$, $p<.001$, $\eta_p^2=.07$.

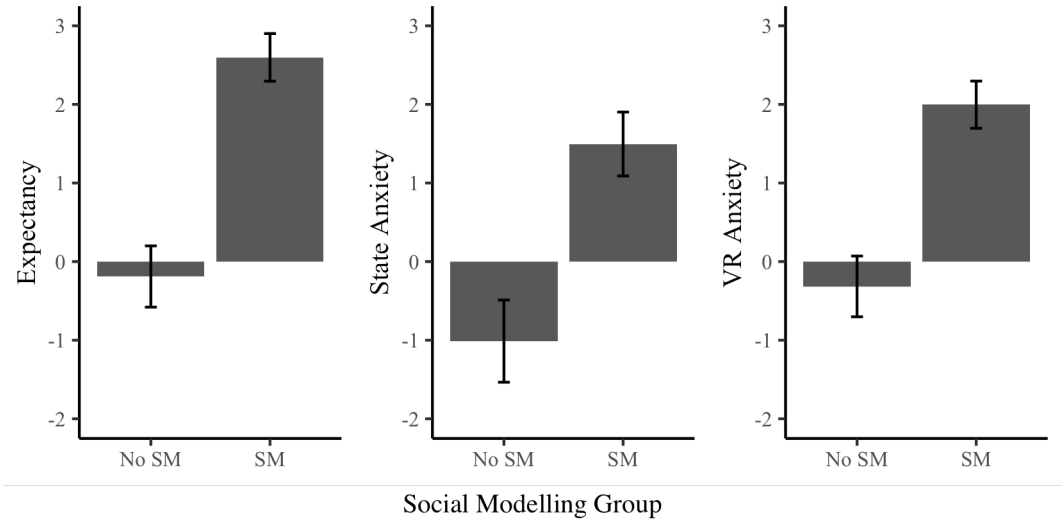
Figure 1 depicts the pooled group means. There was a non-significant main effect of Choice (Choice vs. No Choice), a non-significant effect of Modelling Type (Consistent vs. Inconsistent), and no interaction between Modelled Content and Choice. In summary, social modelling of any type (Consistent or Inconsistent) increased symptoms of cybersickness relative to No Social Modelling, while choice had no effect on socially-acquired cybersickness.

Secondary Outcomes: Expectancy, State Anxiety, VR Anxiety, Control and Affect

To investigate the potential underlying causes of the observed group differences in cybersickness between Social Modelling and No Social Modelling Groups, three one-way between-subjects ANCOVAs were conducted with expectancy, state anxiety, VR anxiety as the dependent variable, Social Modelling (No Social Modelling vs. Social Modelling: Consistent and Inconsistent combined) as the independent variable, and gender as the covariate. Please note that the same analyses for each separate study are presented in Electronic Supplementary Materials 4. Group means from the pooled analysis are depicted in Figure 2. The pattern of results was similar across all three secondary outcomes (with full statistics reported in Table 2). There was a significant effect of the covariate gender on both state anxiety ($p<.001$) and VR Anxiety ($p=.001$) but no significant effect of gender on expectancy ($p=.17$). Controlling for the covariate, Social Modelling significantly increased all three outcomes, relative to the No Social Modelling groups (all *p*s<.001).

Figure 2

Mean baseline adjusted Expectancy, State Anxiety and VR Anxiety: Social Modelling vs. No Social Modelling



Note. All error bars are ± 1 SEM and account for the covariate (gender)

Table 2

ANCOVA results (Contrast: No Social Modelling vs Social Modelling Groups)

	$F(1,332)$	p	η_p^2
Expectancy	93.90	<.001	0.22
State Anxiety	41.95	<.001	0.11
VR Anxiety	65.20	<.001	0.16

As predicted by the literature, Modelled-SSQ was significantly positively correlated with expectancy, $r(334)=.23$, $p<.001$, state anxiety, $r(334)=.24$, $p<.001$, and VR anxiety, $r(334)=.28$, $p<.001$.

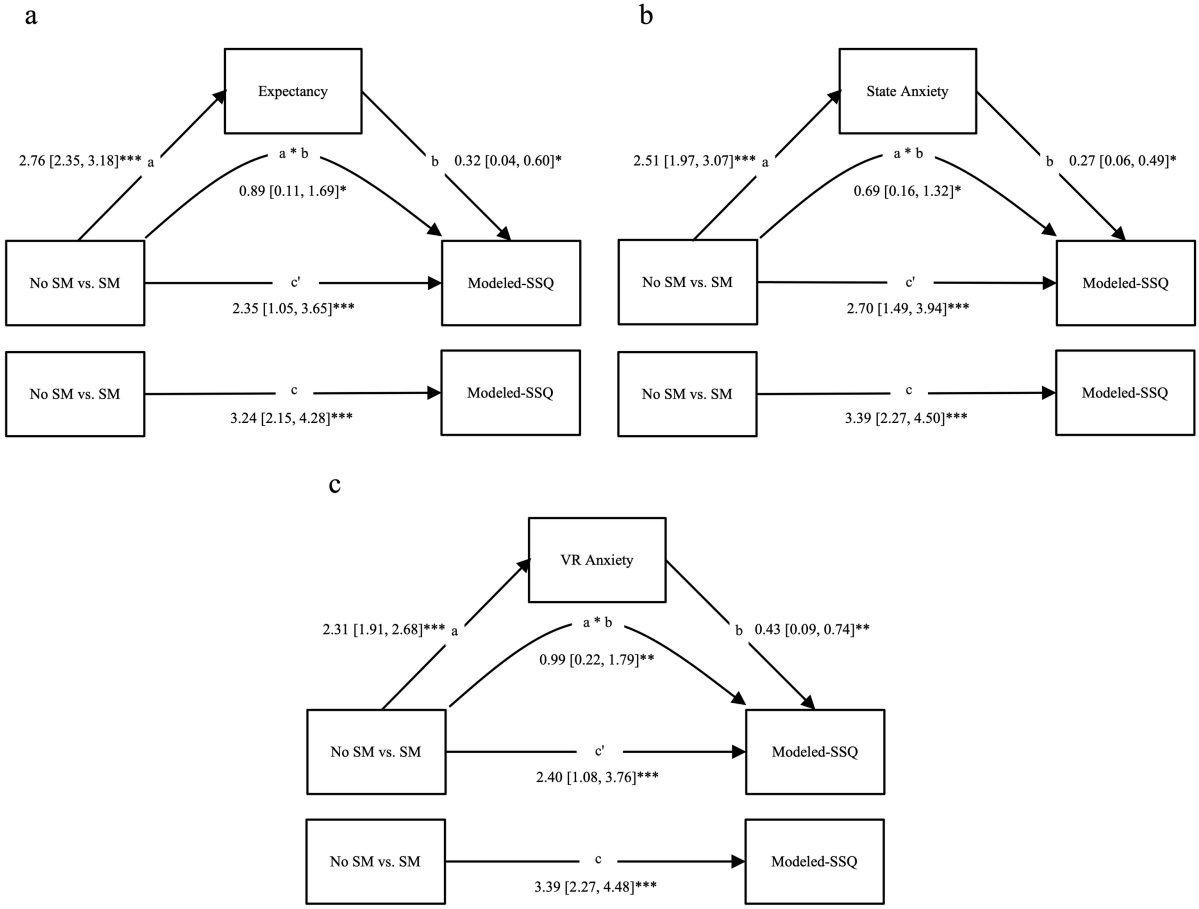
Choice and No Choice groups were compared on perceived control and positive affect scores, but these dimensions did not significantly differ between groups (all *ps*>.05; see Electronic Supplementary Material 4).

Mediation Analyses

As presented in Figure 3, three mediation analyses were conducted, with Social Modelling (No Social Modelling vs. Social Modelling: Consistent and Inconsistent combined, collapsed across choice) as the independent variable, Modelled-SSQ as the dependent variable, and expectancy, state anxiety and VR anxiety, as separate mediators. Gender was included as a covariate in models where there was a significant effect (i.e., state anxiety and VR anxiety, see above). A very small number of participants in each cell self-reported their gender as "other" across the three experiments (n=6; 1.79%), these participants were excluded from the mediation analyses that included gender as a covariate for the model to converge. Bootstrapping with 10,000 samples was conducted to determine 95% confidence intervals (CIs) which were used to determine significance.

Figure 3

Mediatory Effects of Expectancy, State Anxiety and VR Anxiety on Cybersickness



Note. Values are unstandardised beta coefficients with 95% confidence intervals. Figures represent mediatory effects of expectancy (a), state anxiety (b) and VR anxiety (c). Covariate (gender) was included models b and c but is not represented here for brevity. Paths *a*, *b*, and *c* are the direct paths between variables. Curved path *a*b* is the indirect effect with bootstrapped CIs. Path *c'* is the direct association between the group contrast and cybersickness, controlling for the indirect effect.

Expectancy. Expectancy significantly mediated the effect of group on Modelled-SSQ score, direct effect =2.35, 95%CI [1.05,3.65], $p<.01$ and indirect effect =0.89, 95%CI [0.11,1.69], $p=.02$.

State Anxiety. State anxiety significantly mediated the effect of group on Modelled-SSQ score, direct effect =2.70, 95%CI [1.49, 3.94], $p<.001$ and indirect effect =0.69, 95%CI [0.16, 1.32], $p=.01$.

VR Anxiety. VR Anxiety significantly mediated the effect of group on Modelled-SSQ score, direct effect =2.40, 95%CI [1.08,3.76], $p<.01$ and indirect effect =0.99, 95%CI [0.22,1.79], $p<.01$.

Summary

The pooled results from the three experiments provide compelling evidence for an effect of social modelling in producing nocebo effects. Most importantly, they showed that social modelling can produce nocebo effects regardless of whether the experience witnessed is identical or similar to the one subsequently encountered. That is, that socially-acquired nocebo effects can generalise from a specific observed experience to other experiences. Social modelling exacerbated expectancies regarding cybersickness and increased anxiety, and both expectancies and anxiety were found to mediate the relationship between social modelling and cybersickness. Choice, however, was not found to be an effective intervention to reduce socially elicited cybersickness.

General Discussion

The present study explored whether socially modelled nocebo effects would generalise across contexts and whether choice reduced these effects. There was consistent evidence for the effect of social modelling on cybersickness. Critically, this socially-acquired nocebo effect occurred irrespective of whether the participant observed the model undergo an

identical or distinct VR activity, indicating that socially-acquired nocebo effects can generalise. There was, however, no consistent evidence that choice could inhibit these socially-acquired nocebo effects.

Social modelling has been established as a powerful determinant of a range of symptoms (Faasse et al., 2018; Koban & Wager, 2016; Świder & Bąbel, 2013; Vögtle et al., 2013; Vogtle et al., 2019; Vögtle et al., 2016; Yoshida et al., 2013). The present study revealed that social modelling plays an equally important role with respect to nocebo cybersickness (Tan et al., 2022). As hypothesised, witnessing a social model experience cybersickness due to VR immersion exacerbated participants' own experience of cybersickness compared to those that did not view the model. However, prior research has never investigated the effect of modelling *similar* interventions (Bajcar & Bąbel, 2018). The present study therefore investigated the generalisation of socially modelled symptoms beyond identical model/observer experiences. A key novel finding here was that the strength with which social modelling induced nocebo cybersickness did not depend on the similarity between the model and observers' experience – i.e., the social model did not have to undertake the exact same VR activity as the participant to elicit comparable levels of cybersickness. This novel finding has concerning implications, whereby social modelling may be significantly more widespread than previously imagined.

Contrary to hypothesis, choice did not reduce symptoms. Given that choice was not found to enhance perceived control or engender positive affect, the manipulation may have lacked salience. However, the choice provided to participants in the present study was not dissimilar to past research that yielded positive results in the context of explicit instruction and classical conditioning (Geers et al., 2013; Tang et al., 2022). As such, it is equally possible that our measures of control and affect themselves either lacked specificity or were not associated with the choice manipulation. For example, Tang et al. (2019) found an effect

of choice on conditioned placebo analgesia but failed to find a corresponding increase in perceived control, suggesting that these two constructs may be orthogonal. An alternative explanation is that choice may have differential effects based on the mode of induction, with socially modelled nocebo effects being especially resistant to attenuation. The present study was the first to date to investigate choice with respect to social modelled nocebo effects, with past research exclusively concerning explicit instruction (Bartley et al., 2016). Clearly further investigation, employing experimental paradigms concerning choice that have previously been demonstrated to modulate the nocebo effect, are needed to elucidate the role of choice on socially-acquired nocebo effects.

To date, empirical evidence addressing the mechanisms hypothesised to generate socially-modelled nocebo effects has been both limited (Faasse, 2019) and inconsistent (Koban & Wager, 2016; Tan et al., 2022; Vögtle et al., 2013; Vogtle et al., 2019). The present study addressed this concern in a large sample. Consistent with previous research (Koban & Wager, 2016; Tan et al., 2022), expectancies and anxiety appear key to facilitating socially-acquired nocebo effects. Both were found to be elevated after social modelling and to mediate the effect of social modelling on cybersickness. While no effect of choice was observed in the present study, the strength of identifying these mediators is that they can be employed to inform future targeted interventions. As such, research may wish to focus on these mechanisms when developing methods to attenuate socially-acquired nocebo effects.

The present study demonstrated several novel results based on a large representative sample. However, limitations must be noted. First, the study was conducted single-blind, which may have led to experimenter bias. However, care was taken to ensure that all instructions were delivered by the experimenter using identical scripts across experimental sessions. Furthermore, the social model was a pre-recorded video to ensure consistency, and all questionnaires completed by participants were administered remotely via Qualtrics to

reduce biased responding. Second, the study was conducted entirely online via Zoom meaning the quantity of social information conveyed was dependent on the strength of participant's internet connection and limited to what was observable via webcam, introducing experimental noise. Testimony to the strength of social modelling, strong effects were found irrespective of whether the VR environment was consistent or inconsistent, despite these technical limitations. However, social modelling in live settings may be stronger and potentially more receptive to manipulations such as choice. Third, the social model was a male and as such the effect of the model's gender remains unexplored. Further, any gender effects reported may be confounded with gender match between participant and model.

Evidence of generalisation found in the present study is highly problematic with respect to both clinical and non-clinical settings. Results challenge the assumption that socially modelled nocebo effects are limited to identical interventions, suggesting that, as people do not have to observe others experience an identical treatment for social transmission to occur, then opportunity for social modelling may be significantly more widespread than previously imagined. This emphasises the importance of future research into interventions to reduce these negative health effects. Beyond choice, potential avenues that remain unstudied with respect to socially modelled symptoms include: side-effect framing (Barnes, Faasse, et al., 2019; Mao et al., 2021), nocebo education (Crichton & Petrie, 2015; Pan et al., 2019), latent inhibition (Quinn et al., 2017), and affect manipulations (Geers et al., 2020). Importantly, the present study identified negative expectancies and anxiety key mechanisms, meaning that interventions targeting these mechanisms are likely to be most effective. Further exploration of the generalisation of social information is also warranted with respect to different symptom outcomes (e.g., pain, headache, insomnia) within different contexts (e.g., clinically). In addition, future research should investigate to what extent these socially modelled effects can generalise, for example between more dissimilar stimuli (VR

rollercoaster vs. VR walk on the beach), or across modes of nocebo induction (nausea induced via VR vs. GVS).

In summary, results of this study demonstrate that social modelling is a powerful determinant of nocebo effects, with the potential to impact our experiences in both a robust and diffuse manner. As choice was not found to reduce these effects at all, further research concerning negative expectancies and anxieties is critical to reduce the harm that can arise from these socially-acquired side-effects.

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Chapter 4: Investigating whether socially-acquired nocebo effects can spread to other treatments

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Supplementary Materials: Appendix C

Open Science Framework: https://osf.io/m8tdh/overview

Introduction

The nocebo effect refers to adverse health outcomes that cannot be attributed to the treatment itself but rather are due to the psychosocial context in which they occur (Bagaric et al., 2022; Mitsikostas et al., 2020). Growing evidence indicates that social information is a key contributor to the nocebo effect (Saunders et al., 2024)[1]. Simply observing another person (a 'model') experience treatment-related pain, nausea, or itch can elicit or exacerbate these symptoms when the observer subsequently undergoes the same treatment. These socially-acquired nocebo effects can even be demonstrated when the treatment is itself a placebo (e.g., Papoiu et al., 2011; Saunders et al., 2023; Vögtle et al., 2013), and have been implicated in the formation of COVID-19 vaccine side effects (Clemens et al., 2023; Tan et al., 2022). However, research has yet to determine if socially-acquired nocebo effects can spread – or generalise – from one treatment to another. This is critical for understanding the full impact that socially-acquired nocebo effects have, as well as for developing strategies to reduce their burden in healthcare and community settings.

Generalisation has been reliably demonstrated in the context of direct experiential learning both in animals and humans (Ghirlanda & Enquist, 2003). For example, rats trained to learn that a specific tone leads to shock will display a defence response to that specific tone *and* other similar tones (Armory et al., 1997). Recent research has also shown that directly-conditioned placebo and nocebo effects generalise across treatment cues (Kampermann et al., 2021; Koban et al., 2018; Weng et al., 2022) and new environmental contexts (Quinn et al., 2015). However, there has been virtually no research on the extent to which socially-acquired nocebo effects generalise. The only exception that we are aware of is a study by Saunders et al. (2023)[2], which found that observing a model report cybersickness to one virtual reality

[1] This reference refers to Chapter 2 of this thesis
[2] This reference refers to Chapter 3 of this thesis

(VR) setting (a rollercoaster), subsequently increased the observer's nocebo cybersickness both to that setting and another (a VR flight simulation). This demonstrates that socially-acquired nocebo effects can spread across contexts. However, to the best of our knowledge, there is no research examining whether socially-acquired nocebo effects generalise across *medical* treatments (e.g., different types of treatments).

Generalisation of socially-acquired nocebo effects across treatments is both highly concerning and relevant in the context of the significant proliferation of, often negative, information on social media. Seeing or hearing about another's experience of side effects after one type of vaccination may not only lead to nocebo side effects for that specific vaccination—but could also increase nocebo side effects for other vaccinations. Previous research has shown that socially-acquired symptoms arising from a placebo treatment can spread beyond the specific symptoms communicated by the model (Faasse et al., 2018). However, as models and observers received the same treatment, this is distinct from generalisation of socially-acquired nocebo effects *across treatments*. As such there is a significant gap in our knowledge regarding the social transmission of nocebo effects when the model/observer intervention differs.

The current study examined whether nocebo side effects could be elicited via social modelling even when the model apparently received a *different* treatment. This involved simulating a clinical context by administering one of two placebo treatments (capsules) presented as cognitive enhancers, each of which was described as having a *unique* side effect profile. One was described as associated with "Headaches and Dizziness" and the other "Nausea and Stomach Discomfort". Participants were randomised to one of four groups. The three treatment groups comprised: social modelling of side effects associated with the *same* treatment; social modelling of side effects associated with the *different* treatment; and a verbal suggestion only group (i.e., no social modelling). The fourth group was a no-treatment

control group. We hypothesised that there would be an overall nocebo effect, with more side effects reported in the treatment groups than the control group. Most importantly, however, we hypothesised that social modelling would exacerbate this nocebo effect both when the same treatment was received by the observer *and* when a different treatment was received; the latter of which would indicate generalisation of socially-acquired nocebo effects to a novel treatment with unique side-effects. Heart Rate Variability (HRV) and Electrodermal Activity were also collected to explore any effects of social modelling on physiological arousal (See Daniali & Flaten, 2020 for a review with respect to nocebo hyperalgesia).

Methods

The study design and analyses were preregistered (aspredicted.org #109597). Ethics approval was granted by the University of Sydney Human Research Ethics Committee (#2022/532), all methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all participants.

Participants. One hundred and twenty-one healthy volunteers (Female=87, M_{age}=19.52, *SD*=2.28) from the University of Sydney participated and received course credit as compensation. Eligible participants were fluent in English without any known allergy to medication or lactose. Due to the gelatine capsules, those with dietary restrictions were advised not to participate. Participants were required to be in full health at the time of testing and were excluded if they exceeded pre-registered thresholds of physical symptoms at baseline.

Design

The study involved a single-blind one-way between-subjects design with four levels. Participants were told the study was investigating two cognitive enhancers (both actually placebos) of which they may receive one. Participants were warned that one of the treatments

was associated with “headaches and dizziness” and the other with “nausea and stomach discomfort”. The two different side effect profiles, along with the supposed name and branding of the medication container served to distinguish the treatments as distinct. The critical manipulation was if the participant observed the confederate experience side effects, and for those who did, which treatment the confederate had supposedly taken, with participants randomly allocated to one of four groups. R 4.1.1 (R Core Team, 2020) was used as a random number generator to generate a random sequence of group assignment with which to allocate participants in the order in which they were tested. The Social Modelling Consistent group received placebos and observed side effects reported by a model who they believed had taken the same treatment as them. A Social Modelling Inconsistent group received placebos and observed side effects reported by a model who they believed had taken a different treatment to them. A No Social Modelling group received placebos but did not observe a model. A Natural History group did not receive placebos and did not observe a model. This group served as a control, allowing for a comparison with the three treatment groups to isolate the nocebo effect. Any difference in reported symptoms between the Natural History group and the treatment groups would indicate the presence of a nocebo effect overall. The key outcome of interest was the severity of side effects reported by participants.

Materials and Measures

Placebo pills. No participants received active medication. The placebos comprised gelatine capsules filled with lactose. The placebo pills were contained in two distinct fake medication bottles designed to reinforce the cover story and the primary manipulation, see https://osf.io/m8tdh/overview.

Demographics. Participant age and gender were recorded.

Physical Symptoms. Physical symptoms were assessed using a modified version of the General Assessment of Side Effects, GASE (Rief et al., 2009). Symptoms communicated by

the confederate (i.e., stomach discomfort) were added to the questionnaire and symptoms unlikely to occur within the time frame of the experiment were excluded (e.g., diarrhea, insomnia) resulting in a list of 10 symptoms. The original 4-point scale 0(Not Present) to 3(Severe) was modified to a 7-point scale to enhance the sensitivity to changes in symptoms. The full scale was decomposed into three scores: Target Symptoms (Mean severity of symptoms supposedly associated with the participants medication), Non-Target Symptoms (Mean severity of symptoms supposedly associated with the other medication) and General Symptoms (Mean severity of remaining 6 GASE items). The Target Symptoms for participants in the Natural History group (who did not receive medication) were yoked to the Target Symptoms of the previous participant in the No Social Modelling group.

Generalized State Anxiety. General state anxiety was measured via the Spielberger State-Trait Anxiety Inventory-6 (Marteau & Bekker, 1992, Cronbach's alpha=.81).

Side effect specific anxiety. Participants rated their anxiety concerning experiencing side effects on the single item measure: “How anxious are you about experiencing adverse events (e.g., side effects) as a result of participating in this study?” on a visual analogue scale (VAS) ranging from 1(Not Anxious) to 100(Very Anxious).

Expectancy. Participants were asked to rate their expectancy of the experience of side effects on the single item measure: “How much do you expect to experience adverse events (e.g., side effects) as a result of participating in this study?” on a VAS ranging from 1(Not at all) to 100(Very much so).

Expectancy for cognitive enhancement. Participants were asked to rate their expectancy of the efficacy of cognitive enhancement medication on the single item measure: “To what degree do you expect the cognitive enhancement medication to enhance your performance?” on a VAS ranging from 1(No enhancement) to 100(Significant enhancement).

Cognitive performance. The Rapid Visual Information Processing (RVIP) procedure was used to assess sustained attention (Wesnes et al., 1983). Numbers ranging from 1 to 9 were presented on a computer screen at a rate of 100/min for a total duration of five minutes. Participants were required to press the space bar as quickly as possible once either three consecutive even or three consecutive odd numbers appeared. They had 1.5s to make a correct response; all responses outside this time were considered false alarms. The sequence of numbers was semirandom such that the target sequences were separated by a minimum of 5 and maximum of 33 digits. Performance was assessed using proportion (%) of correct responses.

Self-reported cognitive performance. Participants were asked to rate their perceived performance on the RVIP: "How would you rate your performance on the cognitive task?" on a VAS ranging from 1(Very poor) to 100(Very good).

Self-reported influence on cognitive performance. Participants assigned to take the placebo were asked "How effective was the medication at enhancing your cognitive performance?" on a VAS ranging from 1(Not effective at all) to 100(Very effective).

Manipulation check. To ensure participants were aware of their assigned medication they were asked to recall the name of their assigned medication (I was assigned to…: 'Vitatil', 'Monovigil', 'No Treatment Control', 'I took one of the medications but do not recall which one' and 'I do not recall if I received treatment'). To probe more generally about suspicion concerning the confederate they were asked to answer the general probe "Briefly describe (in 2-3 sentences) what you thought the purpose of the experiment was:".

Equivital Sensor Belt and Module. Participant Heart Rate (HR) was measured using an Equivital Sensor Module fitted onto an Equivital Sensor Belt. HR was measured continuously for 15 minutes after administration of the treatment (or lack thereof). HR Variability (HRV) is a measure of the parasympathetic and sympathetic branches that

modulate cardiac activity (Daniali & Flaten, 2020). Frequency domain methodology was used to generate the High Frequency/Low Frequency (HF/LF) ratio using pyHRV (Gomes et al., 2019).

Electrodermal activity (EDA). EDA was recorded as a measure of autonomic arousal in response to the treatment and social communication manipulations. This was achieved by using a PowerLab amplifier and a Galvanic Skin Response amplifier (ADInstruments) with two finger electrodes placed on the middle and index fingers of participants' right hand. EDA was recorded over the same time period as HR. EDA can be decomposed into tonic activity (slower general changes in sympathetic arousal) and phasic activity (reactive fast changes), which each reflect important components of physiological arousal (Braithwaite et al., 2013). A convex optimization approach to electrodermal activity (cvxEDA) was applied to extract the two components (Greco et al., 2016), after which mean Skin Conductance Level (μSCL) was calculated as a measure of the tonic activity and the number of Skin Conductance Responses (nSCR) as a measure of the phasic activity.

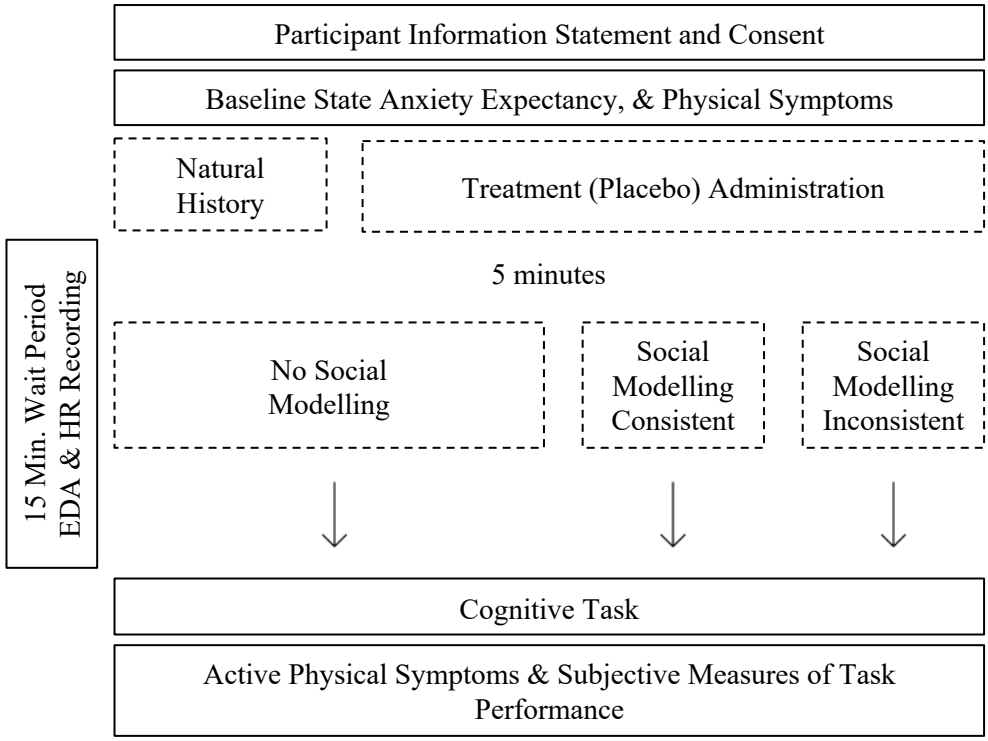
Procedure

Refer to Figure 1 for a flow chart of the study procedure. All participants were tested individually in a single 1hr session conducted by a single experimenter who was a 24-year-old white Australian female. On arrival, participants received a written information sheet, which was reinforced verbally. This outlined the cover story and contained the warning: "*Vitatril* has been associated with the experience of mild nausea and stomach discomfort. *Monovigil* has been associated with the experience of mild headaches and dizziness". Side effect profiles were counterbalanced within each group. Participants who consented were then randomised and verbally informed of their treatment allocation by the researcher (i.e., No Treatment, 'Vitatril' or 'Monovigil'). Next, participants were fitted with the Equivital Harness. Participants then completed demographics and baseline measures including:

physical symptoms, state anxiety, expectancy for side effects and expectancy for cognitive enhancement. Participants were seated facing the door and set up with the electrodes to measure their EDA. The placebo capsules were then administered to treatment groups. All participants were seated and waited for 15 minutes, ostensibly providing time for the medication to take effect in the treatment groups. Exactly five minutes after the HR/EDA recording commenced, participants in the social modelling conditions saw a confederate enter the room. The confederate was a 26-year-old Asian-Australian male perceived as another participant of the study. Within view of the participant, the researcher asked the confederate, "So you received ['Vitatril'/'Monovigil'] around thirty minutes ago, how are you feeling now?". Where the placebo medication either aligned (Social Modelling Consistent) or did not align (Social Modelling Inconsistent) with the supposed treatment the participant had just taken. The confederate then responded with either: "Not great, definitely feeling headachy and a bit dizzy" or "Not great, definitely feeling quite nauseous and my stomach is upset". Importantly, the side effects the confederate reported aligned with the warnings participants had received concerning the treatment the confederate had supposedly taken. At the same timepoint as the social modelling conditions received this side effect modelling, participants in the Natural History and No Social Modelling groups overheard the experimenter have an irrelevant phone call to control for the effect of the conversation. After the 15-minute wait period, all participants were taken to another room to complete the cognitive task to uphold the cover story. Upon completion, participants returned to the main room where they completed the physical symptoms questionnaire again and were also asked to report their perceived efficacy of the medication and complete a manipulation check. All participants then received a written debrief informing them about the true aims of the study.

Figure 1

Flowchart of study procedure



Power and data analysis

We planned to recruit a total of 120 participants (30 participants per-group). This was based on a power analysis on the effect size for the social modelling manipulation (f=.31, derived from Faasse, 2015) with an alpha of .05 with 80% power. Of the 121 participants recruited, one participant was excluded from analysis as their sum-scored baseline physical symptoms exceeded the pre-registered threshold, resulting in a final sample of 120 participants.

Primary data analysis. Statistical analysis was conducted using R 4.1.1 (R Core Team, 2020). The primary data analysis consisted of a one-way (Condition: Natural History, No Social Modelling, Social Modelling Consistent, Social Modelling Inconsistent) ANOVA, using the Target Symptom difference score (Active – Baseline) as the outcome. Orthogonal contrasts were used to determine:

1. Whether there was an overall nocebo effect - No Treatment (Natural History) vs. Treatment (No Social Modelling, Social Modelling Consistent, Social Modelling Inconsistent).

2. The effect of social modelling, above and beyond explicit instruction alone - No Social Modelling vs. Social Modelling (Social Modelling Consistent and Inconsistent).

3. The effect of generalisation - Social Modelling Consistent vs. Inconsistent.

Secondary analysis examined Non-Target Symptoms and General Symptoms as the outcome variable, in similar one-way ANOVAs. Self-reported and actual cognitive performance scores were compared between groups using one-way ANOVAs to assess the presence of a placebo effect but were not the focus of the study.

Analysis of physiological measures. HRV and EDA were extracted in two non-overlapping five-minute periods: (1) the first five minutes of the post-capsule waiting period ("Time 1") and (2) the second five minutes ("Time 2", immediately after the model communication in the social modelling groups). The data was analysed using a two-way mixed ANOVA comprising the within-subject factor Time (Time 1, Time 2) and the between-subject factor Condition. The same three orthogonal contrasts were used to test preregistered hypotheses. We report the Time main effect, each contrast's main effect, and their respective Time × Contrast interactions. Retaining Time as a repeated-measures factor allowed us to both test overall group differences in physiological arousal and evaluate whether the social modelling manipulation altered arousal over time.

For brevity, only the planned orthogonal contrasts are reported in text. Partial eta squared were interpreted with 0.01, 0.06 and 0.14 as thresholds corresponding to small, medium, and large effect sizes (Richardson, 2011). The results of the omnibus tests are available in Supplementary Materials 2 and 6. Exploratory analysis of symptoms is available in Supplementary Materials Figure S3.

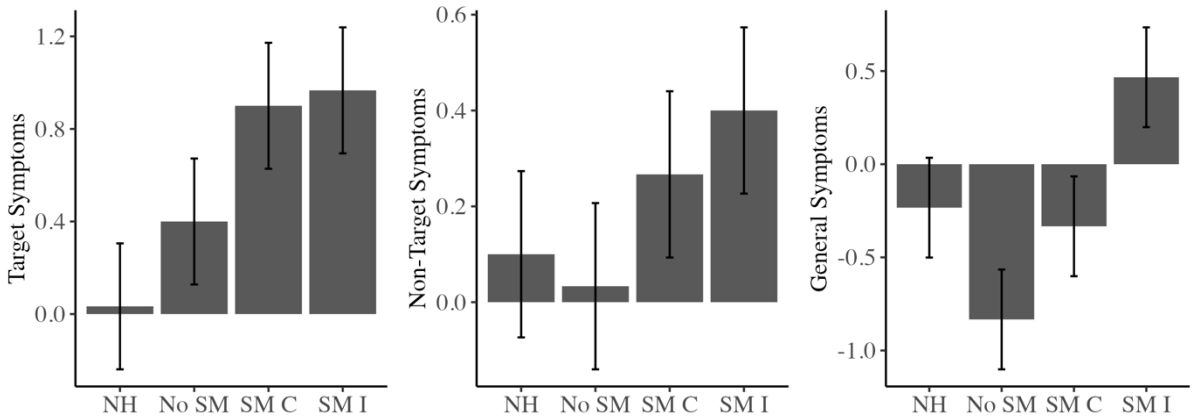
Results

Baseline differences. There were no significant differences between groups in age, gender, or baseline measurements including physical symptoms, state anxiety, general anxiety, expectancy for symptoms, or expected enhancement (all *ps*>.05) indicating randomisation was successful (see Supplementary Materials Table S1).

Target Symptoms. Figure 2 depicts the group means for the three pre-registered outcomes. Orthogonal contrasts revealed that there was a significant overall nocebo effect, where groups that received the placebo reported increased levels of their Target Symptom relative to the Natural History group, $F(1,116)=5.28$, $p=.023$, $\eta_p^2=.04$. There was no significant difference in Target Symptoms between the No Social Modelling group and the social modelling groups combined, $F(1,116)=2.56$, $p=.112$, $\eta_p^2=.02$, nor was there a significant difference in Target Symptoms between the Social Modelling Consistent and Inconsistent groups, $F(1,116)=0.03$, $p=.86$, $\eta_p^2<.001$.

Figure 2

Pre-registered analyses



Note. From left to right, Mean baseline adjusted Target, Non-Target and General Symptom scores by group. Natural History (NH), No Social Modelling (No SM), Social Modelling Consistent (SM C) and Social Modelling Inconsistent (SM I). All error bars are ± 1 SEM.

Non-Target Symptoms. There was no significant overall nocebo effect, $F(1,116)=0.44$, $p=.50$, $\eta_p^2=.004$, social modelling, $F(1,116)=1.99$, $p=.161$, $\eta_p^2=.02$, or generalisation, $F(1,116)=0.30$, $p=.59$, $\eta_p^2=.002$, on severity of Non-Target Symptoms.

General Symptoms. There was no significant overall nocebo effect on severity of General Symptoms, $F(1,116)<.001$, $p>.99$, $\eta_p^2<.001$. However, there was a significant effect of social modelling , $F(1,116)=7.53$, $p=.007$, $\eta_p^2=.06$, where the groups that did not receive social modelling reported a greater reduction in General Symptoms from baseline than those in the social modelling conditions. Similarly, a significant effect of generalisation was found such that participants in the Social Modelling Inconsistent group reported more General Symptoms than Social Modelling Consistent group, $F(1,116)=4.46$, $p=.037$, $\eta_p^2=.04$.

Placebo effects. There was no significant difference in self-reported cognitive performance between groups, $F(3,116)=0.02$, $p>.99$, $\eta^2<.001$, nor was there a significant difference in actual performance, $F(3,116)=0.15$, $p=.93$, $\eta^2=.003$. Within the three groups that received the placebo treatment, there was no significant difference in self-reported influence of treatment on cognitive performance, $F(2,86)=0.67$, $p=.51$, $\eta^2=.02$. See Supplementary Materials Table S7 for group means.

HRV. Refer to Table 1 for group means for the physiological data. Due to technical issues with the Equivital Sensor Module, heart rate data was only available for 81 participants. There was no significant relationship between missing data and participant group, $\chi_3^2=1.63$, $p=.65$, Cramer's $V=.12$. Two-way mixed 2(Time) x 4(Condition) ANOVA was conducted to explore differences in HRV. The two-way mixed ANOVA revealed no significant effect of treatment, $F(1, 77)=0.08$, $p=.773$, $\eta_p^2<0.001$, social modelling, $F(1, 77) = 1.78$, $p=.186$, $\eta_p^2=.02$, nor generalisation, $F(1, 77)=0.33$, $p =.570$, $\eta_p^2= .004$, on HRV. The ANOVA found no significant effect of time $F(1,77)=0.17$, $p=.68$, $\eta^2=.02$, and no interaction

between treatment, social modelling, and generalisation, and time, F(1, 77)=0.09, p=.763, η_p^2=.001, F(1, 77)=0.94, p=.336, η_p^2=.012. F(1, 77)=0.00, p=.969, η_p^2<.001 respectively.

Table 1

Physiological Measures

		Natural History	No Social Modelling	Social Modelling Consistent	Social Modelling Inconsistent
HRV	M	2.11	1.81	2.31	2.64
	SE	0.42	0.41	0.38	0.42
nSCR	M	19.65	28.25	29.59	28.60
	SE	3.08	3.30	2.79	3.22
µSCL	M	-2.83	2.51	3.27	2.31
	SE	1.37	1.47	1.24	1.43

Note. Means are averaged across the factor time.

EDA. Due to technical issues, EDA recordings for 92 participants were available. There was no significant relationship between missing data and participant group, χ_3^2=7.04, p=.07, Cramer's V=.25. Two-way mixed 2(Time) x 4(Condition) ANOVA was conducted to explore differences in tonic (µSCL) and phasic (nSCR) activity separately. Averaged across time, contrasts revealed increased µSCL in groups that received treatment compared to those who did not, F(1,88)=12.17, p<.001, η_p^2=.12. Averaged across the other variables in the model, there was no significant effect of social modelling, F(1,88)=0.02, p=.87, η_p^2<.001, generalisation, F(1,88)=0.26, p=.61, η_p^2=.002, nor time, F(1,88)<0.01 p=.96, η^2<.001. Averaged across time, contrasts revealed increased nSCR in groups that received treatment compared to those who did not, F(1,88)=6.59, p=.01, η_p^2=.07. There was no significant effect

of social modelling, $F(1,88)=0.05$, $p=.83$, $\eta_p^2<.001$, generalisation, $F(1,88)=0.05$, $p=.82$, $\eta_p^2<.001$, nor time, $F(1,88)=3.09$ $p=.08$, $\eta^2=.03$. There was no significant relationship between tonic, B=0.01, $t(89)=0.44$, $p=.67$, or phasic SC, B=0.09, $t(89)=1.00$, $p=.32$, and Target Symptom severity. Table 1 contains group means for the Physiological Measures.

Manipulation check. Most participants correctly recalled the 'treatment' they had taken (93%). The overall social modelling manipulation was successful, with only one participant in the sample reporting suspicion concerning the other participant. A small proportion of participants expressed suspicion that the treatment was a placebo ($N=23$). However, raising suspicion concerning the placebo treatment did not vary between groups, $\chi^2(3, N=120) = 7.05$, $p=.070$, Cramer's $V=0.24$, nor was it associated with a change in target symptom reporting, controlling for group, $F(1, 112)=0.44$, $p=.51$ $\eta_p^2=.004$.

Exploratory Analyses

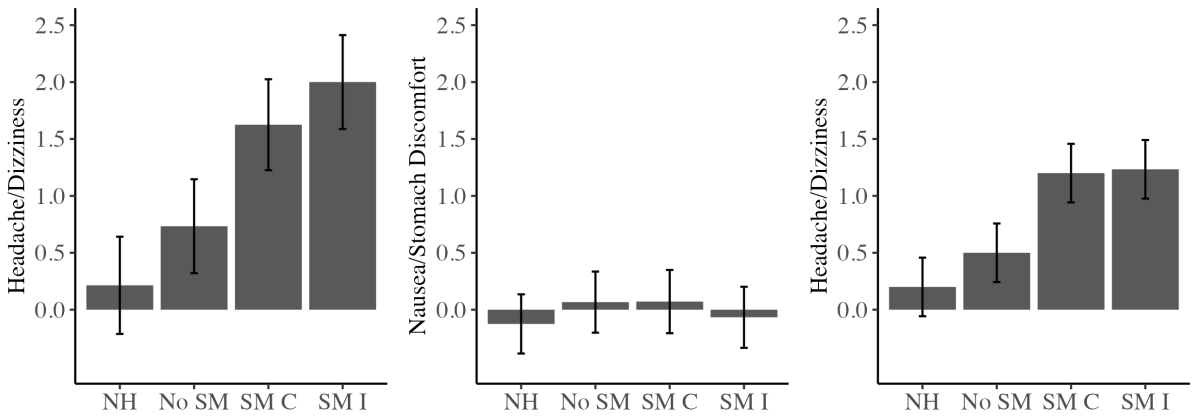
Counterbalancing effect. Contrary to hypotheses, social modelling did not increase Target Symptoms above the effect of instruction alone. To investigate, we conducted exploratory analyses to investigate the influence of counterbalancing side effects. The counterbalancing was intended to increase sensitivity to detect genuine nocebo effects (e.g. Neukirch & Colagiuri, 2015). However, it is possible that if one side effect profile was less responsive to the nocebo manipulation, then this could obscure evidence of social modelling. Further, knowledge regarding the types of symptoms that are most receptive to social modelling is important for future research (Saunders et al., 2024).

To investigate this possibility, we conducted a post-hoc two-sample t-test comparing the Target Symptom severity for participants randomised to headache/dizziness as the target profile versus participants with nausea/stomach discomfort as the target profile, collapsed across the four experimental groups. This revealed participants' whose target was headache/dizziness experienced significantly more of their Target Symptoms ($M=1.17$,

SD=1.71) than the nausea/stomach discomfort participants, (*M*=-0.02, *SD*=1.01), *t*(118)=4.61, *p*<.001, *d*=0.84. This suggested that headache/dizziness was responsive, but nausea/stomach discomfort was not. Therefore, further exploratory analysis was conducted on the sub-group of participants who were warned about headache/dizziness (*n*=60). Despite a reduction in power, this revealed a significant overall nocebo effect, $F(1,56)=6.44$, $p=.014$, $\eta_p^2=.10$, and social modelling effect, $F(1,56)=4.61$, $p=.036$, $\eta_p^2=.08$, but no effect of generalisation, $F(1,56)=0.43$, $p=.52$, $\eta_p^2=.007$, on the severity of headache/dizziness experienced. Similar analyses were conducted with participants warned about nausea/stomach discomfort, which found no significant effect on any contrasts (*p*s >.63), see Supplementary Materials Tables S4 and S5. When the full sample was included using headache/dizziness as the outcome, the pattern of results was replicated, with a significant overall nocebo effect found on severity of headache reported, $F(1,116)=6.85$, $p=.010$, $\eta_p^2=.06$, and significant social modelling effect $F(1,116)=5.17$, $p=.025$, $\eta_p^2=.04$, but no effect of generalisation $F(1,116)=0.008$, $p=.93$, $\eta_p^2<.001$. Results are presented in Figure 3.

Figure 3

Exploratory analyses



Note. From left to right, mean Target Symptoms of headache/dizziness warned participants only; mean Target Symptoms of nausea/stomach discomfort warned participants only. Mean headache/dizziness for all participants. All error bars are ± 1 SEM.

Discussion

The present study investigated whether socially-acquired nocebo effects generalise to similar treatments. Planned analyses revealed an overall nocebo effect, with increased Target Symptom severity in groups that received treatment relative to control. Unexpectedly, there was no significant effect of social modelling above and beyond explicit instruction on Target Symptom severity. Because very few prior studies counter-balance symptom warnings, we conducted a post-hoc, symptom-specific exploration to avoid overlooking differential symptom responsiveness. This exploratory analysis revealed an interesting difference: social modelling increased the nocebo effect when headaches/dizziness were the target profile, but not when nausea/stomach discomfort were, with a large effect of type of target symptom. Most importantly, across both pre-registered and exploratory analyses, the nocebo effect in the Social Modelling Inconsistent group was always as large as, if not larger than, the Social Modelling Consistent group. Taken together, this provides preliminary evidence that while socially-induced nocebo side effects may not always be present, when they are present, they do tend to generalise.

Previous research has established the propensity for directly-conditioned nocebo effects to generalise broadly (Kampermann et al., 2021; Quinn et al., 2017; Weng et al., 2022) and socially-acquired nocebo effects to generalise across VR contexts (Saunders et al., 2023). The present research extends this with preliminary evidence demonstrating generalisation of socially-acquired nocebo effects *across treatments*. The possibility of this type of generalisation of socially-acquired nocebo effects is concerning considering the wealth of treatment-related information communicated between individuals face-to-face, online, and via social media; something which has only been exacerbated by the COVID-19 pandemic (Anderson & Vogels, 2020; Beaunoyer et al., 2020). It suggests that observing another person experience a negative outcome to a specific treatment can cause the observer to experience

nocebo effects not just to that treatment, but to other similar treatments. Interestingly, traditional theories of generalisation from the associative learning literature would predict a weakening of the nocebo effect for different treatments (Ghirlanda & Enquist, 2003). In the current study, as well as in Saunders et al. (2023), the socially-acquired nocebo effect was equally large whether participants received the same or a different treatment to the model. In fact, group means across all analyses trended towards an exacerbation in the Social Modelling Inconsistent group. This indicates the absence of any statistically significant reduction of the nocebo effect due to generalisation was not due to a lack of statistical power. As such, when socially-acquired nocebo effects are present, generalisation across treatments and contexts appears to be as strong as the original effect and hence even more concerning.

Contrary to hypotheses, the primary pre-registered analysis on symptom severity did not find an additive effect of social modelling on side effects above explicit instruction. Importantly however, planned analysis of the secondary outcome general symptoms and exploratory analysis on the subset of participants for whom headaches/dizziness were the Target Symptoms, found significant medium sized effects of social modelling above and beyond instruction. The results of exploratory analyses are consistent with existing studies demonstrating socially-acquired nocebo effects (Barbiani et al., 2018; Faasse et al., 2015; Faasse et al., 2018; Lorber et al., 2007). Notably, these previous studies all included headache as a primary symptom of interest. As such, it may be the case that headache and dizziness are more susceptible to nocebo effects in general and/or in the context of ‘cognitive enhancers’. This can be compared to the concept of cue preparedness’ in learning, where for example rats more readily learn light-shock and taste-nausea contingencies than light-nausea or taste-shock contingencies (Garcia & Koelling, 1966). Understanding if some symptoms are more receptive to social modelling than others could be useful in the development of recommendations regarding the contexts in which interventions might be most appropriate.

Furthermore, given the nature of the exploratory analysis there is a need for pre-registered replication of this result.

Exploratory analyses revealed heightened physiological arousal due to treatment as measured by skin conductance, but no effect when measured using HRV. Physiological arousal was not, however, heightened by social modelling. Previous research has not reached consensus on this topic, with one study finding no effect of social learning on SCR (Egorova et al., 2015) while another has (Koban & Wager, 2016). However, the present analysis of physiological measures is limited due to the lack of pre-treatment baseline measurements. Consequently, it is not clear whether the significantly higher level of arousal among the placebo-treated participants was due to the act of treatment administration itself.

The present study included natural history and treatment-only groups which allowed for a direct assessment of the nocebo effect and the additive effect of social learning above instruction. While this addressed some of the methodological issues in previous studies (Faasse et al., 2015; Faasse et al., 2018), several limitations must be noted. First, the counterbalancing of side effect profiles was intended to increase experimental control and distinguish treatments but appeared to reduce sensitivity to detect socially-acquired nocebo effects because nausea and stomach discomfort appeared non-responsive to the manipulations within the measured timeframe. Because the symptom-specific findings were derived from unplanned exploratory analyses, they should be viewed as hypothesis-generating and warrant replication in future preregistered studies. Second, the study was conducted on a healthy student sample utilising an acute treatment. While this allowed for a large sample size, this translated to an overrepresentation of young, educated females in the sample and as such it is important to replicate this research in clinical samples involving longer treatment timeframes. Third, the modelling procedure took place live (i.e., face-to-face), which may differ from virtual platforms, such as social media. Finally, the manipulation check was brief to avoid

arousing suspicion in the student cohort prior to the study's conclusion. Thus, participant memory of the specific side effects associated with each "medication" was not assessed.

In conclusion, the current study provides mixed evidence for socially-acquired nocebo effects, and also evidence that socially-acquired nocebo effects can generalise from an observed treatment to other treatments, depending on the symptoms measured. The abundance of social information communicated between patients, face-to-face or via mainstream and social media, is therefore a concern due to the potential spread of nocebo effects and the burden they cause. Future studies should seek to examine these processes in clinical settings as well as to identify interventions to inhibit these effects.

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Chapter 5: Positive social modelling attenuates nocebo side effects

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Supplementary Materials: Appendix D

Open Science Framework: https://osf.io/zfas7/overview

Introduction

The nocebo effect, a pervasive psychobiological phenomenon in which individuals develop or experience an exacerbation of symptoms beyond what can be attributed to a treatment's active elements, is increasingly recognised as a significant factor contributing to the experience of side effects. A large-scale review of pharmacological clinical trials involving over half a million participants found that nearly three-quarters of placebo-treated individuals reported side effects and that these rates were often comparable with the drug arm (Mahr et al., 2017). The time and cost associated with the management of side effects impose a substantial burden on our healthcare systems. In the US alone, managing adverse drug reactions is estimated to cost billions annually (Sultana et al., 2013) with side effects often leading to worse treatment adherence and even treatment cessation (Mahr et al., 2017). Given the significant clinical and financial implications, identifying strategies to mitigate nocebo effects is critical.

In the absence of prior direct experience, nocebo effects can arise through instruction. Instruction refers to the information individuals receive about their treatment, such as when a health professional informs a patient that a medication may cause side effects (verbal) or reading the side effect information listed on medication packaging (written). While such side effect warnings are necessary for informed consent, a wealth of evidence indicates that they can produce negative expectancies that exacerbate side effects via the nocebo effect (Mao et al., 2021; Mondaini et al., 2007; Neukirch & Colagiuri, 2015; Schweiger & Parducci, 1981; van Laarhoven et al., 2011). For example, patients receiving analgesia found the injection more painful when told "You will feel a big bee sting; this is the worst part", compared to more neutral wording (Varelmann et al., 2010).

Research to date on strategies to minimise instructed nocebo effects is sparse and inconsistent. One proposed method is side effect framing, which involves presenting

statistical information associated with side effects in a positive manner, e.g., “7 in 10 patients WILL NOT experience headaches” compared to “3 in 10 patients WILL experience headaches” (Barnes et al., 2019). Although Faasse et al. (2018) found that this approach significantly reduced the nocebo effect during a one-hour experimental session, no effect was present when assessed 24 hours later. Furthermore, other empirical studies fail to find any effect of side effect framing (Caplandies et al., 2017; Devlin et al., 2019). Another suggested strategy is “nocebo education,” or informing patients about the nature and mechanisms of the nocebo effect (Crichton & Petrie, 2015; Pan et al., 2019). However, educational interventions can sometimes yield minimal benefits or even backfire (Colgan et al., 2016). For example, one study aimed to improve perceptions of generic medicines via an educational video, but unexpectedly found reduced pain relief and increased symptoms when participants used the generic versus the branded version of the same medication (Colgan et al., 2016). Although the intervention improved perception of generic drugs, it may have unintentionally highlighted differences between generic and branded products or heightened participants’ attention to potential side effects—paradoxically worsening health outcomes, consistent with research concerning educational interventions with respect to other health outcomes (Nyhan & Reifler, 2015). Given the substantial health and societal risks posed by the nocebo effect, it is crucial that novel and more effective strategies be investigated and implemented.

Importantly, in addition to instructions, we also acquire expectations via social learning. Social learning refers to what we learn by observing other’s experiences, such as observing a friend experience headaches after taking a medication, and subsequently expecting and experiencing increased headaches after our own encounter with the medication (Blasini et al., 2017). Socially-induced nocebo effects are robust and can influence a variety of symptom domains including pain, itch, nausea, and general side effects. Furthermore, recent evidence indicates that socially-induced nocebo effects can be passed along social

chains (Mostafa et al., 2024; Tan et al., 2023) and can be triggered by exposure to social media (Tan et al., 2022). Concerningly, this research indicates that observing someone else experience a nocebo effect itself, can lead to the proliferation of nocebo effects. As such, social learning presents a potentially significant cumulative trigger for nocebo-induced side effects across society and health settings.

Yet, while socially-induced nocebo effects are concerning, social learning may also provide an avenue to inhibit nocebo effects via positive social modelling. While placebo and nocebo effects do appear to have some important differences in their psychological and neurobiological mechanisms (Colagiuri & Quinn, 2018), the fact that positive social modelling induces placebo effects raises the possibility that positive social modelling could counteract the negative expectancies induced by nocebo instructions and social learning. Many nocebo social learning studies use a control group in which the model does not report any symptoms (Saunders et al., 2024)[1], which could be considered 'positive' social modelling if the key outcome is presence of side effects. Critically, however, in those studies participants are only ever exposed to either a negative or a positive social model and so they do not provide any evidence regarding whether positive social modelling can counteract nocebo effects.

