Exploring a Potential Facilitating Role for Pain-Related Attentional Bias in Nocebo

Hyperalgesia

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Abstract

The nocebo effect comprises the negative counterpart of the placebo. This occurs when administration of an inert intervention, coupled with negative information or conditioning, results in the occurrence of negative effects. While the literature agrees on the importance of negative expectancies in activating nocebo effects, other potential factors remain relatively overlooked. The aim of the present study was to use a novel gaze-augmented dot-probe task to investigate whether pain-related attentional bias contributes to nocebo effects. This was founded on theories within the pain literature, which propose a causal role for attentional biases in the subsequent experience of pain. Ninety-three participants (60 female, $M = 19.67$) were randomly allocated to one of four groups (nocebo-towards, nocebo-away, controltowards, control-away). A gaze-augmented variant of the the dot-probe training task was designed in an attempt to manipulate attentional biases either towards or away from pain. Participants then received either nocebo or control instruction and conditioning, by pairing a sham TENS device with contingently high pain stimulation (nocebo) or non-contingent pairing (control). Participants were required to rate pain intensity, expectancy and distress during a test phase where all TENS and no-TENS shocks were administered at the same intensity. Results showed an overall nocebo effect – rating TENS paired shocks higher than no-TENS – for all outcomes. No consistent training effect was shown for attentional bias across reaction time and eye-tracking measures. However, attentional bias was shown to interact with nocebo conditioning for intensity ratings, with tentative partial support shown for expectancy. The key interaction showed attentional bias condition to differentially affect nocebo extinction trends. Thus, results provide preliminary validation for exploration of attentional bias as a potential mechanism of nocebo hyperalgesia, however necessarily a more sensitive and dependable measure of attentional bias must be established to allow more definitive conclusions.

Exploring a Potential Facilitating Role for Pain-Related Attentional Bias in Nocebo Hyperalgesia

The placebo effect refers to positive effects induced by an inert substance, generated by an individual's expectations of beneficial outcomes (Amanzio & Benedetti, 1999). Investigations of the placebo effect demonstrate the substantial consequences treatment expectations can produce on health outcomes (Hauser, Hansen, & Enck, 2012). However, the opposite is also apparent: where expectations of sickness and negative affective states results in their occurrence in the expectant (Hahn, 1997). This phenomenon is referred to as the nocebo effect. Despite potential to cause substantial negative health outcomes, the mechanisms of nocebo effects are considerably less understood than those of placebo effects. Current theories agree on a significant role for negative expectations (Benedetti, Lanotte, Lopiano, & Colloca, 2007; Colloca, 2012). Expectancies have been most consistently shown to be produced through verbal suggestion (e.g. Bingel et al., 2011; Jaen & Dalton, 2014; Schweiger & Parducci, 1981; van Laarhoven et al., 2011), and classical conditioning (e.g. Babel et al., 2017; Brasher, Kleinbohl, Holzl, & Becker, 2017).

However, expectancies may also induce attentional processes that contribute to nocebo effects. Expectancies are argued to direct one's attention to relevant information or cues, facilitating interpretation and encoding in accord with the expectation (Geers, Helfer, Weiland, & Kosbab, 2006). Additionally, research has shown that without attending to the relevant stimulus, expectations do not influence subsequent behaviour (Harris, 1990). While there is preliminary evidence for a relationship between attention and nocebo effects (Corbett, 2018; Geers et al., 2006), the primary theoretical rationale for an influential role of attention emerges from pain literature. Here, research proposes the fear-avoidance model as a mechanism where hypervigilance (excessively prioritised attention) towards possible threat cues causes overestimation of subsequent pain intensity (Vlaeyen & Linton, 2000). The

principal implication of this model is that an attentional bias (AB) towards pain-related cues causally amplifies pain perception (Schoth, Nunes, & Liossi, 2012; Sharpe & Jonson, 2012). Given evidence of this within pain research (e.g. McGowan Sharpe, Refshauge, & Nicholas, 2009; Sharpe, Johnson, & Dear, 2015), it would follow that pain-related attention might influence nocebo effect strength.

Previous research regarding attention and nocebo effects includes only correlational measures of related attentional processes, lacking causal explanatory power. Additionally, studies that have successfully manipulated ABs towards pain (McGowan, et al., 2009; Sharpe et al., 2015) did not include a nocebo manipulation. Thus, despite implication of attention in expectancies and in altering pain perception, both of which are core components of nocebo effects, there has been little integration of these areas. Therefore, the present study sought to bridge pain and nocebo literature, via a novel investigation of pain-related AB. Extending the aforementioned literature, this was implemented through manipulation of ABs either towards or away from pain, followed by a nocebo hyperalgesia paradigm, to determine whether AB differentially influenced nocebo hyperalgesia strength.

1.1. The Nocebo Effect

The nocebo effect comprises the negative counterpart of a placebo: whereby an individual expects and thus experiences negative outcomes following administration of an inert substance (Hahn, 1997; Hauser et al., 2012). Importantly, these expectations are dependent on the individual's beliefs regarding the likely effects (Mills, Boakes, & Colagiuri, 2019). For example, placebo groups in clinical trials often report adverse side effects similar to those receiving the active treatment, as a result of participant blinding and clinician warnings (Bartels et al., 2017; Colloca, 2012).

Problematically, the resultant nocebo effects are not confined to the subjective experience of the patient; impacting overall treatment outcomes (Colloca & Miller, 2011). Adverse outcomes such as side effects may effect treatment adherence, potentially leading to withdrawal or inappropriate use (Colloca, 2012). For example, in a multicentre clinical trial for two different active drugs, including warnings of potential gastrointestinal side effects corresponded with a sixfold increase in participant withdrawals (Myers, Cairns, & Singer, 1987). Further, nocebo effects can influence the therapeutic efficacy of an active treatment, potentially diluting positive effects (Klinger, Blasini, Schmitz, & Colloca, 2017). For example, two studies (Aslaksen, Zwarg, Eilertsen, Gorecka, & Bjorkedal, 2015; Bingel et al., 2011) showed that under negative expectancy conditions, the objective effect of an active analgesic on a pain stimulus was completely negated. Given these negative implications, understanding the mechanisms which facilitate nocebo effects is of substantial clinical importance.

Nocebo effects are observed across multiple conditions, including but not limited to headache, asthma, insomnia, caffeine withdrawal (for a review see Webster, Weinman, & Rubin, 2016). However, nocebo hyperalgesia is suggested to be one of the best means to experimentally induce nocebo effects. Nocebo hyperalgesia refers to amplifying one's experience of pain through pairing an inert substance with expectations of increased pain – typically through verbal suggestion, conditioning paradigms or a combination of both (Benedetti et al., 2007). Pain is easily manipulated and can be delivered in a controlled and precise manner (Benedetti et al., 2007; Colloca & Miller, 2011). Thus, the present study focused on the nocebo hyperalgesia paradigm.

1.2. Expectancy and the Nocebo Effect

The most commonly cited mechanism of nocebo effects is negative expectancy, underpinned by Kirsch's (1997) expectancy theory. According to Kirsch (1997), expectancies are self-confirming determinants of behaviour, causing one to interpret events in accordance with what is anticipated. This is through activation of both confirmation and interpretation

biases in the individual. Confirmation biases direct attention towards specific cues, preferentially encoding information consistent with the expectation at the expense of disconfirmatory evidence (Barsky, Saintfort, Rogers, & Borus, 2002; Geers et al., 2006). Similarly, interpretation biases are applied to ambiguous somatic information, causing its interpretation in accord with the expected effect (Geers et al., 2006; Levine, Stern, & Koch, 2006).

As a result, negative expectancies are argued to create adverse responses to an inert stimulus (Hahn, 1997). A meta-analysis of 89 nocebo studies across a variety of outcome variables (such as headache, pain, nausea, caffeine withdrawal, etc.) found learning, perceived dose, verbal suggestion and baseline symptom expectations to be the most robust predictors of nocebo effects (Webster et al., 2016), each of which acts by eliciting negative expectations. From this subset, instruction and conditioning are most consistently associated with inducing expectancies.

1.2.1. Instruction. Verbal suggestion, particularly when originating from a reputable source – such as a researcher or clinician – is capable of manipulating individual expectations. Fortunately, reputability is achieved by nature of the experimental or clinical study: the experimenter or clinician is often automatically recognised as holding a position of authority regarding information and thus more likely to elicit conformity (French & Raven, 1959).

There is significant evidence of the effectiveness of instruction on the nocebo effect. For example, a study by Schweiger and Parducci (1981) instructed participants a low voltage current, known to produce headaches, would be passed through their heads. Despite no activation of a current, approximately 2/3 of subjects reported experiencing headaches. Similarly, Jaen and Dalton (2014) exposed asthmatic subjects to an olfactory, non-irritating stimulus, manipulating instruction as to its nature – asthmogenic or therapeutic. Participants

instructed the stimulus was asthmogenic reported significantly higher irritation and annoyance, and crucially there was an objective increase in airway inflammation.

The power of verbal suggestion is further elucidated through its ability to produce symptoms contradictory to the effects typically associated with a stimulus or procedure. Van Laarhoven et al. (2011) administered participants one of two different somatosensory stimuli known to evoke either itch or pain. The information participants received was manipulated, such that within each stimulus group, participants were told either 95% of people experience itch or 95% of people experience pain. Despite reliable association between each stimuli and its outcome, participants reported significantly higher occurrence of the symptom which they were informed about and thus expected, even where this contradicted the objective effect of the stimuli.

1.2.2. Conditioning. Within a nocebo paradigm, conditioning involves contingently pairing a neutral cue with an aversive stimulus, causing the neutral cue to be associated with the negative response elicited by the aversive stimulus (e.g. Colloca, Petrovic, Wager, Ingvar, & Benedetti, 2010). Often, conditioning is accompanied by verbal instruction, which appears to induce the highest magnitude nocebo hyperalgesia (Petersen et al., 2014). For example, in a similar nocebo hyperalgesia design to that of the present study, a sham device was introduced to participants as a TENS machine which enhances pain sensitivity (Colagiuri & Quinn, 2018). Participants subsequently underwent a conditioning phase, during which activation of the sham was contingently paired with high electro-cutaneous pain. A subsequent test phase administered all stimulations (both with and without sham activation) at medium intensity, however participants consistently rated the sham-paired shocks as significantly more painful.

1.2.3. Attention as a potential mediator of expectancy. Expectancies and their associated mechanisms are clearly associated with nocebo effects. Importantly, attention

appears integral to realising expectancies behaviourally (Harris, 1990). One must attend to the relevant cue in order for it to be associated with the outcome. However, recent evidence suggests attention is not merely a vehicle for the realisation of expectancies, but may have a mediating role in nocebo effects.

Geers et al. (2006) argue that nocebos are likely to have stronger effects when individuals closely attend to their somatic experience, as they are more likely to notice ambiguous symptoms. Correspondingly, a review of nonspecific side effects (those not attributable to the active agent) found tendency to somatisation – excessive attention to somatic state – to be predictive of increased side effect reports (Barsky et al., 2002). In an experimental study, a clinical population of temporomandibular (TMB) disorder patients were asked to give pain intensity ratings during clinical examination of TMB and placebo sites – those not expected to be associated with TMB pain (Wilson, Dworkin, Whitney, & LeResche, 1994). Patients were classified according to degree of somatisation, which found higher somatisation correlated significantly with number of placebo sites recorded as painful.

Pain catastrophizing – tendency to exaggerate the threat of pain – has also been shown to relate to nocebo effect strength. A diagnostic component of pain catastrophizing is disproportionate attention towards pain-related cues (Sharpe & Johnson, 2012; Todd et al., 2015; Vlaeyen & Linton, 2000). Experimental results have shown that higher levels of pain catastrophizing (i.e. those highly fearful of pain) are related to stronger nocebo responses in both a clinical (Sullivan, Lynch, Clark, Mankovsky, & Sawynok, 2008) and non-clinical (Vögtle, Barke, & Kröner-Herwig, 2013) sample.

Importantly, both somatisation and pain catastrophizing relate to increased attention, and appear to modulate the strength of nocebo effect. However, the studies above are limited by their correlational nature, thus are unable to elucidate a potentially causal role for attention. In a study where somatic attention was explicitly manipulated, by instructing

participants receiving placebo treatment to either closely monitor their somatic experience or giving no instruction, differential side effect reports were observed (Geers et al., 2006). Despite identical side effect warnings, the high attention group reported significantly more symptoms than the low attention group. This suggests that relevantly focused attention – in this case, towards somatic experience – is capable of heightening nocebo side effects.

Pain-related ABs, which are discussed following, provide a novel avenue to explore the potential role for attention within nocebo hyperalgesia. Interestingly, despite evidence for causal effects on pain outcomes, pain-related ABs have been largely overlooked in nocebo literature. Figure 1 illustrates a proposed model, where instruction and conditioning are inputs used to generate negative expectancies, which are mediated by ABs to induce nocebo hyperalgesia. Combining this model with the aforementioned correlational evidence, it would be expected that manipulating attention towards pain, through inducing AB, should enhance nocebo hyperalgesia.

Figure 1. Proposed model of nocebo hyperalgesia. *Note.* Solid arrows denote direct inputs, dashed arrows denote mediation.