To address this gap, the present study investigated whether a novel positive social information intervention could reduce nocebo side effects induced by instruction and social modelling. Participants were told they were part of a study investigating the efficacy of a new cognitive enhancement medication - which was actually a placebo. All participants received warnings about side effects and watched a short video concerning the supposed new cognitive enhancement medication. This medication was described to participants in the consent form and via the video as "associated with the experience of headaches and

[1]This refers to Chapter 2 of this thesis

dizziness". Participants in the Intervention condition viewed an additional clip where a social model (actually one of the researchers) reported a positive experience with the medication, finding it effective and communicated their lack of side effect experience. Participants in the No Intervention condition were not exposed to this positive social model. After the placebo was administered in the treatment groups, participants in the Instruction + Side effect Modelling condition then watched a live social model (a confederate participant) experience side effects from the medication. Participants in the Instruction Alone condition were not exposed to this negative social model. We hypothesised that there would be an overall nocebo effect, with increased symptom reporting in the placebo groups compared to the control group. Furthermore, we expected that live social modelling of side effects would exacerbate this nocebo effect compared to instruction alone. Most importantly, we hypothesised that positive social information would reduce nocebo side effects relative to conditions without such information. Finally, we predicted that the Positive Social Modelling Intervention would be more effective in participants exposed to negative social modelling than in those who received instruction alone, reflecting an interaction between side effect modelling and the positive social information intervention.

Methods

The study design and analyses were preregistered (aspredicted.org #163947). Ethics approval was granted by the University of Sydney (#2022/532).

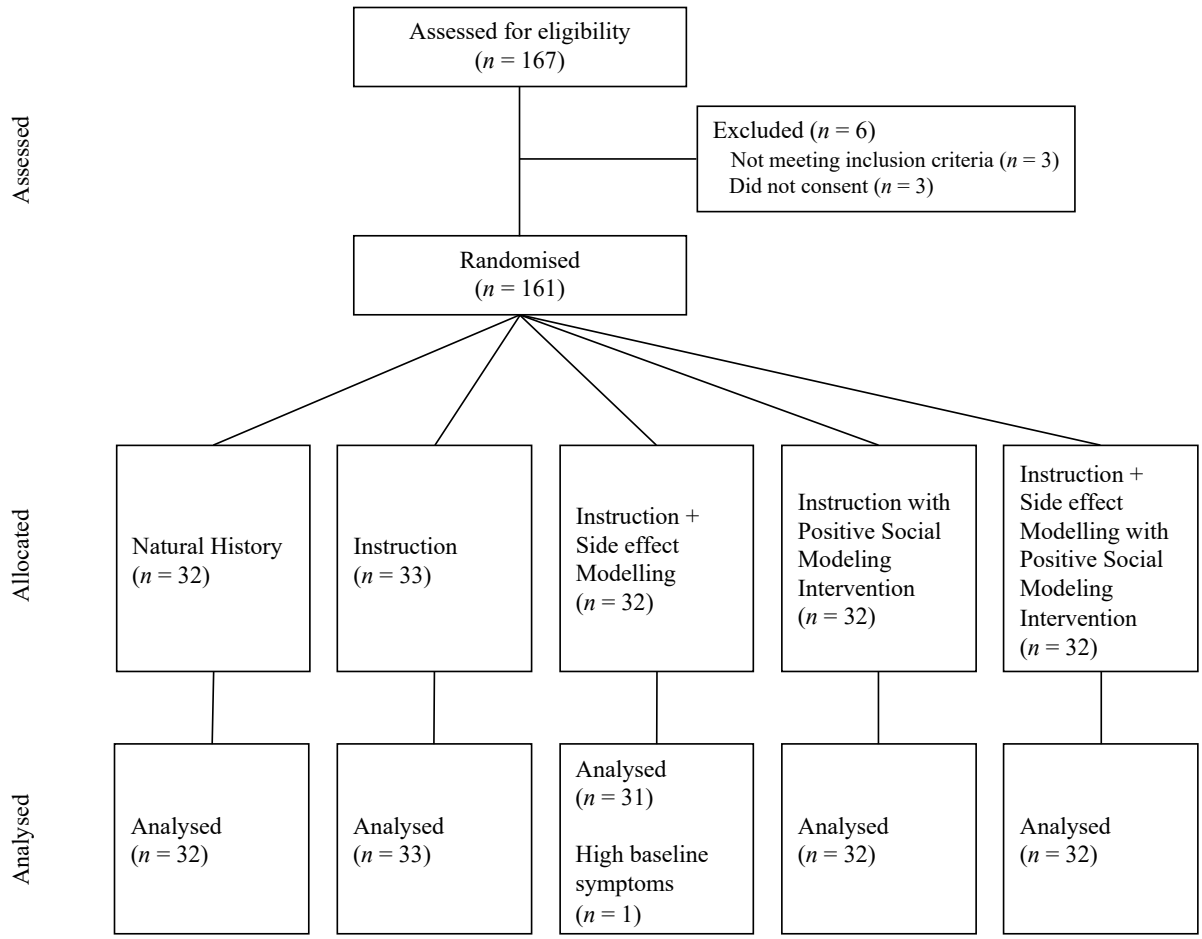
Participants. One hundred and sixty healthy volunteers (Female=110, Male=46, Other=4, M_{age}=20.16, *SD*=3.97, Range 17 - 48) from the University of Sydney participated and received course credit as compensation over the period February – July 2024. Figure

1 presents a CONSORT Flow Diagram of participant selection. Information regarding sample race and socioeconomic status were not collected. Eligible participants

were healthy adults fluent in English without any known allergy to medication or lactose. Due to the gelatine capsules, those with dietary restrictions were advised not to participate. To ensure participants were not experiencing significant symptoms at the time of testing, they were excluded from analysis if they exceeded pre-registered thresholds of physical symptoms pre-treatment (details below).

Figure 1

CONSORT Flow Diagram of Participant Selection Process



Design

The study employed a single-blind between-subjects design with participants randomised using R 4.2.2 (R Core Team, 2024) as a random number generator to one of five conditions based on a 2 (Nocebo Induction Method: Instruction Alone vs. Instruction + Side

effect Modelling) x 2 (Positive Social Modelling Intervention: Positive Model vs. No Positive Model) factorial design with an additional Natural History control group. Participants were told the study was investigating the efficacy of a new cognitive enhancer (actually a placebo). All participants then viewed one of two versions of a five-minute informational video. In the No Intervention condition, the video featured a researcher describing the supposed cognitive enhancer's benefits and potential side effects (i.e., headaches & dizziness), along with a demonstration of the general procedure using footage of a supposed previous participant (actually a confederate). In this version of the video the confederate was only seen up to the point of taking the treatment, so they did not provide any information about the treatment experience or side effects. In the Intervention condition, the same video was presented but it also included an additional 30-second segment at the end, where the supposed previous participant was asked about the cognitive enhancer's efficacy and side effects and explicitly reported the absence of any side effects. The videos are publicly available on OSF https://osf.io/zfas7/. Participants were then further randomised to either encounter a live social model who reported side effects ('Instruction + Side effect Modelling') or not ('Instruction Alone'). This model was a different confederate presented to participants as another participant of the study who was concluding their participant time such that the model was asked about side effects and verbally reported experiencing headaches and dizziness. This led to four groups: Instruction, Instruction with Positive Social Modelling Intervention, Instruction + Side effect Modelling, and Instruction + Side effect Modelling with Positive Social Modelling Intervention. A fifth group was included to create a natural history/control condition to enable an overall assessment of the nocebo effect. This group viewed the 'No Intervention' version of the informational video but did not receive the placebo treatment. The primary dependent variable was the severity of symptoms reported by participants.

Materials and Measures

Physical Symptoms. Physical symptoms were assessed using a 10 item modified version of the General Assessment of Side Effects, GASE (Rief et al., 2009). Each of the 10 symptoms assessed were rated using a 7-point scale 0(Not Present) to 7(Severe). The primary outcome of interest was sum-score of the headaches and dizziness items from the GASE corresponding to the side-effect warnings and symptoms modelled by the live model. In accordance with pre-registration, those with extreme baseline side effects (six or more on any single item, or a mean greater than four) were excluded from analyses.

Symptom expectancy. Participants were asked to rate their expectancy of the experience of side effects on the single item measure: "How much do you expect to experience adverse events (e.g., side effects) as a result of participating in this study?" on a Visual Analogue Scale (VAS) ranging from 1(Not at all) to 100(Very much so).

Expectancy for cognitive enhancement: Participants were asked to rate their expectancy of the efficacy of the cognitive enhancement medication on the single item measure: "To what degree do you expect the cognitive enhancement medication to enhance your performance?" on a VAS ranging from 1(No enhancement) to 100(Significant enhancement).

Generalized State Anxiety. General state anxiety was measured via the Spielberger State-Trait Anxiety Inventory-6 (Cronbach's alpha=.75)(Marteau & Bekker, 1992). Participants rated 6 items like "I am relaxed" on a four-point scale ranging from 1 (not at all) to 4 (very much) based on how they felt at the present.

Side effect specific anxiety. Participants rated their anxiety concerning experiencing side effects on the single item measure: "How anxious are you about experiencing adverse events (e.g., side effects) as a result of participating in this study?" on a VAS ranging from 1(Not Anxious) to 100(Very Anxious).

Objective cognitive performance. Sustained attention was measured using the Rapid Visual Information Processing (RVIP) task (Wesnes et al., 1983). For five minutes, numbers from 1 to 9 were displayed at a speed of 100/min on a computer screen. Participants were instructed to press the space bar when three consecutive even or three consecutive odd numbers appeared in the sequence. They had 1.5 seconds to respond appropriately, or the response was regarded as a false alarm. The target sequences were spaced by a minimum of five and a maximum of 33 digits due to the semirandom nature of the number series. A performance evaluation was conducted using the percentage (%) of correct answers.

Self-reported cognitive performance. Participants were asked to rate their perceived performance on the RVIP: "How would you rate your performance on the cognitive task?" on a VAS ranging from 1(Very poor) to 100(Very good).

Self-reported impact of treatment on cognitive performance. Participants assigned to take the placebo were asked "How effective was the medication at enhancing your cognitive performance?" on a VAS ranging from 1(Not effective at all) to 100(Very effective).

Manipulation check. Participants were asked "Briefly describe (in 2-3 sentences) what you thought the purpose of the experiment was:". The probe was intentionally vague to prevent prematurely raising suspicion regarding the study within the student cohort.

Placebo capsules. All participants assigned to take the "cognitive enhancer" received white and blue gelatine capsules filled with lactose.

Heart rate and electrodermal activity. Participant heart rate and electrodermal activity were measured. Details can be found in Supplementary Materials 6.

Laboratory Setting. The lab was set up like a clinic room to reinforce the cover story. The room contained a medical examination bed and potted plants. The walls were decorated with posters about the anatomy of the brain, memory processes and attention. The researcher

wore a lab coat, and a heart rate monitor was visibly used, all reinforcing the realism of an experimental medication study.

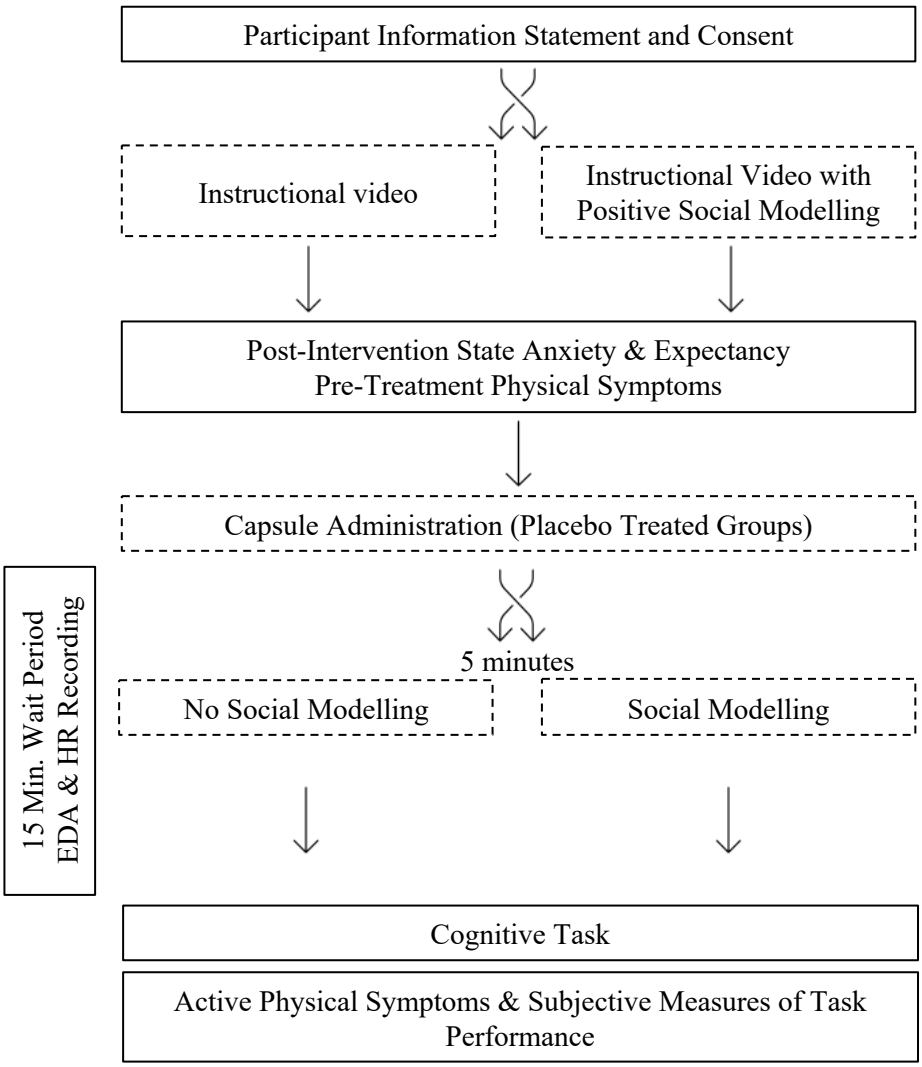
Procedure

Refer to Figure 2 for a flow chart of the study procedure. Participants each attended a 1-hour experimental session. Participants first received an information statement and consent form that outlined the cover story and contained the side effect warning concerning the supposed medication: "*Vitatril* has been associated with the experience of mild headaches and dizziness". Once consent was obtained, participants were asked to watch a video described as a way to inform them of the study aim and procedures. The positive social modelling was implemented via this video. In the No Intervention and Natural History conditions the video detailed: the supposed medication, its mechanism of action, its side effects, and a demonstration of the study procedure with another participant (actually another researcher). Those assigned to the Intervention conditions, watched the same video as those in the No Intervention and Natural History conditions, with an additional scene at the end where the supposed participant was asked how they were feeling. The participant indicated that they felt the positive effects of the medication (i.e., "more focused") and emphasised they did not feel any side effects. The videos are publicly available at https://osf.io/zfas7/. Participants were then fitted with the Equivital Harness and were asked to complete the demographic questions and post-intervention state anxiety and expectancy measures. In addition, a pre-treatment measure of physical symptoms was recorded to identify those who met the exclusion criteria and to control for symptoms being experienced at baseline. Next, participants were seated on a physical exam bed and set up with the electrodes to measure their EDA. The placebo capsules were then administered to treatment groups. All participants were seated and waited for 15 minutes, ostensibly providing time for the medication to take effect in the treatment groups. Exactly five minutes after the physiological recordings commenced, participants in

the side effect modelling conditions saw a confederate enter the room. In view of the participant, the researcher asked the confederate how they were feeling and the confederate responded with “Not great, definitely feeling headachy… and a bit dizzy”. To account for the potential confound of having two different individuals as the positive social model and the side effect model respectively (as necessitated by study design), we counterbalanced which confederate served as the live and video models. Further, to control for gender, age and race, both confederates were Asian Australian men in their 20s. At the timepoint of side effect modelling in the Instruction + Side effect Modelling groups, participants in the other groups overhead the researcher have an irrelevant phone call to control for any generic effects of hearing a conversation. After the 15-minute wait period, all participants completed the cognitive task to uphold the cover story. Next, participants completed the active physical symptoms questionnaire, reported their perceived efficacy of the medication, and completed the manipulation check. At the conclusion of data collection, all participants received a written debrief informing them about the true aims of the study.

Figure 2

Flowchart of study procedure



Note. All participants underwent steps outlined by solid boxes. Boxes with dashed lines indicate a step participants were randomised to undertake. Participants in the Natural History group watched the instructional video with no positive social modelling, did not receive the placebo treatment and did not view the live side effect modelling.

Power and Data Analysis

All data analysis was conducted in R 4.2.2 (R Core Team, 2024) using a threshold of α<.05 to determine significance. The primary data analysis consisted of a 2 (Nocebo Induction Method: Instruction Alone, Instruction + Side effect Modelling) x 2 (Intervention:

No Intervention, Intervention) + 1 (Natural History) ANOVA, using the symptom difference score (active – baseline/pre-treatment) as the dependent variable. Orthogonal contrasts were used to determine the presence of a nocebo effect (Placebo Treatment vs Natural History), the main effect of Nocebo Induction method (Instruction Alone vs Instruction + Side effect Modelling), the main effect of the Positive Social Modelling Intervention (Positive Social Modelling vs No Positive Social Modelling), and the interaction between the Positive Social Modelling Intervention and the Nocebo Induction Method. Secondary analysis explored side effect generalisation with the remaining 8 GASE items sum-scored as the outcome variable, in analyses mirroring those detailed above. Moderation analyses were then conducted to explore group differences revealed in the primary analyses using gender, state anxiety, side-effect anxiety, side-effect expectancy as moderators. Self-reported cognitive performance and actual cognitive performance were compared between groups in a similar way to the primary analyses to assess the presence of a placebo effect. The effect of the Positive Social Modelling Intervention on expectancy and anxiety was assessed using t-tests comparing the groups that received the intervention to those that did not, collapsed across side effect modelling conditions as expectations and anxiety were measured prior to the side effect modelling manipulation. Expectations of side effects that might occur from the supposed treatment were assessed in all participants after the information about the study was delivered, which included the warning about side effects and Positive Social Modelling Intervention in the relevant groups, but before participants knew whether or not they would receive the supposed treatment (i.e., placebo capsules). Mediation analyses were therefore conducted to assess if the effect of the Positive Social Modelling Intervention on side effects was mediated via expectancies. Note, however, that since capsule administration in placebo treatment groups occurred after expectations were measured, we were unable to conduct a

mediation to assess if the overall nocebo effect (Placebo Treatment vs Natural History) was mediated via expectancies.

As per pre-registration, a minimum of 32 participants per-group were recruited. This was based on a power analysis assuming a medium effect size for the Positive Social Modelling Intervention (f=.25, in the absence of prior research to inform the effect size) with an alpha of .05 with the power to detect an effect set at 80%.

Results

Demographic Data

There were no significant differences between groups in age and gender (all $p \geq .291$) indicating randomisation was successful. See Electronic Supplementary Material 1.

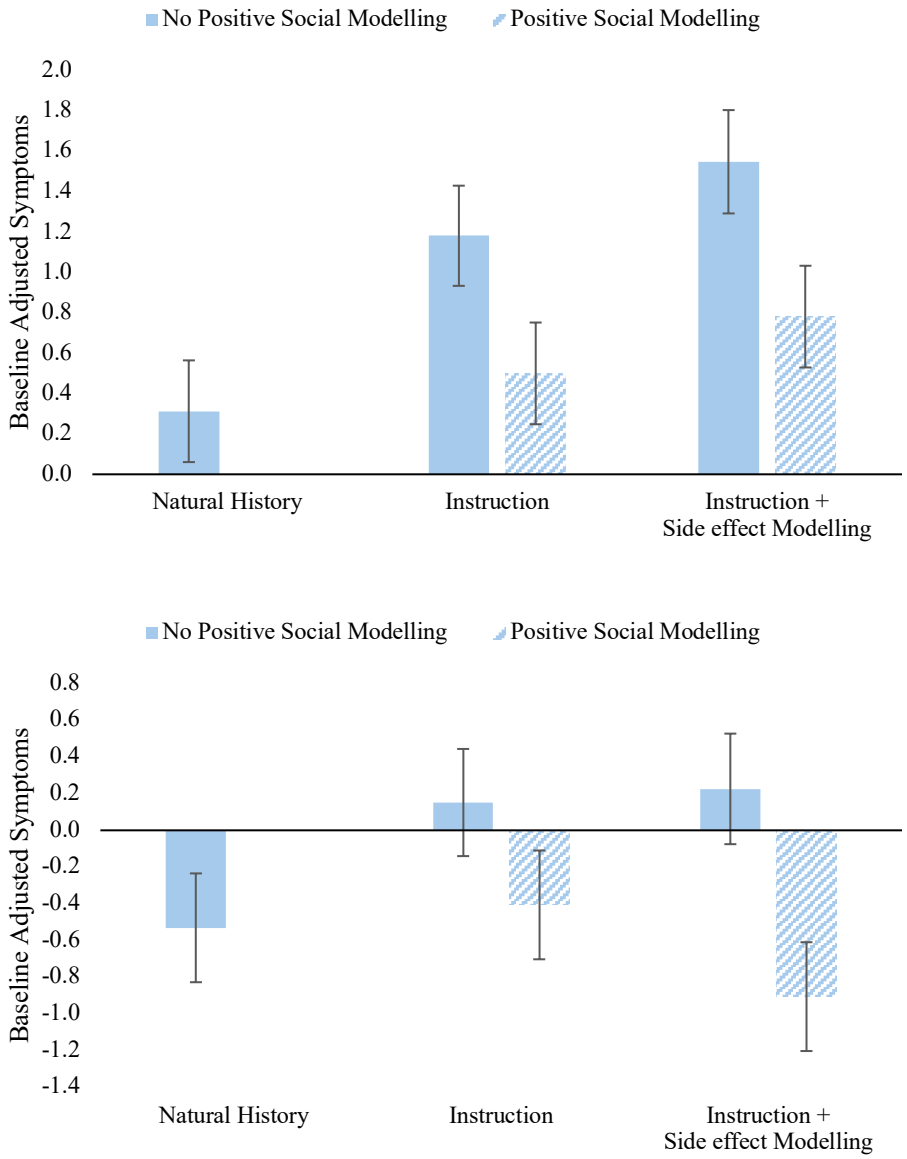
Main Analysis (Pre-registered)

Side effects. Figure 3 depicts the group means for the ANOVA assessing group differences in reported side effect severity. Full statistics are available in the Electronic Supplementary Material 2. Orthogonal contrasts revealed that there was a significant overall nocebo effect, where groups that received the placebo reported increased severity of symptoms relative to the Natural History group, $F(1,155)=6.00$, $p=.015$, $\eta_p^2=.038$. There was no significant difference in symptom severity by induction method, $F(1,155)=1.65$, $p=.201$, $\eta_p^2 =.011$. The positive modelling significantly decreased severity of symptoms reported, $F(1,155)=8.26$, $p=.005$, $\eta_p^2=.051$. There was no significant interaction between induction method and the effect of the positive social modelling $F(1,155)=0.03$, $p=.866$, $\eta_p^2<.001$. The lack of main effect of induction method may have been due to the efficacy of the intervention. To investigate this possibility, a simple effect examined whether induction method had significant effects for those that did not receive the positive modelling

intervention, and this revealed no significant effect of induction method $F(1,62)=0.82$, $p=.369$, $\eta_p^2=.013$.

Figure 3

Baseline adjusted symptoms for each experimental condition



Note. Group means for warned symptoms (top) and non-warned symptoms (bottom). All error bars are ± 1 Standard Error of the Mean (SEM).

Generalisation of side effects. Figure 3 also depicts the group means for the ANOVA assessing group differences in reported side effect severity of all other symptoms assessed by the GASE. Full statistics are available in the Electronic Supplementary Material 3. The

analysis revealed that there was no significant overall effect of the nocebo treatment on other symptoms, $F(1,155)=0.81$, $p=.371$, $\eta_p^2=.005$, and no significant main effect of social induction method, $F(1,155)=0.52$, $p=.474$, $\eta_p^2=.003$. There was a significant effect of the intervention on reducing other symptom's severity, $F(1,155)=8.12$, $p=.005$, $\eta_p^2=.050$. Finally, the interaction between social induction method and the positive intervention was not significant, $F(1,155)=0.937$, $p=.334$, $\eta_p^2=.006$.

Moderation analysis for side effects. Moderation analyses exploring the significant nocebo effect and significant effect of the Positive Social Modelling Intervention are presented in Table 1.

Table 1

Moderation analyses of the nocebo effect and the effect of the positive social modelling intervention

	Nocebo			*Intervention*		
	F(df1,df2)	*p*	η_p^2	*F*(df1,df2)	*p*	η_p^2
Gender	0.06 (1,152)	.814	<.001	0.05 (1,120)	.831	<.001
STAI-6	0.21 (1,156)	.649	.001	2.02 (1,124)	.157	.016
Expectancy	0.32 (1,156)	.572	.003	4.50 (1,124)	.036	.035
Anxiety	0.07 (1,156)	.793	<.001	1.05 (1,124)	.307	.007

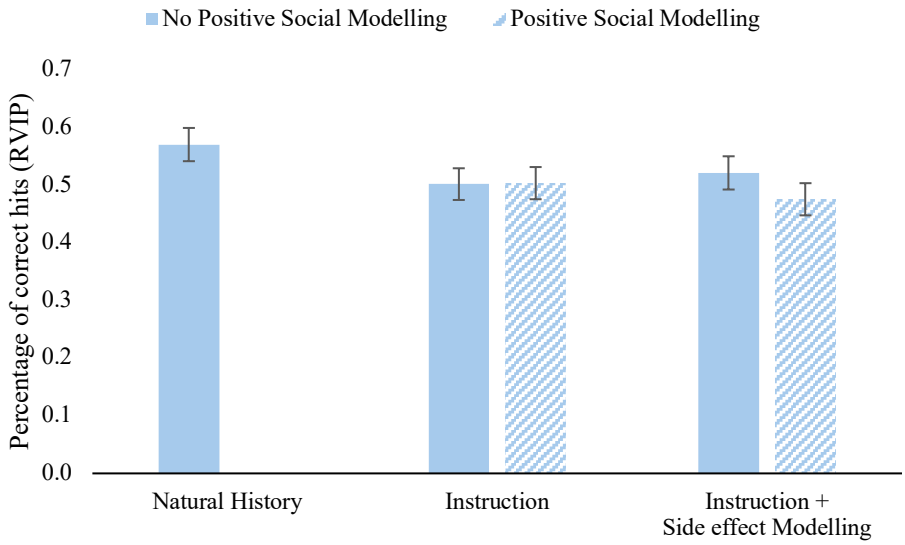
Note. STAI-6 refers to the State-Trait Anxiety Inventory-6 (Marteau & Bekker, 1992). Analyses involving gender have a sample size $N=156$, excluding those who did not identify with either male or female due to insufficient sample size.

Cognitive performance. Refer to Figure 4 for group means of objective cognitive performance. A significant reduction in objective cognitive performance was found in the treatment groups compared to the natural history group, $F(1,152)=4.75$, $p=.030$, $\eta_p^2=.030$.

However, there was no significant effect of side effect modelling, $F(1, 152)=0.02$, $p=.880$, $\eta_p^2<.001$, the Positive Social Modelling Intervention, $F(1, 152)=0.62$, $p=.434$, $\eta_p^2=.004$, nor an interaction, $F(1, 152)=0.72$, $p=.400$, $\eta^2=.005$, on objective cognitive performance. Orthogonal contrasts revealed no significant differences between groups in self-reported cognitive performance all $ps \geq .316$. Within the three groups that received the placebo treatment, there was no significant difference in self-reported influence of treatment on cognitive performance, $F(3, 124)=0.51$, $p=.677$, $\eta^2=.012$. See Electronic Supplementary Materials 5 for full comparisons and group means.

Figure 4

Group means of objective performance on RVIP task



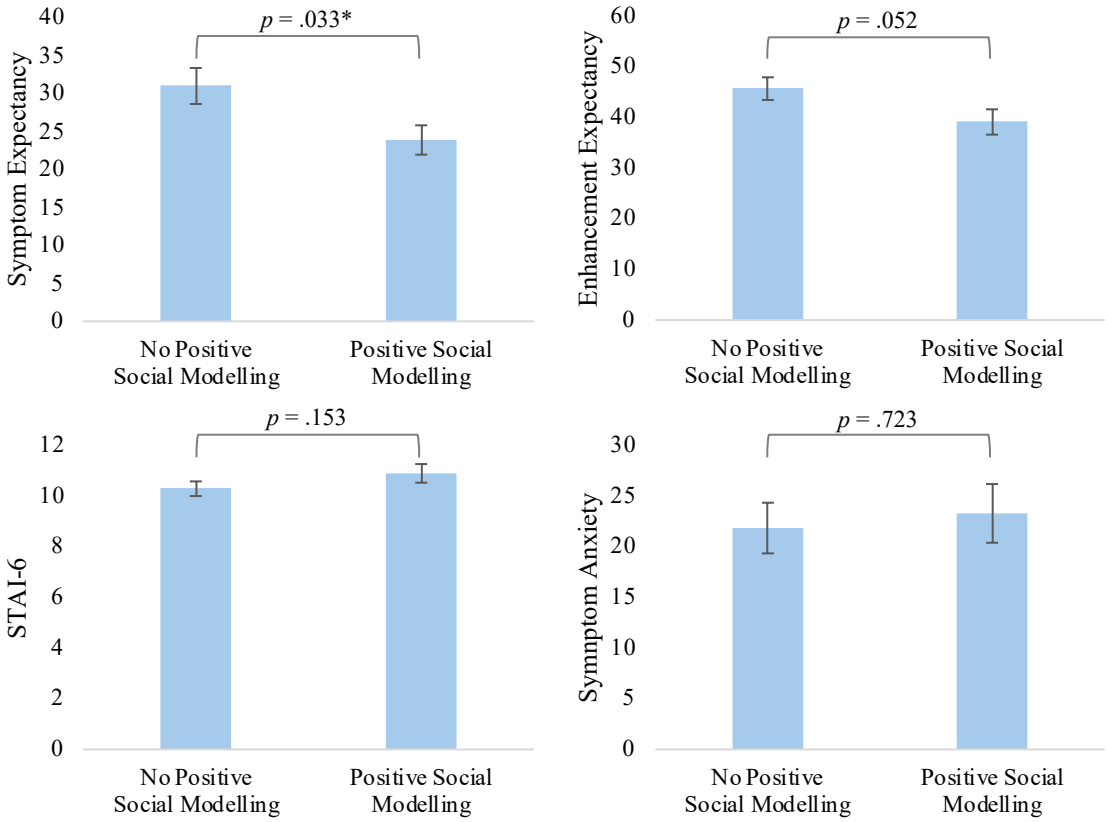
Exploratory Analysis

Effects of the intervention on expectancy and anxiety. T-tests were used to compare expectations for side effects, expectations for cognitive enhancement, side effect anxiety and state anxiety between groups that received the Positive Social Modelling Intervention (i.e., Instruction with Intervention and Instruction + Side effect modelling with Intervention) versus that those who did not (i.e., Natural History, Instruction Alone and Instruction + Side

effect modelling). As shown in Figure 5, the intervention significantly decreased expectancies for symptoms, $t(158)=-2.15$, $p=.033$, $d=-0.35$, but not expected cognitive enhancement, $t(158)=-1.95$, $p=.052$, $d=-0.32$. The Intervention did not significantly affect state anxiety, $t(158)=1.44$, $p=.153$, $d=0.23$, nor symptom-specific anxiety, $t(158)=0.35$, $p=.723$, $d=0.06$.

Figure 5

Comparison of anxiety and expectations between groups that received the Positive Social Modelling intervention and the groups that did not.



Note. * indicates $p<.05$, ** indicates $p<.01$, *** indicates $p<.001$

Mediation of the intervention effect on side effects by expectations. As there were effects of the intervention on both symptom expectancy and symptom severity, a mediation analysis was conducted to investigate if the effect of the intervention on the nocebo effect was mediated by expectations. The independent variable was Intervention: Intervention vs No Intervention, collapsed across induction method, excluding the Natural History group. The

dependant variable was symptom severity and expectancy was the mediator. Bootstrapping with 10,000 samples was conducted to determine 95% confidence intervals (CIs) which were used to determine significance. Expectancy did not significantly mediate the effect of the intervention on symptom severity, direct effect=0.70, 95% CI [0.20,1.22], p=.008 and indirect effect=0.02, 95% CI [-0.05,0.16], p=.671.

Manipulation Check

Both social modelling manipulations were successful, no participants reported suspicion regarding the positive social modelling via the instructional video and only two participants in the sample reported suspicion concerning the live social model. A small proportion of participants expressed suspicion that the treatment was a placebo (N=21, 13%). However, raising suspicion concerning the placebo treatment did not differ statistically between groups, $\chi^2(4, N=160)=3.96$, p=.412, Cramer's V=.16, nor was it associated with a change in target symptom reporting, controlling for group, $F(1, 150)=1.76$, p=.187, η_p^2=.012.

Discussion

This was the first study to investigate whether positive social modelling, i.e., modelling a lack of side effects, could reduce nocebo side effects. As anticipated, we found clear evidence of a nocebo effect, with participants in the (placebo) treatment groups reporting significantly greater side effect severity compared to the Natural History group. Contrary to our hypotheses, the combination of side effect modelling with a side effect warning did not increase nocebo side effects relative to the warning without side effect modelling. Importantly, the novel positive social modelling intervention effectively reduced nocebo symptom severity across treatment groups, demonstrating its utility in mitigating nocebo effects. There was no significant interaction between the nocebo induction method and the positive social modelling intervention, indicating that the intervention's effectiveness

was consistent regardless of the method of nocebo induction. These findings have several important theoretical and clinical implications.

Most importantly, the present study found that providing participants with positive social modelling inhibited nocebo side effects irrespective of whether the nocebo effect was induced by instruction alone or instruction and side effect modelling, and this positive effect extended to other (non-warned) side effects. Positive social modelling has previously been found to lead to placebo effects (Bajcar & Bąbel, 2018; Colloca & Benedetti, 2009), but to the best of our knowledge has never previously been examined as a potential preventive strategy to combat nocebo effects. Two aspects of this finding are particularly interesting. The first is that the positive modelling was video-based whereas the side effect modelling was in person. A recent meta-analysis revealed that, typically, in person modelling produces stronger effects than video-based modelling (Saunders et al., 2024). As such, it is particularly noteworthy that the video-based positive modelling effectively inhibited the nocebo effect even when it involved verbal instruction accompanied by in person side effect modelling. This suggests that video-based positive modelling could be an effective and scalable technique for combatting nocebo effects even when they involve in person observation of another person experiencing adverse symptoms from a treatment. Second, the fact that positive social modelling inhibits nocebo effects means that commonly used 'neutral' control groups in social modelling nocebo research (Saunders et al., 2024) may actually be inhibitory if they involve communication indicating that no adverse symptoms occurred following the treatment, whether direct (as in the current study) or indirect (e.g., absence of a report of side effect). As such, estimating the magnitude of any socially-induced nocebo effect might be more accurate when a true natural history group is used that is not exposed to any social modelling.

Related to this, it was interesting to observe that contrary to predictions, the addition of side effect modelling did not significantly exacerbate the nocebo effect induced via instruction alone. This finding appears inconsistent with a recent meta-analysis demonstrating that instruction with social modelling typically produced larger nocebo effects than verbal instruction alone does (Saunders et al., 2024). However, it is important to note that the current study employed a more formal verbal instruction than is typically used in other studies in that, in addition to being written in the consent form, the side effect warning was presented as part of an explanatory video provided to the participants about the supposed medication and trial. In comparison, in many warning-induced nocebo studies side effect information may only be presented in written materials like the consent form or through brief verbal discussion (e.g., Barbiani et al., 2018; Benedetti et al., 2021; Boehmert et al., 2018; Mao et al., 2021). The use of an explanatory video in the current study may have increased the instructed nocebo effect and created a ceiling effect that reduced the impact of the addition of the side effect social modelling. Supporting this, the effect size of the instructed nocebo effect in the current study was approximately 50% larger than the typical instructed nocebo effect observed in nocebo research (Rooney et al., 2024). It would therefore be interesting for future research to compare the effect of the addition of social modelling to side effect warnings with varying strengths of instructions.

Expectancy and anxiety are key factors hypothesised to facilitate nocebo effects (Rooney et al., 2022). The positive social modelling video intervention successfully reduced expectations for symptoms, however, did not significantly affect participant anxiety. Although symptom expectancy was reduced because of the intervention, side effect expectations did not mediate the reduction in the nocebo effect caused by the intervention. This may suggest that other unmeasured factors are responsible for the intervention's effectiveness. Alternatively, it could be that the timing of the expectancy measurement

resulted in a less sensitive measure and that this undermined evidence of mediation. Symptom expectancy was assessed immediately after the intervention, but prior to placebo administration, potentially making it an outdated measure if there are expectancies that arise once the participant is informed they are assigned to take or not take the supposed 'cognitive enhancer', and from the treatment administration process itself. Additionally, the 15-minute wait period allows ample time to reflect upon and contemplate the information concerning the 'treatment' that the participant received. While we believe it was not feasible in this study to measure side effect expectancy repeatedly without revealing the study's true nature, future research should incorporate expectancy measurements after group allocation and following social modelling manipulations to better understand the role of expectancy in nocebo effects.

Interestingly, we observed no placebo-related improvement on either subjective or objective measures of cognitive performance and in fact, those who received the placebo demonstrated worsened objective cognitive performance. Where previous research has reported placebo cognitive enhancement (Colagiuri & Boakes, 2010; Foroughi et al., 2016; Winkler & Hermann, 2019) the broader study contexts have focused on investigating the primary effect of the placebo (i.e., the cognitive enhancement) with little to no emphasis on side effects. The focus of the current study was on side effects so it may be the case that the instructions delivered concerning cognitive enhancement were less strong than in other studies for which cognitive enhancement is a primary outcome. It is also possible that the experience of side effects due to the nocebo effect in the treatment groups may have engendered discomfort or distraction sufficient to impair cognitive functioning - a hypothesis that warrants investigation in future studies.

Gender was not found to moderate the strength of the nocebo effect, nor influence the efficacy of the intervention. Previous research has found that female observers can be more susceptible to nocebo effects under certain conditions (Faasse et al., 2015; Quinn et al.,

2023), however others suggest it may be the model's gender—or a match between model and observer—that primarily drives observed differences (Saunders et al., 2024; Świder & Bąbel, 2013). In the present study, both the side-effect social model and positive social model were male, leaving questions about the precise role of model and observer gender an avenue for future investigation.

Some limitations to the study are worth discussing. First, the study was conducted with healthy psychology undergraduates and therefore would benefit from replication in clinical settings to investigate if the intervention's benefits translate in clinical practice. Interestingly, the nocebo effect tends to be *larger* in clinical populations (Grosso et al., 2024; Rooney et al., 2024), and factors specific to the clinical environment like presence of other patients and disease comorbidities may influence the nocebo effect and its mitigation in ways not captured here. Additionally, the study did not collect data on participant ethnicity or socioeconomic status, limiting our ability to comment on the generalisability of our findings to the broader population. Second, the study was conducted over the span of one hour, meaning it is unknown how long the positive effects of the intervention can be sustained. Third, several of the measures (e.g., side-effect anxiety and expectancy) were single-item scales that have not been extensively validated in previous research; although they were brief and aligned well with our specific focus, it would be beneficial to replicate our findings with validated instruments. Finally, to translate this intervention into a feasible and useful clinical tool it is crucial to investigate patient acceptability of this intervention. This would indicate whether the positive social modelling is perceived by patients as acceptable and ethical.

In conclusion, this study highlights the role that nocebo effects can play in generating side effects and importantly provides novel evidence that positive social modelling may be a way of combatting these effects. The efficacy of positive social modelling here is particularly noteworthy given that it was video-based and was effective even for a combination of nocebo

instructions and in person side effect modelling. This suggests that positive social modelling may be an effective and scalable method to reduce the significant burden nocebo effects cause. Future research is needed to translate this finding to clinical settings as well as to examine patient perspectives on its acceptability.

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Chapter 6: General Discussion

Summary of Findings

The overarching aim of this thesis was to investigate the formation, modulation and prevention of socially-acquired nocebo effects. To address this aim, three core research questions were posed. First, is there evidence that socially-acquired nocebo effects occur, and how does it compare with other known modes of nocebo induction? Second, to what extent do socially-acquired nocebo effects generalise, that is, can similar but not identical experiences of others also shape one's own symptom experience? Third, what strategies can reduce or prevent the development of socially-acquired nocebo effects? These questions were examined through a systematic review and meta-analysis followed by three studies, each designed to address different aspects of the generalisability, mechanisms, and interventions relevant to socially-acquired nocebo effects. Taken together, this thesis responds to a growing recognition in the nocebo literature that social pathways, whether through face-to-face interactions, mass media, or digital platforms, play a central role in shaping symptom perception and treatment experiences.

Social Learning as a Mode of Nocebo Induction

To address the first aim, Chapter 2 employed a systematic review and meta-analysis of 20 studies to synthesise the current evidence concerning socially-induced nocebo effects. Three principal findings emerged. First, social learning was confirmed as a robust pathway for nocebo induction, eliciting a medium-to-large effect relative to no-treatment controls (Hedges' $g = 0.74$) and a small-to-medium effect when compared with neutral modelling (Hedges' $g = 0.42$). This distinction between how control conditions are operationalised in the field was revealed during the literature review process, which raises important theoretical considerations for interpretation. Specifically, no-treatment controls assess whether nocebo effects can be *elicited* socially, whereas neutral modelling controls examine the impact of *modelling valence*. Second, moderator analyses identified several contextual and

interpersonal factors that magnify the effect of social learning. Stronger nocebo effects were observed with face-to-face modelling relative to video observation, longer modelling exposure, and smaller proportions of female participants and models. Finally, trait empathy emerged as a significant predictor of the magnitude of socially-induced nocebo effects: across seven studies, greater empathy was associated with larger effects (r = .14). Together, these findings demonstrate that social information exerts a substantial influence on nocebo outcomes and highlight both contextual and interpersonal factors that shape susceptibility. The theoretical implications of these outcomes are considered further in the following discussion.

How Nocebo Effects Spread

The meta-analysis in Chapter 2 revealed that observing another person undergoing the same treatment or procedure can elicit nocebo effects. However, a key limitation of the existing empirical literature is that studies unanimously restricted social information to pertain to identical treatment contexts between model and observer. In everyday life, individuals can frequently encounter information about treatments that are similar, but not identical to their own experiences. For example, hearing about side effects following one type of vaccination may not only shape expectations and adverse responses for that specific vaccine but could also generalise to other vaccines or related medical interventions. This process of generalisation is particularly concerning in light of the proliferation of health-related information (and misinformation) through social media (Gage-Bouchard et al., 2018; Suarez-Lledo & Alvarez-Galvez, 2021; Wilson & Wiysonge, 2020), where anecdotal accounts of adverse effects may reach large audiences and extend beyond the original treatment context. Accordingly, Chapters 3 and 4 examined the extent to which socially-acquired nocebo effects generalise across similar but non-identical treatments, addressing a

critical gap in the literature by testing whether exposure to similar experiences can also transmit expectations that amplify symptom burden.

Contextual Generalisation

Chapter 3 was the first empirical investigation in the field to examine whether socially-acquired nocebo effects generalise to novel contexts. Across three studies, evidence converged on a key finding: observing another's adverse experience can elicit nocebo effects even when the observer's own context does not fully match that of the model. Specifically, both groups who observed a social model experience cybersickness—whether the model's VR experience was consistent or inconsistent with their own—reported significantly greater cybersickness compared to participants who did not view the model. Traditional theories of generalisation borrowed from the learning literature would predict that learning weakens as a function of similarity between cues and between contexts (Ghirlanda & Enquist, 2003). However, there was no difference in the magnitude of social learning between consistent and inconsistent groups; in fact, the inconsistent group displayed a numerically larger mean effect when pooled across the three studies. These findings highlight the potential for socially elicited nocebo effects to spread across related but non-identical experiences. Furthermore, mediation analyses identified expectancy and anxiety as key mechanisms driving social learning, with both variables mediating the association between social modelling and nocebo cybersickness. This aligns with broader nocebo research pertaining to classical conditioning and explicit instruction, which consistently implicates negative expectancies and heightened anxiety as central mechanisms of the nocebo effect (Rooney et al., 2022). Together, these results demonstrate that socially-induced nocebo effects are not confined to strictly identical contexts but can generalise across related experiences. This suggests that the opportunity for social information to influence symptom experiences may be significantly broader than previously demonstrated by experimental research.

Treatment Generalisation

Where Chapter 3 demonstrated that socially-acquired nocebo effects can generalise across *environmental contexts* (i.e., VR activity), Chapter 4 extended this investigation to examine whether such effects also spread across different *treatments* in a simulated clinical setting. Using a placebo cognitive enhancer as a cover story, participants were randomised to one of four groups: social modelling of side effects associated with the same treatment, social modelling of side effects associated with a different treatment, instruction only, or no treatment. As hypothesised, participants who received placebo treatments reported increased symptom severity compared to the control group, confirming the induction of a nocebo effect. However, contrary to predictions, social modelling did not significantly enhance target symptom severity beyond the effects of explicit instruction alone. Secondary and exploratory analyses revealed a key caveat. Social modelling increased the reporting of general (non-warned) symptoms and, in particular, produced stronger nocebo effects when headaches and dizziness were the target profile. In contrast, this was not observed when nausea and stomach discomfort were. This suggests that within this experimental design certain symptoms may have been more receptive to social transmission. Importantly, across both pre-registered and exploratory analyses, the magnitude of nocebo effects in the Social Modelling Inconsistent group was always as large as, and in some cases larger than, the Social Modelling Consistent group. These findings reinforce and extend those of Chapter 3, providing further evidence that socially-acquired nocebo effects are not constrained to identical treatment contexts. Instead, they appear able to generalise across related but distinct treatments, amplifying their potential to spread within clinical and everyday health settings.

Taken together, Chapters 3 and 4 underscore the potential for negative social information to generalise, influencing expectations and symptoms in settings beyond the original exposure. By demonstrating that nocebo effects elicited through social observation

are not bound to specific cues, contexts, or treatments, these studies highlight the pervasive nature of social transmission and the heightened risk this poses in clinical and everyday health contexts where individuals frequently encounter others' symptom reports.

Spread to non-modelled symptoms

Existing research suggests that the influence of social modelling may extend beyond the precise symptoms communicated by the model, exerting a more diffuse impact on symptom experience. Evidence from this thesis provides tentative support for this possibility. In Chapter 4, exposure to a social model reporting symptoms led to increased reporting of general symptoms that were neither warned about nor explicitly modelled, indicating a broader spread of socially-acquired symptoms. However, this pattern was not replicated in Chapter 5, where social modelling did not significantly influence these non-warned, non-modelled symptoms. Taken together with prior literature indicating that socially-induced nocebo effects can generalise beyond specific symptoms (Faasse et al., 2018; Tan et al., 2023), these findings suggest that socially modelled side effects may at times spread across symptom domains, but that such generalisation is not inevitable. The mechanisms underpinning this variability remain unclear. Future research is therefore needed to identify the situational, cognitive, and affective factors that facilitate or constrain the diffusion of socially-acquired side effects.

How Nocebo Effects Can Be Reduced

The third primary aim of this thesis, and arguably the most clinically important goal of nocebo research more broadly, was to identify strategies to reduce or prevent the occurrence of nocebo effects. Beyond the immediate unpleasantness experienced by individuals, nocebo effects have wide-ranging consequences for health behaviour and healthcare delivery. They are associated with reduced treatment adherence and increased rates of discontinuation (Barsky et al., 2002; Dunbar-Jacob & Mortimer-Stephens, 2001; Preston et

al., 2000), and may prompt additional prescribing of pharmacological interventions to manage nocebo-related side effects, thereby increasing both costs and the risk of further adverse reactions (Hassett et al., 2006; Zhang et al., 2008). Collectively, these processes place an unnecessary burden on already strained healthcare systems. Despite the clear clinical importance of mitigation, research investigating how to reduce nocebo effects remains relatively preliminary, and work examining interventions targeting socially-acquired nocebo effects is even more limited. This represents a critical gap, given that Chapter 2 found a medium-to-large effect size of social learning in experimental contexts. Moreover, because the mechanisms underlying social transmission may differ from conditioning and explicit instruction, effective intervention strategies may also need to be tailored to this pathway of induction. Prior to the present thesis, no studies had demonstrated a successful attenuation of socially elicited side effects. Chapters 3 and Chapter 5 therefore sought to directly address this gap by assessing the efficacy of two different proposed methods to attenuate socially-induced nocebo effects.

Choice

Chapter 3 examined whether providing participants with choice could attenuate socially-induced nocebo effects, using cybersickness in VR as an analogue symptom model. Pooled analyses of the three studies showed that offering participants a choice of VR environment did not reduce socially-induced cybersickness. This finding is notable given that choice has been shown to reduce nocebo side effects in two different empirical studies (Bartley et al., 2016; Faasse et al., 2023) and substantial body of theory suggesting that choice can exert beneficial effects through enhancing perceived control, reducing anxiety, improving affective state, and positively shape treatment expectations (Geers & Rose, 2011; Leotti & Delgado, 2011; Leotti et al., 2010; Thompson & Schlehofer, 2008). Theoretical implications of this finding are discussed in the following section.

Positive Social Modelling

Chapter 2 demonstrated that the valence of social modelling plays a critical role in shaping nocebo outcomes, such that exposure to a negative social model communicating the presence of symptoms produced a nocebo effect in comparison to exposure to a neutral model communicating the absence of symptoms. Notably, within the context of anticipated side effects, the absence of symptoms may itself function as positively valenced information. Chapter 5 leveraged this finding to assess the effectiveness of a novel nocebo intervention: whether exposure to 'positive' modelling could protect against the development of nocebo side effects. Using a placebo pill paradigm consistent with Chapter 4, Chapter 5 examined nocebo side effects of headache and dizziness, selected given their responsivity to nocebo induction demonstrated in Chapter 4, and avoided difficulties associated with counterbalancing symptom profiles (including reduced statistical power). Side-effect warnings were strengthened through a five-minute video that described the supposed 'treatment' and highlighted the potential for these side effects. Importantly, this video format also enabled the controlled delivery of the novel positive social modelling manipulation. In the positive social modelling condition, participants observed a peer who had ostensibly taken the same treatment but explicitly reported experiencing no side effects.

Replicating prior work, a clear nocebo effect emerged, with placebo-treated participants reporting significantly greater symptom severity than those in the natural history control group. Crucially, exposure to positive social modelling significantly reduced symptom severity relative to groups that did not receive this intervention. This finding provides the first direct evidence that positive social modelling can attenuate nocebo effects. Notably, no significant difference was observed between instruction only and instruction plus side effect modelling conditions, nor was there an interaction between induction method and positive social modelling. The lack of a significant additive effect of side-effect modelling

means the efficacy of the intervention should be interpreted cautiously with respect to socially elicited nocebo effects. These findings indicate that positive social modelling can reduce nocebo symptoms when social information is present, but do not yet demonstrate that it attenuates a standalone social learning nocebo effect. This distinction is important because ethical requirements necessitated side-effect warnings before modelling, which limited isolation of social learning from instruction. Accordingly, the next logical step is replication in paradigms that demonstrate either nocebo effects induced by social modelling alone, or a clear additive social modelling effect above explicit instruction. Only then can the specific efficacy of positive social modelling for socially-acquired nocebo effects be established with confidence. Together, these findings represent an important step toward identifying scalable, ethically viable strategies for reducing nocebo effects.

Theoretical and Practical Implications

The findings of this thesis have several important theoretical and practical implications for understanding and addressing socially-acquired nocebo effects. First, they advance theoretical accounts of social learning in the nocebo literature by clarifying the psychological mechanisms through which socially transmitted information influences symptom experience, with a particular focus on the roles of expectancy and anxiety. Second, the thesis evaluates the utility of proposed interventions aimed at mitigating socially elicited nocebo effects, critically examining choice and positive social modelling. Finally, the findings identify modelling medium as a key moderator of socially-acquired nocebo effects and highlight the substantial influence of video-based modelling.

Mechanisms of Socially-Acquired Nocebo Effects

Expectancy and anxiety have long been recognised as central mechanisms underpinning nocebo effects elicited through explicit instruction and classical conditioning

(Rooney et al., 2022). In contrast, far less is known about the psychological mechanisms driving socially-acquired nocebo effects (Bajcar & Bąbel, 2018; Rooney et al., 2022). The meta-analysis presented in Chapter 2 highlighted this gap clearly; despite robust evidence that social modelling can elicit nocebo responses, only a small subset of studies assessed candidate mediators, with only three studies measuring expectancies following social learning and four assessing anxiety.

Addressing this gap, Chapter 3 demonstrated that both expectancy and anxiety were significantly elevated following exposure to negative social modelling, and critically, this elevation occurred across both social learning conditions. Participants who observed a model experiencing cybersickness reported increased symptom expectancy and heightened anxiety regardless of whether the model's VR context was identical to, or different from, their own. Mediation analyses further showed that expectancy and anxiety each mediated the effect of social modelling on cybersickness severity in both the consistent and inconsistent modelling groups. These findings demonstrate that the generalisation of nocebo cybersickness across contexts is driven by the same expectancy- and anxiety-based mechanisms that underpin the nocebo effect. More broadly, the results of Chapter 3 reinforce expectancy and anxiety as central mechanisms in the acquisition of socially elicited nocebo effects, consistent with other empirical studies (Koban & Wager, 2016; Tan et al., 2023). Therefore, it is recommended that interventions to reduce socially elicited nocebo effects should be designed to directly reduce symptom expectancy and/or state anxiety, as this is likely to maximise efficacy.

Consistent with this framework, Chapter 5 demonstrated that a positive social modelling video intervention significantly reduced participants' symptom expectations, which translated to a reduction in symptom experience. However, reductions in symptom expectancy did not statistically mediate the observed attenuation of nocebo effects. This may reflect limitations in the timing of expectancy measurement, which was assessed immediately

after the intervention but prior to placebo administration. Thus, our measure of expectancy may have been premature given treatment allocation, pill administration, and the subsequent waiting period may modify expectations. It is also possible that positive social modelling operated through additional, unmeasured mechanisms. These findings nevertheless suggest that expectancy remains a clinically relevant target for reducing nocebo effects, while also indicating that the effects of positive social modelling may not be fully explained by expectancy alone. Clarifying these pathways will be essential for optimising and reliably scaling the intervention.

Given empathy is theorised to shape the extent to which an observer understands, internalises, and applies another person's symptomatic experience to the self, it has been hypothesised as a key mechanism underlying acquisition of nocebo effects specifically arising from social information. However, prior evidence in the nocebo literature has been mixed. The meta-analysis in Chapter 2 provided the first robust test of this hypothesis in the context of socially-induced nocebo effects and found a small but significant positive association between trait empathy and nocebo responding, suggesting that individuals higher in empathy may be somewhat more vulnerable to the effects of negative social modelling. At the same time, this finding should be interpreted cautiously, as it was based on only seven studies and a literature characterised by substantial methodological heterogeneity, including variation in symptom domain and modelling medium. Notably, visual inspection of the forest plot suggested that the empathy effect may have been driven primarily by face-to-face paradigms, which is broadly consistent with anecdotal patterns across the literature showing empathy effects in live modelling studies but little evidence in video-based paradigms. As such, comparing live and video-based social modelling provides a logical starting point for future research seeking to clarify when, and by what mechanisms, empathy influences the social acquisition of nocebo effects. It should be noted that a limitation of this thesis is that it

did not include measures of empathy in the experimental studies described in Chapters 3-5 limiting conclusions pertaining to the role of empathy in the development of socially-induced nocebo effects.

Utility of Choice as an Intervention to Reduce Nocebo Effects

The null finding regarding choice in Chapter 3 can be interpreted in two key ways, each with different theoretical and practical implications. First, the choice manipulation employed may not have been sufficiently potent or salient to influence perceived control. Alternatively, the null effect may reflect design differences between Chapter 3 and prior studies that reported protective effects of choice. Both of these accounts are considered in turn below, alongside evidence relevant to their evaluation.

The effectiveness of choice may depend on how choice is operationalised. One explanation for the null effect of choice observed is that the manipulation was not sufficiently salient to meaningfully alter participants' sense of agency. Offering a choice between VR environments (i.e., sunny versus snowy) did not influence perceived control, affect, or arousal, suggesting that this form of choice failed to engender the hypothesised psychological benefits (Geers & Rose, 2011; Leotti & Delgado, 2011; Leotti et al., 2010; Morris & Royle, 1988). It is possible that more substantive choices, like selecting the specific VR task or type of VR headset, are required to meaningfully influence perceptions of control. However, this account is generally not consistent with prior placebo research, which has demonstrated beneficial effects of choice even when the decision itself is relatively superficial (Tang et al., 2022). For example, Brown et al. (2013) found that a trivial choice of a circle or triangle display on screen was sufficient to reduce discomfort to aversive tones, provided the options were framed as potentially efficacious within the study context. Moreover, choice was hypothesised to exert beneficial effects through a generalised sense of control or enhanced positive affect, independent of the specific content of the decision (Geers et al., 2013; Leotti

et al., 2010). An alternative interpretation is that the effectiveness of choice depends on its perceived relevance to managing the stressor or situation at hand (Paterson & Neufeld, 1995). From this perspective, choosing between VR environments may not have been viewed as a meaningful means of exerting control over cybersickness, thereby limiting its psychological impact. Importantly, if choice must be highly salient or directly relevant to be effective, this substantially constrains its practical utility as a simple and scalable intervention. In most medical contexts, autonomy can only be offered within clinically appropriate and ethically constrained bounds, reducing the feasibility of implementing sufficiently meaningful choices to mitigate nocebo effects.

The effectiveness of choice may be situation specific. A second explanation for the null finding is that the effectiveness of choice may differ as a function of study design and other methodological considerations. Although prior studies have reported that choice can reduce nocebo side effects (Bartley et al., 2016; Faasse et al., 2023), the divergence in findings is difficult to interpret given the small and heterogeneous body of existing research. Including Chapter 3, only four studies have examined choice in the context of nocebo effects, and all differ substantially in experimental design. Key differences include the mode of nocebo induction, whether the nocebo outcome constituted a primary effect or a side effect, the specific symptom targeted, the experimental setting (in-person versus online), the timing of the choice manipulation, and the outcome measures employed. Any of these factors may have contributed to the absence of a choice effect observed in Chapter 3. Among these possibilities, the present discussion focuses on two factors with the strongest theoretical and empirical grounding: the mode of nocebo induction and the timing of the choice manipulation.

Existing evidence suggesting that choice can attenuate nocebo side effects comes from studies in which nocebo effects were induced via explicit instruction (Bartley et al.,

2016; Faasse et al., 2023), rather than through social modelling. It is therefore plausible that choice exerts differential effects across induction modes. This matters because different induction pathways may differ in mechanisms and moderators, so benefits observed in one pathway may not transfer to another. In the context of conditioned nocebo effects, it also appears there is no benefit of choice, with Tang et al. (2024) revealing that choice can amplify conditioned nocebo hyperalgesia. Furthermore, choice increased expectancy of pain and the effect of choice on nocebo hyperalgesia was fully mediated by expectancies. Taken together, current evidence suggests choice may be beneficial in some instruction-based contexts, but ineffective or counterproductive in socially modelled or conditioned nocebo effects. Future research should therefore directly compare the impact of choice across instruction, conditioning, and social nocebo induction to determine whether its effects vary systematically as a function of learning pathway.

Another design difference that may have contributed to the null effect of choice may be when choice was offered to participants. In Chapter 3, participants selected their VR environment prior to observing the social model's cybersickness. This may have created the potential for "choice regret," whereby the subsequent observation of the model's cybersickness was perceived as linked to one's chosen option. This stands in contrast to previous research in which choice was exercised after exposure to the nocebo induction (i.e., the side-effect warnings), potentially reducing the likelihood that participants would attribute negative outcomes to their own decision. In Chapter 3, the timing of the choice manipulation was constrained by the primary research question concerning contextual similarity between observer and model. To enable randomisation to consistent and inconsistent social modelling conditions, choice had to be administered prior to the social modelling manipulation. While methodologically justified, this design feature highlights timing as a potentially important moderator of choice effects and identifies an avenue for future research. Importantly, if

choice is only effective when it is offered after symptom expectations have already formed, its practical value as a nocebo intervention may be limited given the likelihood of subsequently encountering additional information in real-world contexts.

Positive Social Modelling as a Useful Intervention to Reduce Nocebo Effects

To date, few interventions have shown reliable efficacy in reducing nocebo effects acquired by any mode of induction, and proposed approaches such as framing manipulations, choice, and nocebo education have produced mixed results with generally small effects (Barnes et al., 2019; Faasse, 2019). Identifying positive social modelling as an effective strategy is therefore a novel contribution to the nocebo literature with important theoretical and clinical implications. From a practical standpoint, two features of this positive social modelling effect are especially important. First, the positive social modelling intervention was delivered via video, whereas the side effect modelling involved in-person observation. This suggests that video-based positive modelling may be sufficient to counteract nocebo effects even when adverse social information is encountered in more direct or immersive forms. The capacity to deliver positive social modelling through pre-recorded video greatly enhances its scalability and feasibility in clinical settings, where live modelling would rarely be practical. Second, this finding raises the possibility that other low-cost formats, such as written patient testimonials, could also deliver these positive social signals. Evidence from patient-information research indicates that the inclusion of testimonials of patient experience can foster positive treatment beliefs (Green et al., 2023). However, it remains unclear whether written formats of positive social modelling would retain the same efficacy as video-based modelling, as reduced salience, credibility, or content (e.g., the absence of facial expressions and vocal tone) may attenuate their impact. Therefore, future research should investigate whether written forms of positive social modelling deliver the same protective benefit to increase feasibly in translating this to clinical practice.

At the same time, important limitations and ethical considerations of this intervention must be acknowledged before translation to clinical practice. In Chapter 5, no independent social modelling effect was observed above and beyond explicit instruction, so presently we can only conclude that positive social modelling can attenuate nocebo symptoms in contexts where social information is present alongside side effect warnings, rather than definitively preventing stand-alone socially elicited nocebo effects. Establishing efficacy in paradigms that isolate social learning, or demonstrate a clear additive social effect, is therefore an important next step.

Ethical concerns also require careful consideration before implementation. For treatments that genuinely carry frequent or severe adverse effects, presenting "no side effects" messages risks minimising valid patient experiences and undermining informed consent requirements (Gelfand, 2020) unless the content is grounded in authentic, representative patient accounts and communicated transparently. In addition, feasibility and patient acceptability should be carefully evaluated in target clinical populations. With these considerations in mind, positive social modelling remains a theoretically grounded and potentially scalable approach that warrants systematic replication and refinement.

Modelling Medium

Across the thesis, converging evidence indicates that video-based social modelling is sufficient to both induce and reduce nocebo effects. The meta-analysis in Chapter 2 demonstrated that although face-to-face modelling elicits larger nocebo effects than video-based modelling, video exposure nevertheless reliably produces meaningful nocebo effects. This was reinforced in Chapter 3, where pre-recorded online videos (presented deceptively so that participants believed they were viewing a live model) successfully generated socially-acquired nocebo effects. Video-based modelling can also attenuate symptom experiences as demonstrated in Chapter 5, testimony to the significant influence video modelling can have.

This has important methodological implications, as it establishes video modelling as a practical, cost-effective, and easily standardised tool for inducing socially learned nocebo effects in large-sample experimental research, reducing reliance on resource intensive and potentially inconsistent live modelling procedures. Beyond the laboratory, the finding that nocebo effects can be elicited through video rather than requiring in-person observation carries significant real-world relevance. As communication increasingly occurs through digital platforms, a trend only amplified by the COVID-19 pandemic, video-based interactions have become embedded in educational, organisational, healthcare, and interpersonal contexts (Anderson & Vogels, 2020; Beaunoyer et al., 2020; Bokolo, 2020; Hacker et al., 2020; Karl et al., 2021; Krome, 2020; Stieglitz & Dang-Xuan, 2013). Demonstrating that adverse symptom expectations can spread through video communication suggests that online environments may serve as fertile grounds for socially transmitted nocebo effects, underscoring the need for careful monitoring and management of symptom-related content in settings where it is feasible to do so.

Limitations

Although study-specific limitations are discussed in their respective chapters, the overall thesis is constrained by challenges inherent to isolating socially-acquired nocebo effects from explicit instruction, practical difficulties in measuring expectancy and anxiety while upholding cover stories, samples consisting of healthy participants, and the reliance on self-report measures and single-blind procedures. These overarching issues limit the inferences that can be drawn and highlight important directions for future research aimed at strengthening the methodological rigour of work in this area.

Isolating the Effect of Social Learning

A central limitation to the findings of the present thesis concerns the difficulty of isolating social modelling as a standalone mode of nocebo induction. Chapter 3 employed a VR model of nocebo cybersickness, which allowed for the investigation of social modelling without explicit cybersickness warnings because it was deemed ethically permissible to omit medication-style risk disclosure in this setting. In contrast, Chapters 4 and 5 examined social modelling in conjunction with explicit warnings about potential side effects due to ethical constraints. Administering a (sham) pill without prior side-effect warnings and subsequently exposing participants to a peer reporting adverse effects was judged to violate informed consent requirements. As a result, the experimental designs used in this thesis reflect a broader pattern in the literature, where social nocebo effects are commonly investigated in the presence of explicit instruction (see Chapter 2). This limits the ability to draw strong theoretical conclusions about the magnitude or mechanisms of social modelling in isolation, as most studies estimate additive effects rather than the unique contribution of social learning alone. Indeed, findings from the meta-analysis in Chapter 2 suggest that social modelling effects may be larger than instruction-based effects, raising the possibility that the influence of social learning may be underestimated when examined only in conjunction with explicit warnings.

At the same time, this limitation is tempered by considerations of ecological validity. In real-world clinical contexts, explicit side-effect information is almost always provided as part of the informed consent process (Gelfand, 2020). For example, before commencing chemotherapy, patients are typically informed by an oncologist or nurse that treatment can cause nausea, fatigue, or other adverse effects, and may then encounter other patients in waiting rooms, treatment centres, or online support forums describing their own symptom experiences. In this way, social information is more likely to be encountered alongside formal

instruction rather than in its absence. As such, the combined instruction and social modelling paradigms employed in Chapters 4 and 5 may demonstrate greater ecological validity. Nevertheless, to more clearly delineate the theoretical role of social modelling, future research should aim to investigate socially elicited nocebo effects in the absence of explicit instruction where ethically permissible. This approach has been successfully implemented in pain-based paradigms and other symptom models that do not require prior risk disclosure (e.g., Vögtle et al., 2013; 2016; 2019), and may offer a valuable avenue for disentangling social learning from instructional effects.

Measurement of Mechanisms

A further limitation of the present thesis concerns the measurement of expectancy and anxiety as mechanisms underlying socially-acquired nocebo effects, and nocebo effects more broadly. In Chapter 3, the remote delivery format and the cover story centred on "learning from others" enabled repeated assessment of cybersickness expectancy without arousing participant suspicion; indeed, only three participants questioned the authenticity of the actor or the broader purpose of the study. In contrast, the social modelling manipulations in Chapters 4 and 5 were designed to appear as incidental encounters rather than integral components of the study's purpose. Under these circumstances, administering expectancy or anxiety measures immediately after the modelling manipulation was judged to pose an unnecessary risk to the cover story, particularly given our concerns that the context and sample characteristics would already weaken the cover story's plausibility. Indeed, both experiments produced higher (though still relatively low) levels of participant suspicion, supporting our caution in minimising potential threats to the cover story. Consequently, these chapters are limited in their ability to comment on expectancy and anxiety as mechanisms of nocebo effects, as these constructs were only assessed after side effect warnings prior to social modelling. Many nocebo studies neglect to measure these mechanisms at any time

point (Faasse, 2019) despite strong evidence of their importance (Rooney et al., 2022). Therefore, while the lack of post modelling assessments limits interpretation, assessing these mechanisms before modelling still represents incremental improvement to many past designs. Given the difficulty in detecting socially elicited effects in Chapters 4 and 5 above and beyond instruction, post-modelling measures of expectancy and anxiety would have been valuable for determining whether the social encounter influenced expectations but failed to translate into symptoms, or whether the modelling manipulation failed to influence these mechanisms. Future research should prioritise designs that allow for measurement of key mechanisms without compromising deception.

Generalising Findings to Clinical Samples

A key limitation of this thesis is that all studies were conducted with healthy participants, using analogue paradigms to simulate clinical side effect experiences. Although Chapter 2 allowed inclusion of clinical samples, no eligible clinical studies were identified; Chapter 3 recruited healthy community participants, and Chapters 4 and 5 recruited healthy University of Sydney students. This limits generalisability to patient populations, where pre-existing symptoms, treatment history, comorbidities, and real interactions with clinicians and other patients may shape learning processes in ways not captured here. Research suggests that nocebo effects are larger in clinical populations (Grosso et al., 2024; Rooney et al., 2024), and therefore future work should prioritise replication in clinical settings to determine the external validity and translational value of these findings.

Self-report Measures

Another limitation of the present thesis is its use of self-report measures for symptoms, expectancies, and anxiety. Self-report data can be susceptible to several sources of bias, including demand characteristics, experimenter effects, socially desirable responding,

and systematic differences in how participants interpret and use rating scales (Chan, 2010; Hamamura et al., 2008; Krumpal, 2013; McCambridge et al., 2012; Rosenthal & Fode, 1963). This criticism is not unique to this thesis and reliance on self-report measures common across placebo and nocebo literature, and indeed many symptoms of health and wellbeing. To strengthen confidence in the validity of findings, where practical to do so future research should incorporate supplementary measures that are less vulnerable to self-report biases. A strength of the present thesis is that it took an important step in this direction by including heart rate variability and electrodermal activity as indices of physiological arousal in Chapters 4 and 5, however results did not always align with the pattern observed in the primary self-report measures. Further research is needed to clarify the precise nature of the relationship between self-reported measures and their hypothesised physiological correlates, and whether social information has an influence on these physiological measures.

Importantly, symptoms such as pain, nausea, expectancy, and anxiety are inherently subjective experiences, and in clinical practice they are most often assessed by asking patients to report what they feel. In that sense, reliance on self-report also reflects the clinical reality of how these constructs are typically measured. Nevertheless, employing physiological measures alongside self-report measures remains important to establish that these effects are not merely artefacts of self-report bias.

Blinding

Finally, the experimental chapters were limited by the blinding procedures employed. All experiments reported in Chapters 3–5 were conducted using a single-blind design, primarily due to resource constraints. To minimise the potential influence of experimenter expectancy, several safeguards were implemented, including the use of standardised experimental scripts and the collection of all outcome measures via the online platform Qualtrics, thereby reducing direct experimenter–participant interaction during data collection.

Nevertheless, single-blind designs cannot fully eliminate the possibility of subtle experimenter effects, and future research should seek to replicate these findings using double-blind methodologies where feasible to further strengthen causal inferences.

Future Directions

Future directions specific to each study are discussed in each chapter. Broadly, two key avenues for future research emerge from the recurrent themes of the thesis:
First, it is necessary for future empirical research to expand how social information is operationalised to more accurately reflect the types of social information encountered in the real world; Second, the thesis identifies many potential moderators of socially elicited effects that warrant careful experimental research in order to synthesise a cohesive and comprehensive theoretical account of these effects.

Expand How Social Learning is Operationalised Within Empirical Research

Existing experimental research, and all research contained in this thesis, has exclusively operationalised social learning as directly observing another person's symptom experience, whether witnessing a peer undergo a painful stimulus, report side effects, or display cybersickness in VR. The field has not yet systematically examined other modalities of social transmission. The closest evidence comes from studies in which participants were shown graphical representations of another person's pain (e.g., ratings displayed on a scale), which have successfully induced socially learned nocebo hyperalgesia despite the absence of direct visual modelling (Koban & Wager, 2016; Rubanets et al., 2024; Yoshida et al., 2013). Future research should therefore explore the extent to which alternative communication channels can transmit nocebo effects, including auditory-only modelling (e.g., hearing another person describe symptoms via microphone) and text-based formats such as written testimonials, online forum posts, or social media content.

Given the widespread and increasing use of social media for health information seeking (Chen & Wang, 2021; Kanchan & Gaidhane, 2023; Suarez-Lledo & Alvarez-Galvez, 2021; Wilson & Wiysonge, 2020), its absence from empirical nocebo research is striking. Emerging observational evidence suggests that social media may act as a powerful channel for socially-induced nocebo effects. For instance, greater exposure to negative social media posts, and higher perceived severity of those posts, has been associated with more severe subsequent COVID-19 vaccine side effects (Clemens et al., 2023; Tan et al., 2022). However, empirical evidence remains limited. To date, no controlled experiment has systematically tested how specific social media features shape nocebo outcomes, including engagement cues (likes, comments, follower counts), source characteristics (friends, strangers, influencers), content valence, and exposure frequency. As a real-world medium for transmitting social information at scale, social media should be treated as a priority for experimental nocebo research. Establishing these causal pathways is essential for developing interventions that reduce harmful expectancy effects and mitigate downstream symptom burden.

Moderators of Socially-induced Nocebo Effects

The meta-analysis in Chapter 2 identified several moderators of socially-induced nocebo effects that warrant targeted experimental follow-up. Stronger effects were associated with face-to-face modelling, longer exposure durations, lower proportions of female participants and models, and higher observer empathy. While these moderators emerged reliably at the meta-analytic level, controlled experimental work is needed to establish causality and clarify the theoretical mechanisms underlying these patterns.

Severity and duration of modelling. The meta-analysis highlighted substantial variability in how modelling is operationalised, and these factors may meaningfully shape the potency of social learning. Future research should therefore systematically investigate core parameters of modelling, including its severity and duration. In particular, it remains unclear

whether increasing symptom severity or exposure time produces linear amplification of nocebo effects, follows an exponential trend, or may lead to ceiling effects. Both factors lend themselves readily to experimental investigation. For example, modelling severity could be tested by comparing the effects of observing a social model report mild, moderate, or severe symptoms. This question also translates easily to pain paradigms, where stimulus intensity can be systematically varied to represent graded levels of adverse experience related to a sham device. Similarly, duration is easily investigated by extending the length of time over which the model communicates symptoms. If social learning is found to be strongest in contexts where more social information is encountered or where more negative attitudes exist, reducing nocebo effects in these situations would be a clinical priority.

Persistence and evolution over time. A critical and largely untested question for future work is how socially-acquired nocebo effects persist and evolve over time. Most experimental studies assess symptoms once following a single exposure, or within a single laboratory session, which leaves open the question of whether socially learned expectancies extinguish quickly or re-emerge with subsequent treatment encounters. To date, only limited evidence speaks to durability, with one study suggesting that social information could influence conditioned placebo and nocebo effects five days later (Zhang et al., 2017). Relatedly, some placebo pill studies include a 24-hour follow-up, but typically do not test whether nocebo effects reappear after a second administration, meaning the conditions under which social nocebo learning is reinforced, extinguished, or reinstated remain unclear.

This gap is important because real-world treatment exposure is dynamic and typically for substantially longer time periods. Consider hormonal contraception as an example. Across their reproductive life, women typically spend around three decades managing pregnancy risk, and commonly switch between multiple contraceptive methods over time (Daniels & Jones, 2013; Sexual & UK, 2020). As with most treatment experiences, there is evidence

consistent with a nocebo contribution to contraceptive side effect experiences (Grimes & Schulz, 2011). One could speculate this is potentially driven in part by the volume of informal social information women encounter through peers' accounts of birth control experiences. This is just one of many situations in which side effect expectations could evolve dynamically overtime interacting with lived treatment experience (classical conditioning), side effect warnings (explicit instruction) and social information. One concrete way to increase ecological validity would be longitudinal experimental designs that (a) induce nocebo learning via social modelling at baseline, (b) reassess symptoms and expectancies at delayed intervals, and (c) include a second (or repeated) exposure to the same treatment cue days or weeks later to assess reinstatement and trajectory. Mapping how symptoms, expectancy, and anxiety evolve across time would help identify when interventions may be most effective, for example whether positive social modelling needs to occur before initial exposure, after symptoms emerge, or periodically across the treatment course.

Multiple models. Another high priority for research is to move beyond single model paradigms and test how social learning unfolds when people are exposed to multiple models. Chapter 2 showed that most studies still rely on one model, yet in real world settings, especially social media, people typically encounter many heterogeneous accounts that differ in severity, credibility, and timing. This shift is theoretically important because learning from multiple sources may not be a simple additive extension of dyadic modelling: effects may depend on how individuals aggregate information across observations, including order effects, distributional features, and conflict between observed experiences and normative risk information. This framework may also contribute to the understanding of community level nocebo phenomena, including episodes of mass psychogenic illness (Bartholomew et al., 2012). This approach would substantially improve ecological validity and directly inform

scalable mitigation strategies, including whether positive social modelling remains protective when adverse information comes from multiple sources.

Conclusion

The nocebo effect is a powerful psychobiological phenomenon with substantial consequences for individuals, healthcare systems, and society. This thesis demonstrates the strength with which social information can shape symptom experience across domains, and how difficult these effects can be to reverse once established. Crucially, results show that socially-acquired nocebo effects are not confined to identical contexts, but can generalise across related experiences, substantially increasing the opportunity for harm in real-world contexts. Across this work, expectancy and anxiety were confirmed as central mechanisms, with trait empathy identified as an important moderator of vulnerability to socially transmitted effects. At the same time, the findings provide cautious optimism: the same social pathways that amplify symptoms may also be harnessed to reduce them, with positive social modelling showing promise as a protective strategy. Even so, development of interventions with which to reduce the nocebo effect remains in its infancy. Advancing robust, ethically acceptable, and scalable approaches that can be integrated into clinical practice will require continued research so that the significant burden of nocebo effects can be reduced for both patients and the wider community.

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Appendices

Appendix A: Supplementary Material, Chapter 2

Pre-registration

NIHR | National Institute for Health and Care Research

PROSPERO
International prospective register of systematic reviews

The magnitude of the effect of social learning on the generation of nocebo effects in healthy and patient populations: a systematic review and meta-analysis

Cosette Saunders, Winston Tan, Kirsten Barnes, Ben Colagiuri, Louise Sharpe, Kate Faasse

Citation
Cosette Saunders, Winston Tan, Kirsten Barnes, Ben Colagiuri, Louise Sharpe, Kate Faasse. The magnitude of the effect of social learning on the generation of nocebo effects in healthy and patient populations: a systematic review and meta-analysis. PROSPERO 2024 Available from https://www.crd.york.ac.uk/PROSPERO/view/CRD42022383720

REVIEW TITLE AND BASIC DETAILS

Review title
The magnitude of the effect of social learning on the generation of nocebo effects in healthy and patient populations: a systematic review and meta-analysis

Review objectives
1. Does social information induce nocebo effects following nocebo exposure relative to a no treatment control group/condition?
2. Is the magnitude of socially-induced nocebo effects greater than that of nocebo effects generated via other sources of information, for example, instruction, classical conditioning?

3. What are the moderators of socially-induced nocebo effects?

Keywords
Nocebo Effect, Observational Learning, Social Learning, Social Modelling

SEARCHING AND SCREENING

Searches
Studies will be identified by searching the following databases: Embase, CINAHL, PubMed, Scopus, PsycINFO, Web of Science. We will also manually search the reference lists of included studies.

Study design
Studies comparing the nocebo effect following social learning relative to no treatment. This could include between-subjects designs where one group is allocated to social learning and another to no treatment or within-subjects designs where participants are exposed to both a social learning manipulation and a no treatment control condition. In both cases the studies must be fully or quasi-randomised, either in terms of allocating participants to groups (between-subjects designs) or counterbalancing the order in which participants undergo each condition (within-subjects designs).

ELIGIBILITY CRITERIA

Condition or domain being studied
This review will focus on the nocebo effects generated via social learning. There are no constraints on the target symptoms/conditions.

Population
The review will include data from healthy and clinical human participants. We anticipate that available studies will only come from adult populations greater than 16 years old. If any child studies are identified these will be included but a sensitivity analysis will be conducted excluding them.

Intervention(s) or exposure(s)
In order to be eligible for inclusion in this review, studies must use a social learning intervention intended to induce nocebo effects. In this context, social learning refers to a form of learning that consists of observing and modelling another's behaviour, attitudes, or emotional expressions regarding side effects or unwanted effects experienced as a result of a treatment or procedure that is described to participants as being active.

Comparator(s) or control(s)
The main comparison is with a no-treatment control group/condition (Q1). Where possible, the nocebo effect generated via social learning will also be compared to the nocebo effect

generated via other sources of information (Q2) including (non-social) instruction and classical conditioning.

Context

The study should induce nocebo effects via the application of either a treatment or manipulation used to modulate symptoms. A 'treatment' is operationalized as an active or sham medical treatment (e.g. placebo pill, sham electrode). A 'manipulation' is operationalized as using a device or procedure to produce or modify symptoms (e.g. virtual reality to induce nausea). Manipulations or suggestions without the administration of a treatment/causal agent will not be considered.
The study should include the use of social learning to induce the nocebo effect. Socially-induced nocebo effects are the expressions of symptoms linked to a treatment or manipulation that result from observing the behaviour or reports of others expressing the symptoms in response to the same treatment or manipulation. The study should measure the nocebo effect as an outcome with regard to a specific symptom or sets of symptoms (e.g. pain, nausea).
Case studies, interviews, reviews, and conference proceedings will be excluded.

OUTCOMES TO BE ANALYSED

Main outcomes

Studies will be included where symptom intensity and/or frequency (or other data, such as unpleasantness, if intensity and frequency are not available) is reported. Where more than one outcome is measured, preference will be given to symptom intensity. Where multiple symptoms or scales are assessed, we will take those that are identified as the primary outcome by the study authors. If no primary outcome is specified, two researchers will review the study methods and rate which outcome should be the primary outcome based on the study design and prior to observing the study's results.

Measures of effect

Differences in the magnitude of symptoms experienced by the social learning group compared to the no treatment control group/condition (Q1) will be estimated via Hedge's g calculated from the means and standard deviations of symptom intensities or by the mean and standard deviation of the cumulative number of symptoms, extracted for treatment versus no treatment condition/group.
The comparison of socially-induced nocebo effects to other forms of induction (Q2) will be estimated 'head-to-head'. Hedge's g calculated from the means and standard deviations of symptom intensities extracted for social learning versus the comparator. This will be done separately for each comparator, i.e. instruction, classical conditioning, and any others identified.
Where data are not available to directly extract means and standard deviations, other relevant statistical information (for example, data from tables or figures) will be used to

calculate the effect size.

Additional outcomes
Relevant variables will be explored as moderators of socially-induced nocebo effects (Q3). These include:

1. The medium of social learning (e.g. face-to-face observation, pre-recorded video observation or showing symbolic pictures of social cues)
2. Experimental design: whether primary vs secondary nocebo effects are induced (where primary nocebo effects relate to situations in which negative outcomes occur without a concomitant benefit, such as when patients are given a warning that a cream will increase skin sensitivity and thus pain. Conversely, secondary nocebo effects occur when there is a beneficial treatment that may also cause adverse effects, such as when patients are given a pain killer and it causes abdominal pain), or whether the study employs a within-subjects vs between-subjects design.
3. Trait empathy
4. Expectancy
5. Anxiety
6. Gender of participants (% female)
7. Gender of models (% female and matched to participant vs not)
8. Type of participant (patient vs. healthy samples)
9. Type of nocebo exposure (active versus inert nocebo)
10. Type of symptoms reported (e.g. pain, itch, nausea)
11. Length of treatment/manipulation
12. Any other potentially relevant variable identified throughout the review process

DATA COLLECTION PROCESS

Data extraction (selection and coding)
Record titles and abstracts from the database search will be transferred to a central database and duplicates will be removed. The remaining records will then be independently reviewed against the inclusion and exclusion criteria by two researchers to determine potentially relevant studies. The full text of potentially relevant studies will be reviewed for eligibility by two researchers, with disagreements being resolved by a third researcher. Two researchers will extract the following data from eligible studies using a standardized form: study authors and date of publication, email address of the corresponding author, country, sample size, participant demographic information, study inclusion criteria, study exclusion criteria, comparators/ control group, main and additional outcome measures.
Means and standard deviations of symptom intensities or mean and standard deviation of the cumulative number of symptoms (or other data if not available) will be extracted to determine the magnitude of effect sizes. In all instances of missing or unclear data in the published report, the corresponding author will be contacted to retrieve the data with one

reminder email sent in case of no reply.

Risk of bias (quality) assessment

The potential risk of bias will be assessed independently by two researchers, and disagreements will be adjudicated by a third independent assessor. Both randomized controlled trials and experimental studies will be assessed using the Risk of Bias 2 (RoB 2) tool provided by the Cochrane Collaboration (Sterne et al., 2019), as highlighted in the PRISMA 2020 Statement (Page et al., 2021).

PLANNED DATA SYNTHESIS

Strategy for data synthesis

Effect sizes will be generated from the data extracted using R version 4.2.2. The inclusion criteria for this systematic review and meta-analysis allows for nocebo studies conducted using different designs and in different populations so that the analyses will be based on a random-effects model in order to take into account the within-study error and the between-study variance. The mean and standard deviation of the symptom intensities or the cumulative number of symptoms will be entered into R. The effect sizes will be calculated and meta-analysed using a random-effects model, which assumes heterogeneity. Measures of the magnitude of heterogeneity, I^2 and Tau, will be calculated for each effect size. Where means and standard deviations are not available, authors will be contacted to request the data, and if unable to provide the data, other statistical parameters in the manuscript will be used to estimate the effect size (if possible).
Where sufficient data exists (categorical variables k greater than 3 / continuous variables k greater than 9: Fu et al., 2010), moderator analysis will be analysed using meta-regression models for continuous moderators and sub-group comparisons.

Analysis of subgroups or subsets

None beyond those specified above.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members

- Miss Cosette Saunders, University of Sydney
- Mr Winston Tan, University of Sydney
- Dr Kirsten Barnes, University of New South Wales
- Professor Ben Colagiuri, University of Sydney
- Professor Louise Sharpe, University of Sydney
- Dr Kate Faasse, University of New South Wales

Review affiliation

University of Sydney

Funding source
The review will be funded by the University of New South Wales

Named contact
Cosette Saunders.
cosette.saunders@sydney.edu.au

TIMELINE OF THE REVIEW

Review timeline
Start date: 19 December 2022. End date: 01 July 2023

Date of first submission to PROSPERO
13 December 2022

Date of registration in PROSPERO
24 December 2022

CURRENT REVIEW STAGE

Publication of review results
The intention is to publish the review once completed.The review will be published in English

Stage of the review at this submission

Review stage	Started	Completed
Pilot work		
Formal searching/study identification		
Screening search results against inclusion criteria		
Data extraction or receipt of IP		
Risk of bias/quality assessment		
Data synthesis		

Review status
The review is currently planned or ongoing.

ADDITIONAL INFORMATION

PROSPERO version history

- Version 1.1 published on 24 Dec 2022
- Version 1.0 published on 24 Dec 2022

Review conflict of interest
None known

Country
Australia

Medical Subject Headings
Conditioning, Classical; Conditioning, Psychological; Control Groups; Humans; Nocebo Effect; Social Learning

Details of any existing review of the same topic by the same authors
This record was previously registered but due to a number of changes a new record has been created:
Please see PROSPERO 2020 CRD42020207161
Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020207161

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The effect of social learning on the nocebo effect: a systematic review and meta-analysis with recommendations for the future

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The effect of social learning on the nocebo effect: a systematic review and meta-analysis with recommendations for the future

Cosette Saunders [a], Winston Tan [a], Kate Faasse [b], Ben Colagiuri [a], Louise Sharpe [a] and Kirsten Barnes [b]

[a]School of Psychology, University of Sydney, Camperdown, Australia; [b]School of Psychology, University of New South Wales, Kensington, Australia

ABSTRACT

Individuals frequently update their beliefs and behaviours based on observation of others' experience. While often adaptive, social learning can contribute to the development of negative health expectations, leading to worsened health outcomes, a phenomenon known as the nocebo effect. This systematic review and meta-analysis examined: whether social learning is sufficient to induce the nocebo effect, how it compares to other forms of induction (classical conditioning and explicit instruction), and factors that influence these effects. The meta-analysis included twenty studies (n = 1388). Social learning showed a medium-large effect size (Hedges' g = .74) relative to no treatment and a to small-medium effect (g = .42) when compared to neutral modelling. The effect of social learning was similar in magnitude to classical conditioning but greater than explicit instruction with a small-medium effect (g = .46). Face-to-face social modelling, longer exposure, higher proportions of female participants and models, and greater observer empathy led to stronger socially-induced nocebo effects. However, further research is essential as only a minority of studies measured important constructs like negative expectancies and state anxiety. Nonetheless, the study highlights social learning as a key pathway for nocebo effects, suggesting it as a target for interventions to reduce the substantial personal and societal burden caused by nocebo effects.

ARTICLE HISTORY
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KEYWORDS
Nocebo effect; social learning; observational learning; symptoms; pain; side effects

Introduction

The nocebo effect is a psychobiological phenomenon in which an individual experiences an increase in the severity, or even the genesis, of adverse health outcomes (e.g., pain, nausea, side effects) that cannot be otherwise explained by a treatment or intervention's active components. As many as 76% of systemic adverse events experienced in the active arms of COVID-19 vaccination trials also occurred in the placebo arms, suggesting a strong role of nocebo effects in ubiquitous experiences such as COVID-19 vaccine side effects (Haas et al., 2022). Beyond the experience of these undesirable symptoms, nocebo effects can lead to perceptions of poorer treatment outcomes (Corsi et al., 2016) and cause non-adherence to otherwise effective treatments (Barsky et al., 2002). As such, it is

CONTACT Cosette Saunders cosette.saunders@sydney.edu.au
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paramount that we identify the mechanisms driving nocebo effects so that interventions to combat them can be devised. Social learning is a potentially key factor in the formation of these nocebo effects.

Social learning occurs when individuals modify their beliefs and behaviours after observing the behaviour of others (Bandura & Walters, 1977). It can play a considerable role in shaping an individual's expectations and experiences, particularly within health contexts. As social learning can occur independent of direct experience, it enables individuals to receive additional, albeit often anecdotal, information about treatments and medications. This information may extend beyond the health information typically disseminated by health professionals. For example, while a doctor may provide written descriptions and verbal suggestions about a treatment's side effects, individuals can also learn by observing another person's treatment experience or receiving experiential information through social channels such as conversations with friends and the use of social media. Consequently, individuals may develop negative expectancies concerning the likelihood or severity of side effects by observing others independently of the information communicated to them by their physicians.

A growing body of literature has demonstrated that social learning can modulate the experience of a variety of health outcomes – e.g., pain (Vögtle et al., 2013; 2016; 2019), medication side effects such as headache and dizziness (Faasse et al., 2015; Faasse et al., 2018), and nausea (Tan et al., 2023). Furthermore, social learning has been proposed to play a central role in community-level nocebo effects including idiopathic environmental intolerance attributed to electromagnetic fields (Witthöft & Rubin, 2013) and wind turbine syndrome (Rubin et al., 2014). Experiential information communicated through social media has also been implicated in the experience of COVID-19 vaccination side effects (Clemens et al., 2023; Tan et al., 2022). Information about the experience of others thus appears to be pivotal in the construction of our own perceptions and experiences of treatments and health-related interventions.

However, it is important to emphasise that what is modelled by an individual can differ in valence. Social modelling can be negative, positive, or neutral in nature. Negative modelling occurs when an individual demonstrates worsened health outcomes following a treatment or intervention (e.g., increased pain). Positive modelling occurs when a model emphasises the alleviation of negative symptoms or an increase in a desired effect (e.g., decreased pain). Last, neutral modelling occurs when the model presents no difference in outcomes before, during, or after exposure to the intervention (e.g., no change in pain). The valence of the social information presented by the model can also be multifaceted, in that an intervention or treatment could lead to positive effects in some domains (e.g., improved cognitive performance) at the same time as negative effects in others (e.g., adverse side effects). This is important because existing studies on socially-induced nocebo effects vary in the types of comparison groups they employ (e.g., negative versus neutral modelling). This may subsequently influence the effect size observed.

In addition to social learning, nocebo effects are known to be induced via other processes such as conditioning and explicit instruction (Blasini et al., 2017). Conditioned nocebo effects arise when a neutral conditioned cue is repeatedly paired with an active unconditioned stimulus such that the conditioned cue elicits adverse outcomes when presented alone (Stewart-Williams & Podd, 2004). For example, elements of the chemotherapy treatment context (e.g., the catheter) can become associated with the chemotherapy-induced nausea such that the appearance of treatment (e.g., connection of the catheter) elicits anticipatory nausea and vomiting prior to the administration of the chemotherapy itself (Kamen et al., 2014). On the other hand, nocebo effects induced by explicit instruction occur when physicians inform patients that they may experience enhanced pain, increased symptom severity, or adverse side effects (Colloca & Miller, 2011). In one instance, when verbally informed that a local anaesthetic injection would 'feel like a big bee sting; this is the worst part of the procedure', participants experienced significantly greater pain relative to those who were told that 'the local anaesthetic injection will numb the area and you will be comfortable during the procedure' (Varelmann et al., 2010). While classical conditioning and explicit instruction

have been shown to be highly influential in placebo and nocebo contexts, social learning has received less theoretical and empirical attention despite its potential relevance to both individual and community-level nocebo effects.

To date, there has not been a comprehensive appraisal of socially-induced nocebo effects. A recent systematic review included social learning as part of a wider exploration of contributing factors to nocebo effects, highlighting that social learning could be one of the strongest forms of nocebo induction (Webster et al., 2016). However, in this systematic review, only three nocebo studies with a social learning manipulation were identified. Recent interest in social learning as a mechanism of nocebo effects means that more studies are currently available, which will allow a meta-analysis of studies. This was not attempted in the Webster et al. (2016) review. A subsequent meta-analysis of 17 studies focused on placebo and nocebo effects arising from social learning specifically for pain (Meeuwis et al., 2023). While interesting for understanding pain itself, the review's focus on pain limits the ability to determine the extent to which social learning can influence other symptom domains often experienced in clinical settings (e.g., headache, dizziness, and nausea). The present meta-analysis therefore aimed to quantify the effect of social learning across a variety of nocebo-related health outcomes. Most recently, a large-scale meta-analysis estimated the nocebo effect size in 130 studies across any induction type and condition, but it only briefly compared social learning to other forms of induction at an omnibus level and did so including indirect cross-study comparisons that do not control for key factors, such as type of sample and target condition (Rooney et al., 2024). Accurately estimating the effect size of socially-induced nocebo effects is essential for developing interventions to minimise their occurrence in clinical and community settings.

In terms of mediators and moderators, negative expectations and state anxiety are two constructs thought to drive the formation of nocebo effects (Faasse, 2019). A meta-analysis of 59 studies found that increased negative expectations for adverse outcomes and higher state anxiety were both associated with larger nocebo effects (Rooney et al., 2022). However, the specific association between these factors and socially-induced nocebo effects has yet to be explored. Individual characteristics such as trait empathy have also been suggested as a contributing factor, with some indication that the affective component of empathy is critical across pain-based (Meeuwis et al., 2023) and side effect-based (Mennitto et al., 2021) symptom domains. Moreover, while there is some indication that females may be more susceptible to the social modelling of nocebo effects (Faasse, 2019), there has yet to be a systematic evaluation of the role of gender. Beyond these factors, there are several other features, particularly those relevant to the content of the modelling itself, that could moderate socially-induced nocebo effects. For example, the mode of delivery (e.g., whether the modelling occurs in a face-to-face setting or through video observation) could be pivotal, given that the complexity of available social cues is likely to vary. Relatedly, it might be intuitive to assume that longer exposure to negative modelling would be positively associated with greater nocebo effects, yet this has not been examined.

In summary, despite increasing research in the area, we currently do not know the effect size of social learning on nocebo effects across multiple symptom domains and relative to other forms of nocebo induction, nor which factors moderate the effect. The present meta-analysis thus aimed to synthesise the current understanding of socially-induced nocebo effects by addressing three key research questions: (1) does social learning elicit nocebo effects?; (2) what is the relative influence of social learning compared to classical conditioning and explicit instruction?; and (3) what are the moderating factors that underpin socially-induced nocebo effects?

Methods

The present meta-analysis protocol was pre-registered on the PROSPERO register (registration ID: CRD42022383720).

Search strategy

Studies were identified by searching the following databases: Embase, CINAHL, PubMed, Scopus, PsycINFO, and Web of Science. A subsequent citation search was conducted by manually searching the reference lists of included studies (backward search) and reviewing studies that had cited included studies (forward search). The search strategy can be found in section 1 of the Supplementary Material.

Selection criteria

Included studies had to report original data where there was at least one social learning manipulation. This manipulation required the observation of another's behaviours, attitudes, or emotional expressions regarding side effects or unwanted effects experienced as a result of a treatment or procedure described to participants as being active.

In addition, included studies required at least one of the following comparator conditions:

a) No treatment control. A condition in which the participant does not receive any social information and/or does not receive treatment.
b) Neutral social modelling control. A condition in which the participants receive modelling of either an absence of negative effects (e.g., not feeling side effects) or no difference between nocebo stimulus and control (e.g., the same reaction to a nocebo cream and control cream).
c) Explicit Instruction. This condition consists of verbal or written information communicated to individuals regarding the supposed effects of a treatment/an intervention that is not social in nature.
d) Classical Conditioning. This condition consists of direct experience with the supposed effects of a treatment/intervention.

In addition, all included studies had to report symptom intensity and/or frequency outcomes (e.g., pain or side effects) or related data (e.g., unpleasantness). Between and within-subject designs were included. In all cases, studies had to fully or quasi-randomise participants, either in terms of group allocation (between-subjects designs) or counterbalancing the order in which participants undergo each condition (within-subjects designs) to be eligible. The review intended to include data from healthy and clinical populations.

Study selection

Two researchers (W.T. and C.S.) conducted an initial search and compiled the retrieved titles and abstracts into Covidence, from which duplicates were removed. The same two researchers then independently performed a title and abstract screening. If any conflicts in the decisions between the researchers existed, the two researchers resolved this conflict via discussion. Following this initial screening, the texts of all potentially relevant studies were independently reviewed in full by the two researchers to determine the final included studies. Conflicts in decisions were reviewed by a third researcher (K.B.), who discussed their own opinion with the first two researchers until consensus was reached.

Data extraction

Data from the included studies were extracted using a Covidence data extraction template designed by the researchers. Extracted information included relevant study characteristics such as publication year, country of origin, sample size, study population (i.e., healthy or clinical), gender (% female), and mean age. The following information was also extracted: experimental

design, medium of social learning, type of nocebo intervention (i.e., primary or secondary), model gender (% female), number of models, type of nocebo exposure (i.e., inert or active nocebo stimulus), modelled symptoms, type of treatment/manipulation, and duration of modelling procedure. Where available, data regarding measures of trait empathy, expectancy, and anxiety were also extracted. Correlations were extracted between individual empathy scores and symptom intensity scores for between-subjects designs (or the social learning stimulus intensity minus the control stimulus intensity if within-subjects or mixed) across social learning conditions. This correlation reflects the relationship between empathy and social learning. In cases where data was not available and authors did not respond to requests for data ($k = 4$; 20%), the R package 'metaDigitise' was used to extract primary outcome, expectancy, and anxiety data from figures with sufficient resolution (Pick et al., 2018).

Independence of results

If a study measured more than one primary outcome (Barbiani et al., 2018), the outcome that most closely aligned with the symptoms that were modelled was chosen. If more than one time point was measured (Lorber et al., 2007; Zhang et al., 2017), measurement closest in time after the nocebo manipulation was extracted. If a study had multiple eligible groups/conditions for analysis within the same research question and thus 'shared' a group in the calculation of each effect size (i.e., Quinn et al., 2023, investigates the effect of both neutral modelling and no treatment), the sample of the shared group (i.e., the negative modelling group) was halved to generate two effect sizes (Higgins et al., 2011). Therefore, all comparisons included can be considered independent. The random effects model implemented accounted for the effect of study in the case that there were multiple independent effects reported from the same study (Harrer et al., 2021).

Outcome data

The meta-analysis was conducted using R 4.2.2 (R Core Team, 2022) using the package 'metafor' (Viechtbauer, 2010). The included studies utilised different designs in different populations, therefore a random-effects model was implemented to take into account the within-study error and the between-study variance. Between-study heterogeneity (τ^2) was estimated using a restricted maximum likelihood procedure recommended by Viechtbauer (2005). Hedges' g values of 0.2, 0.5 and 0.8 were respectively interpreted as small, medium, and large effect sizes (Cohen, 1988).

Heterogeneity and publication bias

To assess the presence of between-study heterogeneity, Cochrane's Q was examined and I^2 was calculated to quantify the percentage of between-study heterogeneity. In accordance with Cochrane recommendation, I^2 was interpreted using the following thresholds: < 40% – not important; 40–60% – moderate heterogeneity; 50–90% substantial heterogeneity, and 75–100% – considerable heterogeneity (Deeks et al., 2022). To test for publication bias, graphical funnel plots were created, and the Egger test subsequently used to assess asymmetry (Egger et al., 1997).

Moderators

Moderator analysis was conducted using sub-groups analysis for categorical moderators and meta-regression for continuous moderators. This analysis was only conducted when sufficient data existed. For categorical variables the minimum number of studies per group was three, and for continuous variables a minimum of nine was required (Fu et al., 2010).

Risk of bias assessment

All included studies were assessed using the Risk of Bias 2 (RoB 2) tool provided by the Cochrane Collaboration (Sterne et al., 2019), as highlighted in the PRISMA 2020 Statement (Page et al., 2021). This assessment was conducted by two researchers (W.T. and C.S.), and disagreements were adjudicated by a third independent assessor (B.C.). Risk of bias for each study was assessed in five domains: randomisation, deviation from intended interventions, missing outcome data, measurement of the outcome, and reporting bias. Within the context of nocebo research, any form of verbal suggestion prevents participants from being blinded to the intervention. Furthermore, the key intervention assessed in the present meta-analysis is social learning, rather than the effects of the specific treatment or intervention. Therefore, deviation from intended intervention bias was assessed based on participant blinding to the social learning manipulation rather than to the treatment/manipulation itself. Reporting bias was weighted less heavily in calculation of overall risk of bias as all included studies were experimental and the pre-registration of studies was not common practice for these studies when most were originally conducted.

Deviations from the registered protocol

Over the course of the literature review and study search, it became apparent that a significant portion of the social learning literature compared the social modelling of negative outcomes to the social modelling of the *absence* of negative outcomes. That is, in the latter scenario, the model experiences the treatment but communicates a lack of negative response. In one example, after taking a supposed beta blocker, the model reported feeling fine, with no experience of side effects (Faasse et al., 2015). Thus, in the interest of accurately reflecting the state of the literature, the first pre-registered research question was expanded to answer: 'Does social learning elicit a nocebo effect in comparison to a control?' and 'Does the type of control group implemented (no treatment vs neutral modelling) affect the size of the nocebo effect elicited?'.

Results

Study selection

A total of 7265 articles were identified through an initial database search, with 4402 remaining following the removal of duplicates. Title and abstract screening resulted in the exclusion of a further 4363 studies. Full text review was conducted on the remaining 39 studies, with 21 identified as ineligible. Of the 18 studies determined eligible, citation searching resulted in the inclusion of an additional 3 studies. Data was unavailable for only one eligible study. Therefore, 20 total studies were included. Refer to section 2 of the Supplementary Materials for the references of included studies (Figure 1).

Study characteristics

A summary of the study characteristics is provided in Table 1. The 20 included studies had an average included sample size of 66 participants, ranging from 20 (Egorova et al., 2015) to 147 (Witthöft & Rubin, 2013) participants. The mean participant age across the included studies ranged from 19 to 43, with the exception of one study conducted with children (Van Lierde et al., 2020). All included studies had a minimum of 50% female participants (overall mean 68%). Most studies originated from Europe ($k = 11$, consisting of studies originating from Germany, UK, Poland, Italy, Netherlands, Belgium, and Turkey) or the United States ($k = 4$). All included studies were based on samples of healthy participants. Nine studies used a mixed design, three used a within-subjects design, and eight used a between-subjects design. There were several types of nocebo stimuli, with placebo

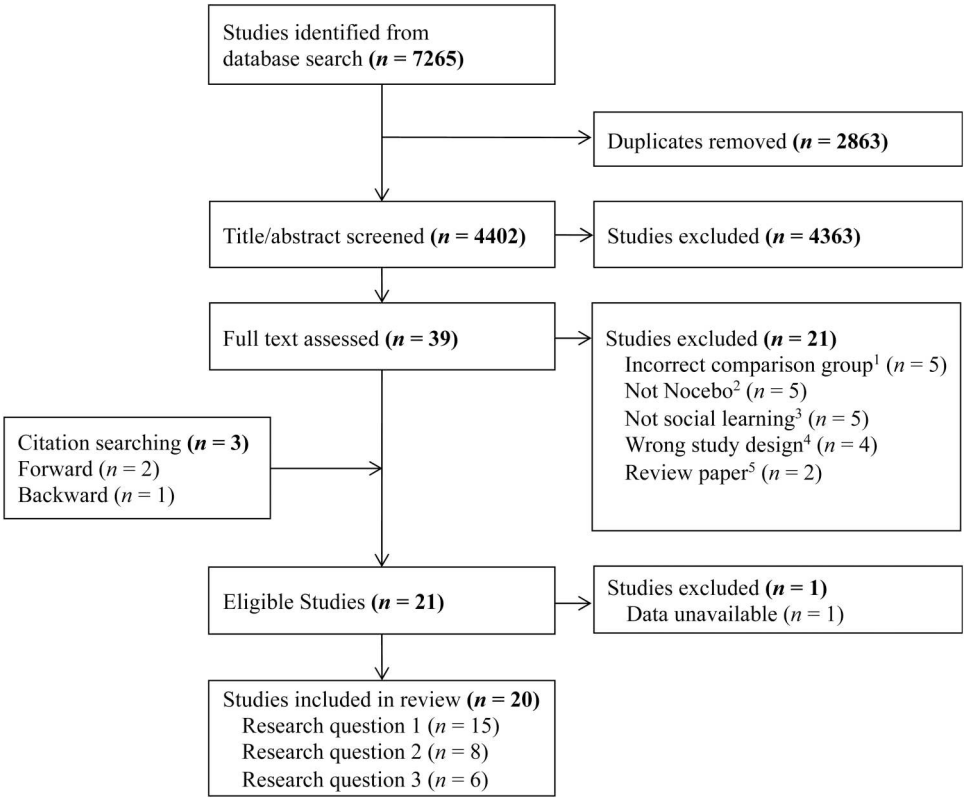

Figure 1. PRISMA flow diagram. Note: [1]Did not have a comparison group that satisfied any of the prespecified criteria. [2]Only assessed placebo effect. [3]No social information communicated, e.g., media reports without explicit social information. [4]Study was not fully or quasi-randomised. [5]Review paper, no original data.

treatments including creams ($k = 4$), pills ($k = 3$), and nasal sprays ($k = 3$), and manipulations such as electrical and heat manipulations ($k = 4$), virtual reality, EEG caps, high altitude, metal rings, cold pressor tasks, and electromagnetic field (EMF) exposure (each $k = 1$). Fourteen studies investigated primary nocebo effects (e.g., where negative health outcomes were the primary or main focus of treatment) and five investigated secondary nocebo effects (e.g., where negative health outcomes existed as a corollary to positive outcomes). The majority of nocebo interventions were inert ($k = 14$), while a minority of studies assessed active nocebo interventions ($k = 6$). Eight studies communicated social information face-to-face, while 12 utilised video observation. Of these 12 video modelling studies, one study utilised live modelling via Zoom (as opposed to pre-recorded videos) (Tan et al., 2023) and Witthöft and Rubin (2013) utilised a pre-recorded media report that contained excerpts of a 'genuine' sufferer of EMF exposure describing their symptoms. Most studies only had one social model deliver the social learning manipulation to participants ($k = 17$), however, three studies investigated social learning with two models. The duration of the social learning manipulation ranged from 1 min (Faasse et al., 2015; Faasse et al., 2018) to 12 h (Barbiani et al., 2018), however with the exception of Barbiani et al. (2018), all other studies had social learning interventions of less than 1 h. A variety of symptom domains were explored, with pain as the most frequently studied ($k = 10$). Other symptoms studied included itch, headache, nausea, and dizziness with many studies assessing more than one symptom. Seven studies measured empathy and reported a correlation between empathy and the nocebo response within the social learning condition. Of the studies that measured empathy, six employed the full form Interpersonal

Table 1. Summary of characteristics for all included studies.