1.3. Attentional Biases

Given the present focus on nocebo hyperalgesia, evidence from literature exploring a relationship between AB and pain is foundational to proposing a facilitative role for attention. Within pain perception, AB refers to preferential attention towards pain-related cues (Crombez, Ryckeghem, Eccleston, & Van Damme 2013). Pain-related AB theories suggest hypervigilance towards pain cues increases vigilance for actual pain detection and biases the interpretation of ambiguous sensations as painful (Pincus & Newman, 2001; Schoth et al., 2012). Similarly, Vlaeyen and Linton's (2000) fear-avoidance model proposes that fear of

pain causes excessive attention to potential threats, negatively influencing the subsequent experience of pain.

Preliminary evidence for a relationship between ABs and pain is supported by their existence in chronic pain samples. Three meta-analyses (Crombez et al., 2013; Schoth et al., 2012; Todd, Van Ryckeghem, Sharpe, & Crombez, 2018) show chronic pain patients to demonstrate a small, yet significant AB to pain relative to healthy controls. Notably, the two most recent meta-analyses observed more robust effects for chronic pain on sensory word stimuli than other types.

1.3.1. Measuring attentional bias. While there are multiple paradigms used to measure AB, the most prevalent and thus focus of the present study is the dot-probe task (Macleod, Mathews, & Tata, 1986). This paradigm measures attentional distribution as the reaction time to detection of a probe, which appears in the location following either a neutral or target stimulus (Macleod et al., 1986). Faster reactions are proposed to occur where the probe appears behind the attended stimuli type (Bar-Haim, 2010; Dear, Sharpe, Nicholas, & Refshauge, 2011).

Initially used in anxiety samples, Dehghani, Sharpe and Nicholas (2003) developed a pain-modified version of the dot-probe task, to allow for AB measurement within pain samples. The pain-modified task, an example of which is shown in Figure 2, accounts for two design factors. Firstly, top-bottom paired stimuli presentation has been shown to achieve better effects and less errors than side by side presentation (Hakamata, et al., 2010). Secondly, probe classification (indicating which of two possibilities appear) encourages a more even monitoring of display than probe identification (indicating whether a single probe appears) (Schoth et al., 2012). Unless specified, the following evidence for pain-related ABs was measured using a similar dot-probe task.

Figure 2. An example of an (a) congruent and (b) incongruent trial for the pain-modified dot probe task using word stimuli. Note that the task used presently follows the same trial design.

1.3.2. Eye-tracking and attentional bias. Despite its prevalence, two interrelated issues arise from the AB literature utilising variants of the dot-probe task: the existence of somewhat contradictory results (Todd et al., 2015), and a reliance on reaction time data. Reaction time as a measure of AB has been shown to have low reliability and internal consistency (Dear et al., 2011). Additionally, reaction time only provides information about the focus of attention at the end of the trial (Mogg, Millar, & Bradley, 2000), confounding hypervigilance with difficulty disengaging. Thus, more recent studies have sought to incorporate eye-tracking measures. As eye movements are guided by attention, eye-tracking over the course of each trial is argued to give a more nuanced account of attentional processing (Yang, Jackson, Gao, & Chen, 2012).

Following success in anxiety literature (e.g. Mogg et al., 2000), this methodological advancement has recently been extended into pain research. In an initial study, Yang et al. (2012) compared eye movements for high and low fear of pain (FOP) groups. Eye-tracking results suggest high FOP were more likely to initially orient attention to the threatening stimuli, with higher reengagement shown for sensory words. Comparisons between chronic pain and no-pain samples show significantly higher initial fixations for chronic pain groups on pain words (Yang, Jackson, & Chen, 2013) and faces (Liossi, Schoth, Godwin, & Liversedge, 2014). Studies in healthy samples where the threat value of an impending pain task was manipulated between subjects show somewhat contradictory results. Both studies (Sharpe et al., 2017; Todd, Sharpe, Colagiuri, & Khatibi, 2016b) show no effect of threat on initial pain fixations. This perhaps suggests that known, short-term threat is not sufficient to foster AB.

1.4. Attentional Bias Modification

Both eye-tracking (Sharpe et al., 2017; Todd et al., 2016b) and reaction time based studies (Boston & Sharpe, 2005; Schoth, Yu, & Liossi, 2014) suggest a threat manipulation is only sometimes successful in inducing observable ABs. However, as attention is predicted to influence interpretation and thus response to pain, inducing ABs is necessary to provide causal evidence for an effect on pain outcomes. Attentional bias modification (ABM) provides an alternative means to achieve this.

Originally, a training version of the dot-probe task was developed by Macleod, Rutherford, Campbell, Ebsworthy and Holker (2002), to investigate attentional retraining on anxiety outcomes. McGowan et al. (2009) used a similar design to revise the pain-modified dot-probe task (Dehghani et al., 2003). This task involves three phases: baseline, training and test. Baseline and test phases consist of a block of trials with equal pain-probe and neutralprobe contingency. The training phase manipulates contingency, such that dependent on group allocation the probe will consistently follow either the pain or neutral stimulus (Macleod et al., 2002). Thus, a learned bias should be induced over the course of the task, such that participants orient attention either towards or away from the pain stimuli set following systematic repetition (Bar-Haim, 2010).

1.4.1. Chronic pain samples. Premised on successful application in anxiety samples (see Bar-Haim, 2010 for a review); ABM has recently been extended to chronic pain samples, providing evidence for subsequently altered pain outcomes. Here, training away from pain – to counteract any bias towards pain – is compared with a non-contingent training group on relevant pain outcomes. While one study showed no effect of training away on immediate or delayed pain outcomes (Heathcote et al., 2018), the remaining three studies (Carleton, Richter, & Asmundson, 2011; Schoth, Georgallis, & Liossi, 2013; Sharpe et al., 2012), despite varied chronic pain types and sample sizes, showed significant decreases in the away-ABM group on relevant pain outcomes. Interestingly, while each of the latter three studies showed improvement on pain outcomes, two (Schoth et al., 2013; Sharpe et al., 2012) showed no significant difference in AB between non-contingent and training away groups, and the third (Carleton et al., 2011) neglected to assess AB.

1.4.2. Experimental pain samples. The predicted relationship between ABM and pain outcomes is illustrated further by experimental results. Bowler et al. (2017) compared word-based training away from pain to non-contingent training, followed by an experimental pain task. Despite no difference in measured ABs, participants who were trained away from pain significantly increased pain threshold (first register of pain) and tolerance (maximum pain withstood) relative to non-contingent training. Where ABM involved either training towards or away from pain stimuli, ABs have been successfully induced (McGowan et al., 2009; Sharpe et al., 2015). In accord with the aforementioned results, both studies showed that training away from pain stimuli significantly increased pain threshold in a subsequent experimental pain task.

Although ABs have not previously been manipulated in a nocebo context, two studies provide relevant parallels. A nocebo hyperalgesia study measured AB during the nocebo paradigm (Corbett, 2018). While ABs were not manipulated, the study found an interaction between nocebo condition and AB. In comparison to control, the nocebo condition showed relative difficulty disengaging from pain-related stimuli. Although the direction of relationship was not elucidated by the study, nor could causality be determined, the existence of a relative effect provides preliminary evidence for a role of AB in nocebo hyperalgesia. By extension, the present study aimed to clarify this finding, through utilising ABM as a means to elucidate potential mediation.

Parallels can also be drawn to manipulation of threat expectancy. McGowan et al. (2009) examined the influence of ABM and a threat manipulation on experimental pain outcomes. Under high threat conditions, ABM training towards pain resulted in decreased pain threshold and higher pain intensity ratings during an experimental pain task when compared with either the high threat-neutral training group or low threat-pain training group. These results would suggest that under nocebo expectancy – which likely parallels high threat expectancy – the effect of attentional training towards pain should be most pronounced.

1.4.3. Eye-tracking and ABM. At present, one study has combined eye-tracking methodologies with pain-related ABM. Todd, Sharpe and Colagiuri (2016a) found no

evidence of change in ABs when measured by either reaction time or eye-tracking. However, somewhat opposing the aforementioned experimental results, the study showed training towards affective pain stimuli, while not observable as an AB, resulted in increased tolerance. Whilst unexpected, this perhaps emerged as a result of study design. The authors compared training towards and away from sensory or affective stimuli in a 2x2 manipulation, such that half of those training towards affective stimuli were simultaneously training away from sensory stimuli – which have been most reliably associated with pain-related ABs (Crombez et al., 2013).

While eye-tracking provides a methodological advancement against reaction time, task-related issues remain. A commonly cited explanation suggests that participants may completely ignore the stimuli, attending only once the probe appears (Ferrari, Mobius, van Opdorp, Becker, & Rinck, 2016). Additionally, specific to the pain-modified version, the typical words drawn from Dehghani et al. (2003) are suggested to be ambiguous, thus perhaps participants do not detect the link between word type and probe appearance (Todd et al., 2016b).

Gaze contingency provides a potential means to overcome these limitations. While this has not been examined in pain literature, a relevant example can be drawn from research in depression. Here, a gaze-contingent dot-probe task required participants to demonstrate specific looking patterns within each trial in order for the probe to appear (Ferrari et al., 2016). Thus, attention was actively engaged across the entire trial, facilitating more direct attentional re-training. The authors compared a positive group (trained to attend to positive affective images) to a negative group. Critically, the positively trained group showed significant increase in positive AB following training (Ferrari et al., 2016). Given the potential for gaze-contingency to address both reaction time and task-based limitations

associated with the dot-probe task, the present study utilised a novel, gaze-augmented dotprobe task to facilitate ABM.

1.5. The Present Study

While the experimental manipulations of pain-related ABs are fairly sparse, there appears to be a consistent relationship with altered pain perception. Additionally, successfully induced nocebo hyperalgesia depends on altered pain perception: through conditioning, instruction and subsequent expectancies. Thus, combining insights from both nocebo and pain-based literature, the aim of the present study was to investigate a potential role for attention in altering nocebo hyperalgesia.

To achieve this, ABs were induced either towards or away from pain-related words through a novel gaze-augmented dot probe paradigm, based on the pain-modified training task designed by McGowan et al. (2009). Two groups (approximately half of each training group) then received nocebo conditioning to a pain stimulus through instruction and conditioning, by pairing increased shock intensity with a sham device (TENS). The remaining two groups formed control, receiving neutral instruction and non-contingent conditioning. The primary outcome was pain intensity ratings, with expectancy and distress measured secondarily.

The use of a novel, gaze augmented dot-probe task rather than the traditional training variant sought to address methodological limitations associated with the traditional version, potentially providing a more dependable means to modify pain-related ABs. Overall, the present study will provide the first evidence for, or against, a causal role of attention in nocebo effects, filling a presently neglected gap in nocebo literature.

1.5.1. Hypotheses. Firstly, conforming with prior studies using a similar nocebo design, it was hypothesised nocebo hyperalgesia would be observed: the nocebo condition would show higher pain intensity, expectancy, and distress ratings for TENS compared with no-TENS trials during test, when compared to control (e.g. Colagiuri & Quinn, 2018; Colagiuri, Quinn & Colloca, 2015; Colloca, et al., 2010).

Secondly, it was hypothesised training ABs towards pain would result in faster reaction times towards pain-related stimuli than neutral during test, and conversely training away from pain would result in faster reaction times towards neutral stimuli than pain-related stimuli during test (McGowan et al., 2009). While this is inconsistent in prior studies utilising a pain-modified ABM task (Section 1.4), the inclusion of eye-tracking and gaze augmentation should enhance potential for inducing significant training effects.

Finally, given AB training should direct attention to pain stimuli (Crombez et al., 2013) it is hypothesised that AB training will interact with nocebo conditioning, such that inducing an AB towards pain will heighten nocebo hyperalgesia for all outcomes compared with training away from pain.

2. Method

2.1. Participants

One hundred and nineteen participants took part in the present study. Participants were recruited using the University of Sydney Psychology Participation Scheme (Appendix A) – in exchange for 1% course credit – and were individually tested in a 1-hour session. Predetermined exclusion criteria – currently experiencing pain, chronic pain diagnosis, current or previous heart condition and previous use of a TENS device – resulted in the exclusion of two participants. Additionally, participants were excluded due to inability to calibrate eyetracking $(n = 7)$, voluntary withdrawal $(n = 3)$, or following data screening (see Section 2.6) (*n=* 14), resulting in a final sample of 93 participants (60 female) with an age range of 18 to 31 years ($M = 19.67$, $SD = 2.33$). The study was approved by The University of Sydney Human Ethics Committee (Appendix B).

2.2. Design

The summary of experimental conditions is presented in Table 1. The key manipulation involved a 2 (ABM: towards pain vs. away from pain) x 2 (nocebo conditioning: nocebo vs. control) between-subjects design. Participants were randomly allocated to one of the four conditions by randomising group codes in sets of eight, generated from random.org/lists. Initially, all groups were informed the experiment was exploring the effect of TENS on pain, with no instruction regarding the expected direction of effect. The dependent variables were pain intensity, expectancy and distress ratings.

Table 1

Summary of Experimental Conditions

Note. $n =$ number of participants in each condition

2.3. Apparatus

2.3.1. 'TENS' device. The TENS device was a sham device, consisting of two electrodes attached to a stimulus isolator (Model FE180, ADInstruments), which was attached to the participant's left dorsal forearm. Although no genuine TENS was delivered to participants during the experiment, to increase credibility the device generated low level

vibrations – square pulses with a pulse width of 0.2ms and an intensity of 2mA – accompanied by a beeping sound when switched on.

2.3.2. Pain stimuli. Pain was induced by electro-cutaneous stimulation. Electrically induced pain was chosen for ease of surreptitious manipulation, to facilitate a conditioned nocebo effect. Each stimulus consisted of an electric shock $-$ a 100-us square pulse, with a total duration of 0.5 seconds and frequency of 100 Hz. This was delivered to the back of the participant's left hand via two silver chloride electrodes, each secured approximately 1cm apart. A pain stimulator (Model SHK1, Contact Precision Instruments) generated each stimulus.