Experiment	Country	*N*	Age (*M*)	% Female	Design	Nocebo stimulus	Type of nocebo intervention	Type of nocebo exposure	Medium	Model gender (% female)	Model (*N*)	Modelled symptoms	Duration of modelling (minutes)
Barbiani et al. (2018)	Italy	36	29	50	mixed	Manipulation: high altitude	Primary	Active	face-to-face	50	2	headache; insomnia	720
Blythe et al. (2021)	Netherlands	58	22	100	between	Treatment: cream/gel/ ointment	Primary	inert	video	100	1	itch	Not Reported
Broderick, Kaplan-Liss, and Bass (2011)	US	39	42	58	between	Treatment: pill	secondary	inert	face-to-face	50	2	headache; dizziness; nausea	Not Reported
Buglewicz-Przewoźnik, Adamczyk, and Bąbel (2022)	Poland	44	24	50	mixed	Manipulation: electrical stimulation	primary	inert	face-to-face	0	1	pain	5
Egorova et al. (2015)	US	20	23	60	within	Manipulation: heat stimulation	primary	Active	video	50	1	pain	Not Reported
Faasse et al. (2015)	NZ	82	21	50	between	Treatment: pill	secondary	inert	face-to-face	100	1	headache; dizziness; drowsiness; dry mouth	1
Faasse et al. (2018)	NZ	96	21	50	mixed	Treatment: nasal spray/inhaler	secondary	inert	face-to-face	50	1	headache; dizziness	1
Lorber et al. (2007)	US	43	Not Reported	59	between	Treatment: nasal spray/inhaler	primary	inert	face-to-face	100	1	headache; drowsiness; itch; nausea	50
Mazzoni et al. (2010)	UK	120	21	50	between	Treatment: nasal spray/inhaler	primary	inert	face-to-face	50	1	headache; drowsiness; itch; nausea	50
Quinn et al. (2023)	Australia	107	19	61	mixed	Treatment: pill	secondary	inert	video	50	2	headache; dizziness; nausea; tiredness	Not Reported
Świder & Bąbel (2013)	Poland	84	23	50	between	Manipulation: electrical stimulation	primary	Active	face-to-face	50	1	pain	5
Tan et al. (2023)	Australia	97	26	61	mixed	Manipulation: virtual reality	primary	Active	video	0	1	nausea; sweating, general discomfort	5
Tu et al. (2019)	US	21	25	57	within	Manipulation: heat stimulation	primary	Active	video	50	1	pain	22
Türkarslan & Çinarbaş (2020)	Turkey	50	22	78	between	Manipulation: EEG cap	secondary	inert	video	Not Reported	1	pain	Not Reported
Van Lierde et al. (2020)	Belgium	44	10	61	within-subjects	Manipulation: cold pressor task	primary	active	video	100	1	pain	2
Vögtle et al. (2013)	Germany	80	23	100	mixed	Treatment: cream/gel/ ointment	primary	inert	video	100	1	pain	10
Vögtle et al. (2016)	Germany	97	43	100	mixed	Treatment: cream/gel/ ointment	primary	inert	video	100	1	pain	10
Vögtle et al. (2019)	Germany	80	22	100	between	Treatment: cream/gel/ ointment	primary	inert	video	100	1	pain	Not Reported
Witthöft & Rubin (2013)	UK	147	30	67	mixed	Manipulation: EMF exposure	primary	inert	video	100	1	headache; nausea; burning skin	9
Zhang et al. (2017)	China	43	21	100	mixed	Manipulation: metal ring	primary	inert	video	0	1	pain	20

Notes. [1]*N* refers to the number of participants analysed in the meta-analysis, and potentially excludes participants in conditions not included in the meta-analysis. [2]Design refers to the design used to calculate the effect size for the meta-analysis, e.g., if the design was originally between-groups pre-post (mixed) but only post scores were able to be extracted, the design was recorded as between subjects.

Reactivity Index (IRI; Davis, 1983) and one the brief version of the IRI (Ingoglia et al., 2016), therefore the analysis of the third research question was conducted on total IRI score.

Risk of bias

The risk of bias assessment is summarised in Table 2. Overall, seven studies were considered low risk of bias. Eleven were judged to have some concerns, primarily based on no specified pre-registration of a data analysis plan (reporting bias). Two were judged to have a high risk of bias. Very few studies showed any risk of bias for deviation from intended intervention ($n = 0$) or outcome measurement ($n = 1$).

Research question 1: effect size of social learning compared to control condition

Fifteen unique studies were included, with a total of 560 participants in social learning conditions, 223 participants in no treatment conditions ($k = 9$) and 317 in neutral modelling conditions ($k = 7$). Figure 2 presents a forest plot of individual study and overall effect sizes. The overall pooled effect size for the nocebo effect elicited social learning was medium ($g = 0.57$; 95%CI [0.40, 0.75]; $p < .001$). Relative to a control condition, social learning significantly increased the nocebo outcome. Visual inspection of the funnel plot and the Egger test indicated potential publication bias ($p = .04$; see section 3 of the Supplementary Material). Duval and Tweedie's trim and fill method suggested there were three missing studies, and produced an adjusted effect size $g = 0.47$, 95%CI [0.27, 0.67]; $p < .001$.[1]

Moderator analysis

Table 3 presents the results of moderator analysis. Meta-regression revealed that the size of the social learning effect did differ significantly between studies that employed a no treatment compared to a neutral modelling control condition ($Q_M = 4.09$, $df = 1$, $p = .04$). Relative to studies that

Table 2. Risk of bias assessment (by category and overall) for each study.

	Randomisation	Deviation from intended intervention	Missing outcome data	Measurement	Reporting	Overall
Barbiani et al. (2018)	Some	Low	Low	Low	Some	Some
Blythe et al. (2021)	Low	Low	Low	Low	Low	Low
Broderick et al. (2011)	Some	Low	Low	Some	High	High
Buglewicz-Przewoźnik et al. (2022)	Some	Low	Low	Low	Some	Some
Egorova et al. (2015)	Low	Low	Low	Low	Some	Low
Faasse et al. (2015)	Low	Low	Low	Low	Some	Low
Faasse et al. (2018)	Low	Low	Low	Low	Some	Low
Lorber et al. (2007)	Some	Low	Low	Low	Some	Some
Mazzoni et al. (2010)	Some	Low	Low	Low	Some	Some
Quinn et al. (2023)	Low	Low	Low	Some	Some	Some
Świder and Bąbel (2013)	Some	Low	Low	Low	Some	Some
Tan et al. (2023)	Low	Low	Low	Low	Low	Low
Tu et al. (2019)	Low	Low	Some	Low	Some	Some
Türkarslan and Çinarbaş (2020)	High	Low	Low	Low	Some	High
Van Lierde et al. (2020)	Some	Low	Low	Low	Some	Some
Vögtle et al. (2013)	Some	Low	Low	Low	Some	Some
Vögtle et al. (2016)	Low	Low	Low	Low	Some	Low
Vögtle et al. (2019)	Low	Low	Low	Low	Some	Low
Witthöft and Rubin (2013)	Some	Low	Low	Low	Some	Some
Zhang et al. (2017)	Some	Low	Low	Low	Some	Some

employed no treatment control conditions, when a neutral modelling condition was employed the effect size for social learning was smaller ($b = -0.32$, 95%CI [−0.63, −0.01]; $p = .04$). The effect size of social learning was inversely associated with the proportion of females in the sample ($b = -0.01$, 95% CI [−0.02, < −0.01]; $p = .02$) and the proportion of models that were female ($b < -0.01$, 95%CI [−0.01, < −0.01]; $p = .04$). Furthermore, the medium through which the modelling was delivered significantly moderated the size of the social learning effect ($Q_M = 9.73$, $df = 1$, $p = .002$). That is, relative to modelling delivered face-to-face, video modelling was associated with a significantly smaller social learning effect ($b = -0.43$, 95%CI [−0.70, −0.16], $p = .002$). The social learning effect size was also positively associated with the duration of the modelling intervention, ($b = 0.09$, 95%CI [<0.01, 0.18]; $p = .05$). No other moderator reached statistical significance, including other social learning related factors (i.e., type of nocebo intervention, number of models, type of nocebo exposure), study/sample characteristics (i.e., mean age, design, year of publication, risk of bias). There were insufficient data to conduct pre-registered moderator analyses of country, type of participant (i.e., healthy, clinical), symptoms modelled, expectancy, and anxiety.

Research question 2: effect size of social learning compared to explicit instruction

There were 4 unique studies, with a total of 135.5 participants in social learning conditions compared to 131.5 participants in explicit instruction conditions.[2] Figure 3 presents a forest plot of overall and individual study effect sizes. The overall pooled effect size for the nocebo effect of social learning relative to explicit instruction was significant, meaning that the size of nocebo effect generated was larger when elicited via social learning than explicit instruction ($g = 0.42$; 95%CI [0.04, 0.80]; $p = .03$). Visual inspection of the funnel plot, the Egger test and moderator analysis could not be performed due to insufficient number of studies (Page et al., 2023).

Research question 2: effect size of social learning compared to classical conditioning

Data from 4 unique studies, with a total of 83 participants in social learning conditions, 82 participants in explicit instruction conditions were included. Figure 4 presents a forest plot of overall and individual study effect sizes. The overall pooled effect size for the nocebo effect of social learning relative to classical conditioning was not significant ($g = -0.09$; 95%CI [−0.40, 0.22]; $p = .56$).

Research question 3: effect size of empathy within social learning condition

Seven studies reported correlations between empathy and social learning resulting in a total sample of 292 participants. The overall pooled effect size for the correlation between the nocebo effect elicited via social learning and empathy was statistically significant, but small ($r = 0.14$; 95%CI [0.01, 0.27]; $p = .03$). Additional analysis at the subscale level (i.e., perspective taking, personal distress, fantasy, and empathic concern) is reported in section 4 of the Supplementary Material (See Figure 5).

Discussion

The present systematic review and meta-analysis had three primary aims. First, to identify the influence of social learning in the formation of the nocebo effect across multiple symptom types. Here, evidence suggests that there was a medium-sized effect of social learning. The second aim was to investigate the magnitude of socially-induced nocebo effects relative to those induced by classical conditioning and explicit instruction. Analyses demonstrated that social learning had a comparable effect size to classical conditioning. Relative to explicit instruction, on the other hand, there was a small-medium increase in the effect size of nocebo outcomes induced by social learning. The third aim was to identify situational and dispositional factors that modulate socially-induced nocebo effects. Several factors, including face-to-face modelling and greater empathy, facilitated

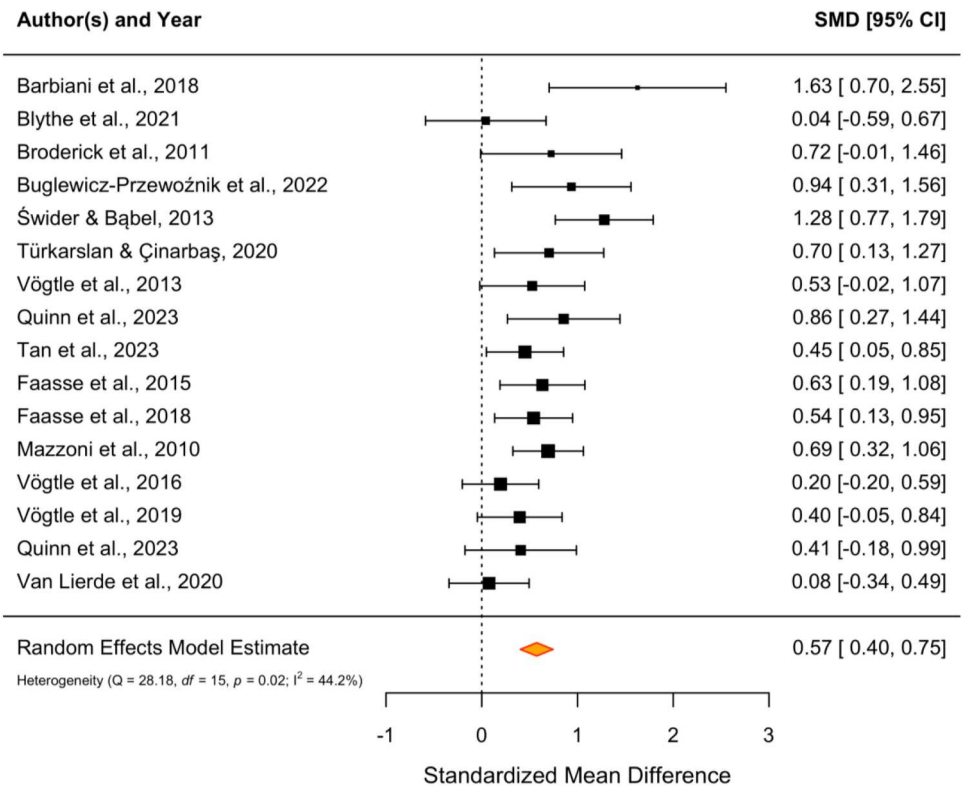

Figure 2. Forest plots displaying Hedges' g (±95%CI) for each included study and an overall effect size (±95%CI) for the effect of social learning. Note. Larger values of Hedges' g indicate larger effects of social learning relative to the control condition.

stronger effects. These outcomes have important theoretical, methodological, and practical implications.

The finding that socially-induced nocebo effects manifest beyond pain to a multitude of other symptomatic contexts including headache, nausea, and drowsiness is important. If social learning can produce the nocebo effect with a medium effect, clinicians need to understand that their

Table 3. RQ1: Moderator analysis of the effect of social learning.

Moderator	K	Subgroup Differences	*b*	95%CI	*p*
Type of control (ref = No treatment)	9	$Q_M = 4.09$, $df = 1$, $p = .04$	0.74	(0.51, 0.98)	<.001
Neutral Modelling	7		−0.32	(−0.64, − 0.01)	.043
Year of publication	16		−0.02	(−0.06, 0.02)	.264
Mean age of sample	16		<0.01	(−0.02, 0.02)	.847
Gender (% Female)	16		−0.01	(−0.02, < −0.01)	.015
Model Gender (% Female)	15		<−0.01	(−0.01, <−0.01)	.043
SM Medium (ref = Face-to-Face)	7	$Q_M = 9.73$, $df = 1$, $p = .002$	0.80	(0.60, 1.01)	<.001
Video	9		−0.43	(−0.70, − 0.16)	.002
Duration of modelling	10		0.09	(<0.01, 0.18)	.049
Design (ref = Between Subjects)	7	$Q_M = 0.65$, $df = 1$, $p = .42$	0.65	(0.40, 0.90)	<.001
Mixed/Within	9		−0.14	(−0.48, 0.20)	.420
Type of nocebo intervention (ref = Primary)	10	$Q_M = 0.20$, $df = 1$, $p = .65$	0.55	(0.33, 0.76)	<.001
Secondary	6		0.09	(−0.29, 0.46)	.652
Number of models (ref = One)	12	$Q_M = 1.65$, $df = 1$, $p = .20$	0.53	(0.34, 0.72)	<.001
Two	4		0.32	(−0.17, 0.81)	.200
Type of nocebo exposure (ref = Active)	4	$Q_M = 0.47$, $df = 1$, $p = .49$	0.69	(0.33, 1.05)	<.001
Inert	12		−0.15	(−0.56, 0.27)	.492
ROB overall (ref = Low)	6	$Q_M = 3.56$, $df = 1$, $p = .06$	0.40	(0.15, 0.64)	.001
Some Concerns & High	10		0.32	(−0.01, 0.64)	.059

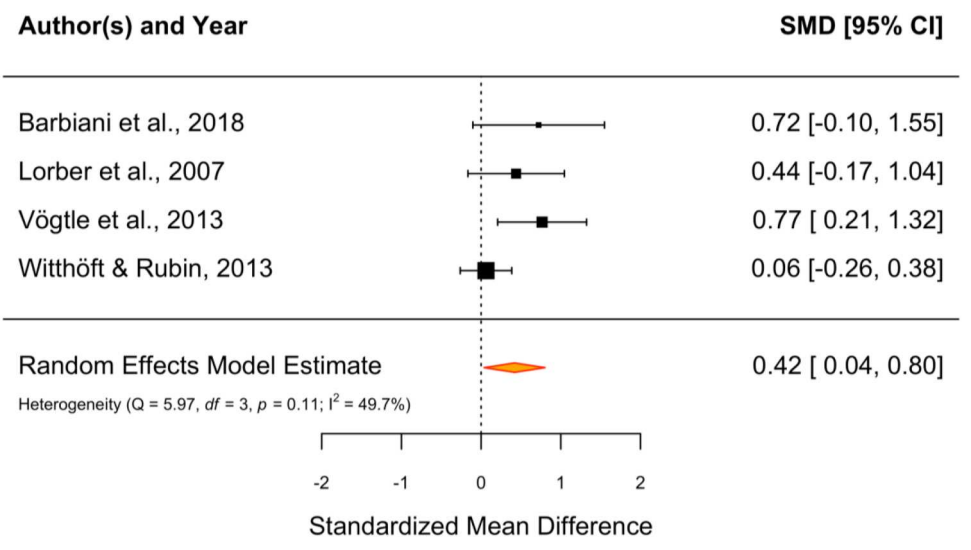

Figure 3. Forest plots displaying Hedges' g (±95%CI) for each included study and an overall effect size (±95%CI) for the effect of social learning in comparison to explicit instruction. Note. Larger values of Hedges' g indicate larger effects of social learning relative to the other modes of nocebo induction.

patients will be influenced by social information across a variety of domains, such as medication side effects, and not just pain. Critically, previous research has often overlooked distinctions between types of control conditions. The present outcomes elucidate that the type of control implemented leads to distinct social learning effect sizes. When compared to a no treatment control, social learning produced a medium to large-sized effect. On the other hand, when compared to a neutral modelling control, this effect was small-medium. This is contrary to prior suggestions that exposure to neutral modelling could be protective, whereby observers are informed that the intervention does not lead to the experience of unwanted or negative health outcomes (Tan et al., 2023). This

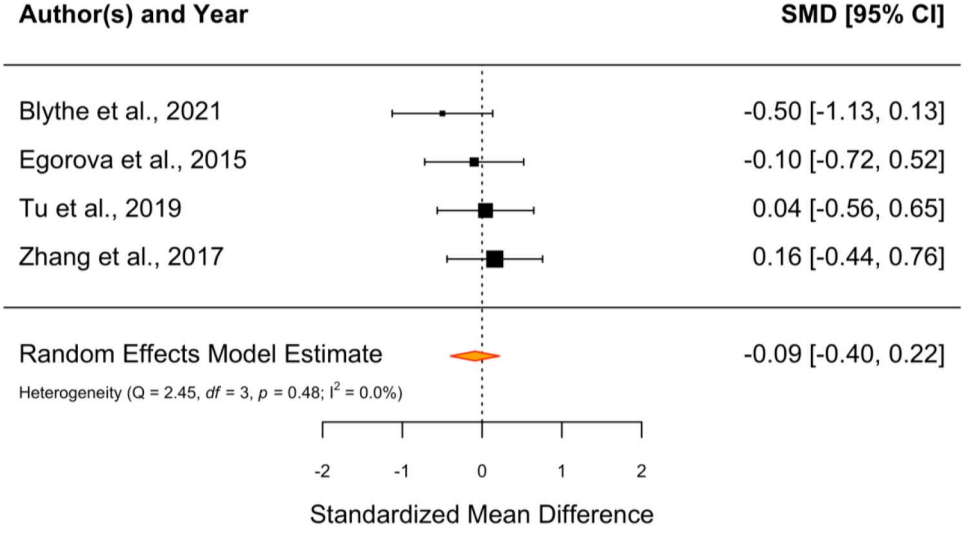

Figure 4. Forest plots displaying Hedges' g (±95%CI) for each included study and an overall effect size (±95%CI) for the effect of social learning in comparison to explicit instruction. Note. Larger values of Hedges' g indicate larger effects of social learning relative to the other modes of nocebo induction.

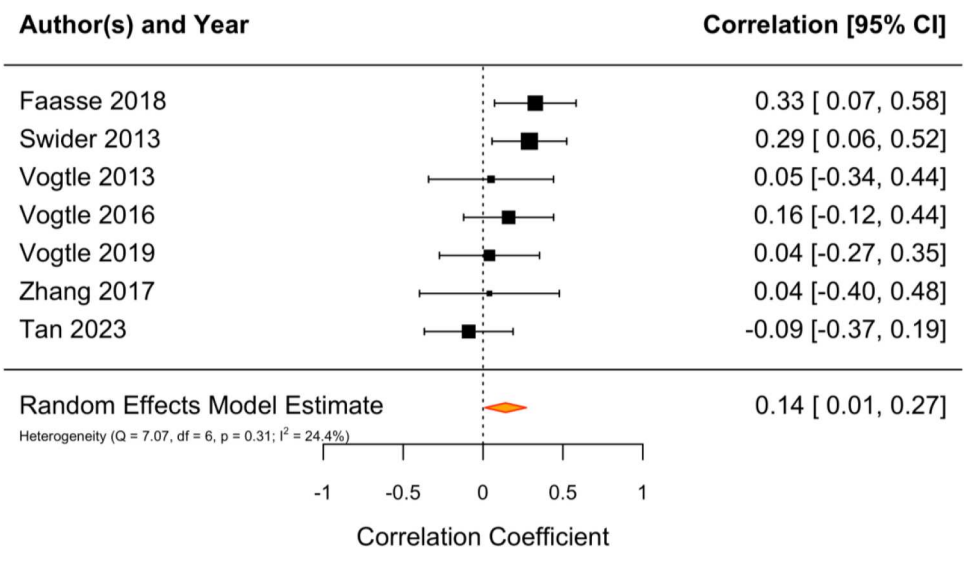

Figure 5. Forest plots displaying Correlation (±95%CI) for each included study and an overall effect size (±95%CI) for the effect of empathy on social learning. Note. Larger values of r indicate larger correlations between empathy and nocebo response.

is an interesting finding in that intuitively it would make sense that modelling the absence of side effects would reduce them, but the results suggest the opposite. One explanation is that modelling the absence of symptoms may highlight the *possibility* of symptoms to the observer, whereas no observation provides no expectation of symptoms at all. This is important because it suggests that in real life scenarios the discussion of either the presence or absence of side effects might both increase the likelihood of side effects. With regards to research, it is crucial to note that the type of control condition studies employ is an important methodological detail to consider.

Though prior research has demonstrated that classical conditioning and explicit instruction have differing effects on the formation of the nocebo effect (Bajcar et al., 2019; Bartels et al., 2014; Bąbel et al., 2017; Colloca, 2014), there has yet to be a comprehensive analysis including social learning comparisons. The present meta-analysis thus employed head-to-head comparisons between social learning and these two other nocebo induction methods. Results indicated that the effect of social learning in inducing nocebo effects was similar in magnitude to classical conditioning and larger than explicit instruction. This implies observing another person's experience can be as influential to health outcomes as our own prior experiences. Moreover, this social learning has a greater influence than explicit instruction. This is of great concern as it suggests the potential for social anecdotal evidence to override information communicated to patients by their health care professionals. Given that it is not feasible to prevent individuals from consuming this social information, further research needs to investigate if the impact of this social information can be minimised in clinical settings. Exposure to experiential information is therefore an important factor that must be considered in healthcare settings.

Moderator analyses highlighted that several individual characteristics and contextual factors modulate the influence of social learning. First, the medium through which a social model is observed is important, with face-to-face modelling producing larger effects than modelling through video. This difference could be attributed to the difficulty in the processing of social cues and non-verbal behaviours (e.g., eye contact) associated with video-based observations (Bohannon et al., 2013; Hietanen et al., 2020). This result is also consistent with the finding that face-to-face and live video interactions prompt stronger social mimicry than pre-recorded video-based observations (Diana et al., 2023), the latter of which was used in seven of the eight included studies utilising video modelling manipulations. As face-to-face modelling elicited greater effects, one might argue that the

experiences we observe in real-world settings are more influential than those observed through video. However, that is not to say that video-based observations are not of importance. The prevalence of the internet and ubiquity of video-based platforms have allowed for interindividual communication and observation to occur on a mass scale, bolstering the ease at which individuals can be socially influenced. For instance, the propagation of tic-like behaviour through video-based modelling has been observed within TikTok communities (Olvera et al., 2021). As such, the large quantity of anecdotal information accessible online may rival the salience of single individual in face-to-face interactions, particularly given that longer exposure leads to stronger nocebo outcomes, though this remains to be investigated.

Surprisingly, studies with higher proportions of female participants and studies in which only female social models could be observed both demonstrated weaker nocebo effects. While unexpected, it is hard to disentangle whether the presence of female observers, the presence of female demonstrators, a match in female gender, or other experimental factors unrelated to gender drove these results. Two studies included in the analysis have reported that a match between female observers and demonstrators increased symptom reporting (relative to other observer/demonstrator configurations) irrespective of whether social modelling occurred (Faasse et al., 2018; Mazzoni et al., 2010). This inflated effect in the no modelling conditions would therefore decrease the effect size associated with modelling itself for female participants. This pattern of results, however, is complicated by other studies that have reported larger social modelling effects in female participants (Quinn et al., 2023). Further, four studies that only included female participant samples also only employed female social models (Blythe et al., 2021; Vögtle et al., 2013; 2016; 2019). These studies had some of the lowest effect sizes, but also shared a common methodology, being conducted within the same laboratory, using a similar design. This complicates interpretation of what is already a varied pattern of results. This ambiguity, however, highlights the need for further systematic investigation into the roles of both observer and model gender. It also appeared that longer modelling manipulations were associated with stronger nocebo outcomes, though this effect was small and should be interpreted with caution as there was a single study with a large effect in which modelling occurred over a twelve-hour period.

Individual differences in empathy may determine whether one understands and applies the experiences of others to their own. There was a small but significant positive association between empathy and nocebo outcomes, indicating that more empathic individuals were more strongly influenced by social modelling. Although there were insufficient studies to investigate moderators of this effect, visual inspection of the Forest plot suggests that the finding was driven primarily by the two studies that employed face-to-face modelling. This is consistent with research indicating that empathy is relevant for face-to-face modelling but not video modelling in placebo paradigms (Hunter et al., 2014) and may explain the finding that face-to-face modelling led to stronger nocebo outcomes than video-based modelling. However, the application of the IRI across the included studies raises questions as its use has not been well-validated, there is no consensus on the factorial structure of empathy (Lima & Osório, 2021), and the personal distress subscale may be more strongly related to negative emotionality than empathy (Murphy et al., 2020). Use of alternative measures such as the Affective and Cognitive Measure of Empathy (ACME;Vachon & Lynam, 2016), which has been used in an existing observational social learning study (Mennitto et al., 2021), should therefore be considered. As such, although the present outcomes suggest that trait empathy plays a small role in socially-induced nocebo effects, the components of trait empathy that contribute to this phenomenon need to be better understood before stronger conclusions can be made. Altogether, the present evidence suggests that the medium and length of social modelling manipulations, the gender of the model and observer, and individual trait empathy moderate the strength of social learning.

Despite several important findings, a number of limitations of the existing literature were also clear. Given the effects of negative expectancies and state anxiety in eliciting the nocebo effect within conditioning and explicit instruction paradigms (Rooney et al., 2022), it has been theorised

that these constructs could also drive socially-induced nocebo effects (Benedetti et al., 2020; Faasse, 2019). Yet, across the literature, only three studies assessed expectancies after social learning and only four measured anxiety. To move beyond theoretical postulations, it is pivotal that measures of expectancies and state anxiety continue to be implemented in future studies, ideally before and after social learning manipulations. Continued implementation of these variables may also elucidate whether their inhibition could be an effective strategy to reduce the occurrence of socially-induced nocebo effects.

Across the included studies, only three designs had participants observe more than one model, with the maximum being two. Whether an individual's expectations and experiences differ based on the number of models observed is an important consideration, particularly given the ease at which anecdotal information spreads through the internet. For example, the exploration of multiple models may help to explain the occurrence of community-level nocebo effects, such as those involving episodes of mass psychogenic illnesses. Mass psychogenic illnesses describe situations in which a population experience physical symptoms that cannot be explained by an observable or medical cause, and are thought to be partially driven by social influence (Bartholomew et al., 2012). Relatedly, whether an individual is influenced by a social model may depend on the interpersonal dynamics between the model and observer. While preliminary research has been conducted on factors such as observers' perceptions of model social status and self-confidence in placebo paradigms (Bajcar et al., 2020; Bieniek & Bąbel, 2022; Brączyk & Bąbel, 2021), these and similar factors, such as warmth and competence, which has attenuated nocebo outcomes in a clinician-patient paradigm (Barnes et al., 2023), have not been investigated in nocebo social modelling contexts.

Regarding social modelling manipulations, it is apparent that some include a form of explicit instruction, making it difficult to isolate the effect of social learning. In one instance, before the observation of a social model, participants were informed that the stimulus was associated with multiple symptoms (Lorber et al., 2007). On the other hand, the provision of risk warnings associated with treatment, such as the potential for side effects, is a cornerstone of individual autonomy in the informed consent process (Gelfand, 2020). As such, these scenarios may in fact better represent clinical settings and thereby demonstrate greater ecological validity. Relatedly, however, no studies with clinical samples were eligible for review, making it difficult to determine if these outcomes do in fact translate to clinical settings.

As mentioned, future research should carefully consider the type of control implemented and how that influences the interpretations that can be drawn regarding the effects of social learning. We posit that comparisons between negative social modelling and no modelling conditions indicate whether social modelling can elicit a nocebo effect. On the other hand, comparisons with neutral modelling may be instead asking how the valence of social modelling affects nocebo outcomes. Neutral modelling therefore highlights to the observer that there is a potential for symptoms to occur but that the model did not experience symptoms themselves. In turn, the observer recognises that there is potential for them to experience symptoms even if the model did not. As such, both types of control conditions have theoretical significance, but researchers need to be explicitly aware of this distinction. It is also clear from the included studies that social modelling in nocebo contexts has only been investigated dichotomously (i.e., negative versus none, or negative versus neutral). If we extend this dichotomy to re-conceptualise that the severity of social modelling may exist on a continuum, the severity of symptoms communicated could correspond with the strength of the nocebo effect elicited. Furthermore, this relationship may not be linear, whereby extremely severe experiences have a disproportionate effect on observers.

Unfortunately, the level of detail provided on social learning manipulations in the existing literature has been relatively inconsistent and vague. As a result, conclusions that could be made with respect to further moderating factors are limited. For instance, two studies may report that their respective social models verbally stated the experience of dizziness and headache to observing participants. However, the tone, duration, and severity of such modelling, and the characteristics of the models themselves, may be substantially different. Furthermore, this raises questions regarding the

'visibility' of the model's symptom severity. Intuitively, more visible physical symptoms (e.g., pain) could be more susceptible to socially induced nocebo effects. While the present study lacked the data to explore this question, it would be prudent for future research to investigate. It would therefore be beneficial for future studies to provide thorough and transparent descriptions of their social learning manipulations or added these to open repositories that could be analysed. Beyond assisting in the determination of social learning elements that most actively contribute to nocebo effects, it would aid in the replication of experimental outcomes. We recommend that design elements are outlined explicitly in text, and ideally, accompanied by a video or transcript of the social interaction on an open data repository such as Open Science Framework. This recommended list of factors is as follows:

(1) the characteristics of the social model including their gender, age, ethnicity, and perceived status (e.g., whether the model is presented as another student, a stranger, or as someone known to the experimenter);
(2) details regarding the interaction with participants (e.g., duration of the contact between participant/model which could influence rapport, and duration of the symptom modelling itself); and
(3) information regarding how the content of the modelling is presented (e.g., whether participants learn through a model's verbal reports, observable behaviours, or other means).

The requested provisions would enable researchers to understand whether there are verbal and behavioural intricacies otherwise missed when only a brief description of the modelling is provided. In addition, studies should pre-register their designs and data analysis plans, as most of the included studies did not, thereby increasing the risk of bias.

The present systematic review and meta-analysis elucidates the key role social learning plays in the development of nocebo effects. The first novel finding demonstrates that social learning has a medium-sized effect on inducing nocebo effects across multiple health outcomes. To the best of our knowledge, it is also the first to directly compare the influence of social learning to the other modes of nocebo induction. Results suggest that social learning has substantial influence on the formation of nocebo effects, with the magnitude of such effects being comparable to classical conditioning and larger than explicit instruction. Analysis of contextual factors showed that face-to-face modelling and longer modelling manipulations elicited stronger nocebo effects, and that individual characteristics, such as the gender of observers and models, as well as the observer's trait empathy, modulate social learning. However, awareness of how design elements, such as the type of control condition implemented, need to be carefully considered by future studies. It is argued that implementations of neutral modelling conditions, where the control is allocated to observe a model experiencing an absence of symptoms, explore the effect of social modelling valence, whereas comparisons with no observation controls indicate whether the nocebo effect can be socially induced. As such, these questions may have differing theoretical and practical implications. Continued measurement and reporting of psychosocial variables, particularly in relation to negative expectations and anxiety, is also critical to understand the underlying mechanisms driving socially-induced nocebo effects. Given the reliable effect of social learning on nocebo effects and the availability of models, particularly online, a key priority for future research is to identify ways to mitigate these effects to reduce the substantial personal and societal harm nocebo effects cause.

Notes

1. Due to the random effect of study included in the original model, the trim and fill method was not able to be applied. Therefore, the trim and fill method was applied to a reduced model without this random effect to generate an approximate adjusted effect size.

2. In one case (Lorber et al., 2007), an estimate of 21–22 participants per group was reported. A request for clarification of group sample sizes was not responded to, and as such, the midpoint of 21.5 participants was used for each group.

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Data availability statement

Accessible at https://osf.io/9avbk/

CRediT authors' contributions

Cosette Saunders – conceptualisation, methodology, formal analysis, investigation, data curation, writing – original draft, writing – review & editing, visualisation, project administration.

Winston Tan – conceptualisation, methodology, formal analysis, investigation, data curation, writing – original draft, writing – review & editing, visualisation, project administration.

Kate Faasse – conceptualisation, methodology, writing – review & editing, supervision, funding acquisition.

Ben Colagiuri – conceptualisation, validation, methodology, writing – review & editing, supervision, funding acquisition.

Louise Sharpe – conceptualisation, writing – review & editing.

Kirsten Barnes – conceptualisation, validation, methodology, writing – review & editing, supervision.

ORCID

Cosette Saunders http://orcid.org/0000-0002-2702-9044
Winston Tan http://orcid.org/0000-0003-4821-7877
Kate Faasse http://orcid.org/0000-0003-3073-3718
Ben Colagiuri http://orcid.org/0000-0003-2157-2641
Louise Sharpe http://orcid.org/0000-0002-8790-6272
Kirsten Barnes http://orcid.org/0000-0001-8328-3998

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Publication Supplementary Materials

Supplementary Material 1. Search Strategy

Studies will be identified by searching the following databases: PubMed, PsycINFO, Web of Science, Embase, CINAHL, Scopus. Search terms will include two concept blocks:

1. (i) Nocebo effect:

   “nocebo” OR "negative placebo" OR “placebo side effect*” OR "psychogenic symptom*" OR "sociogenic symptom*" OR "psychogenic illness" OR "sociogenic illness" in all fields including references

   AND

2. (ii) Social learning:

   “social” OR “video” OR “model*” OR “demonstrat*” OR “observ*” OR "vicarious” in title abstract keywords/headings

Search strategy regarding concept block (i) was informed by the recent nocebo meta-analysis (Rooney et al., 2022)

Supplementary Material 2. References for included studies.

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Tu, Y., Park, J., Ahlfors, S. P., Khan, S., Egorova, N., Lang, C., Cao, J., & Kong, J. (2019). A neural mechanism of direct and observational conditioning for placebo and nocebo responses. *Neuroimage*, 184, 954-963. https://doi.org/10.1016/j.neuroimage.2018.10.020

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Witthöft, M., & Rubin, G. J. (2013). Are media warnings about the adverse health effects of modern life self-fulfilling? An experimental study on idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF). *J Psychosom Res*, *74*(3), 206-212. https://doi.org/10.1016/j.jpsychores.2012.12.002

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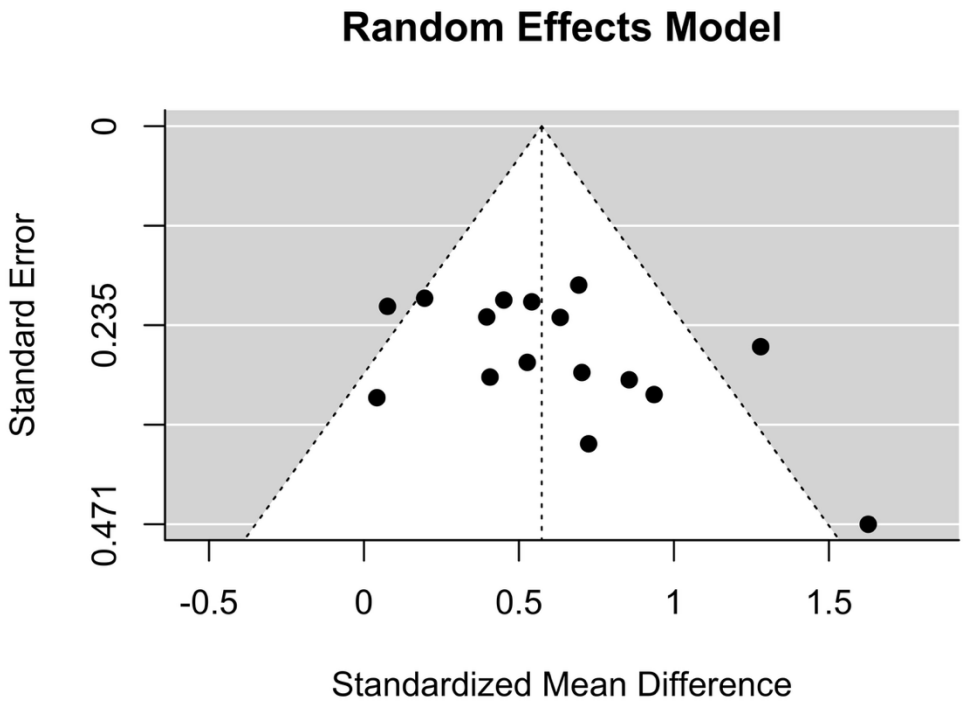
Supplementary Material 3. Figure 1 *RQ1: Funnel Plot*



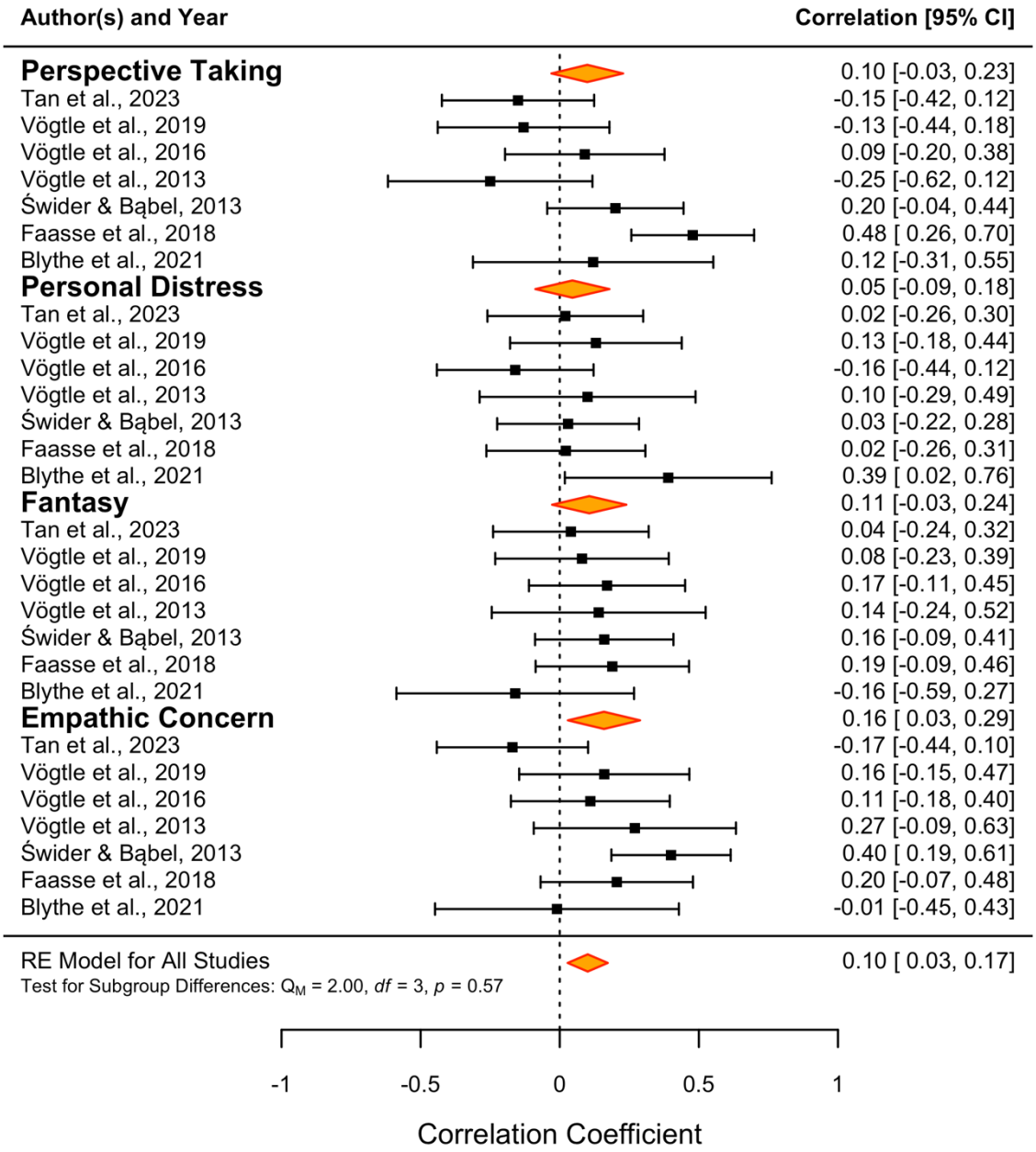
Supplementary Material 4. Empathy analysis at subscale level

Six studies reported correlations between empathy and social learning resulting in a total sample of 271 participants. The overall pooled effect size for the correlation between the nocebo effect elicited via social learning and empathy was statistically significant, but small (r = 0.10; 95%CI [0.03, 0.17]; $p < .001$). The type of IRI subscale did not significantly moderate this effect (Q_M = 2.00, df = 3, p = .57).

Figure 2

Forest plot at subscale level

Forest plots displaying Correlation (+/- 95%CI) for each included study and an overall effect size (+/- 95%CI) for the effect of empathy on social learning.



Note. Larger values of r indicate larger correlations between empathy and nocebo response

Appendix B: Supplementary Material, Chapter 3

Study Approval Letter

THE UNIVERSITY OF SYDNEY

Research Integrity & Ethics Administration
HUMAN RESEARCH ETHICS COMMITTEE

Thursday, 27 May 2021

Dr Kirsten Barnes
Psychology; Faculty of Science
Email: kirsten.barnes@sydney.edu.au

Dear Kirsten,

The University of Sydney Human Research Ethics Committee (HREC) has considered your application.

I am pleased to inform you that after consideration of your response, your project has been approved.

Details of the approval are as follows:

Project No.:	**2021/301**
Project Title:	**Moderating expectancy induced nausea**
Authorised Personnel:	**Barnes Kirsten; Colagiuri Ben; Leung Gavin; Saunders Cosette; Tan Winston; Xu Helen;**
Approval Period:	**27 May 2021** to **27 May 2025**
First Annual Report Due:	**27 May 2022**

Documents Approved:

Date Uploaded	Version Number	Document Name
26/05/2021	Version 1	Project Protocol
26/05/2021	Version 1	New Debrief (Study 5)
26/05/2021	Version 1	Consent form (PILOT STUDY)
26/05/2021	Version 1	PIS (PILOT STUDY)
26/05/2021	Version 1	Other questionnaire measures (secondary predictors)
26/05/2021	Version 1	SONA Advert (PILOT STUDY)
26/05/2021	Version 1	New Debrief (Study 1)
26/05/2021	Version 1	New Debrief (Study 2)
26/05/2021	Version 1	New Debrief (Study 3)
26/05/2021	Version 1	New Debrief (Study 4)
26/05/2021	Version 1	New Debrief (Study 6)
26/05/2021	Version 2	Consent form (all studies, excluding Pilot)
26/05/2021	Version 2	PIS Primary Outcome
26/05/2021	Version 2	PIS No Warning Condition
26/05/2021	Version 1	Debrief (PILOT STUDY)
26/05/2021	Version 2	PIS Side Effect Condition
26/05/2021	Version 1	SSQ (Primary Outcome Measure)
12/04/2021	Version 1	Advert_Image
12/04/2021	Version 1	Participant Info - Studies1-3 Side Effect Condition
12/04/2021	Version 1	SONA Psych Advert
12/04/2021	Version 1	General Advert
12/04/2021	Version 1	Participant Info - Studies1-3: Primary Outcome Condition
12/04/2021	Version 1	Participant Info - Studies 1-2(Control) & Studies 4-6(All)

Special Condition/s of Approval

1. It is a condition of your approval that the following points be corrected in your study documentation:
   - Please check the page numbers on footers of all PIS (they currently show page x of 2 when they are 3 pages in length).
   - Check VR study Primary Outcome PIS section 1 line 3 for typo 'form or motion'

Research Integrity & Ethics Administration
Research Portfolio
Level 3, F23 Administration Building
The University of Sydney
NSW 2006 Australia

T +61 2 9036 9161
E human.ethics@sydney.edu.au
W sydney.edu.au/ethics

ABN 15 211 513 464
CRICOS 00026A

THE UNIVERSITY OF SYDNEY

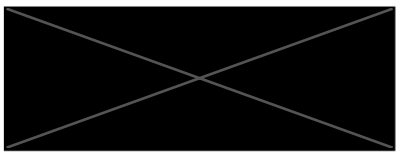
Condition/s of Approval

- Research must be conducted according to the approved proposal.
- An annual progress report must be submitted to the Ethics Office on or before the anniversary of approval and on completion of the project.
- You must report as soon as practicable anything that might warrant review of ethical approval of the project including:
  - Serious or unexpected adverse events (which should be reported within 72 hours).
  - Unforeseen events that might affect continued ethical acceptability of the project.
- Any changes to the proposal must be approved prior to their implementation (except where an amendment is undertaken to eliminate *immediate* risk to participants).
- Personnel working on this project must be sufficiently qualified by education, training and experience for their role, or adequately supervised. Changes to personnel must be reported and approved.
- Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, as relevant to this project.
- Data and primary materials must be retained and stored in accordance with the relevant legislation and University guidelines.
- Ethics approval is dependent upon ongoing compliance of the research with the *National Statement on Ethical Conduct in Human Research*, the *Australian Code for the Responsible Conduct of Research*, applicable legal requirements, and with University policies, procedures and governance requirements.
- The Ethics Office may conduct audits on approved projects.
- The Chief Investigator has ultimate responsibility for the conduct of the research and is responsible for ensuring all others involved will conduct the research in accordance with the above.

This letter constitutes ethical approval only.

Please contact the Ethics Office should you require further information or clarification.

Sincerely,



Dr Haryana Dillon
Chair
Human Research Ethics Committee (HREC 3)

The University of Sydney of Sydney HRECs are constituted and operate in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2018) and the NHMRC's Australian Code for the Responsible Conduct of Research (2018)

Pre-registration

ASPREDICTED

Wharton CREDIBILITY LAB
UNIVERSITY of PENNSYLVANIA

Does choice reduce nocebo cybersickness elicited via social modelling? (#68104)

Author(s)
This pre-registration is currently anonymous to enable blind peer-review.
It has 3 authors.

Pre-registered on: 2021/06/09 - 09:45 PM (PT)

1) Have any data been collected for this study already?
No, no data have been collected for this study yet.

2) What's the main question being asked or hypothesis being tested in this study?
1. Can the social transmission of Virtual Reality (VR) induced cybersickness be elicited even when observing a social model describe symptoms in a different VR environment? Our previous research (AsPredicted #43055) has shown that, relative to no social modelling (i.e., control), social modelling increases symptoms of cybersickness (a type of nocebo effect). We hypothesise that this socially-transmitted cybersickness will generalise across VR environments, occurring even when participants believe they are viewing a model experience symptoms in a VR environment different to their own.

2. Does choice reduce nocebo cybersickness elicited via social modelling? Based on the results of Bartley, Faasse, Horne, and Petrie (2016), we expect that those participants who have a choice over their VR environment will report lower levels of cybersickness.

3) Describe the key dependent variable(s) specifying how they will be measured.
Cybersickness Severity, measured via the Simulator Sickness Questionnaire (SSQ: Kennedy, Lane, Berbaum, & Lilienthal, 1993). Cybersickness will be measured pre and post VR exposure using the 16 item SSQ. As three symptoms from the SSQ (general discomfort, nausea and stomach awareness) are modelled by the confederate, the primary outcome will be based on the sum of these three target items. Secondary analysis will involve the full sum-scored scale and the nausea subscale of the SSQ.

4) How many and which conditions will participants be assigned to?
Participants will be stratified by gender and assigned in quasi-random order to one of six conditions within a factorial 3 (Observational Learning: Observational Learning (Consistent); Observational Learning (Inconsistent); No Observational Learning) x 2 (Choice: Choice; No Choice) design. Participants in the No Choice conditions will be yoked to the previous participants of their gender within the same Observational Learning condition they are assigned to. Participants in the observational learning conditions will watch a social model (actually pre-recorded video footage of one of the experimenters) experience symptoms of cybersickness in either the same (Consistent) or a different (Inconsistent) VR environment before experiencing the VR themselves. Participants in the No Observational Learning condition will not view a social model prior to their VR experience. Participants in the choice condition will choose the VR environment they would like to experience.

5) Specify exactly which analyses you will conduct to examine the main question/hypothesis.
ANCOVA will be employed to analyse the data, controlling for gender (previously found to vary with the strength of social modelling effects: Świder & Bąbel, 2013) using the difference score of the target SSQ items as the dependent variable. Orthogonal contrasts will be used to compare groups that receive social information (Observational Learning: Consistent and Inconsistent) vs. control (No Observational Learning), and Observational Learning Consistent vs. Inconsistent. Choice and No Choice groups, and interactions with Social Learning, will be compared.

Secondary predictor variables are: expectancy regarding symptoms (single-item), VR-specific anxiety (single-item), general anxiety (STAI-6 – Marteua & Bekker, 1992), and sense of control (Self-Assessment Mannikin AM – Bradley & Lang, 1994). Expectancy, anxiety (both VR specific and general) and control will be investigated as potential mediators of significant group differences in nocebo symptoms while controlling for pre-VR cybersickness and gender. This will involve separate linear regressions with relevant difference scores as the outcome variable and each respective secondary measure as the predictor, controlling for gender. Where significant associations exist, mediation analysis will be conducted. This is consistent with our previous research (As Predicted #43055). To extend these analyses, whether a sense of control drives changes in expectancy/anxiety will be explored using a three-path mediation model (IV->Mediator1(M1)->Mediator2(M2)->DV). We will test whether, among the choice vs. no choice groups (IV) the extent to which the participant feels in control (M1) predicts the effect of expectancy (or VR anxiety) (M2) on baseline adjusted cybersickness (DV).

6) Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.
Participants should be in full health at time of testing. Those with extreme pre-VR cybersickness (3 SD above the mean) will be excluded from analyses.

7) How many observations will be collected or what will determine sample size? No need to justify decision, but be precise about exactly how the number will be determined.
We will stop testing once we have collected data from 132 participants (22 participants in each condition) or until September 6th, 2021.

8) Anything else you would like to pre-register? (e.g., secondary analyses, variables collected for exploratory purposes, unusual analyses planned?)
Secondary Analysis: The side effects participants model (or verbalise) to subsequent participants will be recorded and coded. Coding of side effects will be

based on the items of the SSQ and related synonyms (generated through pilot testing). This data may be used to determine how side effects (modelled by the 'actor' vs. not modelled) change across the generations of participants in subsequent analyses.

ASPREDICTED

Wharton CREDIBILITY LAB
UNIVERSITY of PENNSYLVANIA

Does choice reduce nocebo cybersickness elicited via social modelling? (#103304)

Author(s)
This pre-registration is currently anonymous to enable blind peer-review.
It has 3 authors.

Pre-registered on: 2022/07/26 - 01:57 AM (PT)

1) Have any data been collected for this study already?
No, no data have been collected for this study yet.

2) What's the main question being asked or hypothesis being tested in this study?
The present study aims to replicate the results of a previous pre-registered study (AsPredicted #68104).
Our previous research (AsPredicted #43055, #68104) has shown that, relative to no social modelling (i.e., control), social modelling increases symptoms of cybersickness (a type of nocebo effect).
We additionally tested whether this socially-transmitted cybersickness generalised across VR environments and could be attenuated by choice over VR experience (see: #68104). Cybersickness was exacerbated when participants believed they were viewing another individual experience symptoms in a VR environment that was different to their own, while choice attenuated cybersickness but only in this inconsistent VR environment. A secondary study aimed to replicate this unanticipated patten of results, but instead found that the level of cybersickness elicited was similar, regardless of what VR activity the participant believed the other individual experienced. Therefore, it is unclear if generalisation exacerbates nocebo cybersickness and if choice can influence socially induced nocebo cybersickness, which the present study aims to clarify.

3) Describe the key dependent variable(s) specifying how they will be measured.
Cybersickness Severity: measured via the Simulator Sickness Questionnaire (SSQ: Kennedy, Lane, Berbaum, & Lilienthal, 1993). Cybersickness will be measured pre and post VR exposure using the 16 item SSQ. As three symptoms from the SSQ (general discomfort, nausea and stomach awareness) are modelled by the confederate, the primary outcome will be based on the sum of these three target items. Secondary analysis will involve the full sum-scored scale.

4) How many and which conditions will participants be assigned to?
Participants will be stratified by gender and assigned in quasi-random order to one of four conditions within a factorial 2 (Social Modelling: Social Modelling (Consistent); Social Modelling (Inconsistent)) x 2 (Choice: Choice; No Choice) design.
Participants in the No Choice conditions will be yoked to the previous participants of their gender within the same Social Modelling condition they are assigned to. Participants in the Social Modelling conditions will watch a social model (actually pre-recorded video footage of one of the experimenters) experience symptoms of cybersickness in either the same (Consistent) or a different (Inconsistent) VR environment before experiencing the VR themselves. Participants in the choice condition will choose the VR environment they would like to experience.

5) Specify exactly which analyses you will conduct to examine the main question/hypothesis.
ANCOVA will be employed to analyse the data, controlling for gender (previously found to vary with the strength of social modelling effects: Świder & Bąbel, 2013) using the difference score of the target SSQ items as the dependent variable.
Secondary analyses will be consistent with #68104

6) Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.
Participants should be in full health at time of testing. Those with extreme pre-VR cybersickness, scoring 8 or above on any single item on the SSQ or with a sum score SSQ higher than 40 will be excluded from analyses.

7) How many observations will be collected or what will determine sample size? No need to justify decision, but be precise about exactly how the number will be determined.
31 participants per group (124 participants total), powered to detect an effect of partial eta squared =.06, with alpha = .05 with .8 power. The effect size is derived from the interaction effect observed in #68104.