Intensity was individually calibrated for each participant prior to the main task, to control for individual differences in pain tolerance and minimize any potential influence of floor effects. Participants were affirmed of their control over the maximum level of shock they would be receiving, and the ability to decrease intensity if a particular level was too painful. Sensitivity was built in a stepwise procedure of increasing intensity until the participant described the pain as 'painful but tolerable' (as prompted by the experimenter) – aiming for a subjective verbal rating of around 6 out of 10. This was coded as 100% intensity for the participant. Administration was controlled through the PsychLab software.

2.3.3. Dot-probe task. The ABM was conducted using a novel gaze-augmented version of the dot-probe task, based on the training task developed by McGowan et al. (2009). The task was programmed using Inquisit 5 to interface with the Tobii TX300 eyetracker. Stimuli were presented on a 23-inch TX300 display, with a 1920x1080 pixel resolution. Participants were seated approximately 60cm from the monitor, with height adjusted individually. Figure 3 shows the three phase task structure: a 40 trial baseline block; a 160 trial training block; and a 40 trial test block. A 10 second break followed completion of each block.

Figure 3. Diagram of the overall structure of the attentional bias modification task, including distribution of word pairs per phase.

On each trial, a cross appeared in the centre of the screen. The trial progressed once the participant had fixated (150ms) on the cross. A pain-neutral word pair appeared immediately after, with one approximately 1.5cm above and one approximately 1.5cm below where the fixation point had been. A probe, either the letter 'p' or 'q', followed, in the former location of one of the words. Participants were instructed to indicate via response pad (Model RB-530, Cedrus Corporation) which probe appeared, as quickly and accurately as possible. Each trial ended upon response or after 1500ms had elapsed from probe appearance.

Within the baseline and test blocks, word pairs remained on the screen for a fixed period of 500ms. Each pair appeared randomly four times per block, once in each of the 4 possible combinations: target up/probe up; target up/probe down; target down/probe down; target down/probe up. This resulted in equal congruent (where the probe follows the pain word) and incongruent (where the probe does not follow the pain word) trials in both blocks.

During the training block, all trials were either congruent (training towards pain) or incongruent (training away from pain). Critically, in a novel extension to the standard training paradigm, the appearance of the probe was gaze-augmented, such that if the participant fixated (150ms) on the target word (pain for training towards; neutral for training away) the probe appeared immediately in that location. If no fixation on the target word occurred, the trial progressed after 1000ms. Each pair was randomly presented eight times over the training phase, with location counterbalanced.

Unfortunately, there was a minor error in the programming of the training phase. In the training away group, gaze augmentation was not implemented on affective word trials (see below). This meant that the training away group only experienced gaze augmentation of half of their training trials (i.e. sensory words). Importantly, however, all of their trials were still incongruent in that the probe always appeared in the location of the neutral word. The training towards group received full gaze-augmented training.

2.3.3.1. Word stimuli. All words were 7mm tall and presented in white, Arial font on a black background. Two sets of 20 pain-neutral word pairs were used in the dot probe task (Appendix C). Each of these were matched for length and frequency by the authors (Dehghani et al., 2003; McGowan et al., 2009), and have been previously used in experimental ABM (e.g. McGowan et al., 2009; Sharpe et al., 2012). Both sets are split into 10 sensory pain/neutral pairs and 10 affective pain/neutral pairs. The first set, used in baseline and test was drawn from McGowan et al., (2009). Five sensory and five affective pairs were randomly selected to be presented in baseline, with the remaining 10 pairs presented in test, which was kept consistent across participants. The words used in training were drawn from Dehghani et al., (2003). Thus, words in baseline, training and test were always different (see Figure 3).

*2.3.3.2. Eye-tracking***.** Eye movements were tracked throughout the entire task. Eyetracking was calibrated by prompting participants to focus on green dots as they appear in different locations on the screen. The area of interest (AOI) was defined as a 70x25mm rectangle within the centre of the word area. Based on previous literature integrating eyetracking with a dot-probe task, fixations were defined as saccades which remained stable within a one-degree visual angle for at least 150ms (Todd et al., 2016b; Yang et al., 2012) within the set AOI.

2.3.3.3. Attentional bias indices. The primary dependent variable was overall AB index. This was calculated separately for the baseline and test block, to determine if training successfully changed AB towards pain. The following formula was used: AB index = ((*tupl* - *; where* $t =$ *target stimulus,* $p =$ *probe,* $u =$ *upper location, and* $l =$ *lower* location. The formula is based on the difference in reaction time to congruent and incongruent trials, where a positive score indicates an AB towards pain. To conform with previous studies, response times less than 200ms or greater than 1000ms were removed as outliers (Keogh, Ellery, Hunt, & Hannent, 2001).

Additionally, eye-tracking measures were used as supplementary measures of AB. For baseline and test blocks; number of first fixations and total dwell time on pain and neutral words were recorded, to compare whether there was any change in gaze behaviour following training (Schoth et al., 2014; Sharpe et al., 2017; Todd et al., 2016a,b).

2.4. Measures

2.4.1. Fear of Pain Questionnaire-9 (McNeil et al., 2018). The FPQ-9 consists of 9 self-reported items assessing fear of pain, and was used as a baseline measure to control for potential differences in pain fearfulness (Appendix D). The FPQ-9 is highly correlated with the original FPQ-III ($r = .77$, $p < .001$), and has been shown to maintain the reliability and sound psychometric properties of the original version (McNeil et al., 2018).

2.4.2. Depression, Anxiety Stress Scales-21 (Henry & Crawford, 2005). The

DASS-21 is a 21 item self-report questionnaire consisting of three 7-item subscales assessing depression, anxiety and stress (Appendix E). The DASS-21 was used as a baseline measure to control for potential differences in negative affect. Overall, the scale demonstrates high internal consistency ($\alpha = 0.93$), maintaining the reliability and construct breadth of the full length scale (Henry & Crawford, 2005).

2.4.3. Expectancy and distress ratings. Prior to half of the shocks, participants were asked to rate their expectancy of pain with the prompt *"how painful do you EXPECT the next shock to be*" on a computerised visual analogue scale (VAS), where 0 (the left extreme) was labelled as 'not painful' and 100 (the right extreme) was labelled as 'very painful'. For the remaining half of the shocks, participants were asked to rate their current distress with the prompt *"how DISTRESSED do you feel right now?"* on a similar VAS, where 0 was labelled 'not distressed' and 100 was labelled 'very distressed'.

2.4.4. Pain ratings. After each shock, participants were asked to rate pain intensity of the immediately preceding shock with the prompt "*how PAINFUL was the shock*" on a similar VAS, where 0 was labelled as 'not painful' and 100 was labelled as 'very painful'.

2.4.5. Exit questionnaire. Following completion of the experiment, participants were required to complete an exit questionnaire specific to type of conditioning (Appendix F, G). This consisted of two questions referring to demographic data: age and gender, and one question to examine participants' belief in the cover story, consisting of an open-ended prompt asking "*What do you think the study was about?"*.

The final question differed depending on type of conditioning. For participants in the nocebo groups, the question asked participants to rate the effectiveness of TENS in increasing pain on a line scale with integers 0 to 10 numbered. For control group participants, the question asked participants whether the pulse monitor had any effect on increasing pain, on the same 0–10 scale.

2.5. Procedure

A summary of the experimental procedure is provided in Figure 4. Upon arrival, the researcher verbally affirmed compliance with exclusion criteria. Participants were asked to read an information sheet regarding the study (Appendix H) and provide written consent to take part (Appendix I). Following consent, participants were then asked to complete baseline measures.

Figure 4. Flow-chart of the experimental procedure. *N*= total number of participants, *n*= number of participants in each group.

Next, the shock electrodes were introduced and attached to the back of the participant's left hand. Participants were instructed they would be undergoing a calibration phase (Section 2.3.2), to set maximum shock intensity. Following calibration, each participant was assured shocks would never exceed this threshold. Subsequently the sham TENS machine was introduced and attached to the participant. Table 2 summarises the difference in instruction by nocebo condition.

Table 2

Group	Instructions
Nocebo	You have been allocated to receive TENS. TENS stands for
	transcutaneous electrical nerve stimulation, and increases pain by
	amplifying pain signals sent from neurons in your hand to the brain. This
	means shocks will be more painful when the TENS device is active. The
	TENS itself is not painful, but has a noticeable sensation and beeping
	noise when switched on.
Control	You have been allocated to control, meaning you will not receive TENS.
	This device will be used to measure your pulse, however to ensure non-
	interference with other equipment will only be used on half of trials. You
	will feel a slight sensation and beeping noise when the device is active,
	but it isn't painful.

Verbal Instructions According to Nocebo Group Allocation

Participants were then verbally instructed they would be completing an eye-tracking task, and assured no shocks would be administered during its completion. Participants were

instructed to position themselves comfortably in front of the TX300 monitor, and of the importance of remaining still during the course of the task. Instructions were then presented on the computer screen (Appendix J). Following a calibration check and five practice trials, participants completed the dot-probe task, which took approximately 10-15 minutes.

Participants were then instructed to move in front of a second monitor (with no eyetracking function) from which the nocebo task was run. After switching on the monitor, written instructions (Appendix K) appeared on the screen. Participants were prompted to ask any questions, and then to press start.

2.5.1. Nocebo task. The entire pain task consisted of 4 blocks of 16 intermixed TENS and no-TENS trials. A single trial consisted of a 10-second countdown, followed by an 'X' appearing on the screen simultaneous with the shock. At the 7-second mark (following activation of TENS if the trial is a TENS trial) participants were prompted to rate either expectancy or distress by using the mouse to click at an appropriate location on a VAS 100 point scale. Immediately following each shock, participants rated the painfulness on a similar VAS 100-point scale. Each trial was followed by a variable 10-12 second break.

Table 3 shows the task-wise distribution of trial type and intensity. The first two blocks comprised the conditioning phase. For nocebo groups, TENS activation was followed by high pain stimulation, while no-TENS activation was followed by low pain stimulation. For control groups shocks were either of the same two intensities, but not contingent on whether TENS was active. This was delivered in a blocked fashion, counterbalanced within each control group. The test phase commenced immediately following conditioning, without any notification. Participants were presented with a two further blocks of 16 intermixed trials, however all stimulations were medium intensity. In all other respects, the trial procedure was identical.

Table 3

Pain Intensity Structure of the Nocebo Task

Note. % = percentage of calibrated shock intensity for each individual participant.

Finally, participants were detached from all equipment and asked to complete an exit questionnaire. Participants were thanked for participation and informed an appropriate debrief (Appendix L) would be sent via email following completion of data collection for the present experiment.

2.6. Data Analysis

All analyses were conducted in IBM SPSS Version 25 for Mac, and results were considered statistically significant when $p < .05$. Prior to the main analyses, raw data for each participant was manually screened, resulting in the a priori exclusion of 14 participants. This was due to missing training data for ABM task $(n = 3)$, issue with AOI location for ABM task $(n = 5)$ and mean pain scores under 25 (out of 100) for shocks at the participant's calibrated maximum $(n = 6)^1$.

¹ One participant was included due to increasing their maximum intensity during task completion

2.6.1. Preliminary analysis. Preliminary analyses to determine randomisation success were conducted on all baseline measures. Age, FPQ-9, each DASS-21 subscale (Anxiety, Stress, Depression) and maximum calibrated pain were separately analysed using a 2 (AB condition) x 2 (nocebo condition) Analyses of Variance (ANOVA). Gender was analysed using a chi-square test.

2.6.2. Attentional bias. Prior to main analysis, a 2 (AB condition) x 2 (nocebo condition) x (3) (block: baseline/training/test) ANOVA was conducted on accuracy and a 2 (AB condition) x 2 (nocebo condition) ANOVA was conducted on baseline AB, to ensure there were no significant group differences. Main analysis involved a 2 (AB condition) x 2 (nocebo condition) x (2) (block: baseline/test) ANOVA conducted on AB index, to determine whether training successfully manipulated attentional biases.

Additionally, $2(AB)$ condition) x $2(noebo)$ condition) x (2) (block) ANOVAs were conducted on eye-tracking measures: difference between pain and neutral words in proportion of first fixations and mean dwell time. While the majority of AB eye-tracking studies analyse eye movements in relation to only the target stimulus (i.e. pain stimuli) (e.g. Sharpe et al., 2017; Todd et al., 2016a), difference scores were used presently (Sun, Wang, & Luo, 2016). As the experimental design compared two opposing training directions, eye movements towards neutral and pain stimuli should be differentially effected depending on training, warranting the use of a difference score.

2.6.3. Nocebo pain outcomes. The conditioning and test phase were analysed separately, however extraction followed the same procedure. For each phase, difference scores were created for pain intensity, by subtracting no-TENS rating from TENS rating for each of the 16 pairs of TENS no-TENS trials. The 16 resultant difference scores were then collapsed into four blocks of four. Distress and expectancy followed the same procedure, however as these ratings alternated by trial, there were only eight paired TENS no-TENS

trials per phase, thus the blocks were comprised of two rather than four trials. Separate 2 (AB condition) x 2 (nocebo condition) x (4) (block) ANOVAs were conducted for each phase and outcome, which are referred to as cue-evoked intensity, expectancy or distress. Of interest were any main effects and linear trends across blocks.