8) Anything else you would like to pre-register? (e.g., secondary analyses, variables collected for exploratory purposes, unusual analyses planned?)
Secondary variables are: expectancy regarding symptoms (single-item), VR-specific anxiety (single-item), general anxiety (STAI-6 – Marteua & Bekker, 1992), and sense of control (single-item, Tang et al., 2019).
Data from the present study, AsPredicted #68104, and additional data collected in the lab, will be combined for a final pooled analysis consisting of Traditional and Bayesian ANCOVA (default prior, Cauchy width .707). SSQ, state anxiety and expectancy will be explored as outcome variables. This will be consistent with the design outlined above and in #68104
Exploratory variables: Participants will be asked 1) how positive an experience they perceived the social model to have had; 2) to what extent their perceived the social model to have experienced cybersickness; 3) how similar they perceived their own experience to have been relative to that of the social model. The relationship between these variables and cybersickness will be explored.

Questionnaires/Instruments

Start of Block: Participant ID

PID
Please ensure you are completing this survey on a computer, laptop or other non-mobile device.

You will now be asked to answer a few questionnaires. Your answers are confidential, so try to answer as truthfully as possible.
Please enter your Participant ID.

_____

Q113 Please enter the email address that you used to sign up for the study so that we can match your data. This email address will be deleted as soon as you have done so.

_____

End of Block: Participant ID

Start of Block: Baseline SSQ

Q83 An ethical requirement of this study involves monitoring your wellbeing throughout this experiment. As such you will be required to answer some questions regarding physical symptoms and sensations at various stages of the experiment.

Click next to begin the survey.

Page Break

Q1 You will now be asked about your current experiences of a range of physical symptoms and sensations. Please think carefully about each symptom and ask the experimenter if you are unsure about the meaning of any of the words. *How much are you experiencing each of the following sensations or symptoms currently?*

BSSQ_1 General discomfort Not at all Slightly Moderately Strongly Severely

- 0 (12)
- 1 (2)
- 2 (13)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (14)
- 10 (15)

BSSQ_2 Fatigue Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_3 Headache Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_4 Eye strain Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_5 Difficulty focusing Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_6 Salivation increasing Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_Fake Choose option 2 for this question. Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_7 Sweating Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_8 Nausea Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_9 Difficulty concentrating Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_10 Fullness of the head Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_11 Blurred vision Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_12 Dizziness with eyes open Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_13 Dizziness with eyes closed Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_14 Vertigo * *Vertigo is experienced as feeling off balance.* Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_15 Stomach awareness * *Stomach awareness is a feeling of discomfort which is just short of nausea.* Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BSSQ_16 Burping Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

End of Block: Baseline SSQ

Start of Block: Baseline STAI-6

Description A number of statements which people have used to describe themselves are given in the next few questions. Read each statement and choose the most appropriate answer below the statement to indicate **how you feel right now, at this moment.** There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

BSTAI_1 I feel calm

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_2 I am tense

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_3 I feel upset

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_4 I am relaxed

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_5 I feel content

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_6 I am worried

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

End of Block: Baseline STAI-6

Start of Block: Baseline Expectancy and VR Specific Anxiety

Q58 Read each statement and choose the most appropriate number below the statement to indicate how you feel right now, at this moment.

Q88 To what extent do you expect the Virtual Reality experience to feel real?

Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BE How much do you expect to experience feelings of cybersickness (e.g., nausea, general discomfort, sweating) during the Virtual Reality video?

Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

Q90 How much do you believe immersive Virtual Reality experiences can contribute to online learning? Not at all Slightly Moderately Strongly Extremely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

BVRA How anxious do you feel about experiencing the Virtual Reality video? Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

End of Block: Baseline Expectancy and VR Specific Anxiety

Start of Block: Progress Stop 1 (Main Room)

Q173 Please return to Zoom, unmute your microphone and webcam, and await further instructions.

Continue to the next page when instructed to.

End of Block: Progress Stop 1 (Main Room)

Start of Block: Progress Stop 1.2 (IN MAIN ROOM)

Q60
To proceed to the next survey, enter the code provided by the Experimenter.

End of Block: Progress Stop 1.2 (IN MAIN ROOM)

Start of Block: Choice (PID 1###)

Q92 You will now be allowed to choose the VR environment that you would like to experience.

choice_env Please select the environment you would like to experience:

- Sunny Day: A bright sunny afternoon overlooking green fields. (4)
- Snowy Day: A cloudy winter afternoon, with light powdery snow surrounding you. (2)

End of Block: Choice (PID 1###)

Start of Block: No Choice (PID 2###)

Q100 You will now be allowed to review two VR environments. You will be randomly assigned to experience one of the two options below:

no_choice_env Please select the environment you were assigned to experience:

- Sunny Day: A bright sunny afternoon overlooking green fields. (4)
- Snowy Day: A cloudy winter afternoon, with light powdery snow surrounding you. (2)

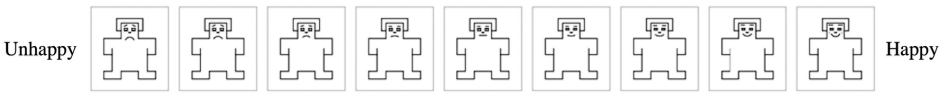
End of Block: No Choice (PID 2###)

Start of Block: Self Assessment Manikin

Q89 Read each scale below and click on the most appropriate picture that represents **how you feel right now, at this moment.**

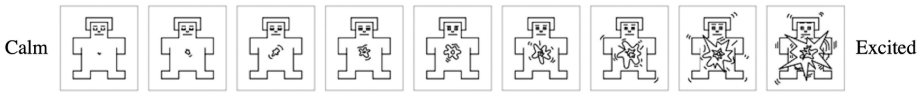
manikin_happy

	Off (1)	On (2)
1 (7)		
2 (8)		
3 (9)		
4 (10)		
5 (11)		
6 (12)		
7 (13)		
8 (14)		
9 (16)		



manikin_calm

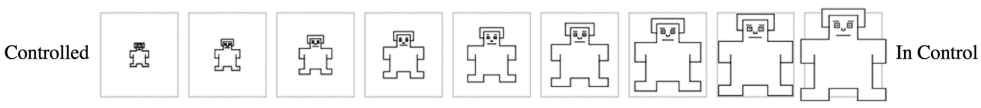
	Off (1)	On (2)
1 (7)		
2 (8)		
3 (9)		
4 (10)		
5 (11)		
6 (12)		
7 (13)		
8 (14)		
9 (16)		



*

manikin_control

	Off (1)	On (2)
1 (7)		
2 (8)		
3 (9)		
4 (10)		
5 (11)		
6 (12)		
7 (13)		
8 (14)		
9 (16)		



End of Block: Self Assessment Manikin

Start of Block: Distractor Task Control Condition only

Q125 Please attempt the following spatial ability questions. If you are unsure of any answers, feel free to answer "Unsure"

Distractor q1 Which figure is identical to the first?

- A (1)
- B (2)
- C (3)
- D (4)
- Unsure (5)

Distractor q2 Which figure is identical to the first?

- A (1)
- B (2)
- C (3)
- D (4)
- Unsure (5)

Distractor q3 How many blocks make up the shape below?

- A (1)
- B (2)
- C (3)
- D (4)
- E (5)
- Unsure (6)

Q118 Which group of shapes can be assembled to make the shape shown?

- A (1)
- B (2)
- C (3)
- D (4)
- Unsure (5)

Q122 Which group of shapes can be assembled to make the shape shown?

- A (1)
- B (2)
- C (3)
- D (4)
- Unsure (5)

Q126 Which box is missing from the picture?

- A (1)
- B (2)
- C (3)
- Unsure (4)

End of Block: Distractor Task Control Condition only

Start of Block: Confirm Choice (Choice Condition Only)

Display this question:

If If Please ensure you are completing this survey on a computer, laptop or other non-mobile device. Yo... Text Response Is Less Than 2000

Q115 Please confirm your choice by sending either "Snowy" or "Sunny" to the experimenter's account via the zoom chat.

End of Block: Confirm Choice (Choice Condition Only)

Start of Block: Progress Stop 2 (IN MAIN ROOM)

Q96
Please return to Zoom, unmute your microphone and webcam, and await further instructions.

Continue to the next page when instructed to.

End of Block: Progress Stop 2 (IN MAIN ROOM)

Start of Block: Progress Stop 2.2 (IN MAIN ROOM)

Q174
To proceed to the next survey, enter the code provided by the Experimenter.

_____

End of Block: Progress Stop 2.2 (IN MAIN ROOM)

Start of Block: Pre-Modelling STAI-6

Q62 A number of statements which people have used to describe themselves are given in the next few questions. Read each statement and choose the most appropriate answer below the statement to indicate how you feel right now, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

PSTAI_1 I feel calm
- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

PSTAI_2 I am tense
- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

PSTAI_3 I feel upset
- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

PSTAI_4 I am relaxed
- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

PSTAI_5 I feel content

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

PSTAI_6 I am worried

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

End of Block: Pre-Modelling STAI-6

Start of Block: Pre-Modelling Expectancy and VR specific anxiety

Q76 Read each statement and choose the most appropriate number below the statement to indicate how you feel right now, at this moment.

Q78 To what extent do you expect the Virtual Reality experience to feel real? Not at all Slightly Moderately Strongly Extremely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

PE How much do you expect to experience feelings of cybersickness (e.g., nausea, general discomfort, stomach awareness) during the Virtual Reality video?

Not at all Slightly

Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

Q82 How much do you believe immersive Virtual Reality experiences can contribute to online learning? Not at all Slightly Moderately Strongly Extremely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

PVRA How anxious do you feel about experiencing the Virtual Reality video?

Not at all Slightly
Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

End of Block: Pre-Modelling Expectancy and VR specific anxiety

Start of Block: Progress Stop 3 (IN MAIN ROOM)

Q72
Please return to Zoom, unmute your microphone and webcam, and await further instructions. Continue to the next page when instructed to.

End of Block: Progress Stop 3 (IN MAIN ROOM)

Start of Block: Progress Stop 3.2 (IN BREAKOUT ROOM)

Q125
To proceed to the next survey, enter the code provided by the Experimenter.

End of Block: Progress Stop 3.2 (IN BREAKOUT ROOM)

Start of Block: Post-Modelling SSQ

Q107 You will now be asked about your current experiences of a range of physical symptoms and sensations. Please think carefully about each symptom and ask the experimenter if you are unsure about the meaning of any of the words. *How much are you experiencing each of the following sensations or symptoms currently?*

		Not at all	Slightly	Moderately	Strongly	Severely
ASSQ_1	General discomfort	• 0 (12) • 1 (2) • 2 (13) • 3 (4) • 4 (5) • 5 (6) • 6 (7) • 7 (8) • 8 (9) • 9 (14) • 10 (15)				

ASSQ_2 Fatigue Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_3 Headache Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_4 Eye strain Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_5 Difficulty focusing Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_6 Salivation increasing Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_FAKE Choose option 2 for this question. Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_7 Sweating Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_8 Nausea Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_9 Difficulty concentrating Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_10 Fullness of the head Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_11 Blurred vision Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_12 Dizziness with eyes open Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_13 Dizziness with eyes closed Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_14 Vertigo * *Vertigo is experienced as feeling off balance.* Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_15 Stomach awareness * *Stomach awareness is a feeling of discomfort which is just short of nausea.* Not at all Slightly Moderately Strongly Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

ASSQ_16	Burping	Not at all	Slightly	Moderately	Strongly	Severely

- 0 (1)
- 1 (2)
- 2 (3)
- 3 (4)
- 4 (5)
- 5 (6)
- 6 (7)
- 7 (8)
- 8 (9)
- 9 (10)
- 10 (11)

End of Block: Post-Modelling SSQ

Start of Block: Memory Questions

Q74 How would you describe the environment around you in the video?

- A rainforest (2)
- A beach (4)
- A forest (5)
- A desert (7)

Q75 Was there a lake present in the video?

- Yes (1)
- No (4)

Q76 What was the weather like?

- Blue sky with no clouds (1)
- Blue sky with clouds (2)
- Snowy with clouds (3)
- Snowy with no clouds (4)

Q77 Roughly what time of day was it?

- Early morning (1)
- Midday (2)
- Evening (3)
- Midnight (5)

Q111 What activity did you experience?

- Aerobatics (stunt flying) (1)
- Rollercoaster (2)
- Rocket Race (3)
- Motorcycling (4)

End of Block: Memory Questions

Start of Block: Progress Stop 4 (IN BREAKOUT ROOM)

Q73 Please return to Zoom, unmute your microphone and webcam, and await further instructions.

Continue to the next page when instructed to.

End of Block: Progress Stop 4 (IN BREAKOUT ROOM)

Start of Block: Progress Stop 4.2 (IN MAIN ROOM)

Q127
To proceed to the next survey, enter the code provided by the Experimenter.

_____

End of Block: Progress Stop 4.2 (IN MAIN ROOM)

Start of Block: Manipulation Check

Q96 Briefly describe (1-2 sentences) what you thought the purpose of this experiment was:

_____

End of Block: Manipulation Check

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Regular Article

Socially Acquired Nocebo Effects Generalize but Are Not Attenuated by Choice

Cosette Saunders, BSci (Hons)[1] · Ben Colagiuri, PhD[1] · Kirsten Barnes, PhD[2]

[1]School of Psychology, University of Sydney, Sydney, Australia
[2]School of Psychology, University of New South Wales, Sydney, Australia

Cosette Saunders
cosette.saunders@sydney.edu.au

Abstract

Background Socially observing a negative treatment-related experience has been shown to modulate our own experience with the same intervention, leading to worsened health outcomes. However, whether this social learning generalizes to similar but distinct interventions has not been explored nor what manipulations can reduce these effects.

Purpose To determine whether socially acquired nocebo effects can be generated by observing a negative experience with a similar, but distinct intervention, and whether choice can reduce these effects.

Methods Across three experiments, a community sample of healthy adults (N = 336) either watched a confederate report cybersickness to the same Virtual Reality (VR) activity they were assigned to (Social Modeling: Consistent); a similar, but different VR activity (Social Modeling: Inconsistent); or did not view the confederate (No Social Modeling). Participants were either given choice over the VR (Choice) or assigned by the experimenter (No Choice).

Results Across the experiments, there was significantly greater cybersickness in both Social Modeling groups relative to No Social Modeling, while the two Social Modeling groups did not differ. There was no significant effect of Choice or a Choice by Social Modeling interaction. Social Modeling elicited greater anxiety and expectancies for cybersickness. Furthermore, these mechanisms mediated the association between social modeling and cybersickness.

Conclusions Socially acquired side-effects were demonstrated to generalize to similar, but distinct interventions, highlighting the diffuse and robust effect social modeling can have on our experiences. However, choice did not attenuate the experience of cybersickness, highlighting the need for alternative methods to counteract the effect of social modeling.

Lay summary

Witnessing someone experience cybersickness during Virtual Reality (VR) generated a nocebo effect in the observer, exacerbating their own symptoms when subsequently encountering VR. The nocebo effect was not specific to the VR activity witnessed, but generalized across different VR experiences, demonstrating that socially acquired nocebo effects are likely to spread rapidly. Choice of VR environment did not reduce the nocebo effect elicited in the observer.

Keywords Nocebo · Social modeling · Choice · Generalization · Virtual Reality · Cybersickness

Introduction

Our prior beliefs and experiences are known to modulate our perception of the world, including the experience of symptoms and side-effects [1]. A primary route through which these symptom-related expectancies are formed concerns the observation of others [2]. For example, witnessing another individual experience side-effects to a treatment can increase side-effect reporting in the observer when the same treatment is subsequently encountered [3–5]. These socially acquired nocebo effects have been documented across a diverse range of symptoms, including pain, headache, and nausea [3, 4, 6–11]. Furthermore, they have significant clinical and societal ramifications given that socially propagated symptoms of this type have been demonstrated to spread at the community level [12].

Somewhat surprisingly, however, studies have yet to investigate: (i) how social information regarding symptoms generalize across similar contexts and interventions, and; (ii) how nocebo effects generated through social modeling (i.e., observing another individual) can be attenuated or blocked. These factors are of importance. As discussed below, not only do they provide novel information about the way socially modeled symptoms are transmitted, but also potential routes to mitigate the burden of nocebo effects.

At present, we know that the social acquisition of negative health outcomes can occur with identical interventions and treatments (e.g., [3, 4, 13]). Of even greater concern, is that socially modeled symptoms may generalize (i.e., spread) to other experiences. That is, observing a person experience a negative outcome to a specific experience or treatment, may not only cause the observer to experience nocebo effects to that specific experience, but also to other similar experiences. Hypothesizing that socially acquired nocebo effects

might generalize in this manner is not unfounded. While not concerned with socially modeled symptoms, nocebo effects induced via direct classical conditioning have been demonstrated to generalize across environmental contexts. For example, participants conditioned to expect nausea from active Galvanic Vestibular Stimulation (GVS), experienced similar levels of nocebo nausea at test, irrespective of whether sham-GVS was delivered in the same room or a different context [14]. Given the mechanisms underlying the nocebo effect have been suggested to be similar across modes of induction (i.e., conditioning, social modeling, and explicit instruction) [15], it is of interest to determine whether socially modeled symptoms can generalize beyond identical interventions, as well as confirm the underlying mediators of any such effect.

Furthermore, given the documented strength of socially modeled nocebo effects [2], it is important to find interventions that can reduce these maladaptive health outcomes. Choice over treatment [16], side-effect framing [17, 18], nocebo education [19–22], latent inhibition [23, 24], and affect manipulations [25] have been proposed as interventions to reduce nocebo effects. A recent meta-analysis established choice as an effective method to enhance placebo effects. As such, choice may be a promising avenue through which to attenuate the nocebo effect, although research in this area has yet to be applied to social modeling [26]. Choice is inherently desirable [27, 28], and thus presents a low cost, nondeceptive, and ethical intervention [16, 29], previously shown to facilitate the placebo effect with respect to pain, discomfort, and sleep [26, 29–31]. Leotti et al. [28] contend that choice is a vehicle for individuals to exercise control, and thereby facilitate a reduction in anxiety and improve mental and physical outcomes [32, 33]. Alternatively, choice may engender a positive affect which could increase placebo effects and reduce nocebo effects [25, 27]. To date, however, only one published study has investigated choice with respect to the nocebo effect [16]. Here, participants who were given choice between two supposed betablockers (actually placebos) reported lower anxiety and fewer side-effects than those assigned to one of the supposed betablockers without any choice. As such, choice provides a potential but untested route through which to diminish socially modeled symptoms.

In order to bridge these two gaps in the literature, the present study investigated the effects of generalization and choice on socially acquired symptoms across three experiments all employing a common methodology. To achieve this a novel Virtual Reality (VR) model was implemented to investigate cybersickness; a constellation of nausea-related symptoms [34] previously reported to be susceptible to social modeling [35]. To explore generalization, participants witnessed a confederate experience cybersickness resulting from a VR activity that was either the same (i.e., Social Modeling Consistent: Confederate undertakes a rollercoaster ride) or different (i.e., Social Modeling Inconsistent: Confederate undertakes aerobatics) to the one that they subsequently experienced. The perception of choice was manipulated by allowing half of the participants to select a VR environment (i.e., choice of sunny or snowy weather) and yoking the remaining participants to their choices. Regardless of the participant's choice, the same VR activity (i.e., the rollercoaster ride) was undertaken by all participants. Finally, expectancy, anxiety, control, and affect were measured throughout the experimental session, allowing for an exploration of potential underlying mechanisms of social modeling and choice.

Past research has repeatedly shown an effect of social observation on the nocebo effect for identical interventions and treatments [3, 4, 6, 7, 35, 36]. Therefore, it was hypothesized that participants assigned to the social modeling groups would report higher levels of cybersickness subsequent to VR exposure when compared with those who received No Social Modeling. This effect of social modeling was expected to generalize, occurring even when participants believed they were viewing a model experience symptoms in a VR environment different to their own. We anticipated that participants given choice over their VR environment would report lower levels of cybersickness across all social modeling conditions [16]. Given a paucity of empirical evidence concerning the role of choice with respect to socially modeled nocebo effects, there was no basis for directional hypotheses and as such interactions between social modeling and choice were explored. Evidence for the influence of psychological factors that mediate socially acquired nocebo effects is inconclusive [1, 8, 10, 35, 37]. Consequently, state anxiety, expectancy, control, and affect were explored as mediators of the social modeling and choice effects. We present details regarding the primary outcome of each of the three experiments in the text (with secondary analyses in Supplementary Materials) and then a pooled analysis of the combined data across the three experiments.

Experiment 1 examined both generalization and choice. Counter to hypotheses, observers who witnessed a social model undergo a different VR experience to the one they subsequently encountered, reported greater cybersickness than those who witnessed a social model undergo the same experience as their own. To assess the validity of this unexpected result of generalization, Experiment 2 focused specifically on generalization independent of choice, finding the nocebo effect to be equivalent across social modeling conditions. Given the discrepant results regarding generalization in Experiments 1 and 2, Experiment 3 was run to adjudicate, while adding choice back into the model to explore its impact on the nocebo effect. Finally, a pooled analysis was run that combined data from all experiments.

Experiment 1

Methods

Experimental design and analyses were preregistered (AsPredicted #68104). Ethical approval was granted by the University of Sydney Human Research Ethics Committee (Protocol 2021/301). The recruitment process for all experiments is depicted in Supplementary Material 1. Data collection occurred between June 30 and August 20, 2021.

Participants

Participants (N = 134) were recruited Australia-wide via Facebook advertisements. The sample comprised of 68 males and 66 females, 18–58 years of age (M = 32.20, SD = 7.06). Information regarding sample race and socioeconomic status (SES) were not collected. In keeping with our previous research [17, 35, 38], participants were ineligible if they had experienced VR > 10 times, had a medical condition increasing postural instability or risk of nausea, were pregnant, had epilepsy, a pacemaker, or preexisting binocular visual abnormalities. Access to a smartphone with diagonal screen size of 4.7–6.4 inches and able to run the latest YouTube application was necessary for participation. All participants were

provided with a VR headset which they kept as compensation for their time.

Design

The current study was presented to participants as an investigation regarding online learning in VR. However, the true purpose was to examine the role of choice and generalization with respect to socially acquired nocebo nausea using a VR-based cybersickness model. Testing took place via the video-conferencing application Zoom, with all participants experiencing a VR rollercoaster ride. A 3(Social Modeling: No Social Modeling, Consistent, Inconsistent) × 2(Choice: No Choice, Choice) between-subjects design was employed. Participants were randomly assigned (via random number generator) to experimental condition and type of VR environment using a gender-stratified yoking procedure based on their order of participation. Full details are provided in Supplementary Material 2. The primary outcome was the severity of symptoms previously modeled by the confederate (general discomfort, nausea, and stomach awareness). State measures of anticipatory anxiety and expectancy were measured as potential mediators of virtually transmitted cybersickness.

Social modeling manipulation

Those randomly assigned to the social modeling groups watched an actor (who they believed was a real participant) experience VR and report symptoms of cybersickness before they experienced VR themselves. In line with previous social modeling research [3, 4, 13] those in the "Consistent" condition observed the actor describe the same VR activity that they chose/were assigned to (i.e., a rollercoaster ride). Importantly, those in the "Inconsistent" condition watched a description of a different environment and activity from their own (i.e., VR Aerobatics). Evidence of similar increased symptom reporting in both the Inconsistent and Consistent groups, relative to control, is therefore indicative of the generalization of a socially modeled nocebo effect across VR activities. The control group did not witness any social modeling prior to their VR experience. The two VR environments were selected from pilot data ($N = 28$), where five VR activities were paired with four environmental conditions. Preference for the snowy versus sunny environment, and rollercoasters vs. aerobatics did not differ (both $ps > .05$).

Choice

Participants assigned to the Choice condition chose which of two VR videos they preferred to watch. To control for differences in cybersickness that could be induced by substantial differences in the content of the VR video (e.g., a rollercoaster vs. aerobatics), participants chose their VR video based on peripheral environmental features (i.e., the weather; a snowy or sunny day). Unbeknownst to participants, the primary property of the VR that may provoke cybersickness (i.e., the rollercoaster ride) was constrained, while they were led to believe that they had chosen this (i.e., "you chose the snowy environment, which is a rollercoaster"). This isolated the manipulation to the perception of choice alone and controlled for the endogenous features of the VR. A manipulation of this type is similar to existing choice studies regarding the placebo effect that typically administer identical sham-treatments with peripheral perceptual differences [26, 29]. Manipulation of these peripheral environmental features (e.g., brightness/contrast associated with the different environments) should not modulate the induction of cybersickness [39].

Materials and measures

Social model

Social modeling took place virtually with live video interactions occurring via webcam on Zoom. While the participant believed the social model to be another participant (referred to as "Julian") who was present in the Zoom session, interactions with the model were actually a series of pre-recorded videos of a male confederate. Open Broadcasting Software was used to pipe the pre-recorded film of the social model into Zoom. This ensured that all participants within each experimental condition were presented with identical social information. The scripts delivered by the confederate were indistinguishable between conditions except for a single reminder concerning the environment (i.e., sunny or snowy), and two reminders of the activity (i.e., rollercoaster or aerobatics). The videos contained subtle cues (e.g., the model looking to the left) that allowed the experimenter to "talk" to the confederate, creating the illusion that he was participating in real time. Only one participant (0.7% of the sample) reported being aware that the model was not real in a post-experiment manipulation check. During the actor's modeling phase, they verbalized and gestured three distinct symptoms of cybersickness (nausea, general discomfort, and stomach awareness). The modeled symptoms were selected from pilot data in the lab so that they were those most likely to occur from VR exposure. See https://youtu.be/AcTfjDa4AjY for an excerpt of an experimental session, containing the script the confederate delivered as he modeled symptoms.

VR headsets and environments

Participants experienced VR using a Shinecon VR G034A head-mounted display. All participants watched one of two VR videos that depicted the same rollercoaster on either a sunny day (see https://youtu.be/19tjefId4oE) or a snowy day (see https://youtu.be/M9Vc-AT-TeM) which served as the "cybersickness-inducing" stimulus. In reality, the short rollercoaster ride served as a plausible activity to experience cybersickness while minimizing the occurrence of cybersickness due to the VR video alone. The videos were created using the custom rollercoaster simulator software NoLimits2 [40] which allowed for the generation of identical videos in length and content while only manipulating the environmental features that participants experienced. Screenshots are presented in Supplementary Material 3.

Primary outcome

Cybersickness

Cybersickness was measured using the 16-item Simulator Sickness Questionnaire (SSQ) [41]. Symptoms were rated on an 11-point scale: 0 (*not at all*) to 10 (*severely*). A baseline measure was taken at the beginning of each session, with the active measure taken immediately after VR. The difference score (active minus baseline) was used to measure cybersickness. Given three symptoms of the SSQ were specifically modeled to participants (general discomfort, nausea, and stomach awareness), cybersickness severity based on these items (referred to hereafter as "Modeled-SSQ") formed

the primary outcome, with the full sum-scored SSQ preregistered as a secondary outcome ("Full-SSQ").

Secondary outcomes

Analysis of secondary outcomes are presented as Supplementary Materials.

Expectancy

Expectancy was assessed with the single item: "How much do you expect to experience feelings of cybersickness (e.g., nausea, general discomfort, stomach awareness) during the VR video?," with an 11-point scale: 0 (*not at all*) to 10 (*severely*).

State anxiety

The short-form State-Trait Anxiety Inventory (STAI-6) [42] was employed with a 4-point rating scale: 1 (*not at all*) to 4 (*very much*). The overall STAI-6 sum score was calculated as the outcome.

VR anxiety

VR-specific state anxiety was measured via the single item: "How anxious do you feel about experiencing the Virtual Reality video?," with the same scale as expectancy.

Baseline measures of secondary outcomes were recorded at the beginning of the study session, and active measures immediately prior to the rollercoaster experience (i.e., following the observation of the social model in the Social Modeling groups). Higher scores indicated greater baseline-adjusted expectancy, state anxiety, and VR anxiety.

Control and affective state

Control and affect were measured via the Self-Assessment Manikin (SAM) [43], with a 9-point pictorial scale [44]. The SAM included the dimensions of valence (unhappy/happy), arousal (calm/agitated), and dominance (controlled/in control). Measurement occurred immediately after participants chose/were assigned their environment. Higher scores indicated a more positive valence, greater arousal, and more perceived control.

Manipulation check

A manipulation check was implemented at the end of each experimental session. Participants were asked to provide an open response to the question "Briefly describe (1–2 sentences) what you thought the purpose of this experiment was":

Procedure

Refer to Supplementary Material 4 for a diagram of experimental procedure. Participants were first screened for eligibility via Qualtrics. Ineligible participants were directed out of the signup process and eligible participants proceeded to the Participant Information Statement and Consent form. Upon consent, participants completed a short demographic survey. Participants were mailed the Headset 1–2 days prior to their scheduled experimental session.

Participants attended the experiment via Zoom, with the same female experimenter and male social model (actually pre-recorded footage). Participants received study information and completed baseline measures via Qualtrics. To maintain the cover story and avoid suspicion concerning repetition of questions regarding their wellbeing, participants were informed that monitoring their wellbeing throughout the experiment was an ethical requirement of the study. Then, all participants viewed information regarding the two VR environments (location—i.e., sunny environment presented on the right or left of the screen—was counterbalanced across participants). Those in the Choice conditions chose their preferred environment, while those in the No Choice conditions were told to click on their assigned environment (controlling for differences in the experience of agency).

All participants then completed the SAM to measure their sense of control and affect after VR selection. Participants in the No Social Modeling condition also completed a 5-min distractor task consisting of spatial reasoning questions (Raven's progressive matrices [45]) aligning the timing of the VR experience between Social Modeling and No Social Modeling groups. This ensured that there was no confounding effect of time on anxiety and expectancy ratings, which may be stronger toward the beginning of the experimental session [35]. Those in the social modeling groups were told the confederate would experience VR first. Depending on the participant's chosen or assigned environment, those in the Social Modeling Consistent condition were told: "both you and Julian [the confederate] chose/were assigned to experience the 'sunny day' environment, which contains a rollercoaster ride," while those in the Social Modeling Inconsistent group were told "You chose/were assigned to experience the 'sunny day' environment which contains a rollercoaster ride, while Julian, you chose/were assigned to experience the 'snowy day' environment which contains 'aerobatics'." These two groups subsequently witnessed the confederate describe the VR environment including the experience of general discomfort, nausea, and stomach awareness (i.e., modeled symptoms). The experimenter then asked the confederate: (i) Could you describe your experience of that VR video?; and (ii) Can you tell me how you feel (physically) at the moment? The confederate responded with the modeled symptoms. After observing the confederate, participants in the social modeling groups completed the active expectancy and anxiety measures. They then underwent the VR experience themselves, with the confederate "watching." Those in the "No Social Modeling" group undertook the same procedure but in reverse (i.e., they underwent the VR experience first while the confederate watched them and then watched the confederate undergo the VR experience). Participants answered the same two questions regarding their VR experience as the confederate (i.e., description and symptoms) and completed the active SSQ measure, several bogus memory questions to uphold the cover story, and the manipulation check. Upon completion participants were thanked for their time and informed they would receive a debriefing statement via email once data collection was complete.

Power and data analysis

Sample size was determined a priori. A minimum of 22 participants per-group were required to achieve 80% power ($\alpha = 0.05$) with an effect size of $\eta_p^2 = 0.07$ (based on the effect size of choice reported by Bartley et al. [16], the hypothesized smaller effect of the two manipulations).

Participants with extreme baseline cybersickness (prespecified as 3 *SD* above the mean, $N = 3$) were excluded from analysis. Participants that failed the manipulation check (by explicitly noting that the social model was not a real participant) were also excluded from the analysis ($N = 1$).

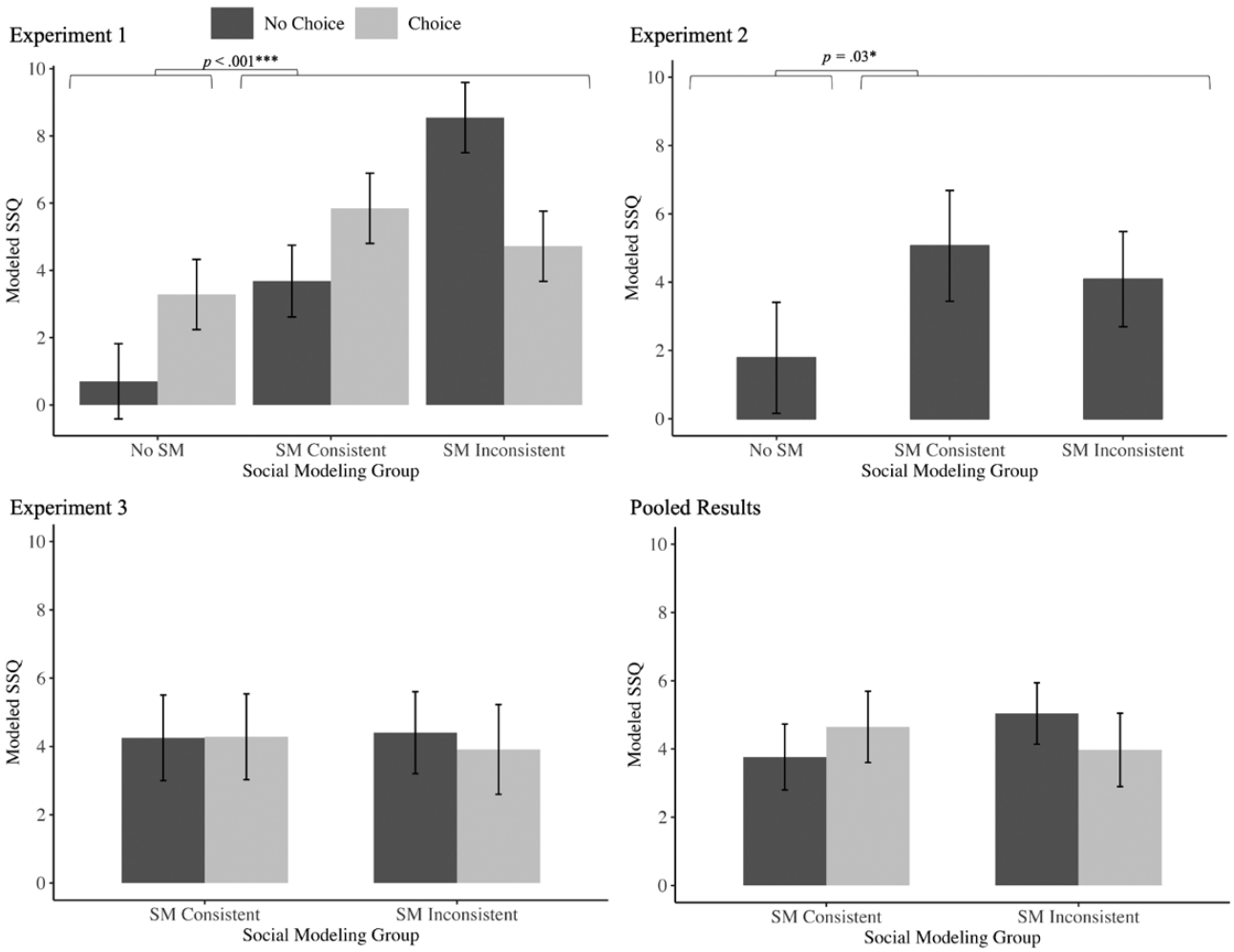

Fig. 1. Mean baseline-adjusted Modeled-SSQ score by group for Experiments 1, 2, and 3. *Note*. All error bars are ± 1 SEM and account for the covariate (gender). Significant main effects are highlighted. Refer to text for significant interaction effects.

Participants were also excluded due to technical difficulties, not following instructions, or withdrawal (N = 7).

The primary analysis was a two-way ANCOVA with the between-subjects factors of social modeling (Social Modeling Consistent, Social Modeling Inconsistent, and No Social Modeling) and choice (Choice and No Choice) as the independent variables and baseline-adjusted Modeled-SSQ score as the dependent variable (active measure minus baseline). Gender was entered as a covariate, as it has previously been shown to moderate socially acquired nocebo effects [7]. Two planned orthogonal contrasts were conducted: (i) social modeling groups (Social Modeling Consistent and Inconsistent, combined) versus control (No Social Modeling); (ii) Social Modeling Consistent versus Social Modeling Inconsistent. Those in the groups that were given choice were compared with those without choice. Unless otherwise specified, all statistical analyses were performed using R version 4.0.3 [46]. The significance value for all tests was set at an alpha rate of .05.

Results

There were no significant between-group differences in age, baseline measures (SSQ, state anxiety, VR anxiety, and expectancy), gender, or prior VR experience (all ps > .05), see Supplementary Material 5.

Figure 1 depicts the group means for the primary outcome. The ANCOVA model revealed that there was no main effect of the covariate, gender $F(1,127) = 1.44$, $p = .23$, $\eta_p^2 = 0.01$, nor was there a main effect of choice $F(1,127) = 0.12$, $p = .72$, $\eta_p^2 < 0.01$. However, a significant main effect of social modeling was observed, $F(2,127) = 9.60$, $p < .001$, $\eta_p^2 = 0.13$ which was qualified by a social modeling × choice interaction $F(2,127) = 5.79$, $p = .004$, $\eta_p^2 = 0.08$. Planned orthogonal contrasts revealed that Modeled-SSQ scores were elevated in the Social Modeling, relative to No Social Modeling, conditions $F(1,127) = 15.94$, $p < .001$, $\eta_p^2 = 0.11$. However, there was no significant overall difference in Modeled-SSQ scores between the Consistent and Inconsistent groups when collapsed across Choice, $F(1,127) = 3.16$, $p = .08$, $\eta_p^2 = 0.02$. There was no significant interaction between Choice and the orthogonal contrast that compared Social Modeling to No Social Modeling conditions on Modeled-SSQ scores, $F(1,127) = 3.38$, $p = .07$, $\eta_p^2 = 0.03$. However, there was an interaction between Choice and the second orthogonal contrast assessing generalization (i.e., comparing Consistent vs. Inconsistent Modeling), $F(1,127) = 8.14$, $p < .001$, $\eta_p^2 = 0.06$. Here, the lack of choice seemingly exacerbating Modeled-SSQ scores in the Inconsistent condition.

Summary

As hypothesized, a main effect of the contrast assessing social modeling was significant. Contrary to hypotheses, however, the generalization effect (i.e., Consistent vs. Inconsistent Modeling) interacted with Choice. In the conditions without the intervention (i.e., the No Choice conditions), watching the confederate undertake a different VR activity exacerbated cybersickness relative to the Social Modeling Consistent condition where the confederate undertook the same VR activity (a significant difference between the No Choice/Consistent and No Choice/Inconsistent groups was confirmed in exploratory analysis; see Supplementary Materials 5). This contradicted expectations, as generalization to a novel stimulus (independent of choice) is typically similar, if not weaker. Therefore, this unanticipated finding warranted further investigation.

Experiment 2

Given the unanticipated pattern of exploratory results concerning the generalization of social modeling found in Experiment 1, which was both complicated by the interaction with the factor of Choice and in an unexpected direction with respect to the No Choice condition specifically, a second study was conducted in an attempt to clarify these findings [47]. Experiment 2 is, therefore, a direct replication of the Social Modeling conditions excluding Choice to provide a clearer test of generalization without introducing the complicating factor of the interaction with the intervention. Choice was also omitted from this experiment to limit the burden on resources and maximize power to detect any general effect of social modeling independent of an additional manipulation.

Methods

Data collection occurred between April 7 and July 13, 2022.

Participants

The sample (N = 78) comprised of 30 males, 46 females, and 2 of other gender identities ranging from 17 to 50 years of age (M = 31.09, SD = 7.96).

Design and procedure

A one way (Social Modeling: Consistent, Inconsistent, No Social Modeling) between-subjects design was employed. All participants underwent the No Choice procedure as described in Experiment 1.

Materials and measures

All methods and materials are consistent with Experiment 1.

Power and data analysis

A minimum of 26 participants per-group were required to achieve 80% power (α = 0.05) with an effect size of η_p^2 = 0.13 (based on the main effect of social modeling found in Experiment 1). Exclusions were extreme baseline cybersickness (N = 2), technical difficulties (N = 1), not following instructions (N = 6), withdrawal (N = 1), or failure of the manipulation check (N = 1).

Results

Figure 1 depicts the group means of the primary outcome. The main ANCOVA model revealed that there was no main effect of the covariate, gender $F(2,73) = 0.48$, $p = .62$, $\eta_p^2 = 0.01$. There was no significant main effect of social modeling $F(2,73) = 2.79$, $p = .07$, $\eta_p^2 = 0.07$. However, planned orthogonal contrasts revealed that Modeled-SSQ scores were elevated in social modeling groups, compared with the No Social Modeling group $F(1,73) = 5.00$, $p = .03$, $\eta_p^2 = 0.06$. However, there was no significant difference in Modeled-SSQ scores between the Consistent and Inconsistent group, $F(1,73) = 0.44$, $p = .51$, $\eta_p^2 = 0.006$.

Summary

In contrast to Experiment 1, those in the Inconsistent (No Choice) group did not experience exacerbated levels of cybersickness relative to the Consistent (No Choice) group (see Fig. 1). Instead, their SSQ scores were comparable to the Social Modeling Consistent group. Combined, both sets of results provide novel evidence of generalization of socially acquired nocebo effects, whereby the model and observer do not need to undertake identical interventions to induce a socially acquired nocebo effect relative to control. However, in Experiment 1, choice was found to reduce cybersickness in the Inconsistent group. It is unclear whether this difference was driven specifically by the exacerbated scores observed among those in the No Choice/Social Modeling Inconsistent condition in Experiment 1, or were associated with the Inconsistent environment more generally (i.e., would have still been observed in Experiment 2 had Choice been tested).

Experiment 3

The discrepancy in results between Experiments 1 and 2 (i.e., whether the Inconsistent condition exacerbates symptoms) calls into question the effect of choice found in the Inconsistent group in Experiment 1. A final experiment was therefore conducted to assess the presence of a differential effect of choice between Social Modeling Consistent and Inconsistent groups, and to confirm that cybersickness elicited in the Inconsistent group is at least similar, if not greater, than the Social Modeling Consistent group. As the control (No Social Modeling) groups in both Experiments 1 and 2 revealed consistently low levels of cybersickness compared with the Social Modeling groups—establishing a robust effect of social modeling consistent with the literature [3, 4, 13, 35], Experiment 3 omitted this condition to minimize burden on resources.

Methods

Small adjustments to refine the method and analyses were preregistered (AsPredicted #103304). Data collection occurred between July 26 and October 9, 2022.

Participants

The sample (N = 124) comprised of 60 males, 60 females, and 4 of other gender identities ranging from 18 to 54 years of age (M = 31.91, SD = 6.60).

Design and procedure

A 2(Social Modeling: Consistent, Inconsistent) × 2(Choice: No Choice, Choice) between-subjects design was employed. All participants underwent the Social Modeling procedure as described in Experiment 1.

Secondary outcomes: materials and measures

Given that no effect of choice on control was observed in Experiment 1 (see Supplementary Materials 4), the measure was adapted to a single item with greater face validity: "How in control do you feel right now?" rated on a VAS from 0 (Not at all), 50 (Moderately) to 100 (Very much). Extra memory questions were included to reinforce the cover story, and participants were asked to rate how positive an experience they perceived the social model to have had during the VR, and to what extent they perceived the social model to have experienced cybersickness.

Power and data analysis

A total of 31 participants per group (124 total) were recruited, powered to detect an effect of $\eta_p^2 = 0.06$, with $\alpha = 0.05$ with 80% power. The effect size is derived from the interaction effect of choice and social modeling observed in Experiment 1. Exclusions were: extreme baseline cybersickness (preregistered as ≥40 sum score baseline SSQ or any single item ≥8, $N = 9$), technical difficulties ($N = 6$), not following instructions ($N = 1$), withdrawal ($N = 1$), or failure of the manipulation check ($N = 1$).

Results

Figure 1 depicts the group means for the primary outcome. The ANCOVA model revealed that there was a main effect of the covariate gender, $F(2,118) = 5.45$, $p = .005$, $\eta_p^2 = 0.08$. However, there was no significant main effect of choice $F(1,118) = 0.06$, $p = .81$, $\eta_p^2 < 0.001$ or social modeling (Consistent vs. Inconsistent) $F(1,118) = 0.01$, $p = .91$, $\eta_p^2 < 0.001$ and no significant social modeling × choice interaction $F(1,118) = 0.08$, $p = .78$, $\eta_p^2 < 0.001$ on Modeled-SSQ scores.

Correlations were run between Modeled-SSQ scores and whether the confederate: (i) was perceived as experiencing cybersickness, and (ii) was perceived as having a positive experience. Neither correlation was statistically significant (both ps > .05).

Summary

Contrary to the results of Experiment 1, no interaction between choice and social modeling was observed. This suggests that the difference reported in Experiment 1 was driven specifically by the exacerbated scores observed among those in the No Choice/Social Modeling Inconsistent condition, which was not replicated in Experiment 2, rather than via choice itself. Consistent with the results of Experiment 2 was the lack of difference in cybersickness elicited between the two Social Modeling groups. This suggests that at a minimum, the Inconsistent group experienced similar levels of cybersickness due to social modeling as the Consistent group, thereby providing consistent novel evidence across the three experiments that socially acquired nocebo effects do generalize.

Pooled Analysis

Results from all experiments were combined for a pooled analysis. Table 1 summarizes the number of pooled participants in each experimental condition. To explore the main effects of Social Modeling and Choice, and their interaction, the analysis was conducted as a 2(Modeling Type: Consistent, Inconsistent) × 2(Choice: No Choice, Choice) + 1(No Social Modeling: both Choice and No Choice groups) ANCOVA controlling for gender as a covariate. There were no significant differences between experiments in the demographics (gender, age, and VR experience) of participants—see Supplementary Materials 5.

Primary Outcome: Modeled-SSQ

Controlling for gender ($F(2,332) = 5.21$, $p = .005$, $\eta_p^2 = 0.04$), participants assigned to the experimental conditions (Modeling type: Consistent Choice, Consistent No Choice, Inconsistent Choice, Inconsistent No Choice) combined had significantly higher Modeled-SSQ scores ($M = 4.50$, $SE = 0.74$) relative to those in the control group (No Social Modeling Choice and No Social Modeling No Choice; $M = 1.11$, $SE = 0.99$) $F(1,332) = 23.21$, $p < .001$, $\eta_p^2 = 0.07$.

Figure 1 depicts the pooled group means. There was a nonsignificant main effect of Choice (Choice vs. No Choice), a nonsignificant effect of Modeling Type (Consistent vs. Inconsistent), and no interaction between Modeled Content and Choice. In summary, social modeling of any type (Consistent or Inconsistent) increased symptoms of cybersickness relative to No Social Modeling, while choice had no effect on socially acquired cybersickness.

Secondary Outcomes: Expectancy, State Anxiety, VR Anxiety, Control, and Affect

To investigate the potential underlying causes of the observed group differences in cybersickness between Social Modeling and No Social Modeling Groups, three one-way between-subjects ANCOVAs were conducted with expectancy, state anxiety, VR anxiety as the dependent variable, Social Modeling (No Social Modeling vs. Social Modeling: Consistent and Inconsistent combined) as the independent variable, and gender as the covariate. Please note that the same analyses for each separate study are presented in Supplementary Materials

Table 1 Count of Participants in Each Condition Across Experiments

Social modeling condition	Choice condition	Experiment 1	Experiment 2	Experiment 3	Total
No Social Modeling	No Choice	20	26	0	46
	Choice	23	0	0	23
Social Modeling Consistent	No Choice	22	26	31	79
	Choice	23	0	31	54
Social Modeling Inconsistent	No Choice	23	26	31	80
	Choice	23	0	31	54
Total (N)		134	78	124	336

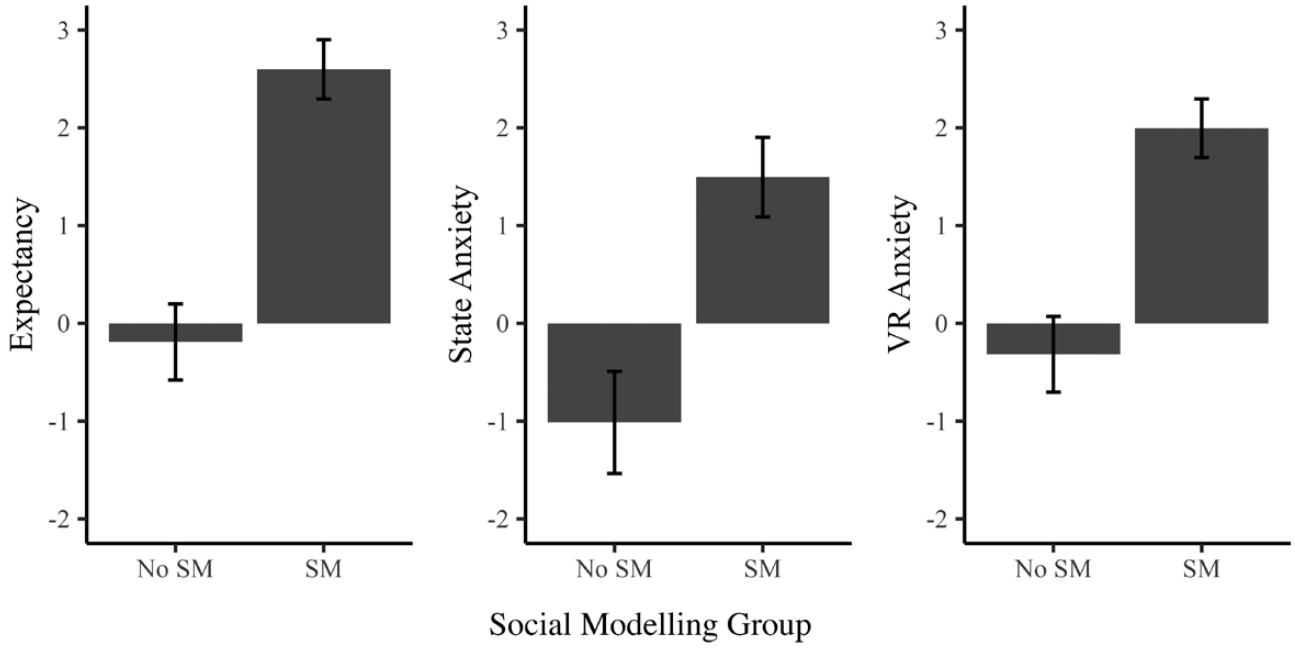

Fig. 2. Mean baseline-adjusted expectancy, state anxiety, and VR anxiety: Social Modeling versus No Social Modeling. *Note.* All error bars are ± 1 SEM and account for the covariate (gender). *VR* Virtual Reality.

5. Group means from the pooled analysis are depicted in Fig. 2. The pattern of results was similar across all three secondary outcomes (with full statistics reported in Table 2). There was a significant effect of the covariate gender on both state anxiety ($p < .001$) and VR anxiety ($p = .001$) but no significant effect of gender on expectancy ($p = .17$). Controlling for the covariate, Social Modeling significantly increased all three outcomes, relative to the No Social Modeling groups (all ps $< .001$). Each Social Modeling group (i.e., Consistent and Inconsistent) was also compared separately to the No Social Modeling group, and the pattern of results remains similar (see: https://osf.io/w2xcp/).

Table 2 ANCOVA Results (Contrast: No Social Modeling vs. Social Modeling Groups)

	$F(1,332)$	p	ηp^2
Expectancy	93.90	<.001	0.22
State anxiety	41.95	<.001	0.11
VR anxiety	65.20	<.001	0.16

VR Virtual Reality.

As predicted by the literature, Modeled-SSQ was significantly positively correlated with expectancy, $r(334) = .23$, $p < .001$, state anxiety, $r(334) = .24$, $p < .001$, and VR anxiety, $r(334) = .28$, $p < .001$.

Choice and No Choice groups were compared on perceived control and positive affect scores, but these dimensions did not significantly differ between groups (all ps $> .05$; see Supplementary Material 5).

Mediation Analyses

As presented in Fig. 3, three mediation analyses were conducted, with Social Modeling (No Social Modeling vs. Social Modeling: Consistent and Inconsistent combined, collapsed across choice) as the independent variable, Modeled-SSQ as the dependent variable, and expectancy, state anxiety, and VR anxiety, as separate mediators. Gender was included as a covariate in models where there was a significant effect (i.e., state anxiety and VR anxiety, see above). A very small number of participants in each cell self-reported their gender as "other" across the three experiments ($n = 6$; 1.79%), these participants were excluded from the mediation analyses that included gender as a covariate for the model to converge. Bootstrapping with 10,000 samples was conducted to determine 95% confidence intervals (CIs) which were used to determine significance.

Expectancy

Expectancy significantly mediated the effect of group on Modeled-SSQ score, direct effect = 2.35, 95% CI [1.05, 3.65], $p < .01$ and indirect effect = 0.89, 95% CI [0.11, 1.69], $p = .02$.

State anxiety

State anxiety significantly mediated the effect of group on Modeled-SSQ score, direct effect = 2.70, 95% CI [1.49, 3.94], $p < .001$ and indirect effect = 0.69, 95% CI [0.16, 1.32], $p = .01$.

VR anxiety

VR anxiety significantly mediated the effect of group on Modeled-SSQ score, direct effect = 2.40, 95% CI [1.08, 3.76], $p < .01$ and indirect effect = 0.99, 95% CI [0.22, 1.79], $p < .01$.

Summary

The pooled results from the three experiments provide compelling evidence for an effect of social modeling in

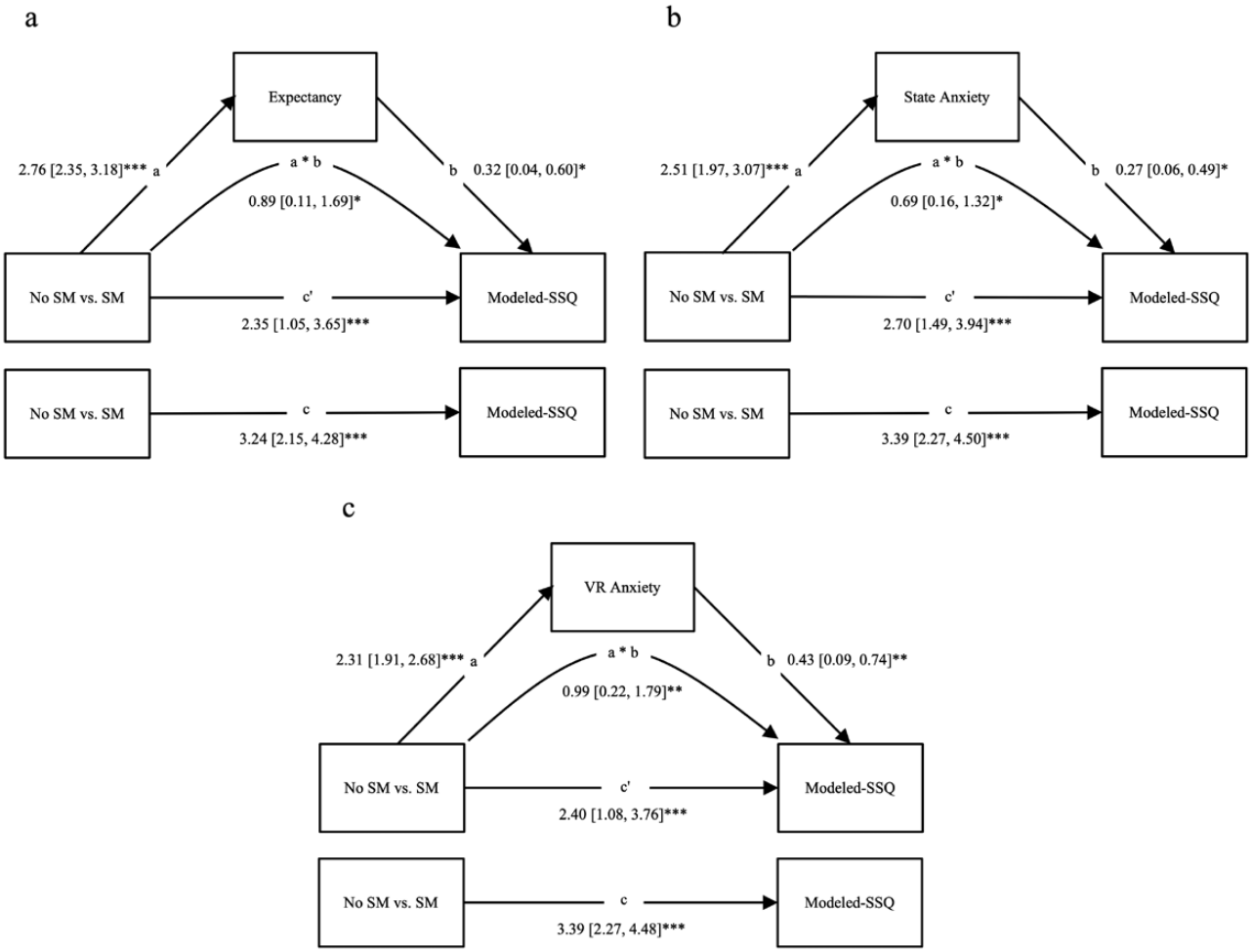

Fig. 3. Mediatory effects of expectancy, state anxiety, and VR anxiety on cybersickness. *Note*. Values are unstandardized beta coefficients with 95% confidence intervals. Figures represent mediatory effects of expectancy (a), state anxiety (b), and VR anxiety (c). Covariate (gender) was included models b and c but is not represented here for brevity. Paths *a*, *b*, and *c* are the direct paths between variables. Curved path $a \times b$ is the indirect effect with bootstrapped CIs. Path *c′* is the direct association between the group contrast and cybersickness, controlling for the indirect effect. *CIs* confidence intervals; *VR* Virtual Reality.

producing nocebo effects. Most importantly, they showed that social modeling can produce nocebo effects regardless of whether the experience witnessed is identical or similar to the one subsequently encountered. That is, that socially acquired nocebo effects can generalize from a specific observed experience to other experiences. Social modeling exacerbated expectancies regarding cybersickness and increased anxiety, and both expectancies and anxiety were found to mediate the relationship between social modeling and cybersickness. Choice, however, was not found to be an effective intervention to reduce socially elicited cybersickness.

General Discussion

The present study explored whether socially modeled nocebo effects would generalize across different experiences and whether choice reduced these effects. There was consistent evidence for the effect of social modeling on cybersickness. Critically, this socially acquired nocebo effect occurred irrespective of whether the participant observed the model undergo an identical or distinct VR activity, indicating that socially acquired nocebo effects can generalize. There was, however, no consistent evidence that choice could inhibit these socially acquired nocebo effects.

Social modeling has been established as a powerful determinant of a range of symptoms [4, 7–10, 36, 37]. The present study revealed that social modeling plays an equally important role with respect to nocebo cybersickness [35]. As hypothesized, witnessing a social model experience cybersickness due to VR immersion exacerbated participants own experience of cybersickness compared with those that did not view the model. However, prior research has never investigated the effect of modeling *similar* interventions [6]. The present study therefore investigated the generalization of socially modeled symptoms beyond identical model/observer experiences. A key novel finding here was that the strength with which social modeling induced nocebo cybersickness did not depend on the similarity between the model and observers experience—that is, the social model did not have to undertake the exact same VR activity as the participant to elicit comparable levels of cybersickness. This novel finding has concerning implications, whereby social modeling may be significantly more widespread than previously imagined. Further research is needed to determine to what extent symptoms can spread, particularly in clinical settings.

Contrary to hypotheses, choice did not reduce symptoms. Given that choice was not found to enhance perceived control or engender positive affect, the manipulation (i.e., choice of sunny vs. snowy weather) may have lacked salience. It was important to hold the VR activity (i.e., the rollercoaster) constant to control for differences in cybersickness elicited. However, a more salient choice like choice of VR activity, or a greater number of choices overall, may have made for a more effective intervention. An important caveat to this limitation is to note that the choice provided to participants in the present study was not dissimilar to past research that yielded positive results in the context of explicit instruction and classical conditioning [26, 29]. As such, it is equally possible that our measures of control and affect themselves either lacked specificity or were not associated with the choice manipulation. For example, Tang et al. [48] found an effect of choice on conditioned placebo analgesia but failed to find a corresponding increase in perceived control, suggesting that these two constructs may be orthogonal. An alternative explanation is that choice may have differential effects based on the mode of induction, with socially modeled nocebo effects being especially resistant to attenuation. Another potential is for the effect of control to be dependent on culture, however the culture of the present sample is consistent with the cultures represented by past research [26]. The present study was the first to date to investigate choice with respect to social modeled nocebo effects, with past research exclusively concerning explicit instruction [16]. Clearly further investigation, employing experimental paradigms concerning choice that have previously been demonstrated to modulate the nocebo effect, are needed to elucidate the role of choice on socially acquired nocebo effects.

To date, empirical evidence addressing the mechanisms hypothesized to generate socially modeled nocebo effects has been both limited [1] and inconsistent [8, 10, 35, 37]. The present study addressed this concern in a large sample. Consistent with previous research [35, 37], expectancies and anxiety appear key to facilitating socially acquired nocebo effects. Both were found to be elevated after social modeling and to mediate the effect of social modeling on cybersickness. While no effect of choice was observed in the present study, the strength of identifying these mediators is that they can be employed to inform future targeted interventions. As such, research may wish to focus on these mechanisms when developing methods to attenuate socially acquired nocebo effects.

The present study demonstrated several novel results based on a large representative sample. However, limitations must be noted. First, the study was conducted single-blind, which may have led to experimenter bias. However, care was taken to ensure that all instructions were delivered by the experimenter using identical scripts across experimental sessions. Furthermore, the social model was a pre-recorded video to ensure consistency, and all questionnaires completed by participants were administered remotely via Qualtrics to reduce biased responding. Second, the study was conducted entirely online via Zoom meaning the quantity of social information conveyed was dependent on the strength of participant's internet connection and limited to what was observable via webcam, introducing experimental noise. Testimony to the strength of social modeling, strong effects were found irrespective of whether the VR environment was consistent or inconsistent, despite these technical limitations. However, social modeling in live settings may be stronger and potentially more receptive to manipulations such as choice. Third, the social model was a male and as such the effect of the model's gender remains unexplored. Furthermore, any gender effects reported may be confounded with gender match between participant and model. Finally, the manipulation check was general. As such, it is possible that the number of participants that recognized the specific purpose of the studies may be underrepresented.

Evidence of generalization found in the present study is highly problematic with respect to both clinical and nonclinical settings. Results extend previous research, demonstrating empirically for the first time that socially modeled nocebo effects are not limited to identical interventions. People do not have to observe others experience an identical intervention for social transmission to occur, meaning symptoms could potentially spread between different brands of similar medication, between similar medical procedures or between similar experiences like VR which is increasingly being used in clinical contexts. This suggests that opportunity for social modeling may be significantly more widespread than previously imagined. This emphasizes the importance of future research into interventions to reduce these negative health effects. Beyond choice, potential avenues that remain unstudied with respect to socially modeled symptoms include: side-effect framing [17, 18], nocebo education [19, 20], latent inhibition [23], and affect manipulations [25]. Importantly, the present study identified negative expectancies and anxieties key mechanisms, meaning that interventions targeting these mechanisms are likely to be most effective. Further exploration of the generalization of social information is also warranted with respect to different symptom outcomes (e.g., pain, headache, insomnia) within different contexts (e.g., clinically). In addition, future research should investigate to what extent these socially modeled effects can generalize, for example between more dissimilar stimuli (VR rollercoaster vs. VR walk on the beach), across modes of nocebo induction (nausea induced via VR vs. GVS) or, if placebo effects elicited via social modeling can generalize in a similar way.

In summary, results of this study demonstrate that social modeling is a powerful determinant of nocebo effects, with the potential to impact our experiences in both a robust and diffuse manner. As choice was not found to reduce these effects at all, further research concerning negative expectancies and anxieties is critical to reduce the harm that can arise from these socially acquired side-effects.

Acknowledgments

The authors thank W. Tan for acting as the social model for the videos used within the experiment. The study was funded by an Australian Government Research Training Program Stipend Scholarship and Australian Research Council Discovery Project (DP200101748).

Compliance with Ethical Standards

Authors' Statement of Conflict of Interest and Adherence to Ethical Standards Cosette Saunders, Ben Colagiuri, and Kirsten Barnes declare that they have no conflict of interest.

Authors' Contributions Cosette Saunders (Conceptualization [equal], Formal analysis [lead], Methodology [equal], Writing – original draft [lead]), Ben Colagiuri (Conceptualization

[equal], Methodology [equal], Writing – review & editing [equal]), and Kirsten Barnes (Conceptualization [equal], Formal analysis [supporting], Methodology [equal], Writing – review & editing [equal])

Open Science Transparency Statements

1. The study was preregistered at AsPredicted.org: https://aspredicted.org/FZN_AFT (Experiments 1 and 2) https://aspredicted.org/HXH_H48 (Experiment 3)

2. The analysis plan was registered prior to beginning data collection at AsPredicted.org: https://aspredicted.org/FZN_AFT (Experiments 1 and 2) https://aspredicted.org/HXH_H48 (Experiment 3)

3. Deidentified data from this study are available in a public archive: https://osf.io/w2xcp/

4. Analytic code used to conduct the analyses presented in this study are available in a public archive: https://osf.io/w2xcp/

5. Some of the materials used to conduct the study are presented in a public archive: https://osf.io/w2xcp/

Supplementary Material

Supplementary material is available at *Annals of Behavioral Medicine* online.

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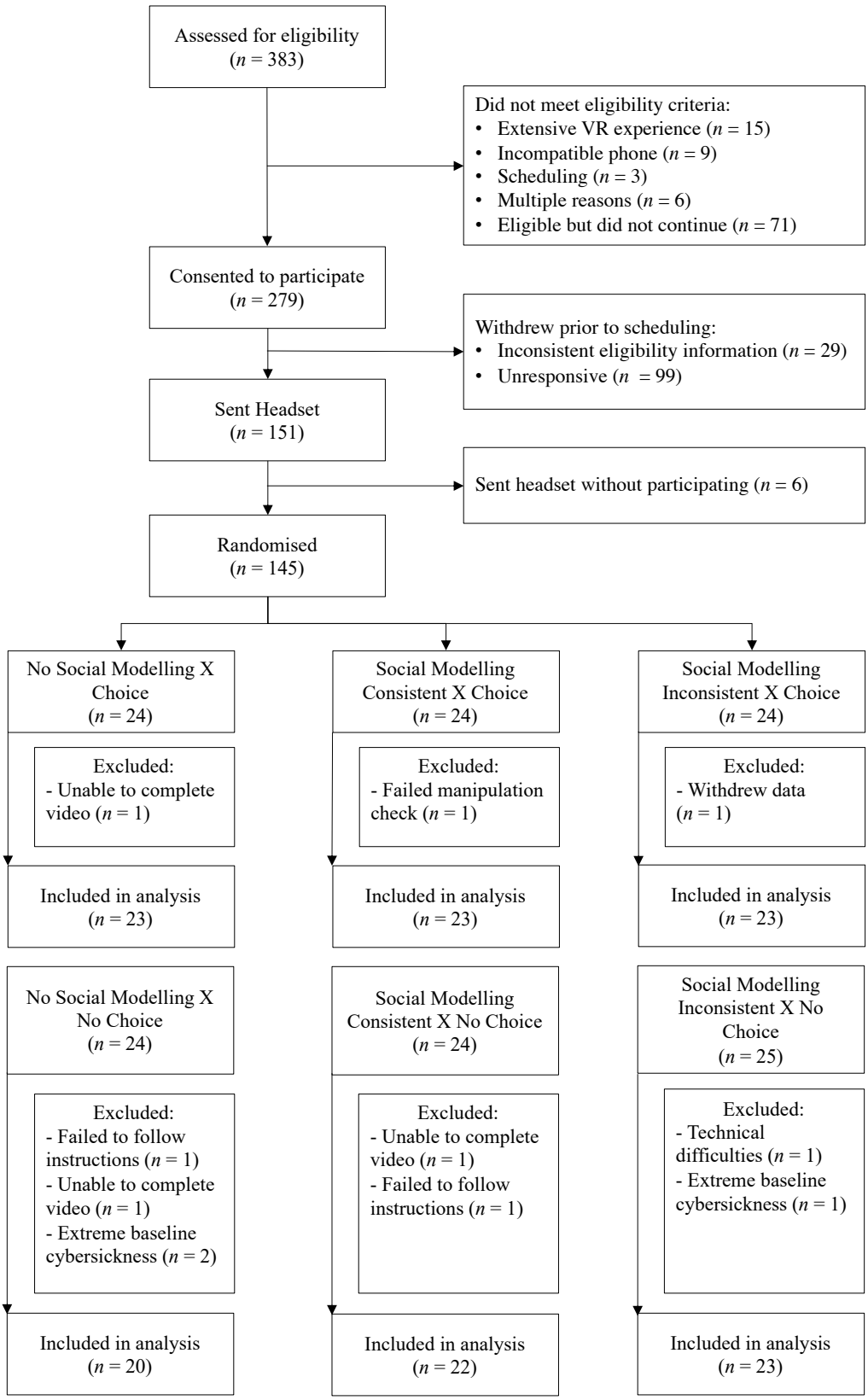
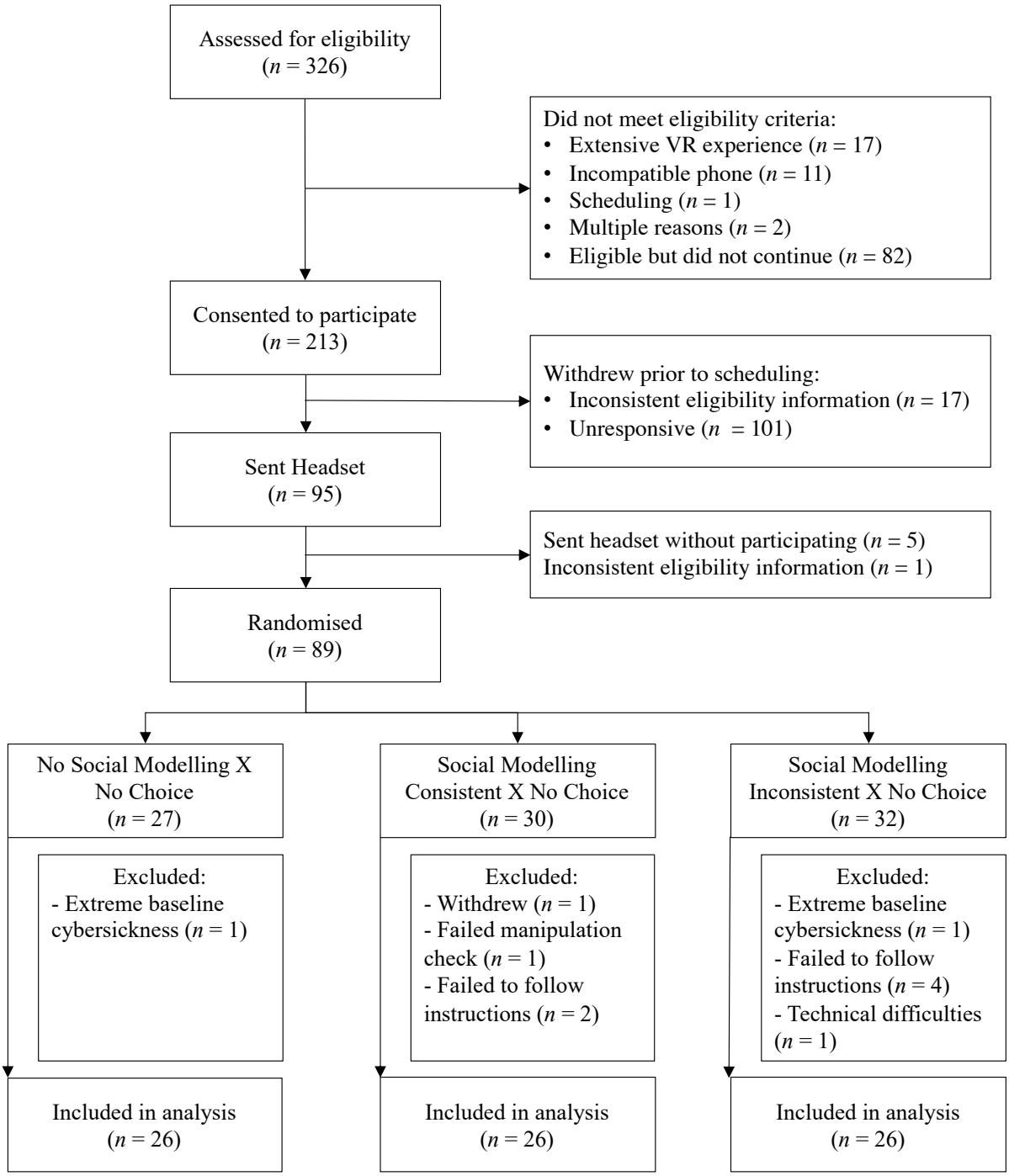
Publication Supplementary Materials

Electronic Supplementary Material 1

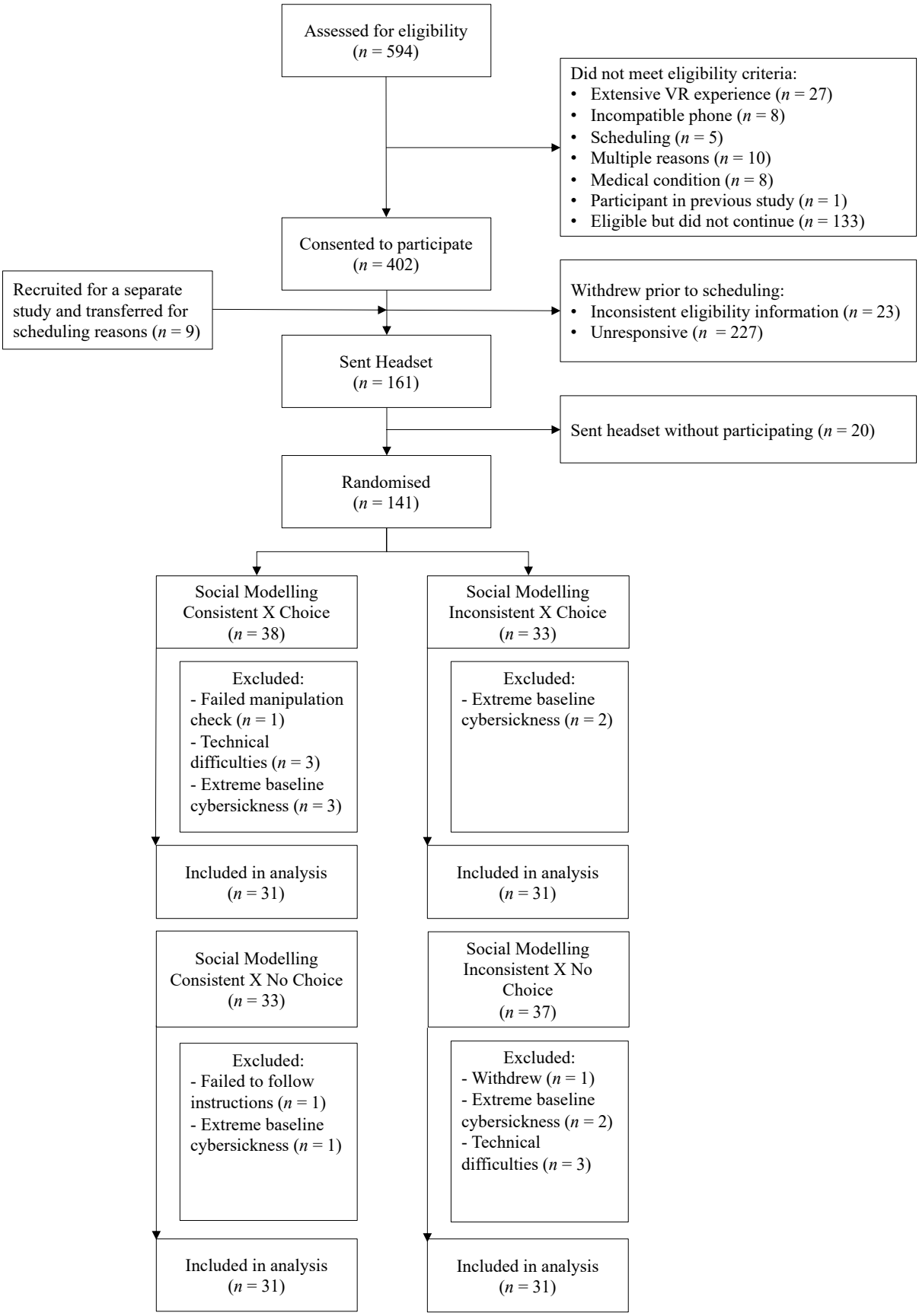
CONSORT Flow Diagram of the Participant Recruitment Process Experiment 1



CONSORT Flow Diagram of the Participant Recruitment Process Experiment 2



CONSORT Flow Diagram of the Participant Recruitment Process Experiment 3



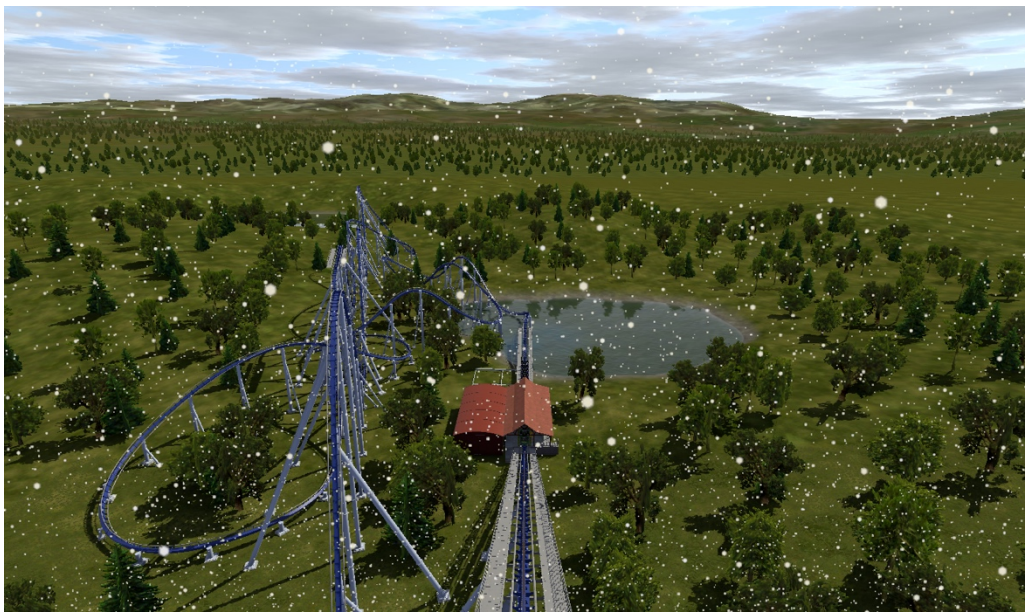
Electronic Supplementary Material 2

Description of yoking procedure

Participants were first stratified by self-report gender. The first participant (of a specified gender) was assigned to the Choice Condition and randomised to one of the three Social Modelling conditions. The second was yoked to the 'No Choice' condition of the same Social Modelling counterpart. The third was assigned to the Choice condition and randomised to one of the two remaining Social Modelling Conditions. The fourth was yoked to the No Choice Condition of the same Social Modelling counterpart. Finally, the fifth participant was assigned to the Choice Condition of the remaining Social Modelling Condition and the sixth participant yoked to the final No Choice Condition. This was performed for each sextuplet in order of their participation.

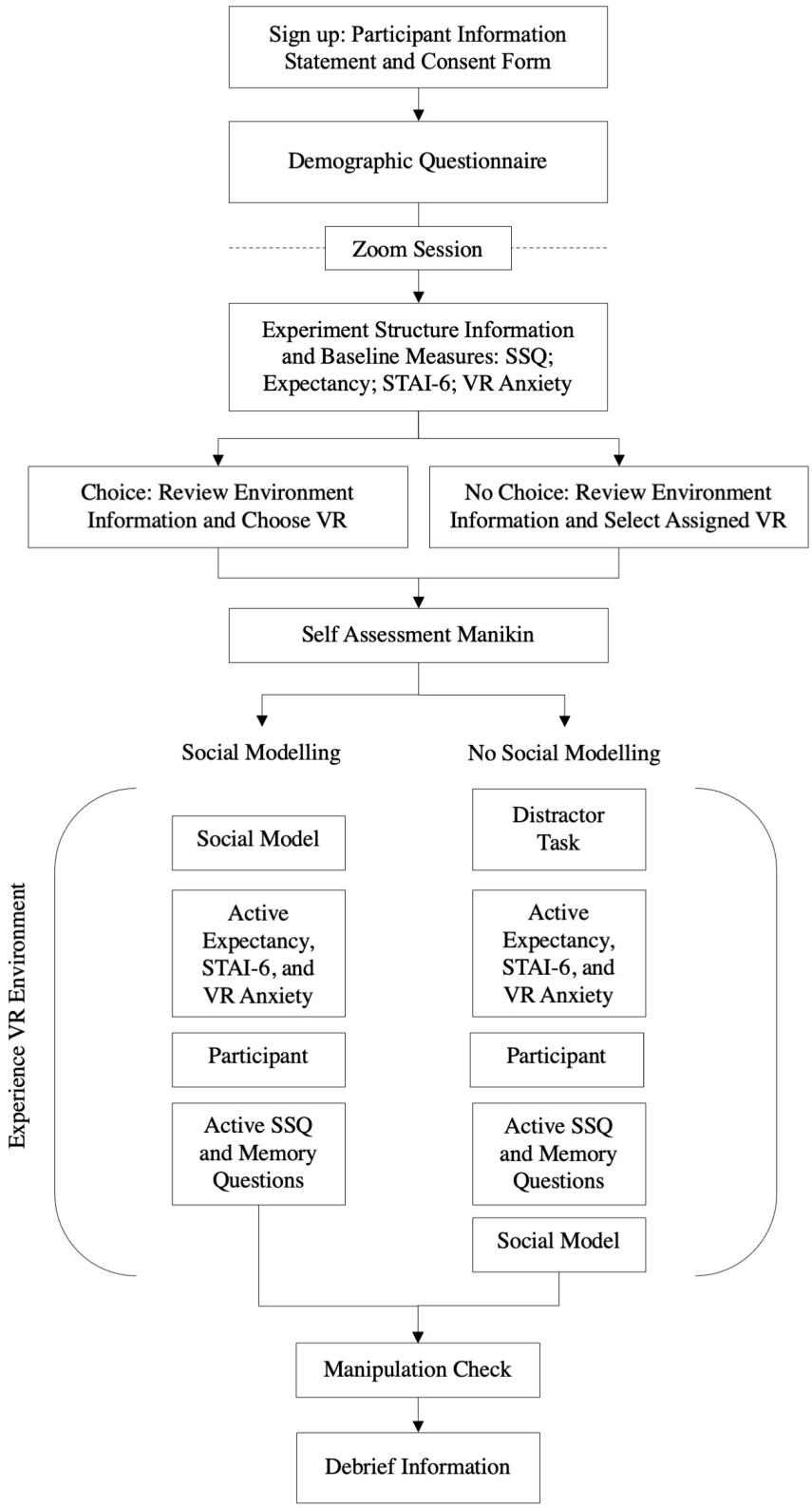
Electronic Supplementary Material 3

Screenshot of the Sunny (top) and Snowy (bottom) rollercoaster experienced by all participants



Electronic Supplementary Material 4

Flow Chart of the Experimental Procedure



Electronic Supplementary Material 5

Supplementary Statistical Analyses

Full statistical analyses, group means, graphical summaries and accompanying code are available at: https://osf.io/w2xcp/?view_only=cafd0e83882844699fd572e6b08d1302.

Table 1

Reliability Statistics (Cronbachs' α)

	Modelled SSQ	Full SSQ	STAI-6
Experiment 1	.83	.89	.71
Experiment 2	.82	.89	.65
Experiment 3	.81	.90	.77

Table 2

Analysis of Baseline Characteristics (Quantitative) Across Experiments

	Experiment 1		Experiment 2		Experiment 3	
	$F(5,128)$	p	$F(2,75)$	p	$F(3,120)$	p
Age	1.05	.39	0.33	.72	0.62	.61
Modelled-SSQ	1.30	.27	0.28	.76	0.59	.62
Full-SSQ	0.44	.82	0.57	.57	0.66	.58
Expectancy	0.74	.60	2.53	.09	1.06	.37
STAI-6	0.53	.75	0.99	.37	0.97	.41
VR Anxiety	0.95	.45	0.40	.67	0.17	.92

Note. Given all baseline characteristics were measured prior to any choice or social modelling manipulation, One-Way ANOVAs were conducted to assess differences in baseline characteristics between the groups.

Table 3

Analysis of Baseline Characteristics (Qualitative) Across Experiments

	Experiment 1		Experiment 2		Experiment 3	
	$\chi^2(5, N = 134)$	*p*	$\chi^2(2, N = 78)$	*p*	$\chi^2(3, N = 124)$	*p*
Gender	0.14	1.00	7.27	.12	2.13	.91
VR Experience	4.62	.46	1.97	.37	1.90	.59

Post-hoc: Social Modelling Consistent vs Inconsistent (No Choice groups only). A two-sided independent samples t-test revealed that the Inconsistent Social Modelling group had significantly higher Modelled-SSQ scores (*M*=8.52, *SD*=5.81) than the Consistent group (*M*=3.68, *SD*=4.81), *t*(43)=-3.03, *p*=.004, *d*=0.90.

Effect of Control. In Experiment 1, there was no significant difference in perceived control as measured by the SAM between Choice (*M*=0.15, *SD*=0.81) and No Choice groups (*M*=0.00, *SD*=1.09), *t*(132)=-0.91, *p*=.18, *d*=0.16.

Between experiment demographics differences. There was no significant difference between experiments with respect to gender, $\chi^2(4, N = 336)=6.97$, *p*=.14, VR experience, $\chi^2(2, N = 336)=1.70$, *p*=.43, or age of participants, $F(2,333)=0.61$, *p*=.54.

Secondary Outcomes: Expectancy, State Anxiety, VR Anxiety, Control and Affect

Table 4

Experiment 1 ANCOVA results (No Social Modelling vs Social Modelling Groups)

	No Social Modelling *M*	Social Modelling *M*	*F*(1,127)	*p*	η_p^2
Expectancy	-0.02	2.22	36.24	<.001	0.22
State Anxiety	0.42	2.75	20.37	<.001	0.14
VR Anxiety	0.25	2.31	29.46	<.001	0.19

Table 5

Experiment 2 ANCOVA results (No Social Modelling vs Social Modelling Groups)

	No Social Modelling	Social Modelling	$F(1,73)$	p	η_p^2
	M	*M*			
Expectancy	-0.18	2.70	29.86	<.001	0.29
State Anxiety	-1.27	1.26	17.08	<.001	0.19
VR Anxiety	-0.10	2.42	27.30	<.001	0.27

Table 6

Baseline-adjusted Expectancy, Anxiety and VR Specific Anxiety for each group

Social Modelling Condition	Choice Condition	Expectancy		STAI		VR Anxiety	
		M	*SE*	*M*	*SE*	*M*	*SE*
No Social Modelling	No Choice	-0.43	0.43	-1.18	0.58	-0.43	0.43
	Choice	0.26	0.53	-0.66	0.72	-0.03	0.53
Social Modelling Consistent	No Choice	2.64	0.37	1.53	0.5	2.12	0.37
	Choice	2.31	0.40	1.65	0.54	1.84	0.40
Social Modelling Inconsistent	No Choice	2.68	0.35	1.44	0.47	1.95	0.34
	Choice	2.69	0.41	1.39	0.56	2.13	0.41

Note. Results are averages across the covariate gender. By dividing the results of the analysis by group the pattern of results does not differ, all social modelling groups experience higher levels of expectancy, state anxiety and VR specific anxiety.

Table 7

Expectancy, State Anxiety and VR Anxiety Aggregated by Gender

Gender		Expectancy		STAI-6		VR Anxiety	
	N	*M*	*SE*	*M*	*SE*	*M*	*SE*
Female	172	2.05	0.17	2.36	0.23	2.12	0.17
Male	158	1.61	0.18	1.36	0.24	1.36	0.18
Other	6	1.42	0.89	-1.63	1.19	0.30	0.88

Note. Results are averaged across experimental groups.

Effect of Choice. See Table 8 for group means. There was no significant difference between Choice and No Choice groups in perceived control, $t(334)=-1.47$, $p = .07$, happiness, $t(210)=0.01$, $p = .50$, or arousal, $t(210)=0.21$, $p = .41$.

Table 8

Group Means for Choice and No Choice Groups

	No Choice		Choice	
	M	*SD*	*M*	*SD*
Perceived Control	-0.06	1.05	0.10	0.91
Happiness	6.94	1.37	6.94	1.37
Arousal	4.27	2.12	4.20	1.65

Note. Averaged across type of Social Modelling

Appendix C: Supplementary Material, Chapter 4

Study Approval Letter

THE UNIVERSITY OF SYDNEY

Research Integrity & Ethics Administration
HUMAN RESEARCH ETHICS COMMITTEE

Wednesday, 10 August 2022

Dr Kirsten Barnes
Psychology; Faculty of Science
Email: kirsten.barnes@sydney.edu.au

Dear Kirsten,

The University of Sydney Human Research Ethics Committee (HREC) has considered your application.

I am pleased to inform you that after consideration of your response, your project has been approved.

Details of the approval are as follows:

Project No.:	**2022/532**
Project Title:	**Socially Acquired Nocebo Effects: The Role of Similarity**
Authorised Personnel:	**Barnes Kirsten; Burchett Alexander; Saunders Cosette; Tan Winston;**
Approval Period:	**10/08/2022** to **10/08/2026**
First Annual Report Due:	**10/08/2023**

Documents Approved:

Date Uploaded	Version Number	Document Name
01/08/2022	Version 2	Consent_Form_All_Studies_v2CLEAN
01/08/2022	Version 1	General_Advert_Info_v1
01/08/2022	Version 2	PIS_study1_v2CLEAN
01/08/2022	Version 2	PIS_study2_v2CLEAN
01/08/2022	Version 2	PIS_study3_v2CLEAN
01/08/2022	Version 2	PIS_study4_v2CLEAN
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10/06/2022	Version 1	Debrief_study3_v1
10/06/2022	Version 1	Debrief_study1_v1
10/06/2022	Version 1	Debrief_study2_v1
10/06/2022	Version 1	Debrief_study4_v1

Condition/s of Approval

- Research must be conducted according to the approved proposal.
- An annual progress report must be submitted to the Ethics Office on or before the anniversary of approval and on completion of the project.
- You must report as soon as practicable anything that might warrant review of ethical approval of the project including:
  - Serious or unexpected adverse events (which should be reported within 72 hours).
  - Unforeseen events that might affect continued ethical acceptability of the project.
- Any changes to the proposal must be approved prior to their implementation (except where an amendment is undertaken to eliminate *immediate* risk to participants).
- Personnel working on this project must be sufficiently qualified by education, training and experience for their role, or adequately supervised. Changes to personnel must be reported and approved.

Research Integrity & Ethics Administration
Research Portfolio
Level 3, F23 Administration Building
The University of Sydney
NSW 2006 Australia

T +61 2 9036 9161
E human.ethics@sydney.edu.au
W sydney.edu.au/ethics

ABN 15 211 513 464
CRICOS 00026A

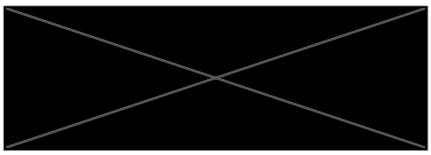
THE UNIVERSITY OF SYDNEY

- Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, as relevant to this project.
- Data and primary materials must be retained and stored in accordance with the relevant legislation and University guidelines.
- Ethics approval is dependent upon ongoing compliance of the research with the *National Statement on Ethical Conduct in Human Research*, the *Australian Code for the Responsible Conduct of Research*, applicable legal requirements, and with University policies, procedures and governance requirements.
- The Ethics Office may conduct audits on approved projects.
- The Chief Investigator has ultimate responsibility for the conduct of the research and is responsible for ensuring all others involved will conduct the research in accordance with the above.

This letter constitutes ethical approval only.

Please contact the Ethics Office should you require further information or clarification.

Sincerely,



Associate Professor Haryana Dhillon
Chair
Human Research Ethics Committee (HREC 3)

The University of Sydney of Sydney HRECs are constituted and operate in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2018) and the NHMRC's Australian Code for the Responsible Conduct of Research (2018)

Pre-registration

ASPREDICTED

Wharton CREDIBILITY LAB
UNIVERSITY of PENNSYLVANIA

Can socially elicited nocebo effects generalise across treatments? (#109597)

Author(s)
This pre-registration is currently anonymous to enable blind peer-review.
It has 2 authors.

Pre-registered on: 2022/10/15 - 06:02 PM (PT)

1) Have any data been collected for this study already?
No, no data have been collected for this study yet.

2) What's the main question being asked or hypothesis being tested in this study?
Can social modelling of side-effects elicit nocebo symptoms, even when the model and observer take different treatments? Participants will be told they may receive no treatment or one of two pills that will enhance cognitive ability and may cause some side effects (Treatment A: headaches and dizziness, Treatment B: nausea and stomach discomfort, counterbalanced). In actuality, the treatment is inert (placebos).

H1. Groups that receive the placebo treatment will demonstrate a nocebo effect, i.e. increased symptoms, relative to those who receive no placebo treatment.
H2. Social modelling will exacerbate the nocebo effect relative to no social modelling.
H3. There will be no difference in nocebo effects for those receiving consistent (observer believes the model has taken the same treatment) and inconsistent (observer believes the model has taken the other treatment) social modelling.

3) Describe the key dependent variable(s) specifying how they will be measured.
Physical symptoms will be assessed using a 10-item modified version of the General Assessment of Side Effects Scale (GASE; Rief, Glombiewski, & Barsky, 2009). The original four-point scale (0-3, not present to severe) will be modified to a seven-point scale to enhance the sensitivity to changes in symptoms. The primary outcome of interest will be mean target symptom severity, defined as mean severity of side effects associated with the participant's assigned medication. Physical symptoms will be measured at the start of the experiment session prior to pill administration in the treatment conditions (Baseline), and at the end of the experimental session (Active). The difference score (Active – Baseline) will form the primary outcome.

Secondary outcome variables include non-target side-effects (mean severity of side effects associated with the other medication) and general side-effects (mean severity of remaining 6 GASE items).

As the natural history group does not receive treatment, their target symptoms and non-target symptoms will be yoked to participants in the No Social Modelling Condition.

State Anxiety: State-Trait Anxiety Inventory-6 (Marteau & Bekker, 1992).

Side-effect specific anxiety, expectancy for side effects, expected cognitive enhancement and self-reported cognitive performance will all be measured using single items on a visual analogue scale (VAS) ranging from 1 to 100.

Cognitive performance: Rapid visual information processing (RVIP) to assess sustained attention (Wesnes et al., 1983).

4) How many and which conditions will participants be assigned to?
Participants will be randomised to one of four conditions: Natural History, No Social Modelling, Social Modelling Consistent, and Social Modelling Inconsistent. All participants will read side-effect warnings concerning two new supposed cognitive enhancement medications (actually placebos), with one supposedly associated with the experience of nausea and stomach discomfort and the other associated with headaches and dizziness. Participants in the social modelling conditions will watch a social model (actually of one of the experimenters) experience side effects from either the same cognitive enhancement medication (Social Modelling Consistent) or from the other medication (Social Modelling Inconsistent). Participants in the No Social Modelling group and the Natural History group will not view a social model and the Natural History group will also not receive any treatment.

5) Specify exactly which analyses you will conduct to examine the main question/hypothesis.
The primary data analysis will consist of a one-way (Condition: Natural History, No Social Modelling, Social Modelling Consistent, Social Modelling Inconsistent) ANOVA, using baseline adjusted (Active – Baseline) mean target symptom severity as the outcome variable. Orthogonal contrasts will be used to compare:
1. No Treatment (Natural History) vs. Treatment (No Social Modelling, Social Modelling Consistent, Social Modelling Inconsistent)
2. No Social Modelling vs. Social Modelling (Social Modelling Consistent, Social Modelling Inconsistent)
3. Social Modelling Consistent vs. Inconsistent

Moderation analyses will then be conducted to explore any group differences revealed in the ANOVA using gender, state anxiety, side-effect anxiety,

side-effect expectancy, Heart Rate Variability (HRV), Electrodermal Activity (EDA) as moderators.
Secondary analysis will explore non-target side effects and general side effects as the outcome variable, in a similar one-way ANOVA.
Self-reported cognitive performance and actual cognitive performance will also be compared between groups (one-way between subjects ANOVA) to assess the presence of a placebo effect.

6) Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.
Participants should be in full health at time of testing. Those with extreme baseline side effects (six or more on any single item, or a mean greater than four) will be excluded from analyses.

A sensitivity analysis will be conducted comparing naive participants to those that correctly identify that the pill they took was a placebo, or that the participant they observed was an actor.

7) How many observations will be collected or what will determine sample size? No need to justify decision, but be precise about exactly how the number will be determined.
A total of 120 participants (30 participants per-group minimum) will be recruited. This is based on a power analysis on the effect size for the social modelling manipulation (f = .31, derived from Faasse, 2015) with an alpha of .05 with the power to detect an effect set at 80%.

8) Anything else you would like to pre-register? (e.g., secondary analyses, variables collected for exploratory purposes, unusual analyses planned?)
Physiological response will be measured using HRV and EDA.

HRV will be measured continuously throughout the session, and EDA measured continuously for 15 minutes after pill administration. A window of time after pill administration (Baseline) will be compared to a window of time after the SM manipulation (Active) between conditions for both physiological measures.

Questionnaires/Instruments

Start of Block: Consent

Q4

Participant Consent Form ***Research Study: Cognitive Enhancement Study*** Dr Kirsten Barnes (Responsible Researcher) School of Psychology, Faculty of Science Phone: +61 2 9351 4589 | Email: kirsten.barnes@sydney.edu.au Miss Cosette Saunders (PhD student) | Email: cosette.saunders@sydney.edu.au I agree to take part in this research study. In giving my consent, I confirm that: The details of my involvement have been explained to me, and I have been provided with a written Participant Information Statement to keep. I understand the purpose of the study is to investigate the efficacy of new cognitive enhancement medications. I acknowledge that the risks and benefits of participating in this study have been explained to me to my satisfaction. I understand that in this study I will be required to Attend a single 1 hour session, conducted in Top South Badham, University of Sydney Provide some basic demographic data, e.g. age, gender Wear a heart rate monitor throughout the session, and have my electrodermal activity monitored. Complete some basic questions about my current state of well-being Complete a simple cognitive performance task I understand that being in this study is completely voluntary. I am assured that my decision to participate will not have any impact on my relationship with the research team or the University of Sydney. I understand that I am free to withdraw from this study and that I can choose to withdraw any information I have already provided (unless the data has already been de-identified or published). I have been informed that the confidentiality of the information I provide will be protected and will only be used for purposes that I have agreed to. I understand that information about me will only be told to others with my permission, except as required by law. I understand that the results of this study may be published, and that publications will not contain my name or any identifiable information about me. I understand that my data may be deposited in electronic repositories, and that no identifying information me will be included in such data sets. I understand that after I sign and return this consent form it will be retained by the researcher, and that I may request a copy at any time.

HREC Approval No.: 2022/532

Q5 Please enter your first and last name.

_____

Q30 I would like feedback on the overall results of this study

- Yes (1)
- No (2)

Display this question:

If I would like feedback on the overall results of this study = Yes

Q31 If yes, please provide your preferred contact email:

_____

Q6

Please select your choice below. Clicking on the "I consent" button below indicates that: • You have read the above information • You voluntarily agree to participate If you do not wish to participate in the research study, please decline participation by clicking on the "I DO NOT consent" button. This will close the current Qualtrics survey and send you to the University of Sydney homepage.

- I consent to take part in the study (1)
- I DO NOT consent to take part in the study (2)

End of Block: Consent

Start of Block: Demographics

Q61 Please pause here and ask the experimenter for instructions to proceed

Page Break

Q36 Please enter the Participant Identification Number provided by the experimenter:

_____

Page Break

age What is your age?

_____

gender What is your gender?

- Male (1)
- Female (2)
- Other (3)

End of Block: Demographics

Start of Block: Baseline GASE

BGASE Rate your experience of each of these symptoms over the past 30 minutes

	Not Present (1)	(2)	Mild (3)	(4)	Moderate (5)	(6)	Severe (7)
Headache (1)							
Dizziness (2)							
Nausea (4)							
Stomach Discomfort (5)							
Breathing Problems (6)							
Palpitation (7)							
Itching (8)							
Abnormal Sweating (9)							
Dry Mouth (11)							
Chest Pain (12)							

End of Block: Baseline GASE

Start of Block: STAI-6

Description A number of statements which people have used to describe themselves are given in the next few questions. Read each statement and choose the most appropriate answer below the statement to indicate **how you feel right now, at this moment.** There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

BSTAI_1 I feel calm

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_2 I am tense

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_3 I feel upset

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_4 I am relaxed

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_5 I feel content

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_6 I am worried

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

End of Block: STAI-6

Start of Block: Baseline Expectancy and Anxiety

Q58 Read each statement and choose the most appropriate number below the statement to indicate how you feel right now, at this moment.

Q21 To what degree do you expect the cognitive enhancement medication to enhance your performance?

	No enhancement			Significant enhancement
	0	25	50	75	100
()					

BE How much do you expect to experience adverse events (e.g. side effects) as a result of participating in this study?

	Not at all			Very much so
	0	25	50	75	100
()					

BA How anxious are you about experiencing adverse events (e.g. side effects) as a result of participating in this study?

	Not anxious			Very anxious
	0	25	50	75	100
()					

End of Block: Baseline Expectancy and Anxiety

Start of Block: Administer Treatment

Q33 Please pause here and ask the experimenter for instructions to proceed

End of Block: Administer Treatment

Start of Block: RVIP

Start of Block: Active GASE

Q34 Please enter the code provided by the experimenter to proceed

_____

Page Break

Q60 Rate your experience of each of these symptoms over the past 30 minutes or since you received medication

	Not Present (1)	(2)	Mild (3)	(4)	Moderate (5)	(6)	Severe (7)
Headache (1)							
Dizziness (2)							
Nausea (4)							
Stomach Discomfort (5)							
Breathing Problems (6)							
Palpitation (7)							
Itching (8)							
Abnormal Sweating (9)							
Dry Mouth (11)							
Chest Pain (12)							

End of Block: Active GASE

Start of Block: Post eval of efficacy

Q32 What Treatment did you receive?

- Monovigil (1)
- Vitatril (2)
- No Treatment Control (3)
- I took one of the medications but do not recall which one (4)
- I do not recall if i received treatment (5)

Q58 How would you rate your performance on the cognitive task?

	Very Poor								Very Good	
	0	10	20	30	40	50	60	70	80	90	100
()											

Display this question:

If What Treatment did you receive? = Monovigil

Or What Treatment did you receive? = Vitatril

Or What Treatment did you receive? = I took one of the medications but do not recall which one

PVRA How effective was the medication at enhancing your cognitive performance?

	Not effective at all								Very effective	
	0	10	20	30	40	50	60	70	80	90	100
()											

Q28 Please describe what you believe the purpose of the study to be:

_____

End of Block: Post eval of efficacy

scientific reports

Check for updates

OPEN

Investigating whether socially acquired nocebo effects can spread to other treatments

Cosette Saunders[1✉], Winston Tan[1], Kirsten Barnes[2], Nicolas McNair[1] & Ben Colagiuri[1]

Observation of another's treatment side effects can elicit side effects in the observer, even when the treatment is a placebo. This study investigated whether these socially acquired side effects can generalise to similar treatments. Healthy volunteers (*N* = 120) participated in a study ostensibly comparing the effect of two cognitive enhancers (placebos). Participants were randomised to one of four experimental groups. The three treatment groups comprised: social modelling of side effects associated with the *same* treatment; social modelling of side effects associated with the *different* treatment; and a verbal suggestion only group (i.e., no social modelling). The fourth group was a no-treatment control group. The primary outcome was severity of side effects reported. Groups that received placebos reported increased symptom severity, i.e., showed a nocebo effect. Surprisingly, primary outcome analysis revealed no significant enhancement of the nocebo effect due to social modelling. However, there was an additive effect of social modelling on general side effects (planned secondary outcome) and specifically for headaches and dizziness (exploratory analysis), both of which generalised across treatments. Therefore, preliminary findings suggest that socially induced nocebo side effects may not always occur, but when they do, they can generalise beyond identical treatments. This warrants replication and raises significant concern given the widespread sharing of treatment-related information, potentially contributing to the societal burden of nocebo effects.

Keywords Nocebo, Social modelling, Symptoms, Side effects, Observational learning, Generalisation

The nocebo effect refers to adverse health outcomes that cannot be attributed to the treatment itself but rather are due to the psychosocial context in which they occur[1,2]. Growing evidence indicates that social information is a key contributor to the nocebo effect[3]. Simply observing another person (a 'model') experience treatment-related pain, nausea, or itch can elicit or exacerbate these symptoms when the observer subsequently undergoes the same treatment. These socially acquired nocebo effects can even be demonstrated when the treatment is itself a placebo [4–6], and have been implicated in the formation of COVID-19 vaccine side effects[7,8]. However, research has yet to determine if socially acquired nocebo effects can spread – or generalise – from one treatment to another. This is critical for understanding the full impact that socially acquired nocebo effects have, as well as for developing strategies to reduce their burden in healthcare and community settings.

Generalisation has been reliably demonstrated in the context of direct experiential learning both in animals and humans[9]. For example, rats trained to learn that a specific tone leads to shock will display a defence response to that specific tone *and* other similar tones[10]. Recent research has also shown that directly-conditioned placebo and nocebo effects generalise across treatment cues[11–13] and new environmental contexts[14]. However, there has been virtually no research on the extent to which socially acquired nocebo effects generalise. The only exception that we are aware of is a study by Saunders et al.[6], which found that observing a model report cybersickness to one virtual reality (VR) setting (a rollercoaster), subsequently increased the observer's nocebo cybersickness both to that setting and another (a VR flight simulation). This demonstrates that socially acquired nocebo effects can spread across contexts. However, to the best of our knowledge, there is no research examining whether socially acquired nocebo effects generalise across *medical* treatments (e.g., different types of treatments).

Generalisation of socially acquired nocebo effects across treatments is both highly concerning and relevant in the context of the significant proliferation of, often negative, information on social media. Seeing or hearing about another's experience of side effects after one type of vaccination may not only lead to nocebo side effects for that specific vaccination—but could also increase nocebo side effects for other vaccinations. Previous research

[1]School of Psychology, A18, University of Sydney, Sydney, NSW 2006, Australia. [2]School of Psychology, University of New South Wales, Sydney, Australia. ✉email: cosette.saunders@sydney.edu.au

has shown that socially acquired symptoms arising from a placebo treatment can spread beyond the specific symptoms communicated by the model[15]. However, as models and observers received the same treatment, this is distinct from generalisation of socially acquired nocebo effects *across treatments*. As such there is a significant gap in our knowledge regarding the social transmission of nocebo effects when the model/observer intervention differs.

The current study examined whether nocebo side effects could be elicited via social modelling even when the model apparently received a *different* treatment. This involved simulating a clinical context by administering one of two placebo treatments (capsules) presented as cognitive enhancers, each of which was described as having a *unique* side effect profile. One was described as associated with "Headaches and Dizziness" and the other "Nausea and Stomach Discomfort". Participants were randomised to one of four groups. The three treatment groups comprised: social modelling of side effects associated with the *same* treatment; social modelling of side effects associated with the *different* treatment; and a verbal suggestion only group (i.e., no social modelling). The fourth group was a no-treatment control group. We hypothesised that there would be an overall nocebo effect, with more side effects reported in the treatment groups than the control group. Most importantly, however, we hypothesised that social modelling would exacerbate this nocebo effect both when the same treatment was received by the observer *and* when a different treatment was received; the latter of which would indicate generalisation of socially acquired nocebo effects to a novel treatment with unique side-effects. Heart Rate Variability (HRV) and Electrodermal Activity were also collected to explore any effects of social modelling on physiological arousal. See Daniali et al. [16] for a review with respect to nocebo hyperalgesia.

Methods

The study design and analyses were preregistered (aspredicted.org #109597). Ethics approval was granted by the University of Sydney Human Research Ethics Committee (#2022/532), all methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all participants.

Participants

One hundred and twenty-one healthy volunteers (Female = 87, M_{age} = 19.52, SD = 2.28) from the University of Sydney participated and received course credit as compensation. Eligible participants were fluent in English without any known allergy to medication or lactose. Due to the gelatine capsules, those with dietary restrictions were advised not to participate. Participants were required to be in full health at the time of testing and were excluded if they exceeded pre-registered thresholds of physical symptoms at baseline.