2.6.4. Regression analysis. To examine whether AB, expectancy or distress individually predicted nocebo hyperalgesia, Pearson correlations were run between baseline AB, test AB, test expectancy, test distress and test nocebo hyperalgesia. Test expectancy, distress and nocebo hyperalgesia were calculated by averaging difference scores (between TENS and no-TENS paired shocks) during the test phase. Where significant zero-order correlation was observed, predictors were entered into a multiple regression to determine potential mediation.

3. Results

3.1. Baseline Characteristics

Baseline and demographic data are reported in Table 4. These variables were examined to screen and thus control for any potential between group differences. 2 (AB condition) x 2 (nocebo condition) ANOVAs were conducted on age, overall FPQ-9 score, each DASS-21 subscale (stress, anxiety and depression) and maximum calibrated pain level. No significant main effects or interactions were found, suggesting no variable differed significantly between groups, $F(1,89) \le 1.09$, $p \ge .3$. Additionally, the chi-squared analysis of gender found no significant group differences, χ^2 ₍₃₎ = .691, *p*= .875 Consequently, covariates were not included in subsequent analysis.
Table 4

Group Means (SD) for Baseline and Demographic Data

Note. $n =$ number of participants in each group; $F =$ number of females in each group; $FPQ-9 =$ Fear of Pain Questionnaire-9; DASS = Depression, Anxiety and Stress Scales-21; Max. Pain = maximum pain level set during calibration**.**

3.2. Attentional Bias Outcomes

3.2.1. Baseline and reaction time outcomes. Means for overall and word-specific AB at baseline and test are displayed in Table 5. For accuracy, operationalised as percentage of correct trials, only a significant linear trend for block emerged, *F*(1,89)= 8.82, *p*= .004. Thus, all groups appeared to improve in accuracy at the same rate as block progressed. For baseline AB index, no significant main effects or interaction were found, suggesting no group's AB significantly differed from each other. Interestingly, there was a trend to significance for nocebo condition, $F(1,89) = 3.00$, $p = .087$. To ensure neither group significantly differed from zero, post-hoc one sample t-tests were conducted separately for nocebo and control. No significant difference was found for nocebo, *t*(46)= 0.492, *p*= .625. A trend to significance was found for control, $t(45)$ = -1.91, p = .063, suggesting at baseline control groups trended towards a significant bias away from pain words.

Table 5

	Towards		Away		
	Nocebo	Control	Nocebo	Control	
Baseline	3.34 (34.58)	$-5.73(41.18)$	1.69(36.92)	$-15.91(35.75)$	
Sensory	5.53 (40.32)	$-8.83(60.37)$	$-1.96(55.11)$	$-16.78(67.02)$	
Affective	3.18(57.74)	$-2.79(51.14)$	3.99(50.34)	$-10.33(44.31)$	
Test	0.40(40.24)	$-3.22(34.79)$	$-4.58(28.18)$	11.00(41.11)	
Sensory	13.72 (39.62)	$-4.36(58.00)$	$-11.03(46.48)$	21.27 (58.13)	
Affective	$-11.31(58.57)$	$-2.94(35.58)$	1.25(45.35)	2.98(49.27)	

Mean AB Index (SD) at Baseline and Test, Overall and by Word Type

A 2 (AB condition) x 2 (nocebo condition) x (2) (block) x (2) (word type: affective vs. sensory) repeated measures ANOVA was subsequently conducted to test the effect of training on AB index. Word type was included as a variable in the analysis to ensure the aforementioned programming error did not result in inconsistent effects for each subset, which could be lost when collapsed over word type as initially planned. No significant main effects or interactions emerged, $F(1,89) \le 2.482$, $p \ge .119$, indicating training did not result in any observable change in AB between baseline and test.

3.2.2. Eye-tracking outcomes. First fixations on pain and neutral words were calculated separately as a proportion of total trials. A difference score was created by subtracting the proportion of neutral fixations from proportion of pain fixations, thus a score >0 indicates greater first fixations to pain words, and <0 indicates greater first fixations to neutral words. Difference in proportion of fixations at baseline and test, for each experimental group, are shown in Figure 5.

Figure 5. Mean difference in proportion of first fixations (\pm standard error), calculated as the difference in proportion of first fixations between pain and neutral words, for each experimental group at baseline and test. *Note.* >0 indicates more first fixations to pain words, <0 indicates more first fixations to neutral words.

A 2 (AB condition) x 2 (nocebo condition) x (2) (block) was conducted on proportion of first fixations, to determine if this changed as a function of training. A significant main effect for block, $F(1,89) = 4.18$, $p = .044$, was qualified by a significant interaction between block and AB group, $F(1,89)= 5.10$, $p = .026$. Simple effects analysis by block revealed no differences between AB group at baseline, $F(1,89)= 0.55$, $p = .460$. However, there was a significant main effect of AB condition within the test block, *F*(1,89)= 5.94, *p*= .017. It appears the interaction was driven by differences following training, where – contrary to predictions – training towards groups fixated on pain words significantly less than training away.

For mean dwell time, difference scores were created by subtracting mean dwell time for neutral words from pain words. Thus, a score >0 indicates greater dwell time on pain words, and <0 indicates greater dwell time on neutral words. Dwell time difference for each group at baseline and test is shown in Figure 6. A 2 (AB condition) x 2 (nocebo condition) x (2) (block) ANOVA was conducted on dwell time difference, to determine if this changed as a function of training. No significant main effects or interactions with block were observed, $F(1,89) \le 2.93$, $p \ge .091$. As such, the amount of time spent looking at pain words did not appear to change as a function of training.

Figure 6. Mean dwell time difference (\pm standard error), calculated as the difference in dwell time between pain and neutral words, for each experimental group at baseline and test. *Note.* >0 indicates greater dwell time on pain words, and <0 indicates greater dwell time on neutral words.

3.3. Conditioning Phase

The main focus of the study were nocebo effects on intensity, expectancy and distress during the test phase, where all shocks were of equal, medium intensity. Hence, detailed analysis of the conditioning phase for each outcome is provided in Appendix M. Briefly, a main effect of nocebo conditioning was found on intensity and expectancy, confirming nocebo conditioning successfully increased intensity and expectancy on TENS trials. Interactions with block were found for intensity and distress, suggesting the difference between nocebo and control increased across the conditioning phase. Overall, this suggested nocebo conditioning had the intended effect.

3.4. Test Phase

3.4.1. Intensity ratings. Figure 7 shows mean pain ratings for paired TENS and no-TENS trials, across all experimental blocks for each group. Note that during test, any difference between TENS and no-TENS intensity ratings represents nocebo hyperalgesia as all shocks were administered at equal intensity. Figure 8 shows nocebo hyperalgesia by group across each test block.

Figure 7. Mean pain ratings (\pm standard error) across each block, separated by TENS and no-TENS, for each experimental group: (a) Nocebo Towards, (b) Nocebo Away, (c) Control Towards and (d) Control Away. *Note.* Block 1-4 = Conditioning phase, Block 5-8 = Test phase.

Figure 8. Mean nocebo hyperalgesia (\pm standard error), calculated as the difference between TENS and No-TENS pain intensity ratings, for each group by test block of four trials.

Analysis found a significant main effect of nocebo conditioning, $F(1,89) = 17.74$, $p \le$.001. On average, across test block and AB group, nocebo groups rated TENS-paired shocks 7.35 points more painful than control groups, indicating nocebo hyperalgesia. The main effect of AB condition and its interaction with nocebo conditioning were not significant, $F(1,89) \le 0.071$, $p \ge 0.780$, suggesting averaged over test block, attentional training did not appear to influence cue-evoked intensity or nocebo hyperalgesia strength. Additionally, there was no main effect of block nor a significant nocebo conditioning by block interaction, $F(1,89) \le 1.81$, $p \ge 1.83$, suggesting that averaged across AB condition, nocebo hyperalgesia did not trend towards extinction.

However, a significant linear interaction between AB group and test block, *F*(1,89)= 4.81, *p*= .031, was observed. Simple effects analysis for AB group revealed a significant

linear effect for training towards, $F(1,45)= 6.32$, $p= .016$, suggesting difference in cueevoked pain decreases linearly by block, averaged over nocebo condition. No significant linear interaction with block was observed for training away, $F(1,89)= 0.36$, $p= .554$. This was qualified by a significant three-way linear interaction between AB group, nocebo group and test block, $F(1,89)=4.41$, $p=.038$. Simple effects analysis by nocebo group was conducted to comprehend these interactions. A significant interaction between AB group and the linear trend across blocks was observed within the nocebo group, $F(1,45)= 6.87$, $p= .012$. Within control, there was no significant linear interaction between AB group and block. These results suggest that the difference in nocebo hyperalgesia strength between nocebo towards and nocebo away appears to decrease as a function of time.

Thus, additional pairwise comparisons were run to compare the magnitude of nocebo hyperalgesia for nocebo towards and nocebo away in each test block. In block one, nocebo hyperalgesia was significantly stronger (7.25 points) for nocebo towards compared with nocebo away, $F(1,89) = 4.72$, $p = .032$. For each subsequent test block, there was no significant difference in nocebo hyperalgesia between nocebo towards and nocebo away, all $F(1,89) \le 1.37$, $p \ge .246$. Nocebo hyperalgesia appears to be initially stronger for training towards compared with training away, however the interaction suggests this difference decreases linearly as a function of block. Given the decreasing linear trend observed overall for training towards but not away, it appears that as test block progresses, the nocebo towards group trends towards extinction, while nocebo away does not appear to.

Figure 9. Mean pain expectancy ratings (\pm standard error) across each block, separated by TENS and no-TENS, for each experimental group: (a) Nocebo Towards, (b) Nocebo Away, (c) Control Towards and (d) Control Away. *Note.* Block 1-4 = Conditioning phase, Block 5-8 = Test phase.

3.4.2. Expectancy ratings. Figure 9 shows mean pain expectancy ratings for paired TENS and no-TENS trials, across all experimental blocks, for each group. Figure 10 shows cue-evoked expectancy by group across test blocks. Results for test phase cue-evoked

expectancy found a significant main effect of nocebo condition, $F(1,89) = 17.89$, $p < .001$. On average, across test block and AB group, cue-evoked expectancy was 10.94 points higher for nocebo groups compared to control. Additionally, a significant linear trend for block was observed, $F(1,89) = 4.53$, $p = .036$, suggesting across all conditions, difference in cue-evoked expectancy decreased linearly by block. Neither the AB or nocebo conditioning interaction with block was significant, $F(1,89) \le 2.811$, $p \ge .097$, suggesting although expectancy decreased linearly overall, there was no difference in rate within conditions. Thus, the nocebo effect on expectancy did not appear to extinguish.

Figure 10. Mean cue-evoked expectancy (\pm standard error) for each group, by test block of two trials.

Figure 11. Mean distress ratings (\pm standard error) across each block, separated by TENS and no-TENS, for each experimental group: (a) Nocebo Towards, (b) Nocebo Away, (c) Control Towards and (d) Control Away. *Note.* Block 1-4 = Conditioning phase, Block 5-8 = Test phase.

3.4.3. Distress ratings. Figure 11 shows mean distress ratings for paired TENS and no-TENS trials, across all experimental blocks for each group. Figure 12 shows cue-evoked distress by group across test blocks. A main effect of nocebo condition was found, $F(1,89)$ = 6.48, *p*= .013. On average, across test block and AB group, cue-evoked distress was 4.34 points higher for nocebo groups compared to control. Additionally, a significant linear trend for block was observed, *F*(1,89)= 4.67, *p*= .033. Across all conditions, cue-evoked distress appeared to decrease linearly over time. However, this was qualified by an interaction between nocebo condition and linear trend across block, *F*(1,89)= 5.74, *p*= .019. Averaged over AB condition, it appears that as block progressed, the difference between cue-evoked distress for nocebo and control decreased linearly. Simple effects analysis by nocebo group observed a significant linear trend for the nocebo group, $F(1,45)= 13.92$, $p = .001$, while no significant linear trend was observed for control, $F(1,44) = 0.02$, $p = .883$. These results suggest, averaged over AB training, cue-evoked distress trends towards extinction for nocebo groups.

Figure 12. Mean cue-evoked distress (\pm standard error) for each group, by test block of two trials.

3.5. Regression Analysis

Pearson correlations between nocebo hyperalgesia and expected predictors are displayed in Table 6. Interestingly, a trend towards significance was observed for baseline AB and nocebo hyperalgesia, *r*= .197, *p*= .059, suggesting higher AB towards pain at baseline trended to increased nocebo hyperalgesia during test. Additionally, a significant correlation was found between baseline AB and test cue-evoked expectancy, $r = .220$, $p =$.034. This suggests that higher AB towards pain predicted significantly greater nocebo hyperalgesia expectancy during test.

Table 6

Pearson Correlations between Baseline AB, Test AB, Average Cue-Evoked Expectancy at Test, Average Cue-Evoked Distress at Test, and Nocebo Hyperalgesia

	Nocebo	Baseline	Test AB	Test	Test Distress
	Hyperalgesia	AB		Expectancy	
Baseline AB	.197				
Test AB	.005	$-.156$	1		
Test Expectancy	.448**	$.220*$.066		
Test Distress	$.418**$.067	.127	$.667**$	

Note. Nocebo hyperalgesia = average of pain intensity difference scores during test phase. Baseline $AB =$ Attentional Bias Index during the baseline phase of the dot-probe task. Test AB = Attentional Bias Index during the test phase of the dot-probe task. Test expectancy = average of expectancy difference scores during test phase. Test distress = average of distress difference scores during test phase.