Design

The study involved a single-blind one-way between-subjects design with four levels. Participants were told the study was investigating two cognitive enhancers (both actually placebos) of which they may receive one. Participants were warned that one of the treatments was associated with "headaches and dizziness" and the other with "nausea and stomach discomfort". The two different side effect profiles, along with the supposed name and branding of the medication container served to distinguish the treatments as distinct. The critical manipulation was if the participant observed the confederate experience side effects, and for those who did, which treatment the confederate had supposedly taken, with participants randomly allocated to one of four groups. R 4.1.1[17] was used as a random number generator to generate a random sequence of group assignment with which to allocate participants in the order in which they were tested. The Social Modelling Consistent group received placebos and observed side effects reported by a model who they believed had taken the same treatment as them. A Social Modelling Inconsistent group received placebos and observed side effects reported by a model who they believed had taken a different treatment to them. A No Social Modelling group received placebos but did not observe a model. A Natural History group did not receive placebos and did not observe a model. This group served as a control, allowing for a comparison with the three treatment groups to isolate the nocebo effect. Any difference in reported symptoms between the Natural History group and the treatment groups would indicate the presence of a nocebo effect overall. The key outcome of interest was the severity of side effects reported by participants.

Materials and measures

Placebo pills

No participants received active medication. The placebos comprised gelatine capsules filled with lactose. The placebo pills were contained in two distinct fake medication bottles designed to reinforce the cover story and the primary manipulation, see https://osf.io/m8tdh/.

Demographics

Participant age and gender were recorded.

Physical symptoms

Physical symptoms were assessed using a modified version of the General Assessment of Side Effects, GASE[18]. Symptoms communicated by the confederate (i.e., stomach discomfort) were added to the questionnaire and symptoms unlikely to occur within the time frame of the experiment were excluded (e.g., diarrhea, insomnia) resulting in a list of 10 symptoms. The original 4-point scale 0(Not Present) to 3(Severe) was modified to a 7-point scale to enhance the sensitivity to changes in symptoms. The full scale was decomposed into three scores: Target Symptoms (Mean severity of symptoms supposedly associated with the participants medication), Non-Target Symptoms (Mean severity of symptoms supposedly associated with the other medication) and General Symptoms (Mean severity of remaining 6 GASE items). The Target Symptoms for participants in the Natural

History group (who did not receive medication) were yoked to the Target Symptoms of the previous participant in the No Social Modelling group.

Generalized state anxiety
General state anxiety was measured via the Spielberger State-Trait Anxiety Inventory-6[19], (Cronbach's alpha = 0.81).

Side effect specific anxiety
Participants rated their anxiety concerning experiencing side effects on the single item measure: "How anxious are you about experiencing adverse events (e.g., side effects) as a result of participating in this study?" on a visual analogue scale (VAS) ranging from 1(Not Anxious) to 100(Very Anxious).

Expectancy
Participants were asked to rate their expectancy of the experience of side effects on the single item measure: "How much do you expect to experience adverse events (e.g., side effects) as a result of participating in this study?" on a VAS ranging from 1(Not at all) to 100(Very much so).

Expectancy for cognitive enhancement
Participants were asked to rate their expectancy of the efficacy cognitive enhancement medication on the single item measure: "To what degree do you expect the cognitive enhancement medication to enhance your performance?" on a VAS ranging from 1(No enhancement) to 100(Significant enhancement).

Cognitive performance
The Rapid Visual Information Processing (RVIP) procedure was used to assess sustained attention[20]. Numbers ranging from 1 to 9 were presented on a computer screen at a rate of 100/min for a total duration of five minutes. Participants were required to press the space bar as quickly as possible once either three consecutive even or three consecutive odd numbers appeared. They had 1.5s to make a correct response; all responses outside this time were considered false alarms. The sequence of numbers was semirandom such that the target sequences were separated by a minimum of 5 and maximum of 33 digits. Performance was assessed using proportion (%) of correct responses.

Self-reported cognitive performance
Participants were asked to rate their perceived performance on the RVIP: "How would you rate your performance on the cognitive task?" on a VAS ranging from 1(Very poor) to 100(Very good).

Self-reported influence on cognitive performance
Participants assigned to take the placebo were asked "How effective was the medication at enhancing your cognitive performance?" on a VAS ranging from 1(Not effective at all) to 100(Very effective).

Manipulation check
To ensure participants were aware of their assigned medication they were asked to recall the name of their assigned medication (I was assigned to…: 'Vitatil', 'Monovigil', 'No Treatment Control', 'I took one of the medications but do not recall which one' and 'I do not recall if I received treatment'). To probe more generally about suspicion concerning the confederate they were asked to answer the general probe "Briefly describe (in 2–3 sentences) what you thought the purpose of the experiment was:".

Equivital sensor belt and module
Participant Heart Rate (HR) was measured using an Equivital Sensor Module fitted onto an Equivital Sensor Belt. HR was measured continuously for 15 min after administration of the treatment (or lack thereof). HR Variability (HRV) is a measure of the parasympathetic and sympathetic branches that modulate cardiac activity[16]. Frequency domain methodology was used to generate the High Frequency/Low Frequency (HF/LF) ratio using pyHRV[21].

Electrodermal activity (EDA)
EDA was recorded as a measure of autonomic arousal in response to the treatment and social communication manipulations. This was achieved by using a PowerLab amplifier and a Galvanic Skin Response amplifier (ADInstruments) with two finger electrodes placed on the middle and index fingers of participants' right hand. EDA was recorded over the same time period as HR. EDA can be decomposed into tonic activity (slower general changes in sympathetic arousal) and phasic activity (reactive fast changes), which each reflect important components of physiological arousal[22]. A convex optimization approach to electrodermal activity (cvxEDA) was applied to extract the two components[23], after which mean Skin Conductance Level (μ SCL) was calculated as a measure of the tonic activity and the number of Skin Conductance Responses (nSCR) as a measure of the phasic activity.

Procedure

Refer to Fig. 1 for a flow chart of the study procedure. All participants were tested individually in a single 1 h session conducted by a single experimenter who was a 24-year-old white Australian female. On arrival, participants received a written information sheet, which was reinforced verbally. This outlined the cover story and contained the warning: "*Vitatril* has been associated with the experience of mild nausea and stomach

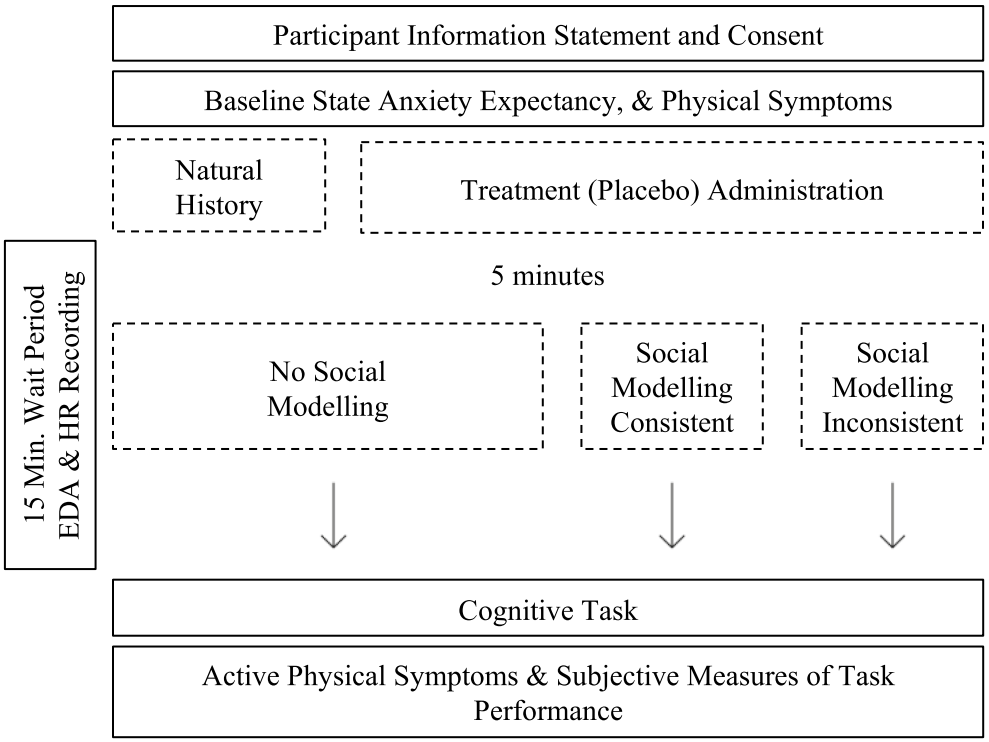


Fig. 1. Flowchart of study procedure.

discomfort. *Monovigil* has been associated with the experience of mild headaches and dizziness". Side effect profiles were counterbalanced within each group. Participants who consented were then randomised and verbally informed of their treatment allocation by the researcher (i.e., No Treatment, 'Vitatril' or 'Monovigil'). Next, participants were fitted with the Equivital Harness. Participants then completed demographics and baseline measures including: physical symptoms, state anxiety, expectancy for side effects and expectancy for cognitive enhancement. Participants were seated facing the door and set up with the electrodes to measure their EDA. The placebo capsules were then administered to treatment groups. All participants were seated and waited for 15 min, ostensibly providing time for the medication to take effect in the treatment groups. Exactly five minutes after the HR/EDA recording commenced, participants in the social modelling conditions saw a confederate enter the room. The confederate was a 26-year-old Asian-Australian male perceived as another participant of the study. Within view of the participant, the researcher asked the confederate, "So you received ['Vitatril'/'Monovigil'] around thirty minutes ago, how are you feeling now?". Where the placebo medication either aligned (Social Modelling Consistent) or did not align (Social Modelling Inconsistent) with the supposed treatment the participant had just taken. The confederate then responded with either: "Not great, definitely feeling headachy and a bit dizzy" or "Not great, definitely feeling quite nauseous and my stomach is upset". Importantly, the side effects the confederate reported aligned with the warnings participants had received concerning the treatment the confederate had supposedly taken. At the same timepoint as the social modelling conditions received this side effect modelling, participants in the Natural History and No Social Modelling groups overheard the experimenter have an irrelevant phone call to control for the effect of the conversation. After the 15-min wait period, all participants were taken to another room to complete the cognitive task to uphold the cover story. Upon completion, participants returned to the main room where they completed the physical symptoms questionnaire again and were also asked to report their perceived efficacy of the medication and complete a manipulation check. All participants then received a written debrief informing them about the true aims of the study.

Power and data analysis

We planned to recruit a total of 120 participants (30 participants per-group). This was based on a power analysis on the effect size for the social modelling manipulation (f = 0.31, derived from Faasse, 2015) with an alpha of 0.05 with 80% power. Of the 121 participants recruited, one participant was excluded from analysis as their sum-scored baseline physical symptoms exceeded the pre-registered threshold, resulting in a final sample of 120 participants.

Primary data analysis

Statistical analysis was conducted using R 4.1.1[17]. The primary data analysis consisted of a one-way (Condition: Natural History, No Social Modelling, Social Modelling Consistent, Social Modelling Inconsistent) ANOVA,

using the Target Symptom difference score (Active – Baseline) as the outcome. Orthogonal contrasts were used to determine:

1. Whether there was an overall nocebo effect—No Treatment (Natural History) vs. Treatment (No Social Modelling, Social Modelling Consistent, Social Modelling Inconsistent).
2. The effect of social modelling, above and beyond explicit instruction alone—No Social Modelling vs. Social Modelling (Social Modelling Consistent and Inconsistent).
3. The effect of generalisation—Social Modelling Consistent vs. Inconsistent.

Secondary analysis examined Non-Target Symptoms and General Symptoms as the outcome variable, in similar one-way ANOVAs. Self-reported and actual cognitive performance scores were compared between groups using one-way ANOVAs to assess the presence of a placebo effect but were not the focus of the study.

Analysis of physiological measures

HRV and EDA were extracted in two non-overlapping five-minute periods: (1) the first five minutes of the post-capsule waiting period ("Time 1") and (2) the second five minutes ("Time 2", immediately after the model communication in the social modelling groups). The data was analysed using a two-way mixed ANOVA comprising the within-subject factor Time (Time 1, Time 2) and the between-subject factor Condition. The same three orthogonal contrasts were used to test preregistered hypotheses. We report the Time main effect, each contrast's main effect, and their respective Time × Contrast interactions. Retaining Time as a repeated-measures factor allowed us to both test overall group differences in physiological arousal and evaluate whether the social modelling manipulation altered arousal over time.

For brevity, only the planned orthogonal contrasts are reported in text. Partial eta squared were interpreted with 0.01, 0.06 and 0.14 as thresholds corresponding to small, medium, and large effect sizes[24]. The results of the omnibus tests are available in Supplementary Materials 2 and 6. Exploratory analysis of symptoms is available in Supplementary Materials Figure S3.

Results

Baseline differences

There were no significant differences between groups in age, gender, or baseline measurements including physical symptoms, state anxiety, general anxiety, expectancy for symptoms, or expected enhancement (all $ps > 0.05$) indicating randomisation was successful (see Supplementary Materials Table S1).

Target symptoms

Figure 2 depicts the group means for the three pre-registered outcomes. Orthogonal contrasts revealed that there was a significant overall nocebo effect, where groups that received the placebo reported increased levels of their Target Symptom relative to the Natural History group, $F(1,116) = 5.28$, $p = 0.023$, $\eta_p^2 = 0.04$. There was no significant difference in Target Symptoms between the No Social Modelling group and the social modelling groups combined, $F(1,116) = 2.56$, $p = 0.112$, $\eta_p^2 = 0.02$, nor was there a significant difference in Target Symptoms between the Social Modelling Consistent and Inconsistent groups, $F(1,116) = 0.03$, $p = 0.86$, $\eta_p^2 < 0.001$.

Non-target symptoms

There was no significant overall nocebo effect, $F(1,116) = 0.44$, $p = 0.50$, $\eta_p^2 = 0.004$, social modelling, $F(1,116) = 1.99$, $p = 0.161$, $\eta_p^2 = 0.02$, or generalisation, $F(1,116) = 0.30$, $p = 0.59$, $\eta_p^2 = 0.002$, on severity of Non-Target Symptoms.

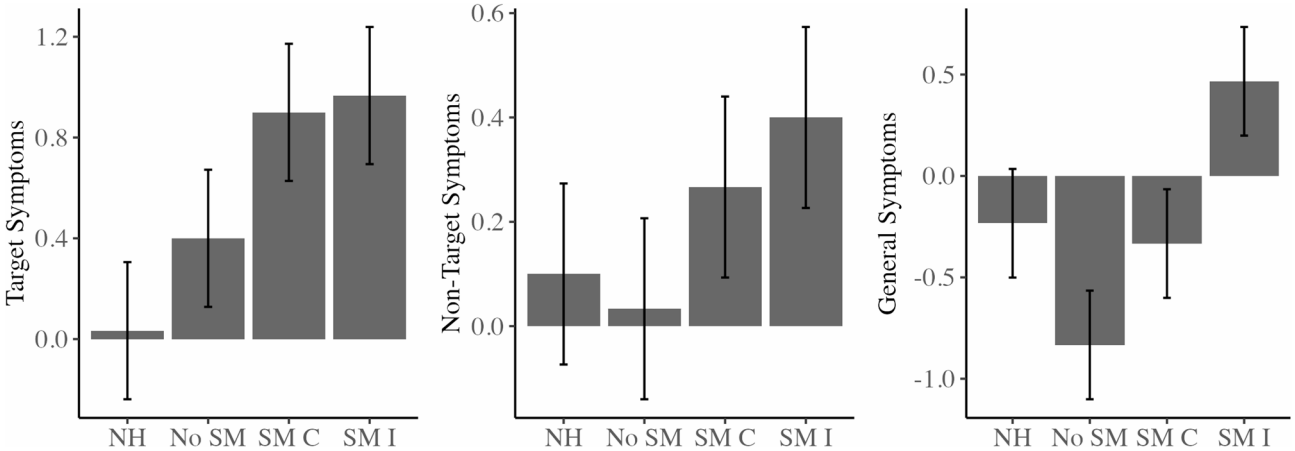


Fig. 2. Pre-registered analyses. Note. From left to right, Mean baseline adjusted Target, Non-Target and General Symptom scores by group. Natural History (NH), No Social Modelling (No SM), Social Modelling Consistent (SM C) and Social Modelling Inconsistent (SM I). All error bars are ± 1 SEM.

General symptoms

There was no significant overall nocebo effect on severity of General Symptoms, $F(1,116) < 0.001$, $p > 0.99$, $\eta_p^2 < 0.001$. However, there was a significant effect of social modelling, $F(1,116) = 7.53$, $p = 0.007$, $\eta_p^2 = 0.06$, where the groups that did not receive social modelling reported a greater reduction in General Symptoms from baseline than those in the social modelling conditions. Similarly, a significant effect of generalisation was found such that participants in the Social Modelling Inconsistent group reported more General Symptoms than Social Modelling Consistent group, $F(1,116) = 4.46$, $p = 0.037$, $\eta_p^2 = 0.04$.

Placebo effect

There was no significant difference in self-reported cognitive performance between groups, $F(3,116) = 0.02$, $p > 0.99$, $\eta^2 < 0.001$, nor was there a significant difference in actual performance, $F(3,116) = 0.15$, $p = 0.93$, $\eta^2 = 0.003$. Within the three groups that received the placebo treatment, there was no significant difference in self-reported influence of treatment on cognitive performance, $F(2,86) = 0.67$, $p = 0.51$, $\eta^2 = 0.02$. See Supplementary Materials Table S7 for group means.

HRV. Refer to Table 1 for group means for the physiological data. Due to technical issues with the Equivital Sensor Module, heart rate data was only available for 81 participants. There was no significant relationship between missing data and participant group, $\chi_3^2 = 1.63$, $p = 0.65$, Cramer's $V = 0.12$. Two-way mixed 2(Time) × 4(Condition) ANOVA was conducted to explore differences in HRV. The two-way mixed ANOVA revealed no significant effect of treatment ($F(1, 77) = 0.08$, $p = 0.773$, $\eta_p^2 < 0.001$), social modelling ($F(1, 77) = 1.78$, $p = 0.186$, $\eta_p^2 = 0.02$), nor generalisation ($F(1, 77) = 0.33$, $p = 0.570$, $\eta_p^2 = 0.004$) on HRV. The ANOVA found no significant effect of time $F(1,77) = 0.17$, $p = 0.68$, $\eta^2 = 0.02$, and no interaction between treatment, social modelling, and generalisation, and time, $F(1, 77) = 0.09$, $p = 0.763$, $\eta_p^2 = 0.001$, $F(1, 77) = 0.94$, $p = 0.336$, $\eta_p^2 = 0.012$. $F(1, 77) = 0.00$, $p = 0.969$, $\eta_p^2 < 0.001$ respectively.

EDA. Due to technical issues, EDA recordings for 92 participants were available. There was no significant relationship between missing data and participant group, $\chi_3^2 = 7.04$, $p = 0.07$, Cramer's $V = 0.25$. Two-way mixed 2(Time) × 4(Condition) ANOVA was conducted to explore differences in tonic (μSCL) and phasic (nSCR) activity separately. Averaged across time, contrasts revealed increased μSCL in groups that received treatment compared to those who did not, $F(1,88) = 12.17$, $p < 0.001$, $\eta_p^2 = 0.12$. Averaged across the other variables in the model, there was no significant effect of social modelling, $F(1,88) = 0.02$, $p = 0.87$, $\eta_p^2 < 0.001$, generalisation, $F(1,88) = 0.26$, $p = 0.61$, $\eta_p^2 = 0.002$, nor time, $F(1,88) < 0.01$ $p = 0.96$, $\eta^2 < 0.001$. Averaged across time, contrasts revealed increased nSCR in groups that received treatment compared to those who did not, $F(1,88) = 6.59$, $p = 0.01$, $\eta_p^2 = 0.07$. There was no significant effect of social modelling, $F(1,88) = 0.05$, $p = 0.83$, $\eta_p^2 < 0.001$, generalisation, $F(1,88) = 0.05$, $p = 0.82$, $\eta_p^2 < 0.001$, nor time, $F(1,88) = 3.09$ $p = 0.08$, $\eta^2 = 0.03$. There was no significant relationship between tonic, $B = 0.01$, $t(89) = 0.44$, $p = 0.67$, or phasic SC, $B = 0.09$, $t(89) = 1.00$, $p = 0.32$, and Target Symptom severity. Table 1 contains group means for the Physiological Measures.

Manipulation check

Most participants correctly recalled the 'treatment' they had taken (93%). The overall social modelling manipulation was successful, with only one participant in the sample reporting suspicion concerning the other participant. A small proportion of participants expressed suspicion that the treatment was a placebo ($N = 23$). However, raising suspicion concerning the placebo treatment did not vary between groups, $\chi^2(3, N = 120) = 7.05$, $p = 0.070$, Cramer's $V = 0.24$, nor was it associated with a change in target symptom reporting, controlling for group, $F(1, 112) = 0.44$, $p = 0.51$ $\eta_p^2 = 0.004$.

Exploratory analyses

Counterbalancing effect

Contrary to hypotheses, social modelling did not increase Target Symptoms above the effect of instruction alone. To investigate, we conducted exploratory analyses to investigate the influence of counterbalancing side effects. The counterbalancing was intended to increase sensitivity to detect genuine nocebo effects[25]. However, it is possible that if one side effect profile was less responsive to the nocebo manipulation, then this could obscure evidence of social modelling. Further, knowledge regarding the types of symptoms that are most receptive to social modelling is important for future research[3].

To investigate this possibility, we conducted a post-hoc two-sample t-test comparing the Target Symptom severity for participants randomised to headache/dizziness as the target profile versus participants with nausea/stomach discomfort as the target profile, collapsed across the four experimental groups. This revealed participants' whose target was headache/dizziness experienced significantly more of their Target Symptoms

		Natural history	No social modelling	Social modelling consistent	Social modelling inconsistent
HRV	M	2.11	1.81	2.31	2.64
	SE	0.42	0.41	0.38	0.42
nSCR	M	19.65	28.25	29.59	28.60
	SE	3.08	3.30	2.79	3.22
μSCL	M	−2.83	2.51	3.27	2.31
	SE	1.37	1.47	1.24	1.43

Table 1. Physiological measures. *Note*. Means are averaged across the factor time.

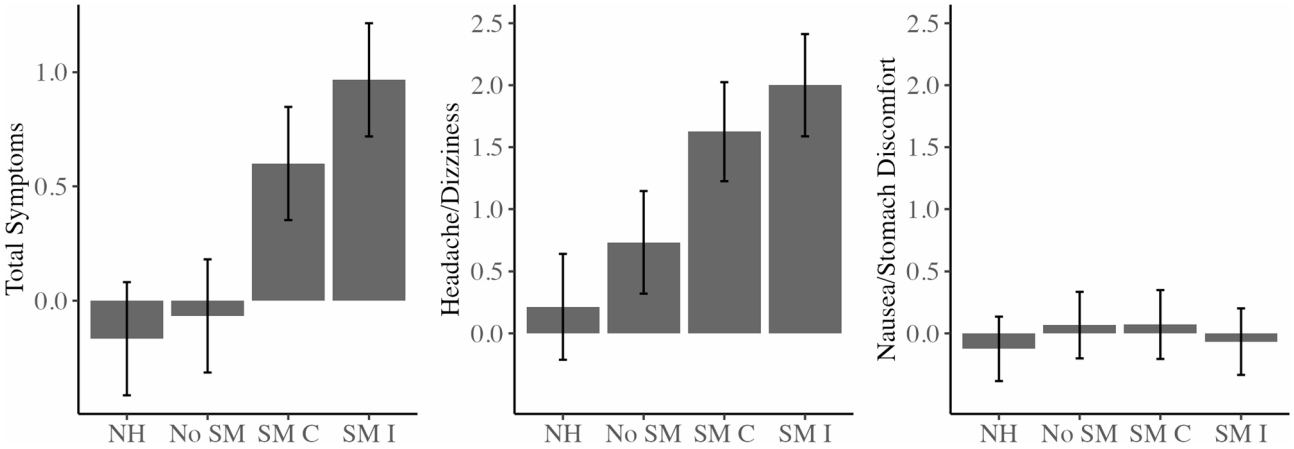


Fig. 3. Exploratory analyses. Note. From left to right, mean Target Symptoms of headache/dizziness warned participants only; mean Target Symptoms of nausea/stomach discomfort warned participants only. Mean headache/dizziness for all participants. All error bars are ± 1 SEM.

($M = 1.17$, $SD = 1.71$) than the nausea/stomach discomfort participants, ($M = -0.02$, $SD = 1.01$), $t(118) = 4.61$, $p < 0.001$, $d = 0.84$. This suggested that headache/dizziness was responsive, but nausea/stomach discomfort was not. Therefore, further exploratory analysis was conducted on the sub-group of participants who were warned about headache/dizziness ($n = 60$). Despite a reduction in power, this revealed a significant overall nocebo effect, $F(1,56) = 6.44$, $p = 0.014$, $\eta_p^2 = 0.10$, and social modelling effect, $F(1,56) = 4.61$, $p = 0.036$, $\eta_p^2 = 0.08$, but no effect of generalisation, $F(1,56) = 0.43$, $p = 0.52$, $\eta_p^2 = 0.007$, on the severity of headache/dizziness experienced. Similar analyses were conducted with participants warned about nausea/stomach discomfort, which found no significant effect on any contrasts ($ps > 0.63$), see Supplementary Materials Tables S4 and S5. When the full sample was included using headache/dizziness as the outcome, the pattern of results was replicated, with a significant overall nocebo effect found on severity of headache reported, $F(1,116) = 6.85$, $p = 0.010$, $\eta_p^2 = 0.06$, and significant social modelling effect $F(1,116) = 5.17$, $p = 0.025$, $\eta_p^2 = 0.04$, but no effect of generalisation $F(1,116) = 0.008$, $p = 0.93$, $\eta_p^2 < 0.001$. Results are presented in Fig. 3.

Discussion

The present study investigated whether socially acquired nocebo effects generalise to similar treatments. Planned analyses revealed an overall nocebo effect, with increased Target Symptom severity in groups that received treatment relative to control. Unexpectedly, there was no significant effect of social modelling above and beyond explicit instruction on Target Symptom severity. Because very few prior studies counter-balance symptom warnings, we conducted a post-hoc, symptom-specific exploration to avoid overlooking differential symptom responsiveness. This exploratory analysis revealed an interesting difference: social modelling increased the nocebo effect when headaches/dizziness were the target profile, but not when nausea/stomach discomfort were, with a large effect of type of target symptom. Most importantly, across both pre-registered and exploratory analyses, the nocebo effect in the Social Modelling Inconsistent group was always as large as, if not larger than, the Social Modelling Consistent group. Taken together, this provides preliminary evidence that while socially induced nocebo side effects may not always be present, when they are present, they do tend to generalise.

Previous research has established the propensity for directly-conditioned nocebo effects to generalise broadly[11,12,26] and socially acquired nocebo effects to generalise across VR contexts[6]. The present research extends this with preliminary evidence demonstrating generalisation of socially acquired nocebo effects *across treatments*. The possibility of this type of generalisation of socially acquired nocebo effects is concerning considering the wealth of treatment-related information communicated between individuals face-to-face, online, and via social media; something which has only been exacerbated by the COVID-19 pandemic[27,28]. It suggests that observing another person experience a negative outcome to a specific treatment can cause the observer to experience nocebo effects not just to that treatment, but to other similar treatments. Interestingly, traditional theories of generalisation from the associative learning literature would predict a weakening of the nocebo effect for different treatments[9]. In the current study, as well as in Saunders et al.[6], the socially acquired nocebo effect was equally large whether participants received the same or a different treatment to the model. In fact, group means across all analyses trended towards an exacerbation in the Social Modelling Inconsistent group. This indicates the absence of any statistically significant reduction of the nocebo effect due to generalisation was not due to a lack of statistical power. As such, when socially acquired nocebo effects are present, generalisation across treatments and contexts appears to be as strong as the original effect and hence even more concerning.

Contrary to hypotheses, the primary pre-registered analysis on symptom severity did not find an additive effect of social modelling on side effects above explicit instruction. Importantly however, planned analysis of the secondary outcome general symptoms andexploratory analysis on the subset of participants for whom headaches/dizziness were the Target Symptoms, found significant medium sized effects of social modelling above and beyond instruction. The results of exploratory analyses are consistent with existing studies demonstrating

socially acquired nocebo effects[15,29–31]. Notably, these previous studies all included headache as a primary symptom of interest. As such, it may be the case that headache and dizziness are more susceptible to nocebo effects in general and/or in the context of 'cognitive enhancers'. This can be compared to the concept of cue preparedness' in learning, where for example rats more readily learn light-shock and taste-nausea contingencies than light-nausea or taste-shock contingencies[32]. Understanding if some symptoms are more receptive to social modelling than others could be useful in the development of recommendations regarding the contexts in which interventions might be most appropriate. Furthermore, given the nature of the exploratory analysis there is a need for pre-registered replication of this result.

Exploratory analyses revealed heightened physiological arousal due to treatment as measured by skin conductance, but no effect when measured using HRV. Physiological arousal was not, however, heightened by social modelling. Previous research has not reached consensus on this topic, with one study finding no effect of social learning on SCR[33] while another has[34]. However, the present analysis of physiological measures is limited due to the lack of pre-treatment baseline measurements. Consequently, it is not clear whether the significantly higher level of arousal among the placebo-treated participants was due to the act of treatment administration itself.

The present study included natural history and treatment-only groups which allowed for a direct assessment of the nocebo effect and the additive effect of social learning above instruction. While this addressed some of the methodological issues in previous studies[15,31], several limitations must be noted. First, the counterbalancing of side effect profiles was intended to increase experimental control and distinguish treatments but appeared to reduce sensitivity to detect socially acquired nocebo effects because nausea and stomach discomfort appeared non-responsive to the manipulations within the measured timeframe. Because the symptom-specific findings were derived from unplanned exploratory analyses, they should be viewed as hypothesis-generating and warrant replication in future preregistered studies. Second, the study was conducted on a healthy student sample utilising an acute treatment. While this allowed for a large sample size, this translated to an overrepresentation of young, educated females in the sample and as such it is important to replicate this research in clinical samples involving longer treatment timeframes. Third, the modelling procedure took place live (i.e., face-to-face), which may differ from virtual platforms, such as social media. Finally, the manipulation check was brief to avoid arousing suspicion in the student cohort prior to the study's conclusion. Thus, participant memory of the specific side effects associated with each "medication" was not assessed.

In conclusion, the current study provides mixed evidence for socially acquired nocebo effects, and also evidence that socially acquired nocebo effects can generalise from an observed treatment to other treatments, depending on the symptoms measured. The abundance of social information communicated between patients, face-to-face or via mainstream and social media, is therefore a concern due to the potential spread of nocebo effects and the burden they cause. Future studies should seek to examine these processes in clinical settings as well as to identify interventions to inhibit these effects.

Data availability

The study was preregistered at aspredicted. org (#109,597) before data collection, including a detailed analysis plan. Deidentified data and analytic code used to conduct the analyses presented in this study are available in a public archive: https://osf.io/m8tdh/.

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Author contributions

All authors (C.S., W.T., K.B., N.M., & B.C.) were involved with study conception and design. C.S. and W.T. ran the experiment sessions with participants. C.S. conducted statistical analyses under the supervision of B.C., N.M. & K.B. C.S. wrote the first draft of the main manuscript text. All authors reviewed the manuscript (C.S., W.T., K.B., N.M., & B.C.).

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to C.S.

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Publication Supplementary Materials

Table S1. Baseline Characteristics

		Natural History	No Social Modelling	Social Modelling Consistent	Social Modelling Inconsistent	χ^2_3	p
Gender	F	21	26	21	19	4.47	.21
	M	9	4	9	11		
						$F(3,116)$	
Age	M	19.60	19.80	18.93	19.77	0.94	.42
	SE			0.42			
Baseline GASE	M	10.96	12.53	12.10	11.66	1.34	.26
	SE			0.57			
Baseline STAI-6	M	9.86	10.60	9.93	10.20	0.37	.78
	SE			0.55			
Baseline Anxiety	M	32.10	25.50	23.27	32.30	1.33	.27
	SE			4.28			
Expectancy (Symptoms)	M	45.40	38.03	43.86	38.83	0.75	.53
	SE			4.23			
Expectancy (Enhance-ment)	M	42.03	45.47	41.40	33.43	1.70	.17
	SE			3.90			

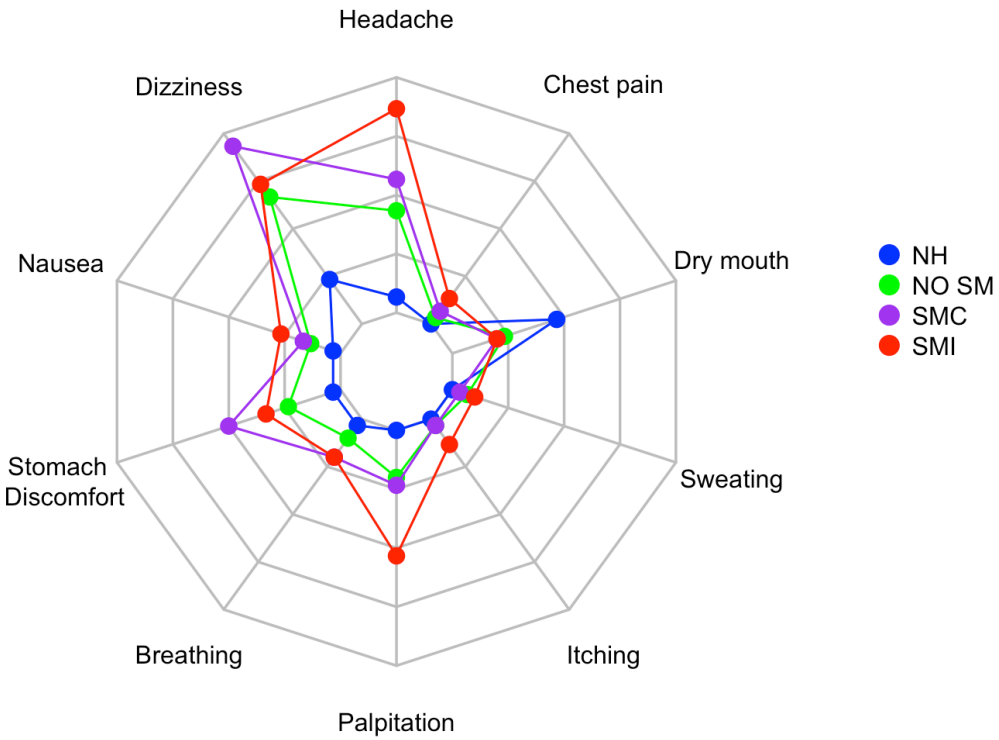
S2. Omnibus ANOVA Results

Target Symptoms. The one-way ANOVA revealed no significant main effect of condition on Target Symptoms, $F(3,116)=2.62$, $p=.054$, $\eta^2=.06$.

Non-Target Symptoms. The one-way ANOVA revealed no significant main effect of condition on Non-Target Symptoms , $F(3,116)=0.91$, $p=.44$, $\eta^2=.02$.

General Symptoms. The one-way ANOVA revealed a significant main effect of condition on General Symptoms, $F(3,116)=4.00$, $p=.009$, $\eta^2=.09$.

Figure S3. Active symptom means, Exploratory.



Counterbalancing. There was a main effect of condition within participants warned about headache and dizziness, on Target symptom severity, $F(3,56)=3.82$, $p=.015$, $\eta^2=.17$.

Table S4. *Group means for Target Symptom severity for subset of participants warned about 'Headaches and Dizziness'*

		Natural History	No Social Modelling	Social Modelling Consistent	Social Modelling Inconsistent
Target profile H/D	M	0.21	0.73	1.63	2.00
	SE	0.43	0.41	0.40	0.41

Similar analyses were conducted with participants warned about Nausea/Stomach discomfort, which found no main effect of condition, $F(3,56)=0.14$, $p=.94$, $\eta^2=.007$. Orthogonal contrasts also revealed no significant overall nocebo effect, $F(1,56)=0.24$, $p=.63$, $\eta_p^2=.004$, no significant effect of social modelling, $F(1,56)=0.03$, $p=.85$, $\eta_p^2<.001$, and no significant effect of generalisation, $F(1,56)=0.13$, $p=.72$, $\eta_p^2=.002$ on severity of nausea and stomach discomfort experienced.

Table S5. *Group means for Target Symptom severity for subset of participants warned about 'Nausea and Stomach Discomfort"*

		Natural History	No Social Modelling	Social Modelling Consistent	Social Modelling Inconsistent
Target Profile N/SD	M	-0.12	0.07	0.07	-0.07
	SE	0.26	0.27	0.28	0.27

S6. Physiological Measures

EDA Omnibus results.

The ANOVA comparing μSCL by time and condition revealed a significant main effect of condition on μSCL, $F(3,88)=4.27$, $p=.007$, $\eta^2=.12$, but not time, $F(1,88)<0.01$ $p=.96$., $\eta^2<.001$, nor an interaction effect $F(3,88)=0.50$, $p=.68$, $\eta^2=.17$.

The ANOVA comparing nSCR by time and condition revealed no significant main effects of condition $F(3,88)=2.29$, $p=.08$, $\eta^2=.07$, or time, $F(1,88)=3.09$ $p=.08$, $\eta^2=.03$, nor an interaction effect $F(3,88)=1.56$, $p=.21$, $\eta^2=.05$. nSCR did not significantly predict severity of target symptoms, B=0.09, $t(89)=1.00$, $p=.32$.

Table S7. Summary of Placebo Effects

		Natural History	No Social Modelling	Social Modelling Consistent	Social Modelling Inconsistent	$F(3,116)$	p
Perceived Performance	M	39.63	38.87	38.67	39.67	0.67	.51
	SE			3.93			
Objective Performance	M	50.70%	53.16%	52.37%	51.06%	0.15	.93
	SE			2.96%			
						$F(2,86)$	
Estimated Enhancement	M		28.96	26.60	22.75	0.67	.51
	SE			3.77			

Appendix D: Supplementary Material, Chapter 5

Study Approval Letter

THE UNIVERSITY OF SYDNEY

Research Integrity & Ethics Administration
HUMAN RESEARCH ETHICS COMMITTEE

Monday, 9 October 2023

Dr Ben Colagiuri
Psychology; Faculty of Science
Email: ben.colagiuri@sydney.edu.au

Dear Ben,

Your request to modify this project, which was submitted on 07/09/2023, has been considered.

After consideration of your response to the comments raised, this project has been approved to proceed with the proposed amendments.

Protocol Number: **2022/532**
Protocol Title: **Socially Acquired Nocebo Effects: The Role of Similarity**

Addition of Authorised Persons: David Ng
Removal of Authorised Persons:

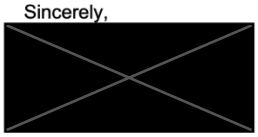
New Completion Date:
Annual Report Due: **10/08/2024**

Documents Approved:

Date Uploaded	Version Number	Document Name
03/10/2023	Version 2	Debrief
03/10/2023	Version 2	PIS CLEAN

Please contact the ethics office should you require further information.

Sincerely,



Dr Joanne Hart
Chair
Modification Review Committee (MRC 3)

The University of Sydney of Sydney HRECs are constituted and operate in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2018) and the NHMRC's Australian Code for the Responsible Conduct of Research (2018)

Research Integrity & Ethics Administration
Research Portfolio
Level 3, F23 Administration Building
The University of Sydney
NSW 2006 Australia

T +61 2 9036 9161
E human.ethics@sydney.edu.au
W sydney.edu.au/ethics

ABN 15 211 513 464
CRICOS 00026A

Pre-registration

ASPREDICTED

Wharton CREDIBILITY LAB
UNIVERSITY of PENNSYLVANIA

Can positive social information reduce socially acquired nocebo effects? (#163947)

Author(s)
This pre-registration is currently anonymous to enable blind peer-review.
It has 2 authors.

Pre-registered on: 02/27/2024 03:44 PM (PT)

1) Have any data been collected for this study already?
No, no data have been collected for this study yet.

2) What's the main question being asked or hypothesis being tested in this study?
Can positive social modelling reduce the effect of subsequent negative social modelling on nocebo side effects?
Participants will be told they may receive no treatment or a pill that will enhance cognitive ability and may cause headaches and dizziness. In actuality, the treatment is inert (placebos).
H1. Groups that receive the placebo treatment will demonstrate a nocebo effect, i.e., increased symptoms, relative to those who receive no placebo treatment [Main effect of placebo treatment].
H2. Social modelling of side effects by confederate will increase the nocebo effect relative to explicit instruction [Main effect of social modelling]
H3. Positive social information will reduce nocebo side effects relative to no positive social information [Main effect of positive social information, i.e., the intervention being assessed].
H4. The positive social modelling will be more effective on participants who receive negative social modelling compared to participants who only receive explicit instruction. [Interaction between social modelling and positive social information intervention]

3) Describe the key dependent variable(s) specifying how they will be measured.
Physical symptoms will be assessed using a 10-item modified version of the General Assessment of Side Effects Scale (GASE; Rief, Glombiewski, & Barsky, 2009). The original four-point scale (0-3, not present to severe) will be modified to a seven-point scale to enhance the sensitivity to changes in symptoms.
The primary outcome of interest will be sum score severity of headache and dizziness (hereafter 'symptom severity'). Physical symptoms will be measured at the start of the experiment session prior to pill administration in the treatment conditions (Baseline), and at the end of the experimental session (Active). The difference score (Active – Baseline) will form the primary outcome.
State Anxiety: State-Trait Anxiety Inventory-6 (Marteau & Bekker, 1992).
Side effect specific anxiety, expectancy for side effects, expected cognitive enhancement and self-reported cognitive performance will all be measured using single items on a visual analogue scale (VAS) ranging from 1 to 100.
Cognitive performance: Rapid visual information processing (RVIP) to assess sustained attention (Wesnes et al., 1983).

4) How many and which conditions will participants be assigned to?
Participants will be randomised to one of five conditions within a 2(Induction method: Explicit Instruction alone, Social Modelling + Explicit Instruction) x 2(Positive Social Information Intervention: No Intervention, Intervention)+1(Natural History) between-subjects design.
All participants will read side effect warnings and watch a short video concerning a new supposed cognitive enhancement medication (actually a placebo). This medication will be described to participants as "previously associated with the experience of headaches and dizziness".
Participants in the Intervention condition will also view an additional clip at the end of the instructional video with a social model (actually one of the experimenters) reporting a positive experience with the medication. Participants in the No Intervention condition will not receive this positive social information.
All participants except those in the Natural History group will receive the treatment.
Participants in the Social Modelling + Explicit Instruction condition will then watch a social model live (actually of one of the experimenters) experience side effects from the cognitive enhancement medication. Participants in the Explicit Instruction alone condition will not receive this negative social information.

5) Specify exactly which analyses you will conduct to examine the main question/hypothesis.
The primary data analysis will consist of a one way five level ANOVA(Induction method x Positive Social information Intervention + control group), using baseline adjusted (Active – Baseline) symptom severity as the outcome variable.
Four contrasts will determine: effect of treatment (H1, natural history control vs all other groups), the effect of induction method (H2), the effect of the intervention (H3) and the interaction between induction method and the intervention (H4)
In the case that the intervention is highly effective at symptom reduction in the Social Modelling + Explicit instruction group, it may mean that the main effect of the Induction method is not significant. In this case a simple effect will be used to compare the Social Modelling group to the Explicit Instruction group (Both in the No Positive Social Information Intervention condition) which will be used to assess the effect of social modelling.
Moderation analyses will then be conducted to explore any group differences revealed in the above analyses using gender, state anxiety, side-effect anxiety, side-effect expectancy, Heart Rate Variability (HRV), Electrodermal Activity (EDA) as moderators.
Secondary analysis will explore side effect generalisation with the remaining GASE items sum-scored as the outcome variable, in analyses mirroring those detailed above.
Self-reported cognitive performance and actual cognitive performance will also be compared between groups in a similar way to the primary analyses to

assess the presence of a placebo effect.

6) Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.
Participants should be in full health at time of testing. Those with extreme baseline side effects (six or more on any single item, or a mean greater than four) will be excluded from analyses.
A sensitivity analysis will be conducted comparing naive participants to those that correctly identify that the pill they took was a placebo, or that the participant they observed was an actor.

7) How many observations will be collected or what will determine sample size? No need to justify decision, but be precise about exactly how the number will be determined.
A total of 160 participants (32 participants per-group minimum) will be recruited. This is based on a power analysis assuming a medium effect size for the intervention manipulation (f = .25, the intervention effect size is hypothesised to be smaller than that of social modelling) with an alpha of .05 with the power to detect an effect set at 80%.

8) Anything else you would like to pre-register? (e.g., secondary analyses, variables collected for exploratory purposes, unusual analyses planned?)
Physiological response will be measured using HRV and EDA.
HRV will be measured continuously throughout the session, and EDA measured continuously for 15 minutes after pill administration. A window of time after pill administration (Baseline) will be compared to a window of time after the SM manipulation (Active) between conditions for both physiological measures.

Questionnaires/Instruments

Q4

Participant Consent Form ***Research Study: Cognitive Enhancement Study*** Prof. Ben Colagiuri (Responsible Researcher) School of Psychology, Faculty of Science Phone: +61 2 9351 4589 | Email: ben.colagiuri@sydney.edu.au Miss Cosette Saunders (PhD student) | Email: cosette.saunders@sydney.edu.au I agree to take part in this research study. In giving my consent, I confirm that: The details of my involvement have been explained to me, and I have been provided with a written Participant Information Statement to keep. I understand the purpose of the study is to investigate the efficacy of new cognitive enhancement medications. I acknowledge that the risks and benefits of participating in this study have been explained to me to my satisfaction. I understand that in this study I will be required to Attend a single 1 hour session, conducted in Top South Badham, University of Sydney Provide some basic demographic data, e.g. age, gender Wear a heart rate monitor throughout the session, and have my electrodermal activity monitored. Complete some basic questions about my current state of well-being Complete a simple cognitive performance task I understand that being in this study is completely voluntary. I am assured that my decision to participate will not have any impact on my relationship with the research team or the University of Sydney. I understand that I am free to withdraw from this study and that I can choose to withdraw any information I have already provided (unless the data has already been de-identified or published). I have been informed that the confidentiality of the information I provide will be protected and will only be used for purposes that I have agreed to. I understand that information about me will only be told to others with my permission, except as required by law. I understand that the results of this study may be published, and that publications will not contain my name or any identifiable information about me. I understand that my data may be deposited in electronic repositories, and that no identifying information me will be included in such data sets. I understand that after I sign and return this consent form it will be retained by the researcher, and that I may request a copy at any time.

HREC Approval No.: 2022/532

Q5 Please enter your first and last name.

_____

Q30 I would like feedback on the overall results of this study

- Yes (1)
- No (2)

Display this question:

If I would like feedback on the overall results of this study = Yes

Q31 If yes, please provide your preferred contact email:

_____

consent

Please select your choice below. Clicking on the "I consent" button below indicates that: • You have read the above information • You voluntarily agree to participate If you do not wish to participate in the research study, please decline participation by clicking on the "I DO NOT consent" button. This will close the current Qualtrics survey and send you to the University of Sydney homepage.

- I consent to take part in the study (1)
- I DO NOT consent to take part in the study (2)

End of Block: Consent

Start of Block: Intervention

Q66 Please pause here and ask the experimenter for instructions to proceed

Page Break

pid Please enter the Participant Identification Number provided by the experimenter:

_____

Page Break

Q62 The following video will provide the information you will need to watch for the study. Please watch:

End of Block: Intervention

Start of Block: Fit Equivital

Q78 The experimenter will now fit you with the Eqivital heart rate harness.

Page Break

Q79 Please enter the code provided by the experimenter to proceed

_____

End of Block: Fit Equivital

Start of Block: Demographics

Q61 Please answer the following questions

age What is your age?

_____

gender What is your gender?

- Male (1)
- Female (2)
- Other (3)

End of Block: Demographics

Start of Block: Baseline GASE

BGASE Rate your experience of each of these symptoms over the past 30 minutes

	Not Present (1)	(2)	Mild (3)	(4)	Moderate (5)	(6)	Severe (7)
Headache (1)							
Dizziness (2)							
Nausea (4)							
Stomach Discomfort (5)							
Breathing Problems (6)							
Palpitation (7)							
Itching (8)							
Abnormal Sweating (9)							
Dry Mouth (11)							
Chest Pain (12)							

End of Block: Baseline GASE

Start of Block: STAI-6

Description A number of statements which people have used to describe themselves are given in the next few questions. Read each statement and choose the most appropriate answer below the statement to indicate **how you feel right now, at this moment.** There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

BSTAI_1 I feel calm

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_2 I am tense

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_3 I feel upset

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_4 I am relaxed

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_5 I feel content

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

BSTAI_6 I am worried

- Not at all (1)
- Somewhat (2)
- Moderately (3)
- Very Much (4)

End of Block: STAI-6

Start of Block: Baseline Expectancy and Anxiety

Q58 Read each statement and choose the most appropriate number below the statement to indicate how you feel right now, at this moment.

Q21 To what degree do you expect the cognitive enhancement medication to enhance your performance?

	No enhancement 0	25	50	75	Significant enhancement 100
()					

BE How much do you expect to experience adverse events (e.g. side effects) as a result of participating in this study?

	Not at all 0	25	50	75	Very much so 100
()					

BA How anxious are you about experiencing adverse events (e.g. side effects) as a result of participating in this study?

	Not anxious 0	25	50	75	Very anxious 100
()					

End of Block: Baseline Expectancy and Anxiety

Start of Block: Administer Treatment

Q33 Please pause here and ask the experimenter for instructions to proceed

End of Block: Administer Treatment

Start of Block: RVIP

Start of Block: Active GASE

Q34 Please enter the code provided by the experimenter to proceed

_____

Page Break

Q60 Rate your experience of each of these symptoms over the past 30 minutes or since you received medication

	Not Present (1)	(2)	Mild (3)	(4)	Moderate (5)	(6)	Severe (7)
Headache (1)							
Dizziness (2)							
Nausea (4)							
Stomach Discomfort (5)							
Breathing Problems (6)							
Palpitation (7)							
Itching (8)							
Abnormal Sweating (9)							
Dry Mouth (11)							
Chest Pain (12)							

End of Block: Active GASE

Start of Block: Post eval of efficacy

Q32 What Treatment did you receive?

- Vitatril (2)
- No Treatment Control (3)
- I took one of the medications but do not recall which one (4)
- I do not recall if i received treatment (5)

Q58 How would you rate your performance on the cognitive task?

Very Poor Very Good

0 10 20 30 40 50 60 70 80 90 100

  ()

Display this question:

If What Treatment did you receive? =

Or What Treatment did you receive? = Vitatril

Or What Treatment did you receive? = I took one of the medications but do not recall which one

PVRA How effective was the medication at enhancing your cognitive performance?

Not effective at all Very effective

0 10 20 30 40 50 60 70 80 90 100

  ()

Q28 Please describe what you believe the purpose of the study to be:

_____

End of Block: Post eval of efficacy

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Regular Article

Positive social modeling attenuates nocebo side effects

Cosette Saunders, BSc (Hons)[1,*], Winston Tan, PhD[1], David Ng, PhD[1], Alexander Burchett, BAdvSt (Hons) (Psych)[1], Nicolas McNair, PhD[1], Ben Colagiuri, PhD[1]

[1]School of Psychology, University of Sydney, Sydney, Australia

[*]**Corresponding author:** Cosette Saunders, BSc(Hons), School of Psychology, University of Sydney, Australia (cosette.saunders@sydney.edu.au)

Abstract

Background: Receiving negative instructions and observing another's adverse treatment-related experience can lead to worsened health outcomes via the nocebo effect. However, it is unknown whether the observation of a positive treatment-related experience can mitigate these effects.

Purpose: To investigate whether a positive social modeling intervention can reduce nocebo side effects induced by instruction and social modeling.

Methods: Participants ($N = 160$) were told the study assessed a new cognitive enhancer (actually a placebo). Participants received side effect warnings and viewed an informational video describing the medication. Placebo-treated groups were randomized to either watch an additional clip where a peer reported a positive experience with no side effects or not. These groups were further randomized to either encounter a live model exhibiting side effects or not. A Natural History group did not view any modeling nor receive the placebo. The primary outcome was the severity of side effects.

Results: A significant nocebo effect was observed, with increased symptom severity in placebo-treated groups compared to the Natural History group. The positive social modeling intervention (i.e., viewing a peer experience no side effects) significantly reduced symptom severity. No significant difference in symptom severity was found between instruction alone and instruction with side effect modeling, nor was there an interaction between the induction method and the positive social modeling intervention.

Conclusions: Positive social modeling reduces nocebo side effects induced by instruction alone and instruction with side effect modeling. Positive social modeling may be an effective method to mitigate the burden of nocebo side effects in clinical settings.

Lay Summary

Negative expectancies can trigger adverse symptoms via the nocebo effect. These nocebo effects significantly increase the burden of side effects patients experience. This study tested whether positive social modeling—providing a video recording of another person reporting no adverse symptoms—can counteract nocebo effects. We found that participants who received warnings about side effects or who watched another person experience side effects reported more adverse symptoms after receiving a fake cognitive enhancer than a control group. Most importantly, we also found that providing positive social modeling counteracted this effect. These results suggest that providing positive social information can help reduce the nocebo effect and has the potential to reduce the burden of side effects.

Keywords: instruction; nocebo effect; placebo; social learning; social modeling; side effects.

Open Science Transparency Statements

1. The study was pre-registered at AsPredicted.org: https://aspredicted.org/hk9p-h5tr.pdf
2. The analysis plan was registered prior to beginning data collection at AsPredicted.org: https://aspredicted.org/hk9p-h5tr.pdf
3. De-identified data from this study are available in a public archive: https://osf.io/zfas7/
4. Analytic code used to conduct the analyses presented in this study are available in a public archive: https://osf.io/zfas7/
5. Some of the materials used to conduct the study are presented in a public archive: https://osf.io/zfas7/

Introduction

The nocebo effect, a pervasive psychobiological phenomenon in which individuals develop or experience an exacerbation of symptoms beyond what can be attributed to a treatment's active elements, is increasingly recognized as a significant factor contributing to the experience of side effects. A large-scale review of pharmacological clinical trials involving over half a million participants found that nearly 3-quarters of placebo-treated individuals reported side effects and that these rates were often comparable with the drug arm.[1] The time and cost associated with the management of side effects impose a substantial burden on our healthcare systems. In the US alone, managing adverse drug reactions is estimated to cost billions annually[2] with side effects often leading to worse treatment

adherence and even treatment cessation.[1] Given the significant clinical and financial implications, identifying strategies to mitigate nocebo effects is critical.