Test cue-evoked expectancy was positively correlated with nocebo hyperalgesia, *r*= .448, *p*< .001. Similarly, test cue-evoked distress was positively correlated with nocebo hyperalgesia, $r = .418$, $p < .001$. Distress and expectancy were also significantly correlated

with each other, $r = .667$, $p < .001$, suggesting greater difference in distress was associated with a greater difference in expectancy, and vice versa. Given the significant main effects of nocebo conditioning for both expectancy and distress, each could be explored as a potential mediating variable.

Separate multiple regressions were run for each potential mediator and nocebo condition, to determine whether each maintained a significant relationship with nocebo hyperalgesia when controlling for nocebo group allocation. Controlling for nocebo conditioning, expectancy significantly predicted nocebo hyperalgesia, β = .339, *p*= .001. Thus, as shown in Figure 13, expectancy appeared to partially mediate the effect of nocebo condition on nocebo hyperalgesia. Additionally, distress continued to significantly predict nocebo hyperalgesia when controlling for the effect of nocebo condition, β = .335, p = .001. As shown in Figure 14, distress ratings likewise appear to partially mediate the effect of nocebo condition on nocebo hyperalgesia.

Indirect Effect= -.14**

Figure 13. Mediation model depicting the relationship between nocebo condition, expectancy and nocebo hyperalgesia. Standardised coefficients are shown. *Note.* Nocebo groups were coded 1 = nocebo and 2 = control; $* =$ significant at 0.05, $** =$ significant at 0.01.

Indirect Effect= -.09*

Figure 14. Mediation model depicting the relationship between nocebo condition, distress and nocebo hyperalgesia. Standardised coefficients are shown. *Note.* Nocebo groups were coded 1 = nocebo and 2 = control; $*$ = significant at 0.05, $**$ = significant at 0.01.

4. Discussion

The aim of the present study was to bridge a blatant gap in the nocebo literature, through integrating AB theories of pain. A manipulation of pain-related ABs, through a novel gaze-augmented variant of the dot-probe task, was combined with nocebo instruction and conditioning to explore whether this ABM subsequently changed nocebo hyperalgesia. As the first study to incorporate ABM into a nocebo design, the study is the first to investigate a potentially causal role for attention in nocebo hyperalgesia.

As hypothesised, nocebo instruction and conditioning successfully induced nocebo hyperalgesia during the test phase. This was shown for all outcomes: intensity, expectancy and distress. It was further hypothesised that training ABs would result in differential AB index depending on AB group. For the primary outcome, reaction time, and both supplementary eye-tracking outcomes this hypothesis was not supported by results. Training did not appear to result in any consistent bias either towards or away from pain.

Finally, it was hypothesised AB training would interact with nocebo conditioning, such that training towards pain should heighten nocebo hyperalgesia at test. For pain intensity, results partially supported the hypothesis in the form of a three-way interaction between training, nocebo conditioning and test block. Results for pain expectancy once again partially supported the hypothesis, through significant correlation between baseline AB and heightened cue-evoked expectancy. However, this must be cautiously interpreted as it is correlational by nature of the failed manipulation. Finally, results for distress did not support the hypothesis.

Collectively, the present findings suggest AB does interact with nocebo conditioning, despite failure to observe a training effect. Thus, this study is the first to demonstrate that pain-related attention differentially influences nocebo hyperalgesia, providing initial evidence necessary for more comprehensive exploration of attentional mediation, an area which has been largely overlooked in nocebo literature.

4.1. Nocebo Hyperalgesia Outcomes

The primary hypothesis predicted that following nocebo instruction and conditioning, a nocebo hyperalgesia effect would occur. This was observed during the test phase as a main effect of nocebo condition for all three outcome variables: pain intensity, pain expectancy and distress. Despite identical shock intensities for TENS and no-TENS trials, nocebo groups consistently rated the TENS-paired trials higher on each outcome when compared to control groups. These results align with existing literature which utilise classical conditioning and verbal instruction to induce nocebo hyperalgesia (Colagiuri & Quinn, 2018; Colagiuri et al., 2015; Colloca et al., 2010). Additionally, no overall trend towards extinction for nocebo groups was observed for pain intensity, however this will be elaborated on below.

While expectancy was measured as a secondary outcome, it is more commonly cited as a mechanism of nocebo effects (Benedetti et al., 2007). It is proposed that nocebo effects

are realised through one's self-confirming expectancies (Hahn, 1997), which are produced by instruction or conditioning. Mediation analysis validated this in the present study. Controlling for nocebo group allocation, expectancy was shown to partially mediate the effect of nocebo conditioning on pain intensity. It is interesting to note that although expectancy across all groups decreased across the test block, the rate this occurred did not differ depending on nocebo conditioning. Thus, nocebo expectancy similarly failed to extinguish across the test phase, bolstering its implication as a key mechanism in maintaining nocebo hyperalgesia (Benedetti et al., 2007).

Additionally, the relationship between distress and nocebo hyperalgesia is notable. Previous studies including a subjective measure of fear (Babel et al., 2017) or anxiety (Colagiuri & Quinn, 2018) found no evidence of a predictive relationship with pain intensity. Contrarily, present results suggest that nocebo conditioning induced significantly heightened cue-evoked distress, and moreover that distress partially mediates the effect of nocebo conditioning on nocebo hyperalgesia.

The present finding is buttressed by the crucial distinction between fear and anxiety. Fear is associated with a cued response to a predictable, identifiable threat, while anxiety is associated with a more generalised response to a less predictable threat (Grillon, 2008). As the present study utilised an explicit, cue-evoked nocebo hyperalgesia paradigm, negative emotional responses more likely map to fear than anxiety. Differences are therefore most likely a result of study design. The choice of subjectively rating how 'distressed' rather than 'anxious', more strongly implicates fear, accounting for the discrepancy with Colagiuri and Quinn (2018). Additionally, though Babel et al. (2017) utilised a similar subjective fear rating, their design involved a conditioning paradigm without explicit instruction as to the salience of the cue. Thus, there was no certain, isolatable threat, accounting for the lack of association found with fear.

Moreover, the mediating role of distress found presently lends a degree of support to the primary rationale for the present study, through aligning with the predictions of the fearavoidance model of pain (Vlaeyen & Linton, 2000). Pain-related fear is proposed to foster hypervigilance towards cues of threat, heightening the subsequent experience of pain. Thus, theoretically pain-related fear is implicated in ABs (Keogh et al., 2001; Schoth et al., 2012). However, this cannot be overstated as the present, as the relationship is established only by correlation. Additionally, no measure of ABs was included following the conditioning manipulation, thus it cannot be ascertained whether heightened fear was empirically related to increased ABs. Tentatively, there appears to be substantial merit to integrating pain-related theories of attention into the nocebo context, however the specific role of pain-related fear and its relationship with AB must necessarily be explored further to provide strong, causal evidence.

It is worth briefly noting that a significant relationship between expectancy and distress was observed. As both were measured as secondary outcomes for the present study and not explicitly manipulated, this correlational relationship must be interpreted cautiously. In accord with the aforementioned link to the fear-avoidance model, an interesting postulation could be that negative expectancy heightens pain-related fear, which in turn heightens nocebo hyperalgesia. However, this possibility would require direct experimental manipulation to establish a more conclusive link.

4.2. Attentional Bias Modification

The second hypothesis predicted that undergoing training towards or away from pain words, via a novel gaze-augmented ABM, would create detectable differences in AB depending on training group. Against predictions, training did not produce any consistent changes to AB.

4.2.1. Reaction time. No interaction between training and time was observed for AB index overall or for either sensory or affective words, suggesting AB was not significantly different from baseline. Unfortunately, it is not surprising reaction time did not result in detectable differences in AB following training. The majority of ABMs using a painmodified variant of the dot-probe task show no training effects on ABs (Bowler et al., 2017; Schoth et al., 2013; Sharpe et al., 2012; Todd et al., 2016a). However, all bar one (Todd et al., 2016a) compared training away with a non-contingent training, while presently contingent training away was compared with contingent training towards pain. Theoretically, this should produce stronger effects as two opposing directions are compared, rather than comparing one direction to zero. Indeed, in two of the three studies which have compared opposing training directions, evidence for changes in ABs following training were shown (McGowan et al., 2009; Sharpe et al., 2015).

Alterations made to the present dot-probe task likely account for this discrepancy. Due to time pressures, the duration of each phase of the dot-probe task was halved, such that there were only 160 training trials. It has previously been suggested that the length of assessment phase may dilute any potential training effects (Sharpe et al., 2012). Presently, this was halved from 80 to 40 trials, which should preclude potential dilution. Thus, the obvious difference lies in the shortened training block. Empirically, stronger training effects are associated with longer training phases (Hakamata et al., 2010). It was presently hypothesised that adding gaze-augmentation would account for the shortened training phase duration. Unfortunately, the present results suggest that this was insufficient for participants to (a) consistently detect associations between the target stimuli and the probe location and (b) consistently detect associations between the target stimuli themselves as pain-related (Todd et al., 2015). Ambiguity is another commonly cited issue with the stimuli used in the dot-probe task. Words such as 'boring', 'sharp', 'burning' and 'cruel' are typically not

immediately associated with pain (Todd et al., 2015). Extensive repetition appears necessary for contingencies to be detected by participants, and learned associations to subsequently be induced.

It is interesting to note the trend to significance for nocebo group on baseline AB, which appeared to be driven by a tendency for control groups to avoid pain-related words. This was perhaps fostered by elements specific to the study design, as healthy participants tend not to show significant biases towards or away from pain (Crombez et al., 2013). Tentative parallels can be drawn to the results of Schoth et al. (2014), who found participants under low threat conditions displayed bias away from sensory pain words. Presently, all participants received instruction as to their nocebo group allocation (whether or not they would experience TENS during the experiment) prior to the completion of the dot-probe task. This can be somewhat likened to a threat manipulation, as nocebo groups are subsequently wary of potential for increased pain associated with TENS activation. It is possible the trend to significance observed is a function of the reduced threat associated with control instruction, however, this is speculative at present, and would need to be replicated significantly for stronger postulations to be made.

4.2.2. Mean dwell time. No changes were observed in mean dwell time between pain and neutral words as a function of training. This suggests that AB training did not influence avoidance or difficulty disengaging behaviours. Avoidance would be indicated by reduced dwell time on the target stimulus, while difficulty disengaging would be conveyed as increased dwell time on target stimulus (Todd et al., 2016a).

As only one prior study investigated eye-tracking in an ABM, there is limited direct empirical comparison. In accord with the present results, Todd et al., (2016a) found no interaction between training and mean dwell time. However, both Todd et al. (2016a) and the present study failed to find the expected effect of training on overall AB index. Thus it cannot be discounted that perhaps training does influence avoidance and difficulty disengaging behaviours, and these were not presently observed by nature of the failed overall manipulation.

However, eye-tracking outcomes were included in the present design to account for low reliability and internal consistency associated with reaction time (Dear et al., 2011). While it may be the case that reaction time data is certain evidence of failed training manipulation and thus lack of gaze differentiation by training condition, alternative factors must be considered. Firstly, perhaps the gaze-augmented training phase prevented observable effects on mean dwell time. During training, participants could only dwell for extended periods on the non-target word, as a fixation on the target word would cause the trial to progress. Thus, if participants failed to associate the gaze-contingent element with the appearance of the probe, it is foreseeable that this would subsequently influence mean dwell time following training, barring significant differences from emerging.

Secondly, during baseline and test, word pairs were presented for only 500ms, therefore mean dwell time only measured early attentional distribution. This differs from previous AB measurement studies incorporating eye-tracking, which present stimuli for at least 1250ms (Liossi et al., 2014; Sharpe et al., 2017; Yang et al., 2012; Yang et al., 2013). While each of these studies found no effect on attentional maintenance or late attentional processing as measured by dwell time, a key difference is that each was measuring ABs, whereas the present study involved a manipulation. Thus, it cannot be ruled out that perhaps the shorter presentation time of probes during baseline and test was insufficient to capture differences in dwell time, nor whether training impacts later attentional processing. While 500ms was presently chosen to conform with successful ABM studies (McGowan et al., 2009; Sharpe et al., 2015), longer presentation times should necessarily be explored.

4.2.3. First fixation. Results for first fixations were unexpected, both in relation to previously discussed outcomes and the hypothesised direction. The interaction between block and AB group suggested training towards pain words resulted in significantly fewer first fixations on pain words during the test block relative to training away from pain words, indicating avoidance.

However, the significance of this result must not be overstated. Firstly, if the present results truly reflected learnt avoidance, it would be expected this trend would be observed in at least one of the other outcome measures. Indeed, first fixation is the most consistently associated eye-tracking outcome with factors that predict AB (Liossi et al., 2014; Yang et al., 2012; Yang et al., 2013). As the training manipulation should predict AB, this finding is consequently inconsistent with the majority of eye-tracking studies. To this point, as the overall results for the ABM suggest no change in AB, it is possible this significant result is extraneous. Comparison of group means augments this assumption: both towards (*M*= -.026) and away (*M*=0.009) are very close to 0, which represents no bias. Secondly, as could be the case with dwell time, it is possible that failing to associate the gaze-contingent element with probe appearance prompted avoidance of the training group specific target word, which was then subsequently reflected in higher first fixations for the non-target word at test.

4.3. ABM and Nocebo Hyperalgesia

The final hypothesis, and primary rationale for the study, predicted that AB training would interact with nocebo conditioning, such that training towards pain would strengthen nocebo hyperalgesia for each outcome relative to training away from pain. It was predicted this would emerge as a main effect interaction between nocebo conditioning and AB training, such that training towards pain would heighten nocebo hyperalgesia across the whole test phase. For pain intensity and expectancy, the hypothesis was partially supported. No interaction was observed for distress, disconfirming the hypothesis.

4.3.1. Pain intensity. For pain intensity, an interaction between test block, AB training and nocebo conditioning was observed. While unexpected, this finding aligns with the hypothesised interaction. Additional analysis of simple effects revealed the three-way interaction to be determined by an interaction between training and time within the nocebo groups, driven by a trend to extinction for nocebo towards which was not observed in nocebo away. Cumulatively, the three-way interaction augments the hypothesised link between attention and nocebo effect strength, whereby ABM does appear to have a differential effect on nocebo hyperalgesia. Pairwise comparisons tentatively suggest nocebo hyperalgesia is initially stronger when trained towards pain, however this appears to trend to extinction. When trained away from pain, nocebo groups show a milder, yet persistent nocebo hyperalgesia effect.

Thus, it appears that although the ABM presently employed was unsuccessful at producing observable ABs, there was a later effect on objective pain outcomes. While unexpected, this does not conflict findings in pain. Indeed, the majority of dot-probe ABM studies found no objective effects on ABs, yet significant effects on later pain-related outcomes (Bowler et al., 2017; Schoth et al., 2013; Sharpe et al., 2012; Todd et al., 2016a).

The differing extinction trends observed for nocebo towards and nocebo away can be likened to findings of ABM and pain outcomes. Training away from pain is most consistently associated with increased threshold (Todd et al., 2015). Importantly, pain threshold is the most direct experimental measure of hypervigilance for pain detection (Sharpe et al., 2015), which is causally implicated in the fear-avoidance model: ABs create hypervigilance, which amplifies one's experience of pain (Pincus & Newman, 2001).

Hypervigilance induced by training towards pain would suggest initially the experience of pain is heightened, in accord with the fear-avoidance model, thus accounting for the initial difference in nocebo hyperalgesia strength. However, this induced

hypervigilance to pain cues could promote stronger sensitivity to change, perhaps making those trained towards pain more likely to notice the surreptitious drop in intensity, reflected in decreasing difference scores across test trials.

As away groups have theoretically been trained to attend away from pain, the resultant hypervigilance should not be present, thus reducing sensitivity to the surreptitious decrease in TENS-paired shock intensity between conditioning and test, and accounting for the overall lack of extinction. Additionally, on the grounds healthy participants do not show significant bias to pain words (Crombez et al., 2013), training away somewhat parallels a nocebo design without attentional manipulation. Thus, the trend observed for training away corroborates previous findings of lack of extinction for nocebo effects (Colagiuri et al., 2015; Colagiuri & Quinn, 2018).

The trend to significant correlation observed for baseline AB and nocebo hyperalgesia is worth noting. While entirely speculative at present, it is certainly interesting that higher AB at baseline trended towards increasing the strength of nocebo hyperalgesia during the test phase. At most, this finding bolsters the importance of considering attention as a factor in nocebo effects.

4.3.2. Expectancy. Results for expectancy provided cautious partial support for the hypothesis. While no interactions with AB condition were observed for expectancy ratings during test, a higher AB at baseline correlated positively with increased expectancy difference during test. However, as no significant correlation was observed between baseline AB and nocebo hyperalgesia, the conditions for additional mediation analysis were not fulfilled. Thus, this finding must be interpreted cautiously.

The presently proposed model of nocebo hyperalgesia (Figure 1) suggests negative expectancies, provoked by instruction and conditioning paradigms, are mediated by ABs to pain in facilitating nocebo hyperalgesia. The aforementioned results have confirmed that

expectancy is a significant predictor of nocebo hyperalgesia, and moreover demonstrated a relationship between ABs and expectancy. However, as this is founded on baseline AB due to the failure of the present ABM to produce any observable change in AB, further clarification and successful manipulation is required to determine the nature of this relationship.

4.3.3. Distress. Across conditioning, test, and regression analysis, there appears to be no relationship between AB training and distress. The relationship between pain-related ABM and distress in the literature is somewhat unclear. Carleton et al. (2011) found significant effects of training away from pain on fear of pain. Todd et al. (2016a), using a similar, albeit single item distress measure to that of the present study, found a significant relationship between training towards affective pain and increased distress. However, Sharpe et al. (2012) found no relationship between ABM training and changes in fear of pain.

Presently, distress was used to capture participants' fear specific to the impending shock. Thus, differences between the present findings and those of Carleton et al. (2011) are likely attributed to generalisability. Their fear-related outcome was a general measure of removed pain, while the present measure is explicitly associated with the specific situation. While both the present study and that of Todd et al. (2016a) used a similar, situation-specific measure of distress, presently distress was measured and analysed as a cue-paired difference score. Thus, it appears that attentional training does not influence the magnitude of cueevoked distress, however whether it influences overall distress, regardless of cue, cannot be determined. As this was not presently hypothesised, required analysis was not undertaken. However, it would be interesting to determine if ABM does have any effect on overall fear, as this may provide further insight into the mechanisms by which ABs influence nocebo hyperalgesia, potentially linking to aforementioned extrapolations of the fear-avoidance model.

4.4. Limitations and Future Research

Necessarily, there are important limitations that should be addressed for future research within ABM and nocebo hyperalgesia. Firstly, while care was taken in post-analysis to ensure there was no negative influence on results, a programming error meant gazeaugmentation was only implemented for half of the trials for the training away group. While all trials were still incongruent in terms of probe location, missing half of the gazeaugmentation may have influenced the ability of training away groups to determine contingencies. Additionally, this precluded analysis of whether gaze-augmentation was successful, in regard to whether the number of gaze-augmented trials per 40 trials increased across the training block. Stronger effects may have been observed had the training away group received fully gaze-augmented training, though present results do not appear to suggest this.

Secondly, the present shortening of the dot-probe task may have resulted in a lack of detectable change to AB. This was given strong consideration in the study design, however given time stipulations it was unfeasible to include the full length version of both the dotprobe task and the nocebo protocol. The decision to shorten the dot-probe task was made in the interest of preserving investigation of extinction trends, and under the prospect that perhaps gaze-augmentation would account for the shortened number of trials. As this did not presently appear to be the case, future designs could include a 320 training trial of the dotprobe task, perhaps shortening the nocebo task to two test blocks and foregoing investigation of extinction.

Finally, while presently a novel variant of the dot-probe task was utilised, incorporating eye-tracking technologies, it remains that no significant differences in ABs were found. Thus, the limited reliability of the dot-probe task remains an issue to be contended with in future studies of ABs. Extending on the present study, perhaps gazecontingency could be incorporated rather than gaze-augmentation, such that the trial does not progress unless the participant shows the required looking pattern. This should encourage more active engagement with the task (Ferrari et al., 2016), hopefully facilitating detection of contingencies both between the words themselves and the appearance of the probe.

4.5. Practical and Theoretical Implications

Despite the aforementioned limitations, there are a number of key implications which follow from the present results. Firstly, as the first study within nocebo literature to include an ABM, and given the significant interaction that emerged, the results provide empirical evidence for the previously overlooked role of attention in nocebo effects. In accord with results found in pain literature, AB training resulted in changes to nocebo hyperalgesia outcomes. However, the ABM was unsuccessful, which must be addressed in future research to conclusively associate these outcomes with ABs. This does not negate the significance of the present relationship. Given the poor reliability of the dot-probe task (Dear et al., 2011) and the trend within pain literature to show objective pain outcomes without observable changes in ABs (e.g. Sharpe et al., 2012; Todd et al., 2016a), these results should not be understated.

Conceptually, the results provide some support for the proposed model of nocebo hyperalgesia (Figure 1). It does appear that attention has a role in changing nocebo effects, although at present the conditions were not met for mediation to be empirically tested. Increasing understanding of the mechanisms underlying nocebo hyperalgesia, and nocebo effects more generally is necessary to appropriately mitigate their potential for harm in clinical and non-clinical contexts. Further research should seek to clarify the relationship between attention nocebo hyperalgesia proposed by the present results, which could potentially allow for attention-related interventions to be implicated in the reduction of nocebo hyperalgesia.

Additionally, fear was found to significantly mediate the relationship between nocebo conditioning and nocebo hyperalgesia. While this is a tentative conclusion grounded on a correlational finding, it does suggest a role for fear in the strength of nocebo hyperalgesia. This should necessarily be replicated following an empirical manipulation, to lend weight to the present finding. Thus, interventions aimed to minimise fear directly associated with a procedure or side effect – such as distraction or mindfulness – may serve to decrease the strength of nocebo effects in a clinical context.

4.6. Conclusions

The present study aimed to remedy a significant deficiency in nocebo literature, through exploring the potential for pain-related attention to influence nocebo hyperalgesia. While observable ABs towards pain were not successfully induced following a novel variant of the dot-probe task, the novel finding at present was the differing extinction trends for nocebo towards compared with nocebo away. While this should necessarily be replicated before strong conclusions can be drawn, the present study provides an important foundation for further exploration of attention in the context of nocebo effects, which has been largely overlooked to present.

Additionally, the study represents the first to trial a gaze-augmented variant of the dot-probe task, in the interest of accounting for the lack of reliability plaguing the traditional version. However, gaze-augmentation did not appear to observably change ABs. It is thus perhaps necessary that this task is further extended to gaze-contingency, however this must be empirically tested.

Importantly, the implications and applications that follow from the present results can be generalised beyond the experimental context. The identification of attention and distress as relevant to nocebo hyperalgesia strength suggests attentional and fear-reduction interventions could potentially be implicated in its reduction. Further, while additional research is

necessary, the continued clarification of the mechanisms underlying the nocebo effect provides more insightful means as to not only how this eventuates, but also how this can be clinically mitigated.

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List of Appendices

Appendix A: SONA Advertisement

Study Information

Appendix B: University of Sydney Human Research Ethics Committee Approval

Human Ethics <human.ethics@sydney.edu.au> $\begin{array}{ccccccc}\n\Delta & \zeta & \zeta & \zeta & \to & \cdots\n\end{array}$ Thu 11/04/2019 2:51 PM Creating_a_Form_in_IRMA_Gu... 698 KB

Project Title: Exploring the mechanisms of placebo effects Project number: 2017/989

Modification outcome

Your request to modify the above project was reviewed on 03/04/2019.

The Modification Review Committee approved this modification in principle, subject to the following information being sought and reviewed by the Ethics Office

Please note that you may not implement your requested modifications until your response has been reviewed and final approval has been granted.

1. Please provide SONA_Paid notice board advertisement, and amend the PIS to state the study is also advertised via SONA Paid

Your request will be further considered when these matters have been addressed.

How to submit your response

Please provide your response using the 'Response to existing application' form in IRMA. Detailed instructions on how to submit are attached.

You should provide a cover letter which includes each of the numbered points above followed by your response to each point.

If the Committee has requested that you amend documents, such as the Participant Information Statement or Consent Form, please ensure version numbers/dates are updated and provide both a copy with the changes underlined (or tracked) and a final (clean) copy of the document.

Please note if you do not submit a response within three months from the date of this email the application may lapse and a new application will be required.

If you have any queries you can contact us on the details below.

Regards, The Ethics Office

Questions?

Research Integrity and Ethics Administration I Research Portfolio THE UNIVERSITY OF SYDNEY Level 3, Administration Building (F23) I The University of Sydney I NSW I 2006 T+61 2 9036 9161 | E human.ethics@sydney.edu.au | W http://sydney.edu.au/ethics

Appendix B (Cont.): University of Sydney Human Research Ethics Committee Approval

After consideration of your response to the comments raised, this project has been approved to proceed with the proposed amendments.

Documents Approved:

Please contact the ethics office should you require further information.

Sincerely,

Associate Professor Mark Arnold Chair **Modification Review Committee Chair (MRC 2)**

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 (2007) and the NHMRC's Australian Code for the Responsible **Conduct of Research (2007)**

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

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ABN 15211 513464
CRICOS 00026A

Appendix C: Word Stimuli for the Attentional Bias Modification

C1. Training Block Words (Dehghani et al., 2003)

C2. Baseline and Test Block Words (McGowan et al., 2009)

Baseline.

Test.

Appendix D: Fear of Pain Questionnaire-9 (McNeil et al., 2018)

FEAR OF PAIN QUESTIONNAIRE

 ID

Date:

INSTRUCTIONS: The items listed below describe painful experiences. Please look at each item and think about how **FEARFUL** you are of experiencing the **PAIN** associated with each item. If you have never experienced the PAIN of a particular item, please answer on the basis of how FEARFUL you expect you would be if you had such
an experience. Circle one number for each item below to rate your FEAR OF PAIN in relation to each event.

Appendix E: Depression, Anxiety Stress Scales-21 (Henry & Crawford, 2005)

Appendix F: Exit Questionnaire – Nocebo Groups

ABN 15 211 513 464

Faculty of Science

End-of-experiment questionnaire

ID Number: ________________

1. What do you think the study was about?

2. Have you used TENS previously?

3. How effective would you say the TENS was at increasing pain?

Thank you for your participation!

TENS and Psychophysiological Responses to Pain

Appendix G: Exit Questionnaire – Control Groups

Thank you for your participation!

TENS and Psychophysiological Responses to Pain

Page 1 of 1

Appendix H: Participant Information Statement

School of Psychology Faculty of Science

ABN 15 211 513 464

TENS and Psychophysiological Responses to Pain

PARTICIPANT INFORMATION STATEMENT

(1) What is this study about?