In the absence of prior direct experience, nocebo effects can arise through instruction. Instruction refers to the information individuals receive about their treatment, such as when a health professional informs a patient that a medication may cause side effects (verbal) or reading the side effect information listed on medication packaging (written). While such side effect warnings are necessary for informed consent, a wealth of evidence indicates that they can produce negative expectancies that exacerbate side effects via the nocebo effect.[3–7] For example, patients receiving analgesia found the injection more painful when told "You will feel a big bee sting; this is the worst part," compared to more neutral wording.[8]

Research to date on strategies to minimize instructed nocebo effects is sparse and inconsistent. One proposed method is side effect framing, which involves presenting statistical information associated with side effects in a positive manner, e.g., "7 in 10 patients WILL NOT experience headaches compared to "3 in 10 patients WILL experience headaches."[9] Although Faasse et al.[10] found that this approach significantly reduced the nocebo effect during a one-hour experimental session, no effect was present when assessed 24 hours later. Furthermore, other empirical studies fail to find any effect of side effect framing.[11,12] Another suggested strategy is "nocebo education," or informing patients about the nature and mechanisms of the nocebo effect.[13,14] However, educational interventions can sometimes yield minimal benefits or even backfire.[15] For example, one study aimed to improve perceptions of generic medicines via an educational video, but unexpectedly found reduced pain relief and increased symptoms when participants used the generic versus the branded version of the same medication.[15] Although the intervention improved the perception of generic drugs, it may have unintentionally highlighted differences between generic and branded products or heightened participants' attention to potential side effects—paradoxically worsening health outcomes, consistent with research concerning educational interventions with respect to other health outcomes.[16] Given the substantial health and societal risks posed by the nocebo effect, it is crucial that novel and more effective strategies be investigated and implemented.

Importantly, in addition to instructions, we also acquire expectations via social learning. Social learning refers to what we learn by observing other's experiences, such as observing a friend experience headaches after taking a medication, and subsequently expecting and experiencing increased headaches after our own encounter with the medication.[17] Socially induced nocebo effects are robust and can influence a variety of symptom domains including pain, itch, nausea, and general side effects. Furthermore, recent evidence indicates that socially induced nocebo effects can be passed along social chains[18,19] and can be triggered by exposure to social media.[20] Concerningly, this research indicates that observing someone else experience a nocebo effect itself, can lead to the proliferation of nocebo effects. As such, social learning presents a potentially significant cumulative trigger for nocebo-induced side effects across society and health settings.

Yet, while socially induced nocebo effects are concerning, social learning may also provide an avenue to inhibit nocebo effects via positive social modeling. While placebo and nocebo effects do appear to have some important differences in their psychological and neurobiological mechanisms,[21] the fact that positive social modeling induces placebo effects raises the possibility that positive social modeling could counteract the negative expectancies induced by nocebo instructions and social learning. Many nocebo social learning studies use a control group in which the model does not report any symptoms,[22] which could be considered "positive" social modeling if the key outcome is the presence of side effects. Critically, however, in those studies participants are only ever exposed to either a negative or a positive social model and so they do not provide any evidence regarding whether positive social modeling can counteract nocebo effects.

To address this gap, the present study investigated whether a novel positive social information intervention could reduce nocebo side effects induced by instruction and social modeling. Participants were told they were part of a study investigating the efficacy of a new cognitive enhancement medication—which was actually a placebo. All participants received warnings about side effects and watched a short video concerning the supposed new cognitive enhancement medication. This medication was described to participants in the consent form and via the video as "associated with the experience of headaches and dizziness." Participants in the Intervention condition viewed an additional clip where a social model (actually one of the researchers) reported a positive experience with the medication, finding it effective and communicating their lack of side effect experience. Participants in the No Intervention condition were not exposed to this positive social model. After the placebo was administered in the treatment groups, participants in the Instruction + Side effect Modeling condition then watched a live social model (a confederate participant) experience side effects from the medication. Participants in the Instruction Alone condition were not exposed to this negative social model. We hypothesized that there would be an overall nocebo effect, with increased symptom reporting in the placebo groups compared to the control group. Furthermore, we expected that live social modeling of side effects would exacerbate this nocebo effect compared to instruction alone. Most importantly, we hypothesized that positive social information would reduce nocebo side effects relative to conditions without such information. Finally, we predicted that the Positive Social Modeling Intervention would be more effective in participants exposed to negative social modeling than in those who received instruction alone, reflecting an interaction between side effect modeling and the positive social information intervention.

Methods

The study design and analyses were pre-registered (aspredicted.org #163947). Ethics approval was granted by the University of Sydney (#2022/532).

Participants. One hundred and sixty healthy volunteers (Female = 110, Male = 46, Other = 4, M_{age} = 20.16, *SD* = 3.97, Range 17 - 48) from the University of Sydney participated and received course credit as compensation over the period February–July 2024. Figure 1 presents a CONSORT Flow Diagram of participant selection. Information regarding sample race and socioeconomic status was not collected. Eligible participants were healthy adults fluent in English without any known allergy to medication or lactose. Due to the gelatin capsules, those with dietary restrictions were advised not to participate. To ensure participants were not

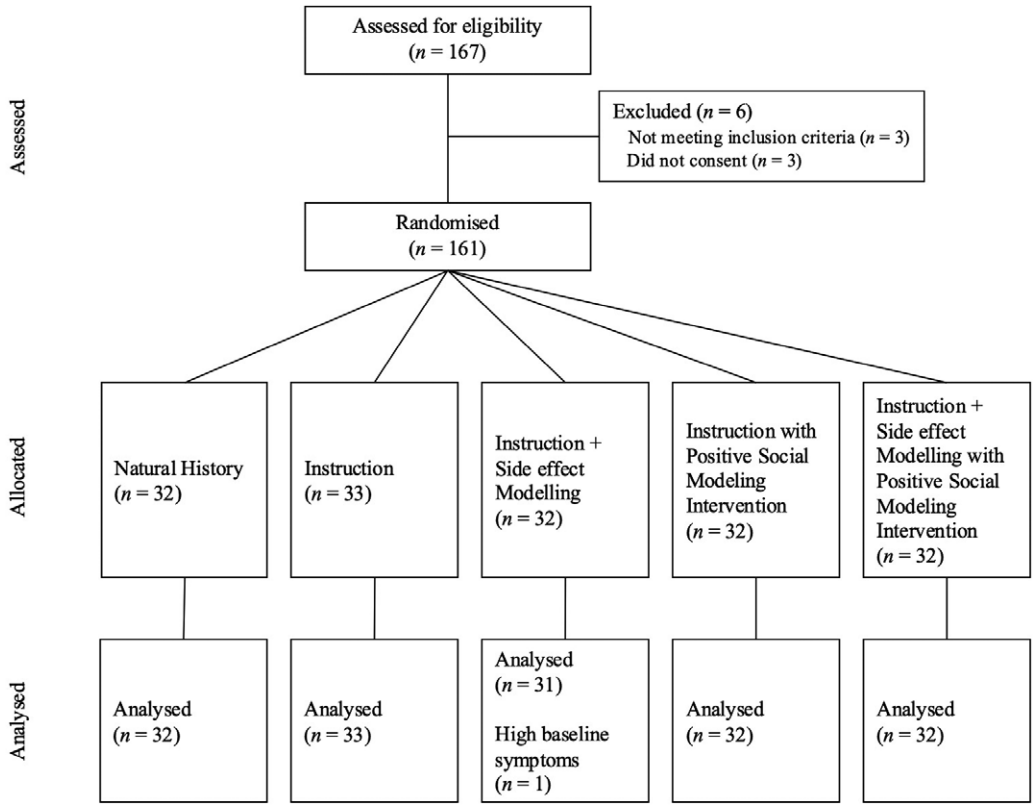

Figure 1. CONSORT flow diagram of participant selection process.

experiencing significant symptoms at the time of testing, they were excluded from analysis if they exceeded pre-registered thresholds of physical symptoms pre-treatment (details below).

Design

The study employed a single-blind between-subjects design with participants randomized using R 4.2.2[23] as a random number generator to 1 of 5 conditions based on a 2 (Nocebo Induction Method: Instruction Alone vs. Instruction + Side effect Modeling) × 2 (Positive Social Modeling Intervention: Positive Model vs. No Positive Model) factorial design with an additional Natural History control group. Participants were told the study was investigating the efficacy of a new cognitive enhancer (actually a placebo). All participants then viewed one of 2 versions of a 5-minute informational video. In the No Intervention condition, the video featured a researcher describing the supposed cognitive enhancer's benefits and potential side effects (i.e., headaches & dizziness), along with a demonstration of the general procedure using footage of a supposed previous participant (actually a confederate). In this version of the video the confederate was only seen up to the point of taking the treatment, so they did not provide any information about the treatment experience or side effects. In the Intervention condition, the same video was presented but it also included an additional 30-second segment at the end, where the supposed previous participant was asked about the cognitive enhancer's efficacy and side effects and explicitly reported the absence of any side effects. The videos are publicly available on OSF https://osf.io/zfas7/. Participants were then further randomized to either encounter a live social model who reported side effects ("Instruction + Side effect Modeling") or not ("Instruction Alone"). This model was a different confederate presented to participants as another participant of the study who was concluding their participant time such that the model was asked about side effects and verbally reported experiencing headaches and dizziness. This led to 4 groups: Instruction, Instruction with Positive Social Modeling Intervention, Instruction + Side effect Modeling, and Instruction + Side effect Modeling with Positive Social Modeling Intervention. A fifth group was included to create a natural history/control condition to enable an overall assessment of the nocebo effect. This group viewed the "No Intervention" version of the informational video but did not receive the placebo treatment. The primary dependent variable was the severity of symptoms reported by participants.

Materials and measures

Physical symptoms.

Physical symptoms were assessed using a 10-item modified version of the General Assessment of Side Effects, GASE.[24] Each of the 10 symptoms assessed was rated using a 7-point scale 0 (not present) to 7 (severe). The primary outcome of interest was sum-score of the headaches and dizziness items from the GASE corresponding to the side effect warnings and symptoms modeled by the live model. In accordance with pre-registration, those with extreme baseline side effects (6 or more on any single item, or a mean greater than 4) were excluded from analyses.

Symptom expectancy.

Participants were asked to rate their expectancy of the experience of side effects on the single item measure: "How much do you expect to experience adverse events (e.g., side effects) as

a result of participating in this study?" on a Visual Analogue Scale (VAS) ranging from 1 (not at all) to 100 (very much so).

Expectancy for cognitive enhancement.

Participants were asked to rate their expectancy of the efficacy of the cognitive enhancement medication on the single item measure: "To what degree do you expect the cognitive enhancement medication to enhance your performance?" on a VAS ranging from 1(No enhancement) to 100(Significant enhancement).

Generalized state anxiety.

General state anxiety was measured via the Spielberger State-Trait Anxiety Inventory-6 (Cronbach's alpha = .75).[25] Participants rated 6 items like "I am relaxed" on a 4-point scale ranging from 1 (not at all) to 4 (very much) based on how they felt at the present.

Side effect specific anxiety.

Participants rated their anxiety concerning experiencing side effects on the single item measure: "How anxious are you about experiencing adverse events (e.g., side effects) as a result of participating in this study?" on a VAS ranging from 1(Not Anxious) to 100(Very Anxious).

Objective cognitive performance.

Sustained attention was measured using the Rapid Visual Information Processing (RVIP) task.[26] For 5 minutes, numbers from 1 to 9 were displayed at a speed of 100/min on a computer screen. Participants were instructed to press the space bar when 3 consecutive even or 3 consecutive odd numbers appeared in the sequence. They had 1.5 seconds to respond appropriately, or the response was regarded as a false alarm. The target sequences were spaced by a minimum of 5 and a maximum of 33 digits due to the semi-random nature of the number series. A performance evaluation was conducted using the percentage (%) of correct answers.

Self-reported cognitive performance.

Participants were asked to rate their perceived performance on the RVIP: "How would you rate your performance on the cognitive task?" on a VAS ranging from 1(Very poor) to 100(Very good).

Self-reported impact of treatment on cognitive performance.

Participants assigned to take the placebo were asked "How effective was the medication at enhancing your cognitive performance?" on a VAS ranging from 1(Not effective at all) to 100(Very effective).

Manipulation check.

Participants were asked "Briefly describe (in 2-3 sentences) what you thought the purpose of the experiment was". The probe was intentionally vague to prevent prematurely raising suspicion regarding the study within the student cohort.

Placebo capsules.

All participants assigned to take the "cognitive enhancer" received white and blue gelatin capsules filled with lactose.

Heart rate and electrodermal activity.

Participant heart rate and electrodermal activity were measured. Details can be found in Supplementary Materials 6.

Laboratory setting.

The lab was set up like a clinic room to reinforce the cover story. The room contained a medical examination bed and potted plants. The walls were decorated with posters about the anatomy of the brain, memory processes, and attention. The researcher wore a lab coat, and a heart rate monitor was visibly used, all reinforcing the realism of an experimental medication study.

Procedure

Refer to Figure 2 for a flow chart of the study procedure. Participants each attended a 1-hour experimental session. Participants first received an information statement and consent form that outlined the cover story and contained the side effect warning concerning the supposed medication: "*Vitatril* has been associated with the experience of mild headaches and dizziness." Once consent was obtained, participants were asked to watch a video described as a way to inform them of the study aim and procedures. The positive social modeling was implemented via this video. In the No Intervention and Natural History conditions the video detailed: the supposed medication, its mechanism of action, its side effects, and a demonstration of the study procedure with another participant (actually another researcher). Those assigned to the Intervention conditions, watched the same video as those in the No Intervention and Natural History conditions, with an additional scene at the end where the supposed participant was asked how they were feeling. The participants indicated that they felt the positive effects of the medication (i.e., "more

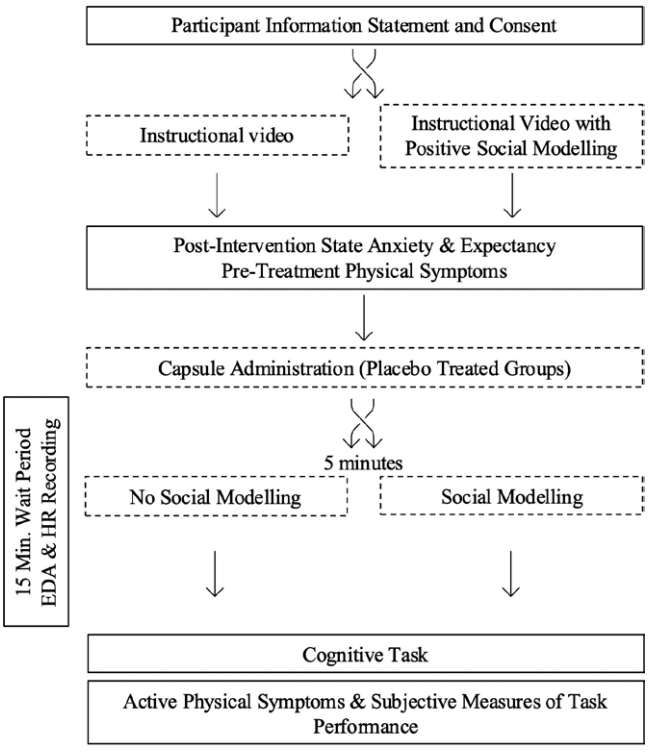

Figure 2. Flowchart of study procedure. All participants underwent steps outlined by solid boxes. Boxes with dashed lines indicate a step participants were randomized to undertake. Participants in the Natural History group watched the instructional video with no positive social modeling, did not receive the placebo treatment and did not view the live side effect modeling.

focused") and emphasized they did not feel any side effects. The videos are publicly available at https://osf.io/zfas7/. Participants were then fitted with the Equivital Harness and were asked to complete the demographic questions and post-intervention state anxiety and expectancy measures. In addition, a pre-treatment measure of physical symptoms was recorded to identify those who met the exclusion criteria and to control for symptoms being experienced at baseline. Next, participants were seated on a physical exam bed and set up with the electrodes to measure their EDA. The placebo capsules were then administered to treatment groups. All participants were seated and waited for 15 minutes, ostensibly providing time for the medication to take effect in the treatment groups. Exactly 5 minutes after the physiological recordings commenced, participants in the side effect modeling conditions saw a confederate enter the room. In view of the participant, the researcher asked the confederate how they were feeling and the confederate responded with "Not great, definitely feeling headachy… and a bit dizzy." To account for the potential confound of having 2 different individuals as the positive social model and the side effect model respectively (as necessitated by study design), we counterbalanced which confederate served as the live and video models. Further, to control for gender, age and race, both confederates were Asian Australian men in their 20s. At the timepoint of side effect modeling in the Instruction + Side effect Modeling groups, participants in the other groups overhead the researcher have an irrelevant phone call to control for any generic effects of hearing a conversation. After the 15-minute wait period, all participants completed the cognitive task to uphold the cover story. Next, participants completed the active physical symptoms questionnaire, reported their perceived efficacy of the medication, and completed the manipulation check. At the conclusion of data collection, all participants received a written debrief informing them about the true aims of the study.

Power and data analysis

All data analysis was conducted in R 4.2.2[23] using a threshold of $\alpha < .05$ to determine significance. The primary data analysis consisted of a 2 (Nocebo Induction Method: Instruction Alone, Instruction + Side effect Modeling) × 2 (Intervention: No Intervention, Intervention) + 1 (Natural History) ANOVA, using the symptom difference score (active - baseline/pre-treatment) as the dependent variable. Orthogonal contrasts were used to determine the presence of a nocebo effect (Placebo Treatment vs Natural History), the main effect of Nocebo Induction method (Instruction Alone vs Instruction + Side effect Modeling), the main effect of the Positive Social Modeling Intervention (Positive Social Modeling vs No Positive Social Modeling), and the interaction between the Positive Social Modeling Intervention and the Nocebo Induction Method. Secondary analysis explored side effect generalization with the remaining 8 GASE items sum-scored as the outcome variable, in analyses mirroring those detailed above. Moderation analyses were then conducted to explore group differences revealed in the primary analyses using gender, state anxiety, side effect anxiety, side effect expectancy as moderators. Self-reported cognitive performance and actual cognitive performance were compared between groups in a similar way to the primary analyses to assess the presence of a placebo effect. The effect of the Positive Social Modeling Intervention on expectancy and anxiety was assessed using t-tests comparing the groups that received the intervention to those that did not, collapsed across side effect modeling conditions as expectations and anxiety were measured prior to the side effect modeling manipulation. Expectations of side effects that might occur from the supposed treatment were assessed in all participants after the information about the study was delivered, which included the warning about side effects and Positive Social Modeling Intervention in the relevant groups, but before participants knew whether or not they would receive the supposed treatment (i.e., placebo capsules). Mediation analyses were therefore conducted to assess if the effect of the Positive Social Modeling Intervention on side effects was mediated via expectancies. Note, however, that since capsule administration in placebo treatment groups occurred after expectations were measured, we were unable to conduct a mediation to assess if the overall nocebo effect (Placebo Treatment vs Natural History) was mediated via expectancies.

As per pre-registration, a minimum of 32 participants per-group were recruited. This was based on a power analysis assuming a medium effect size for the Positive Social Modeling Intervention (f = .25, in the absence of prior research to inform the effect size) with an alpha of .05 with the power to detect an effect set at 80%.

Results

Demographic data

There were no significant differences between groups in age and gender (all $p \geq .291$) indicating randomization was successful. See Electronic Supplementary Material 1.

Main analysis (pre-registered)

Side effects.

Figure 3 depicts the group means for the ANOVA assessing group differences in reported side effect severity. Full statistics are available in the Electronic Supplementary Material 2. Orthogonal contrasts revealed that there was a significant overall nocebo effect, where groups that received the placebo reported increased severity of symptoms relative to the Natural History group, $F(1,155) = 6.00$, $p = .015$, $\eta_p^2 = .038$. There was no significant difference in symptom severity by induction method, $F(1,155) = 1.65$, $p = .201$, $\eta_p^2 = .011$. The positive modeling significantly decreased severity of symptoms reported, $F(1,155) = 8.26$, $p = .005$, $\eta_p^2 = .051$. There was no significant interaction between induction method and the effect of the positive social modeling $F(1,155) = 0.03$, $p = .866$, $\eta_p^2 < .001$. The lack of main effect of induction method may have been due to the efficacy of the intervention. To investigate this possibility, a simple effect examined whether induction method had significant effects for those that did not receive the positive modeling intervention, and this revealed no significant effect of induction method $F(1,62) = 0.82$, $p = .369$, $\eta_p^2 = .013$.

Generalization of side effects.

Figure 3 also depicts the group means for the ANOVA assessing group differences in reported side effect severity of all other symptoms assessed by the GASE. Full statistics are available in the Electronic Supplementary Material 3. The analysis revealed that there was no significant overall effect of the nocebo treatment on other symptoms, $F(1,155) = 0.81$, $p = .371$, $\eta_p^2 = .005$, and no significant main effect of social induction method, $F(1,155) = 0.52$, $p = .474$, $\eta_p^2 = .003$. There was a significant

effect of the intervention on reducing other symptom's severity, $F(1,155) = 8.12$, $p = .005$, $\eta_p^2 = .050$. Finally, the interaction between social induction method and the positive intervention was not significant, $F(1,155) = 0.937$, $p = .334$, $\eta_p^2 = .006$.

Moderation analysis for side effects.

Moderation analyses exploring the significant nocebo effect and significant effect of the Positive Social Modeling Intervention are presented in Table 1.

Cognitive performance.

Refer to Figure 4 for group means of objective cognitive performance. A significant reduction in objective cognitive performance was found in the treatment groups compared to the natural history group, $F(1,152) = 4.75$, $p = .030$, $\eta_p^2 = .030$. However, there was no significant effect of side effect modeling, $F(1, 152) = 0.02$, $p = .880$, $\eta_p^2 < .001$, the Positive Social Modeling Intervention, $F(1, 152) = 0.62$, $p = .434$, $\eta_p^2 = .004$, nor an interaction, $F(1, 152) = 0.72$, $p = .400$, $\eta^2 = .005$ on objective cognitive performance. Orthogonal contrasts revealed no significant differences between groups in self-reported cognitive performance all $p >= .316$. Within the 3 groups that received the placebo treatment, there was no significant difference in self-reported influence of treatment on cognitive performance, $F(3, 124) = 0.51$, $p = .677$, $\eta^2 = .012$. See Electronic Supplementary Materials 5 for full comparisons and group means.

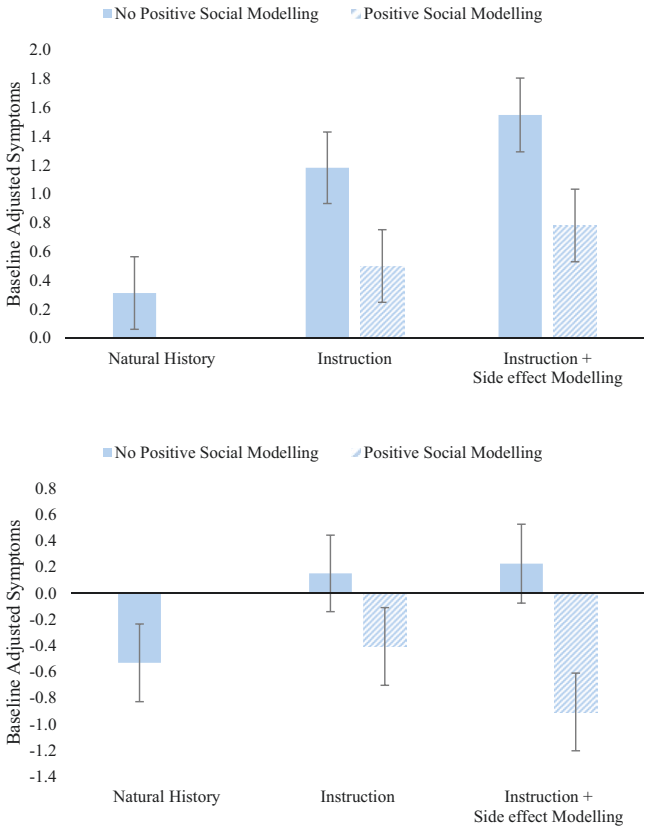

Figure 3. Baseline adjusted symptoms for each experimental condition. Group means for warned symptoms (top) and non-warned symptoms (bottom). All error bars are ± 1 Standard Error of the Mean (SEM).

Exploratory analysis

Effects of the intervention on expectancy and anxiety.

T-tests were used to compare expectations for side effects, expectations for cognitive enhancement, side effect anxiety and state anxiety between groups that received the Positive Social Modeling Intervention (i.e., Instruction with Intervention and Instruction + Side effect modeling with Intervention) versus that those who did not (i.e., Natural History, Instruction Alone and Instruction + Side effect modeling). As shown in Figure 5, the intervention significantly decreased expectancies for symptoms, $t(158) = -2.15$, $p = .033$, $d = -0.35$, but not expected cognitive enhancement, $t(158) = -1.95$, $p = .052$, $d = -0.32$. The Intervention did not significantly affect state anxiety, $t(158) = 1.44$, $p = .153$, $d = 0.23$, nor symptom-specific anxiety, $t(158) = 0.35$, $p = .723$, $d = 0.06$.

Mediation of the intervention effect on side effects by expectations.

As there were effects of the intervention on both symptom expectancy and symptom severity, a mediation analysis was conducted to investigate if the effect of the intervention on the nocebo effect was mediated by expectations. The independent variable was Intervention: Intervention vs No Intervention, collapsed across induction method, excluding the Natural History group. The dependant variable was symptom severity and expectancy was the mediator. Bootstrapping with 10,000 samples was conducted to determine 95% confidence intervals (CIs) which were used to determine significance. Expectancy did not significantly mediate the effect of the intervention on symptom severity, direct effect = 0.70, 95% CI [0.20,1.22], $p = .008$ and indirect effect = 0.02, 95% CI [-0.05,0.16], $p = .671$.

Manipulation check

Both social modeling manipulations were successful, no participants reported suspicion regarding the positive social modeling via the instructional video and only 2 participants in the sample reported suspicion concerning the live social

Table 1. Moderation analyses of the nocebo effect and the effect of the positive social modeling intervention.

	Nocebo			Intervention		
	F(df1,df2)	*P*	η_p^2	*F*(df1,df2)	*P*	η_p^2
Gender	0.06 (1,152)	.814	<.001	0.05 (1,120)	.831	<.001
STAI-6	0.21 (1,156)	.649	.001	2.02 (1,124)	.157	.016
Expectancy	0.32 (1,156)	.572	.003	4.50 (1,124)	.036	.035
Anxiety	0.07 (1,156)	.793	<.001	1.05 (1,124)	.307	.007

STAI-6 refers to the State-Trait Anxiety Inventory-6.[25] Analyses involving gender have a sample size $N = 156$, excluding those who did not identify with either male or female due to insufficient sample size.

model. A small proportion of participants expressed suspicion that the treatment was a placebo ($N = 21$, 13%). However, raising suspicion concerning the placebo treatment did not differ statistically between groups, $\chi^2(4, N = 160) = 3.96$, $p = .412$, Cramer's V = .16, nor was it associated with a change in target symptom reporting, controlling for group, $F(1, 150) = 1.76$, $p = .187$, $\eta_p^2 = .012$.

Discussion

This was the first study to investigate whether positive social modeling, i.e., modeling a lack of side effects, could reduce nocebo side effects. As anticipated, we found clear evidence of a nocebo effect, with participants in the (placebo) treatment groups reporting significantly greater side effect severity compared to the Natural History group. Contrary to our hypotheses, the combination of side effect modeling with a side effect warning did not increase nocebo side effects relative to the warning without side effect modeling. Importantly, the novel positive social modeling intervention effectively reduced nocebo symptom severity across treatment groups, demonstrating its utility in mitigating nocebo effects. There was no significant interaction between the nocebo induction method and the positive social modeling intervention, indicating that the intervention's effectiveness was consistent regardless of the method of nocebo induction. These findings have several important theoretical and clinical implications.

Most importantly, the present study found that providing participants with positive social modeling inhibited nocebo side effects irrespective of whether the nocebo effect was induced by instruction alone or instruction and side effect modeling, and this positive effect extended to both other (non-warned) side effects. Positive social modeling has previously been found to lead to placebo effects,[27,28] but to the best of our knowledge has never previously been examined as a potential preventive strategy to combat nocebo effects. Two aspects of this finding are particularly interesting. The first is that the positive modeling was video-based whereas the side effect modeling was in person. A recent meta-analysis revealed that, typically, in person modeling produces stronger effects than video-based modeling.[22] As such, it is particularly noteworthy that the video-based positive modeling effectively inhibited the nocebo effect even when it involved verbal instruction accompanied by in person side effect modeling. This suggests that video-based positive modeling could be an effective and scalable technique for combatting nocebo effects even when they involve in person observation of another person experiencing adverse symptoms from a treatment.

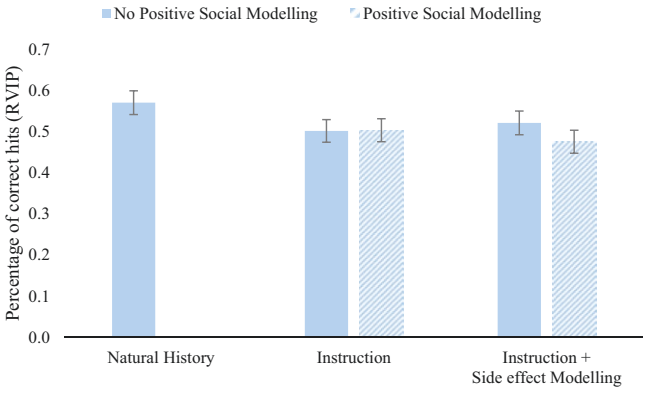

Figure 4. Group means of objective performance on the RVIP task.

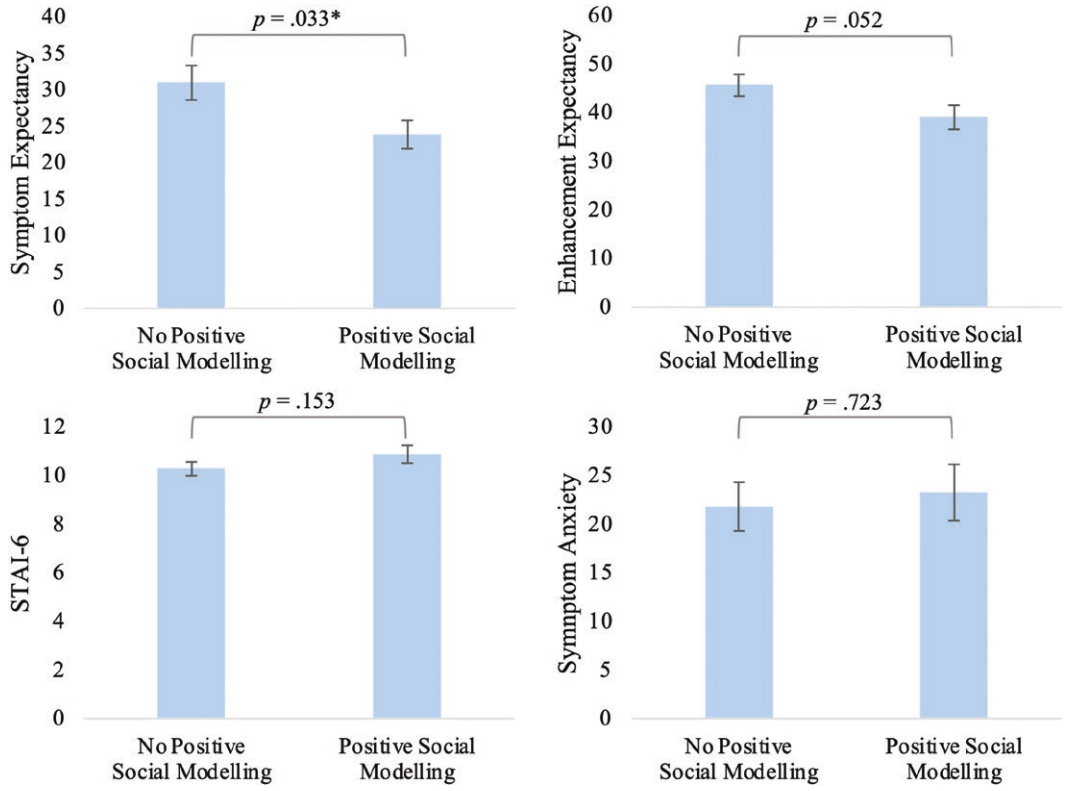

Figure 5. Comparison of anxiety and expectations between groups that received the Positive Social Modeling intervention and the groups that did not. * indicates $p < .05$, ** indicates $p < .01$, *** indicates $p < .001$.

Second, the fact that positive social modeling inhibits nocebo effects means that commonly used "neutral" control groups in social modeling nocebo research[22] may actually be inhibitory if they involve communication indicating that no adverse symptoms occurred following the treatment, whether direct (as in the current study) or indirect (e.g., absence of a report of side effect). As such, estimating the magnitude of any socially induced nocebo effect might be more accurate when a true natural history group is used that is not exposed to any social modeling.

Related to this, it was interesting to observe that contrary to predictions, the addition of side effect modeling did not significantly exacerbate the nocebo effect induced via instruction alone. This finding appears inconsistent with a recent meta-analysis demonstrating that instruction with social modeling typically produced larger nocebo effects than verbal instruction alone does.[22] However, it is important to note that the current study employed a more formal verbal instruction than is typically used in other studies in that, in addition to being written in the consent form, the side effect warning was presented as part of an explanatory video provided to the participants about the supposed medication and trial. In comparison, in many warning-induced nocebo studies side effect information may only be presented in written materials like the consent form or through brief verbal discussion [e.g.,.[4,29–31]] The use of an explanatory video in the current study may have increased the instructed nocebo effect and created a ceiling effect that reduced the impact of the addition of the side effect social modeling. Supporting this, the effect size of the instructed nocebo effect in the current study was approximately 50% larger than the typical instructed nocebo effect observed in nocebo research.[32] It would therefore be interesting for future research to compare the effect of the addition of social modeling to side effect warnings with varying strengths of instructions.

Expectancy and anxiety are key factors hypothesized to facilitate nocebo effects.[33] The positive social modeling video intervention successfully reduced expectations for symptoms, however, did not significantly affect participant anxiety. Although symptom expectancy was reduced because of the intervention, side effect expectations did not mediate the reduction in the nocebo effect caused by the intervention. This may suggest that other unmeasured factors are responsible for the intervention's effectiveness. Alternatively, it could be that the timing of the expectancy measurement resulted in a less sensitive measure and that this undermined evidence of mediation. Symptom expectancy was assessed immediately after the intervention, but prior to placebo administration, potentially making it an outdated measure if there are expectancies that arise once the participant is informed they are assigned to take or not take the supposed "cognitive enhancer," and from the treatment administration process itself. Additionally, the 15-minute wait period allows ample time to reflect upon and contemplate the information concerning the "treatment" that the participant received. While we believe it was not feasible in this study to measure side effect expectancy repeatedly without revealing the study's true nature, future research should incorporate expectancy measurements after group allocation and following social modeling manipulations to better understand the role of expectancy in nocebo effects.

Interestingly, we observed no placebo-related improvement on either subjective or objective measures of cognitive performance and in fact, those who received the placebo demonstrated worsened objective cognitive performance. Where previous research has reported placebo cognitive enhancement[34–36] the broader study contexts have focused on investigating the primary effect of the placebo (i.e., the cognitive enhancement) with little to no emphasis on side effects. The focus of the current study was on side effects so it may be the case that the instructions delivered concerning cognitive enhancement were less strong than in other studies for which it's a primary outcome. It is also possible that the experience of side effects due to the nocebo effect in the treatment groups may have engendered discomfort or distraction sufficient to impair cognitive functioning—a hypothesis that warrants investigation in future studies.

Gender was not found to moderate the strength of the nocebo effect, nor influence the efficacy of the intervention. Previous research has found that female observers can be more susceptible to nocebo effects under certain conditions,[37,38] however others suggest it maybe the model's gender—or a match between model and observer—that primarily drives observed differences.[22,39] In the present study, both the side effect social model and positive social model were male, leaving questions about the precise role of model and observer gender an avenue for future investigation.

Some limitations to the study are worth discussing. First, the study was conducted with healthy psychology undergraduates and therefore would benefit from replication in clinical settings to investigate if the intervention's benefits translate in clinical practice. Interestingly, the nocebo effect tends to be *larger* in clinical populations,[32,40] and factors specific to the clinical environment like presence of other patients and disease comorbidities may influence the nocebo effect and its mitigation in ways not captured here. Additionally, the study did not collect data on participant ethnicity or socioeconomic status, limiting our ability to comment on the generalisability of our findings to the broader population. Second, the study was conducted over the span of one hour, meaning it is unknown how long the positive effects of the intervention can be sustained. Third, several of the measures (e.g., side effect anxiety and expectancy) were single-item scales that have not been extensively validated in previous research; although they were brief and aligned well with our specific focus, it would be beneficial to replicate our findings with validated instruments. Finally, To translate this intervention into a feasible and useful clinical tool it is crucial to investigate patient acceptability of this intervention. This would indicate whether the positive social modeling is perceived by patients as acceptable and ethical.

In conclusion, this study highlights the role that nocebo effects can play in generating side effects and importantly provides novel evidence that positive social modeling may be a way of combatting these effects. The efficacy of positive social modeling here is particularly noteworthy given that it was video-based and was effective even for a combination of nocebo instructions and in person side effect modeling. This suggests that positive social modeling may be an effective and scalable method to reduce the significant burden nocebo effects cause. Future research is needed to translate this finding to clinical settings as well as to examine patient perspectives on its acceptability.

Supplementary Material

Supplementary material is available at *Annals of Behavioral Medicine* online.

Author contributions

Cosette Saunders (Conceptualization, Methodology, Investigation, Data Analysis, Formal Analysis, Writing—Original Draft), Winston Tan (Conceptualization, Methodology, Writing—Review & Editing), David Ng (Conceptualization, Methodology, Writing—Review & Editing), Alexander Burchett (Conceptualization, Methodology, Writing—Review & Editing), Nicolas McNair (Conceptualization, Formal Analysis, Writing—Review & Editing), and Ben Colagiuri (Conceptualization, Supervision, Writing—Review & Editing)

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Publication Supplementary Materials

All analytic code and further results can be found at OSF *https://osf.io/zfas7/*

Supplementary Material 1. Demographic Data

ANOVA (Age ~ Group)

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	65026.56482	1	4152.18860	0.00000
group	78.35213	4	1.25077	0.29188
Residuals	2427.42287	155	NA	NA

group	emmean	SE	df	lower.CL	upper.CL
NH	20.21875	0.69957	155	18.83683	21.60067
NINSM	19.48485	0.68889	155	18.12402	20.84567
INSM	21.46875	0.69957	155	20.08683	22.85067
NISM	19.67742	0.71076	155	18.27338	21.08146
ISM	19.96875	0.69957	155	18.58683	21.35067

Gender (N)

	NH	NINSM	INSM	NISM	ISM
Female	23	24	23	18	22
Male	9	8	8	12	9
other	0	1	1	1	1

Supplementary Material 2. Pre-registered Analysis: Side effects

ANOVA (Primary side effects ~ Group)

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	119.61140	1	58.86944	0.00000
group	32.04474	4	3.94288	0.00447
Residuals	314.93026	155	NA	NA

	eta.sq	eta.sq.part
group	0.09235	0.09235

Supplementary Material 3. Generalisation of side effects

ANOVA (Other side effects ~ Group)

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	13.75726	1	4.89001	0.02848
group	29.12572	4	2.58818	0.03901
Residuals	436.06803	155	NA	NA

	eta.sq	eta.sq.part
group	0.06261	0.06261

group	emmean	SE	df	lower.CL	upper.CL
NH	-0.53125	0.29651	155	-1.11697	0.05447
NINSM	0.15152	0.29198	155	-0.42526	0.72829
INSM	-0.40625	0.29651	155	-0.99197	0.17947
NISM	0.22581	0.30125	155	-0.36928	0.82090
ISM	-0.90625	0.29651	155	-1.49197	-0.32053

Supplementary Material 4. Moderation analyses

*Moderation analyses: Gender * Nocebo effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	90.69960	1	41.65812	0.00000
treat	11.07577	1	5.08708	0.02553
gender	0.80632	1	0.37034	0.54373
treat:gender	0.12143	1	0.05577	0.81362
Residuals	330.94000	152	NA	NA

	eta.sq	eta.sq.part
treat	0.03218	0.03238
gender	0.00234	0.00243
treat:gender	0.00035	0.00037

*Moderation analyses: Gender * Intervention effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	98.50784	1	42.63673	0.00000
intervention	11.79430	1	5.10488	0.02566
gender	0.69994	1	0.30295	0.58306
intervention:gender	0.10567	1	0.04574	0.83102
Residuals	277.24781	120	NA	NA

	eta.sq	eta.sq.part
intervention	0.04025	0.04080
gender	0.00239	0.00252

	eta.sq	eta.sq.part
intervention:gender	0.00036	0.00038

*Moderation analyses: STAI * Nocebo effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	16.44058	1	7.70897	0.00617
treat	0.03902	1	0.01830	0.89258
stai	1.92178	1	0.90112	0.34395
treat:stai	0.44356	1	0.20798	0.64899
Residuals	332.69439	156	NA	NA

	eta.sq	eta.sq.part
treat	0.00011	0.00012
stai	0.00554	0.00574
treat:stai	0.00128	0.00133

*Moderation analyses: STAI * Intervention effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	10.85273	1	4.89887	0.02870
intervention	1.06105	1	0.47895	0.49019
stai	0.15129	1	0.06829	0.79427
intervention:stai	4.47274	1	2.01897	0.15785
Residuals	274.70393	124	NA	NA

	eta.sq	eta.sq.part
intervention	0.00358	0.00385
stai	0.00051	0.00055
intervention:stai	0.01511	0.01602

*Moderation analyses: Expectancy * Nocebo effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	31.78131	1	14.87155	0.00017
treat	1.82112	1	0.85216	0.35737
expect_sideeffect	0.99458	1	0.46540	0.49612
treat:expect_sideeffect	0.68426	1	0.32019	0.57231
Residuals	333.38048	156	NA	NA

	eta.sq	eta.sq.part
treat	0.00525	0.00543
expect_sideeffect	0.00287	0.00297
treat:expect_sideeffect	0.00197	0.00205

*Moderation analyses: Expectancy * Intervention effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	25.94094	1	11.94602	0.00075
intervention	23.25469	1	10.70898	0.00138
expect_sideeffect	3.54802	1	1.63389	0.20355
intervention:expect_sideeffect	9.77452	1	4.50125	0.03586

	Sum Sq	Df	F value	Pr(>F)
Residuals	269.26771	124	NA	NA

	eta.sq	eta.sq.part
intervention	0.07856	0.07950
expect_sideeffect	0.01199	0.01301
intervention:expect_sideeffect	0.03302	0.03503

*Moderation analyses: Anxiety * Nocebo effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	49.45199	1	23.16513	0.00000
treat	5.30536	1	2.48522	0.11695
anxiety	1.77175	1	0.82995	0.36369
treat:anxiety	0.14768	1	0.06918	0.79288
Residuals	333.02252	156	NA	NA

	eta.sq	eta.sq.part
treat	0.01529	0.01568
anxiety	0.00511	0.00529
treat:anxiety	0.00043	0.00044

*Moderation analyses: Anxiety * Intervention effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	50.39221	1	22.74410	0.00001

	Sum Sq	Df	F value	Pr(>F)
intervention	16.49757	1	7.44604	0.00728
anxiety	2.38783	1	1.07772	0.30123
intervention:anxiety	2.33197	1	1.05251	0.30693
Residuals	274.73650	124	NA	NA

	eta.sq	eta.sq.part
intervention	0.05574	0.05665
anxiety	0.00807	0.00862
intervention:anxiety	0.00788	0.00842

*Moderation analyses: Phasic EDA * Nocebo effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	63.74393	1	26.51682	0.00000
treat	3.41091	1	1.41890	0.23581
phasic_mean	0.08049	1	0.03348	0.85510
treat:phasic_mean	0.52625	1	0.21891	0.64067
Residuals	305.29600	127	NA	NA

	eta.sq	eta.sq.part
treat	0.01084	0.01105
phasic_mean	0.00026	0.00026
treat:phasic_mean	0.00167	0.00172

*Moderation analyses: Phasic EDA * Intervention effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	67.29748	1	27.44087	0.00000
intervention	6.65726	1	2.71453	0.10255
phasic_mean	0.08328	1	0.03396	0.85417
intervention:phasic_mean	1.60220	1	0.65330	0.42083
Residuals	247.69786	101	NA	NA

	eta.sq	eta.sq.part
intervention	0.02484	0.02617
phasic_mean	0.00031	0.00034
intervention:phasic_mean	0.00598	0.00643

Moderation analyses: Tonic EDA Nocebo effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	91.78827	1	38.23864	0.00000
treat	8.59044	1	3.57874	0.06080
tonic_mean	0.32913	1	0.13712	0.71178
treat:tonic_mean	0.69777	1	0.29069	0.59072
Residuals	304.85157	127	NA	NA

	eta.sq	eta.sq.part
treat	0.02729	0.02741
tonic_mean	0.00105	0.00108
treat:tonic_mean	0.00222	0.00228

*Moderation analyses: Tonic * Intervention effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	92.05180	1	37.46959	0.00000
intervention	14.34777	1	5.84024	0.01746
tonic_mean	0.50252	1	0.20455	0.65204
intervention:tonic_mean	0.41648	1	0.16953	0.68141
Residuals	248.12741	101	NA	NA

	eta.sq	eta.sq.part
intervention	0.05354	0.05466
tonic_mean	0.00188	0.00202
intervention:tonic_mean	0.00155	0.00168

*Moderation analyses: HRV * Nocebo effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	89.90681	1	41.98440	0.00000
treat	9.58692	1	4.47687	0.03608
lf.hf_mean	10.56606	1	4.93411	0.02789
treat:lf.hf_mean	2.21120	1	1.03258	0.31126
Residuals	308.36648	144	NA	NA

	eta.sq	eta.sq.part
treat	0.02911	0.03015
lf.hf_mean	0.03209	0.03313

	eta.sq	eta.sq.part
treat:lf.hf_mean	0.00671	0.00712

*Moderation analyses: HRV * Intervention effect*

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	91.05585	1	41.26568	0.00000
intervention	5.70098	1	2.58363	0.11072
lf.hf_mean	9.31627	1	4.22205	0.04217
intervention:lf.hf_mean	0.15499	1	0.07024	0.79146
Residuals	253.75618	115	NA	NA

	eta.sq	eta.sq.part
intervention	0.02029	0.02197
lf.hf_mean	0.03315	0.03541
intervention:lf.hf_mean	0.00055	0.00061

Supplementary Material 5. Cognitive performance

ANOVA (Self Reported Performance on RVIP ~ Group)

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	231716.1987	1	526.56617	0.00000
group	746.8709	4	0.42431	0.79093
Residuals	68207.9729	155	NA	NA

	eta.sq	eta.sq.part
group	0.01083	0.01083

group	emmean	SE	df	lower.CL	upper.CL
NH	35.84	3.71	155	28.52	43.17
NINSM	36.76	3.65	155	29.54	43.97
INSM	36.75	3.71	155	29.42	44.08
NISM	41.84	3.77	155	34.40	49.28
ISM	39.12	3.71	155	31.80	46.45

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	231716.19874	1	526.56617	0.00000
treat	196.98483	1	0.44764	0.50445
social	444.53419	1	1.01019	0.31642
intervention	59.21421	1	0.13456	0.71425
social:intervention	58.55667	1	0.13307	0.71577

	Sum Sq	Df	F value	Pr(>F)
Residuals	68207.97290	155	NA	NA

ANOVA (Estimated enhancement ~ Group)

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	99200.3582	1	215.25400	0.0000
group	702.5012	3	0.50812	0.6774
Residuals	57145.7176	124	NA	NA

	eta.sq	eta.sq.part
group	0.01214	0.01214

group	emmean	SE	df	lower.CL	upper.CL
NINSM	27.81818	3.73701	124	20.42160	35.21477
INSM	24.03125	3.79495	124	16.51998	31.54252
NISM	30.06452	3.85567	124	22.43306	37.69597
ISM	29.46875	3.79495	124	21.95748	36.98002

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	99313.5084	1	216.92832	0.00000
social	472.2914	1	1.03162	0.31174
intervention	157.1440	1	0.34325	0.55902
Residuals	57227.1461	125	NA	NA

ANOVA (Proportion correct hits ~ group)

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	41.46437	1	1663.57103	0.00000
group	0.15271	4	1.53171	0.19575
Residuals	3.78859	152	NA	NA

	eta.sq	eta.sq.part
group	0.03875	0.03875

group	emmean	SE	df	lower.CL	upper.CL
NH	0.57018	0.02882	152	0.51323	0.62712
NINSM	0.50159	0.02748	152	0.44730	0.55589
INSM	0.50329	0.02791	152	0.44815	0.55843
NISM	0.52105	0.02882	152	0.46410	0.57800
ISM	0.47533	0.02791	152	0.42019	0.53047

	Sum Sq	Df	F value	Pr(>F)
(Intercept)	41.46437	1	1663.57103	0.00000
treat	0.11840	1	4.75046	0.03083
social	0.00057	1	0.02300	0.87967
intervention	0.01537	1	0.61660	0.43353
social:intervention	0.01783	1	0.71518	0.39906
Residuals	3.78859	152	NA	NA

	eta.sq	eta.sq.part
treat	0.03004	0.03031
social	0.00015	0.00015
intervention	0.00390	0.00404
social:intervention	0.00452	0.00468

Supplementary Material 6. Physiological Measures

Materials and measures

Equivital Sensor Belt and Module. Participant Heart Rate (HR) was measured using an Equivital Sensor Module fitted onto an Equivital Sensor Belt. HR was measured continuously for 15 minutes after administration of the treatment (or lack thereof). HR Variability (HRV) is measure of the parasympathetic and sympathetic branches that modulate cardiac activity (Daniali & Flaten, 2020). Spectral analysis was used to investigate the High Frequency/Low Frequency (HF/LF) ratio using the pyHRV package (Gomes et al., 2019).

Electrodermal activity (EDA). EDA was recorded as a measure of autonomic arousal in response to the treatment and social communication manipulations. This was achieved by using a PowerLab DAQ and Galvanic Skin Response amplifier (ADInstruments) with two electrodes placed on the middle and index fingers of participants' right hand. EDA was recorded over the same time period as HR. EDA can be decomposed into tonic activity (slower general changes in sympathetic arousal) and phasic activity (reactive fast changes), which each reflect important components of physiological arousal (Braithwaite et al., 2013). A convex optimization approach to electrodermal activity was applied to extract the two components (Greco et al., 2016), after which mean Skin Conductance Level (μSCL) was calculated as a measure of the tonic activity and the Skin Conductance Response (SCR) as a measure of the phasic activity.

Results

HRV. Due to technical issues with the Equivital Sensor Module, complete heart rate data was available for 148 participants ($N_{Missing}$=12). There was no significant relationship between missing data and participant group, χ_4^2=0.48, p=.98, Cramer's V=.05. Three-way mixed 2(Time: first five minutes vs second five minutes, where five minutes is the time point side effect modelling occurred in groups that received modelling) x 2(Induction Method) x

2(Intervention) + 1(Natural History) ANOVA was conducted to explore differences in HRV. There was no significant effect of Time, Induction Method, Intervention, nor interactions, all p>.060.

EDA. Due to technical issues, complete EDA recordings for 131 participants were available ($N_{Missing}$=29). There was no significant relationship between missing data and participant group, χ_4^2=4.75, p=.31, Cramer's V=.17. Three-way mixed 2(Time) x 2(Induction Method) x 2(Intervention) + 1(Natural History) ANOVA was conducted to explore differences in tonic and phasic activity, separately. Holding the other factors constant, there was a significant interaction between treatment and time on Tonic activity, such that there was a larger increase in tonic activity in treatment groups than the Natural History group. With respect to phasic activity, there was a main effect of time such that the second time period (i.e., after social modelling in the social modelling groups) had higher phasic activity than the first. There was a main effect of the intervention, such that those who received the intervention had reduced phasic activity than those who did not. No other effects reached significance, all p>.066.

EDA ANOVA Contrasts

	Tonic (μSCL)			Phasic (SCR)		
	t(133)	p	η_p^2	t(133)	p	η_p^2
Time	0.835	0.405	0.005	2.016	0.046	0.030
Treatment	0.109	0.914	0.000	0.440	0.660	0.001
Intervention	1.422	0.157	0.015	2.213	0.029	0.036
Induction Method	-1.625	0.107	0.019	0.525	0.600	0.002

Treatment*Time	-1.668	0.098	0.020	-0.942	0.348	0.007
Intervention*Time	-2.029	0.044	0.030	-0.355	0.723	0.001
Induction Method*Time	1.300	0.196	0.013	0.470	0.639	0.002
Intervention* Induction Method* Time	0.859	0.392	0.006	1.855	0.066	0.025

Group Means Tonic EDA

group	name	emmean	SE	df	lower.CL	upper.CL
nh	tonic_BW	0.157	1.433	133	-2.677	2.991
ninsm	tonic_BW	5.054	1.489	133	2.108	7.999
nism	tonic_BW	3.670	1.383	133	0.935	6.405
insm	tonic_BW	0.820	1.383	133	-1.914	3.555
ism	tonic_BW	3.222	1.407	133	0.439	6.005
nh	tonic_AW	0.634	2.033	133	-3.386	4.655
ninsm	tonic_AW	5.685	2.112	133	1.506	9.863
nism	tonic_AW	5.195	1.961	133	1.315	9.074
insm	tonic_AW	-0.358	1.961	133	-4.237	3.522
ism	tonic_AW	2.872	1.996	133	-1.076	6.820

Group Means Phasic EDA

group	name	emmean	SE	df	lower.CL	upper.CL
nh	phasic_BW	0.622	0.177	133	0.272	0.971
ninsm	phasic_BW	0.865	0.184	133	0.502	1.228
nism	phasic_BW	0.709	0.171	133	0.372	1.047
insm	phasic_BW	0.432	0.171	133	0.095	0.769

group	name	emmean	SE	df	lower.CL	upper.CL
ism	phasic_BW	0.606	0.174	133	0.262	0.949
nh	phasic_AW	0.966	0.236	133	0.499	1.433
ninsm	phasic_AW	0.936	0.245	133	0.451	1.421
nism	phasic_AW	0.955	0.228	133	0.505	1.406
insm	phasic_AW	0.698	0.228	133	0.247	1.148
ism	phasic_AW	1.103	0.232	133	0.645	1.562

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Appendix E: Conference Presentations Related to Thesis

FEB. 2025	"The interaction of positive and negative social modelling in nocebo effects", **talk** at 2025 Australian Placebo & Nocebo Symposium
JUN. 2025	"Positive social modelling attenuates nocebo side effects", **poster** at 2025 Society for Interdisciplinary Placebo Studies (SIPS) Conference
JUN. 2025	"From this treatment to that: Do socially-acquired nocebo effects spread to other treatments?", **poster** at 2025 Society for Interdisciplinary Placebo Studies (SIPS) Conference