You are invited to take part in a research study investigating the acute effect of Transcutaneous Electrical Nerve Stimulation (TENS) on psychophysiological responses to pain. TENS involves passing a high frequency, low voltage electrical current through the skin that stimulates the nerves below the skin. The psychophysiological responses that will be recorded are your subjective pain ratings and autonomic arousal, assessed non-invasively via skin conductance.

You have been invited to participate in this study because you responded to an advertisement about the study. This Participant Information Statement tells you about the research study. Knowing what is involved will help you decide if you want to take part in the research. Please read this sheet carefully and ask questions about anything that you don't understand or want to know more about.

Participation in this research study is voluntary.

By giving your consent to take part in this study you are telling us that you:

- ✓ Understand what you have read.
- $\sqrt{ }$ Agree to take part in the research study as outlined below.
- ✓ Agree to the use of your personal information as described.

You will be given a copy of this Participant Information Statement to keep.

(2) Who is running the study?

The study is being carried out by the following researchers:

This study is being funded by the Australian Research Council.

(3) What will the study involve for me?

If you agree to participate you will be asked to:

- ✓ Attend a single 60 min session in the Badham Building, University of Sydney
- ✓ Provide some basic demographic data, e.g. age, gender
- \checkmark Complete a computerized attention task, where two words will be presented simultaneously followed by a probe, which you are asked to identify as quickly and accurately as possible
- \checkmark Complete some questionnaires about your emotional state, including fear of pain, depression, anxiety, and stress
- ✓ Have recordings of your skin conductance (to measure arousal) taken. This will require an eight minute baseline period
- ✓ Receive a series of electrical shocks set at a level of your choosing and rate your pain following each shock
- ✓ Have TENS (described above) applied to your arm
- ✓ Complete computerised questions assessing your expectancy and anxiety

(4) How much of my time will the study take?

The study involves a single 60 min session.

(5) Who can take part in the study?

Healthy adults who are not currently suffering from pain are invited to participate in this study. Although the risk is extremely low, participants who are pregnant or have a heart condition are not eligible to participate in the study.

(6) Do I have to be in the study? Can I withdraw from the study once I've started?

Being in this study is completely voluntary and you do not have to take part. Your decision whether to participate will not affect your current or future relationship with the researchers or anyone else at the University of Sydney.

If you decide to take part in the study and then change your mind later, you are free to withdraw at any time. You can do this by informing the researcher that you wish to withdraw. There will be no negative consequences should you wish to withdraw.

(7) Are there any risks or costs associated with being in the study?

Possible risks may include, but are not limited to:

- $\sqrt{ }$ The electric shocks will cause mild temporary pain or distress. Risk to you is minimised by allowing you to set the maximum shock level that you will receive.
- $\sqrt{ }$ There is a minor risk of fainting. Participants with a history of fainting should discuss this with the researcher.

(8) Are there any benefits associated with being in the study?

Psychology students participating via SONApsych will receive 1 hour of course credit. All other participants (including those participating via SONApaid) will receive \$20 to cover the costs of their participation.

It is also expected that by conducting this study, we will enhance knowledge of psychophysiological responses to pain that may help us develop new ways of treating pain in the future.

(9) What will happen to information about me that is collected during the study?

By providing your consent, you are agreeing to us collecting personal information about you for the purposes of this research study. Your information will only be used for the purposes outlined in this Participant Information Statement, unless you consent otherwise.

Your information will be stored securely and your identity/information will be kept strictly confidential, except as required by law. Study findings may be published, but you will not be individually identifiable in these publications*.*

(10) Can I tell other people about the study?

As prior knowledge of the experimental aims and methods may alter results, it would be appreciated if you could refrain from discussing the experiment with others.

(11)What if I would like further information about the study?

When you have read this information, The Ben Colagius will be available to discuss it with you further and answer any questions you may have. If you would like to know more at any stage during the study, please feel free to contact Dr Ben Colagither via phone 9351 or email

(12)Will I be told the results of the study?

You have a right to receive feedback about the overall results of this study. You can tell us that you wish to receive feedback by ticking the appropriate box on the Participant Consent Form. This feedback will be in the form of a one page lay summary. You will receive this feedback after the study is finished.

(13)What if I have a complaint or any concerns about the study?

Research involving humans in Australia is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this study have been approved by the HREC of the University of Sydney (2017/989)*.* As part of this process, we have agreed to carry out the study according to the *National Statement on Ethical Conduct in Human Research (2007).* This statement has been developed to protect people who agree to take part in research studies.

If you are concerned about the way this study is being conducted or you wish to make a complaint to someone independent from the study, please contact the university using the details outlined below. Please quote the study title and protocol number.

The Manager, Ethics Administration, University of Sydney:

- **Telephone:** +61 2 8627 8176
- **Email:** human.ethics@sydney.edu.au
- **Fax:** +61 2 8627 8177 (Facsimile)

Appendix I: Consent Form

School of Psychology Faculty of Science

ABN 15 211 513 464

Associate Professor

TENS and Psychophysiological Reponses to Pain

PARTICIPANT CONSENT FORM

I, [PRINT NAME], agree to take part in this research study.

In giving my consent I state that:

- I understand the purpose of the study, what I will be asked to do, and any risks/benefits involved.
- I have read the Participant Information Statement and have been able to discuss my involvement in the study with the researchers if I wished to do so.
- The researchers have answered any questions that I had about the study and I am happy with the answers.
- I understand that being in this study is completely voluntary and I do not have to take part. My decision whether to be in the study will not affect my relationship with the researchers or anyone else at the University of Sydney now or in the future.
- I understand that I can withdraw from the study at any time.
- 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 consent to:

I would like to receive feedback about the overall results of this study YES NO

If you answered **YES**, please indicate your preferred form of feedback and address:

Appendix J: Computer Instructions for the Dot-Probe Task

In this task a cross will appear in the centre of the screen.

After it disappears, two words will appear, one above where the cross was, and one below.

When you see words, it is important that you read BOTH words silently.

After the words disappear, either a 'p' or a 'q' will appear on the screen.

Simply press 'p' on the response box as fast as you can when you see 'p' on the screen and

press the 'q' on the response box as fast as you can when you see 'q' on the screen.

It will be easier if you place your fingers near the response box before the task starts.

You will also be given some practice trials before you start.

Please ask the experimenter if you have any questions now, otherwise click below to proceed.

Appendix K: Computer Instructions for the Nocebo Task

K1. Instructions for Nocebo Groups

You will receive a series of electrical shocks and your task is to rate the intensity of the pain caused by each shock on a scale from 0-100.

A score of 0 indicates the shock caused NO PAIN

A score of 100 indicates the shock was VERY PAINFUL

All shocks will be signalled by a 10 sec countdown. The shock will occur when an X appears.

You will NEVER receive a shock during the rest periods in between each of the trials.

On some of the trials you will receive TENS on other trials you will not receive TENS.

At various points throughout the experiment, you will also be asked to rate some of your

emotions, e.g. expectancy & distress. Distress includes emotions like feeling anxious or being afraid.

Please try to rate these as accurately as honestly as you can.

Please ask the experimenter if you have any questions now, otherwise click below to proceed.

K2. Instructions for Control Groups

You will receive a series of electrical shocks and your task is to rate the intensity of the pain caused by each shock on a scale from 0-100.

A score of 0 indicates the shock caused NO PAIN

A score of 100 indicates the shock was VERY PAINFUL

All shocks will be signalled by a 10 sec countdown. The shock will occur when an X appears.

You will NEVER receive a shock during the rest periods in between each of the trials.

At various points throughout the experiment, you will also be asked to rate some of your

emotions, e.g. expectancy & distress. Distress includes emotions like feeling anxious or being afraid.

Please try to rate these as accurately as honestly as you can.

Please ask the experimenter if you have any questions now, otherwise click below to proceed.

ABN 15 211 513 464

Associate Professor

Appendix L: Debrief Form

Email:

Telephone: Facsimile:

http://www.sydney.edu.au/

TENS and Psychophysiological Responses to Pain

PARTICIPANT DEBRIEF STATEMENT

Thank you for participating in this study. The aim of this study was to investigate the nocebo effect. The nocebo effect is when people experience negative physiological and/or psychological responses to treatments that are not due to the actual substances contained in the treatment. The nocebo effect is an important area of research because it may help practitioners maximize positive and reduce negative treatment outcomes in health settings.

In this study, no participants actually received Transcutaneous Electrical Nerve Stimulation (TENS). Participants that were told they were receiving TENS actually were given electrodes that were attached to a fake, or inactive, TENS machine that never produced an electrical current. Some people were told it might increase their pain sensitivity, and others still were given no suggestion about TENS' likely effect on pain sensitivity and instead told it was a heart rate monitor. We were interested in understanding how psychological processes such as learning and attention influence whether or not you experienced a nocebo effect. To examine this, some participants received training that made it initially feel like TENS was effective for increasing pain and others did not. Further, some participants completed attentional bias training to increase their attention towards or away from pain related stimuli.

Because the nocebo effect requires that people believe they are receiving an active treatment it was necessary for us to keep the real purpose of this study hidden from you. The reason for delaying this information until now is so that other potential participants did not know that the study investigated the relationship between rumination and the nocebo effect before they participated. We apologise for the deception and for the delay in revealing the study's true aims. After reading this you have the right to withdraw your data from the study. Please inform one of the researchers if you wish to do this. Please be assured that there will be no repercussions if you choose to do this.

If you would like to know more about this study, or are interested in the outcome, please contact **Dr Bene Colagius** or **beneficial properties** who will organize to make the results of the study available to you. Meanwhile, because it is important that other participants do not know precisely what we are looking for before they are tested, we ask for your help by not telling other people who might participate in this study future.

Once again, thank you for participating.

Appendix M: Analysis of the Conditioning Phase

For the conditioning phase, 2 (AB condition) x 2 (nocebo condition) x (4) (block) ANOVAs were conducted separately on difference scores for pain intensity, expectancy and distress.

Pain Intensity

A significant main effect of conditioning was found, $F(1,89) = 264.28$, $p < .001$. Averaged over block and AB condition, cue-evoked pain was 34.61 points higher for nocebo groups than control. A significant linear trend for block, $F(1,89) = 29.77$, $p < .001$, suggested across all groups, pain intensity ratings increased as conditioning progressed. Additionally, a linear interaction between nocebo group and conditioning block, $F(1,89) = 34.09$, $p < .001$, was qualified by a significant quadratic trend, $F(1,89) = 8.41$, $p = .005$. This indicates that as block increased, the difference between nocebo and control difference scores increased at a decreasing rate. No main effect or interaction related to AB was significant, $F(1,89) \le 1.33$, *p* \geq .252 suggesting this did not influence pain intensity difference scores during conditioning.

Expectancy

A significant main effect of nocebo condition was found, $F(1,89) = 14.23$, $p < .001$. Averaged over the entire conditioning phase and AB group, cue-evoked expectancy was 11.88 points higher for nocebo groups than control. Additionally, the three way linear interaction between AB group, nocebo condition and block, $F(1,89) = 4.04$, $p = .048$ was significant. Follow up analysis of each AB group separately showed a significant linear interaction between block and nocebo condition within training away, $F(1,45) = 4.60$, $p =$.037. Between the nocebo away and control away groups, the difference between cue-evoked expectancy appeared to increase linearly with block. Interestingly, no linear interaction with nocebo group was observed for training towards, $F(1,44) = 0.034$, $p = .855$, suggesting the

difference in cue-evoked expectancy between nocebo towards and control towards did not change as a function of time.

Distress

No main effects on distress were significant, $F(1,89) \le 1.14$, $p \ge .288$, suggesting averaged over block, the difference in distress between TENS and no-No-TENS trials did not differ depending on nocebo condition or AB condition. However, a significant linear interaction between block and nocebo condition emerged, $F(1,89)=4.21$, $p=.043$. It appears that as block increases, the difference in cue-evoked distress between nocebo and control groups increased linearly, averaged over AB training.

Appendix N: Statistical Analysis of Baseline Characteristics

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N1. Gender

```
CROSSTABS
 /TABLES=Group BY Gender
 /FORMAT=AVALUE TABLES
 /STATISTICS=CHISQ
 /CELLS=COUNT
 /COUNT ROUND CELL.
```
Group * Gender Crosstabulation

Count

Chi-Square Tests

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 8.16.

N2. Age

```
UNIANOVA Age BY ABGroup Ngroup
  /METHOD=SSTYPE(3)
  /INTERCEPT=INCLUDE
 /PRINT DESCRIPTIVE
 /CRITERIA=ALPHA(.05)
  /DESIGN=ABGroup Ngroup ABGroup*Ngroup
```
Descriptive Statistics

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Dependent Variable: Age

Tests of Between-Subjects Effects

Dependent Variable: Age

a. R Squared = $.028$ (Adjusted R Squared = $-.005$)

N3. Fear of Pain

```
UNIANOVA FOP BY ABGroup Ngroup
 /METHOD=SSTYPE(3)
 /INTERCEPT=INCLUDE
 /PRINT DESCRIPTIVE
 /CRITERIA=ALPHA(.05)
 /DESIGN=ABGroup Ngroup ABGroup*Ngroup.
```
Descriptive Statistics

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Dependent Variable: FOP

Tests of Between-Subjects Effects

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Dependent Variable: FOP

a. R Squared = $.009$ (Adjusted R Squared = $-.024$)

N4. DASS – Stress Scale

```
UNIANOVA DASS_S BY ABGroup Ngroup
/METHOD=SSTYPE(3) /INTERCEPT=INCLUDE
 /PRINT DESCRIPTIVE
 /CRITERIA=ALPHA(.05)
 /DESIGN=ABGroup Ngroup ABGroup*Ngroup.
```
Descriptive Statistics

Tests of Between-Subjects Effects

a. R Squared = .017 (Adjusted R Squared = -0.016)

N5. DASS – Anxiety Scale

```
UNIANOVA DASS_A BY ABGroup Ngroup
 /METHOD=SSTYPE(3)
 /INTERCEPT=INCLUDE
 /PRINT DESCRIPTIVE
 /CRITERIA=ALPHA(.05)
  /DESIGN=ABGroup Ngroup ABGroup*Ngroup.
```
Descriptive Statistics

Tests of Between-Subjects Effects

a. R Squared = .007 (Adjusted R Squared = -0.027)

N6. DASS – Depression Scale

```
UNIANOVA DASS_D BY ABGroup Ngroup
 /METHOD=SSTYPE(3)
 /INTERCEPT=INCLUDE
 /PRINT DESCRIPTIVE
 /CRITERIA=ALPHA(.05)
 /DESIGN=ABGroup Ngroup ABGroup*Ngroup.
```
Descriptive Statistics

Tests of Between-Subjects Effects

a. R Squared = $.008$ (Adjusted R Squared = $-.025$)

N7. Maximum Calibrated Shock Intensity

```
UNIANOVA MaxPain BY ABGroup Ngroup
 /METHOD=SSTYPE(3)
 /INTERCEPT=INCLUDE
 /PRINT DESCRIPTIVE
 /CRITERIA=ALPHA(.05)
  /DESIGN=ABGroup Ngroup ABGroup*Ngroup.
```
Descriptive Statistics

Dependent Variable: MaxPain

Tests of Between-Subjects Effects

a. R Squared = $.020$ (Adjusted R Squared = $-.013$)

Appendix O: Statistical Analysis of Attentional Bias Outcomes

O1. Baseline Attentional Bias

```
GLM acc_base acc_train acc_test BY ABGroup Ngroup
 /WSFACTOR=Block 3 Polynomial
 /MEASURE=accuracy
 /METHOD=SSTYPE(3)
 /PRINT=DESCRIPTIVE
 /CRITERIA=ALPHA(.05)
 /WSDESIGN=Block
 /DESIGN=ABGroup Ngroup ABGroup*Ngroup.
```
Within-Subjects Factors

Measure: accuracy

Tests of Within-Subjects Contrasts

Measure: accuracy

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Tests of Between-Subjects Effects

UNIANOVA BaseAB BY ABGroup Ngroup

```
 /METHOD=SSTYPE(3)
/INTERCEPT=INCLUDE
/PRINT DESCRIPTIVE
/CRITERIA=ALPHA(.05)
```
/DESIGN=ABGroup Ngroup ABGroup*Ngroup.

Tests of Between-Subjects Effects

Dependent Variable: BaseAB

Measure: accuracy

a. R Squared = .042 (Adjusted R Squared = .010)

SORT CASES BY Ngroup. SPLIT FILE LAYERED BY Ngroup. T-TEST /TESTVAL=0 /MISSING=ANALYSIS /VARIABLES=BaseAB /CRITERIA=CI(.95).

One-Sample Statistics

One-Sample Test

O2. Reaction Time

GLM BaseABSensory BaseABAff TestABSensory TestABAff BY ABGroup Ngroup /WSFACTOR=Block 2 Polynomial Word_Type 2 Polynomial /MEASURE=AB_Index /METHOD=SSTYPE(3) /PRINT=DESCRIPTIVE /CRITERIA=ALPHA(.05) /WSDESIGN=Block Word_Type Block*Word_Type /DESIGN=ABGroup Ngroup ABGroup*Ngroup.

Within-Subjects Factors

Tests of Within-Subjects Contrasts

Measure: AB_Index

Tests of Between-Subjects Effects

O3. Eye-Tracking – Proportion of First Fixations

```
GLM Base Prop FF D Test Prop FF D BY ABGroup Ngroup
 /WSFACTOR=Block 2 Polynomial
 /MEASURE=prop_ff
 /METHOD=SSTYPE(3)
 /CRITERIA=ALPHA(.05)
  /WSDESIGN=Block
  /DESIGN=ABGroup Ngroup ABGroup*Ngroup.
```
Within-Subjects Factors

Measure: prop_ff

Tests of Within-Subjects Contrasts

Measure: prop_ff

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Tests of Between-Subjects Effects

Measure: prop_ff

Transformed Variable: Average

×.
UNIANOVA Base_Prop_FF_D BY ABGroup Ngroup $/$ METHOD=SSTYPE (3) /INTERCEPT=INCLUDE /CRITERIA=ALPHA(0.05) /DESIGN=ABGroup Ngroup ABGroup*Ngroup.

Tests of Between-Subjects Effects

a. R Squared = $.026$ (Adjusted R Squared = $-.006$)

```
UNIANOVA Test_Prop_FF_D BY ABGroup Ngroup
 /METHOD=SSTYPE(3)
 /INTERCEPT=INCLUDE
 /CRITERIA=ALPHA(0.05)
 /DESIGN=ABGroup Ngroup ABGroup*Ngroup.
```
Tests of Between-Subjects Effects

a. R Squared = .084 (Adjusted R Squared = .053)

O4. Eye-Tracking – Mean Dwell Time

GLM Base DW D Test DW D BY ABGroup Ngroup /WSFACTOR=Block 2 Polynomial /MEASURE=diff_dw $/$ METHOD=SSTYPE (3) /PRINT=DESCRIPTIVE /CRITERIA=ALPHA(.05) /WSDESIGN=Block /DESIGN=ABGroup Ngroup ABGroup*Ngroup.

Within-Subjects Factors

Measure: diff_dw

Tests of Within-Subjects Contrasts

Measure: diff_dw

Tests of Between-Subjects Effects

Measure: diff_dw

Transformed Variable: Average

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Appendix P: Statistical Analysis of Pain Intensity (Conditioning Phase)

GLM DpainCB1 DpainCB2 DpainCB3 DpainCB4 BY ABGroup Ngroup /WSFACTOR=Block 4 Polynomial /MEASURE=intensity diff /METHOD=SSTYPE(3) /PRINT=DESCRIPTIVE /CRITERIA=ALPHA(.05) /WSDESIGN=Block /DESIGN=ABGroup Ngroup ABGroup*Ngroup.

Within-Subjects Factors

Tests of Within-Subjects Contrasts

Tests of Between-Subjects Effects

Appendix Q: Statistical Analysis of Pain Expectancy (Conditioning Phase)

GLM DExpCB1 DExpCB2 DExpCB3 DExpCB4 BY ABGroup Ngroup /WSFACTOR=Block 4 Polynomial /MEASURE=expect_diff /METHOD=SSTYPE(3) /PRINT=DESCRIPTIVE /CRITERIA=ALPHA(.05) /WSDESIGN=Block /DESIGN=ABGroup Ngroup ABGroup*Ngroup.

Within-Subjects Factors

Tests of Within-Subjects Contrasts

Tests of Between-Subjects Effects

SORT CASES BY ABGroup. SPLIT FILE LAYERED BY ABGroup. GLM DExpCB1 DExpCB2 DExpCB3 DExpCB4 BY ABGroup Ngroup /WSFACTOR=Block 4 Polynomial /MEASURE=expect_diff /METHOD=SSTYPE(3) /PRINT=DESCRIPTIVE /CRITERIA=ALPHA(.05) /WSDESIGN=Block /DESIGN=ABGroup Ngroup ABGroup*Ngroup.

Tests of Within-Subjects Contrasts

Measure: expect_diff

Appendix R: Statistical Analysis of Distress (Conditioning Phase)

GLM DDistCB1 DDistCB2 DDistCB3 DDistCB4 BY ABGroup Ngroup /WSFACTOR=Block 4 Polynomial /MEASURE=distress_diff /METHOD=SSTYPE(3) /PRINT=DESCRIPTIVE /CRITERIA=ALPHA(.05) /WSDESIGN=Block /DESIGN=ABGroup Ngroup ABGroup*Ngroup.

Within-Subjects Factors

Tests of Within-Subjects Contrasts

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Measure: distress_diff

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Measure: distress_diff

Tests of Between-Subjects Effects

Appendix S: Statistical Analysis of Pain Intensity (Test Phase)

```
GLM DPainTB1 DpainTB2 DPainTB3 DPainTB4 BY ABGroup Ngroup
  /WSFACTOR=Block 4 Polynomial
  /MEASURE=intensity_diff
 /METHOD=SSTYPE(3)
  /PRINT=DESCRIPTIVE
  /CRITERIA=ALPHA(.05)
  /WSDESIGN=Block
 /DESIGN=ABGroup Ngroup ABGroup*Ngroup.
```
Within-Subjects Factors

Tests of Within-Subjects Contrasts

Measure: intensity_diff

Tests of Between-Subjects Effects

Measure: intensity_diff

Transformed Variable: Average

SORT CASES BY ABGroup. SPLIT FILE LAYERED BY ABGroup. GLM DPainTB1 DpainTB2 DPainTB3 DPainTB4 BY ABGroup Ngroup /WSFACTOR=Block 4 Polynomial /MEASURE=intensity_diff /METHOD=SSTYPE(3) /PRINT=DESCRIPTIVE /CRITERIA=ALPHA(.05) /WSDESIGN=Block /DESIGN=ABGroup Ngroup ABGroup*Ngroup.

Tests of Within-Subjects Contrasts

Measure: intensity_diff

SORT CASES BY Ngroup. SPLIT FILE LAYERED BY Ngroup. GLM DPainTB1 DpainTB2 DPainTB3 DPainTB4 BY ABGroup Ngroup /WSFACTOR=Block 4 Polynomial /MEASURE=intensity_diff /METHOD=SSTYPE(3) /PRINT=DESCRIPTIVE /CRITERIA=ALPHA(.05) /WSDESIGN=Block /DESIGN=ABGroup Ngroup ABGroup*Ngroup.

Tests of Within-Subjects Contrasts

Measure: intensity_diff

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```
GLM DPainTB1 DpainTB2 DPainTB3 DPainTB4 BY ABGroup Ngroup
 /WSFACTOR=Block 4 Polynomial
/MEASURE=intensity diff
 /METHOD=SSTYPE(3)
  /EMMEANS=TABLES(ABGroup*Ngroup)
  /EMMEANS=TABLES(ABGroup*Ngroup*Block) compare (ABgroup)
  /CRITERIA=ALPHA(.05)
  /WSDESIGN=Block
  /DESIGN=ABGroup Ngroup ABGroup*Ngroup.
```
Pairwise Comparisons

Measure: intensity_diff

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Least Significant Difference (equivalent to no adjustments).

Univariate Tests

Each F tests the simple effects of ABGroup within each level combination of the other effects shown. These tests are based on the linearly independent pairwise comparisons among the estimated marginal means.

Appendix T: Statistical Analysis of Pain Expectancy (Test Phase)

GLM DExpTB1 DExpTB2 DExpTB3 DExpTB4 BY ABGroup Ngroup /WSFACTOR=Block 4 Polynomial /MEASURE=expectancy_diff /METHOD=SSTYPE(3) /PRINT=DESCRIPTIVE /CRITERIA=ALPHA(.05) /WSDESIGN=Block /DESIGN=ABGroup Ngroup ABGroup*Ngroup.

Within-Subjects Factors

Measure: expect_diff

Tests of Within-Subjects Contrasts

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Measure: expect_diff

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Tests of Between-Subjects Effects

Appendix U: Statistical Analysis of Distress (Test Phase)

```
GLM DDistTB1 DDistTB2 DDistTB3 DDistTB4 BY ABGroup Ngroup
  /WSFACTOR=Block 4 Polynomial
  /MEASURE=distress_diff
 /METHOD=SSTYPE(3)
  /PRINT=DESCRIPTIVE
  /CRITERIA=ALPHA(.05)
  /WSDESIGN=Block
 /DESIGN=ABGroup Ngroup ABGroup*Ngroup.
```
Within-Subjects Factors

Tests of Within-Subjects Contrasts

Measure: distress_diff

Measure: distress_diff

Tests of Between-Subjects Effects

SORT CASES BY Ngroup. SPLIT FILE LAYERED BY Ngroup. GLM DDistTB1 DDistTB2 DDistTB3 DDistTB4 BY ABGroup Ngroup /WSFACTOR=Block 4 Polynomial /MEASURE=distress_diff /METHOD=SSTYPE(3) /PRINT=DESCRIPTIVE /CRITERIA=ALPHA(.05) /WSDESIGN=Block /DESIGN=ABGroup Ngroup ABGroup*Ngroup.

Tests of Within-Subjects Contrasts

Measure: distress_diff

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Appendix V: Regression Analysis

CORRELATIONS

 /VARIABLES=Ngroup BaseAB TestAB T_pain_diff T_exp_diff T_distress_diff /PRINT=TWOTAIL NOSIG /MISSING=PAIRWISE.

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

```
REGRESSION
 /MISSING LISTWISE
 /STATISTICS COEFF OUTS R ANOVA
 /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT T_pain_diff
  /METHOD=ENTER Ngroup T_exp_diff.
```


a. Predictors: (Constant), T_exp_diff, Ngroup

ANOVA^a

a. Dependent Variable: T_pain_diff

b. Predictors: (Constant), T_exp_diff, Ngroup

Coefficients^a

a. Dependent Variable: T_pain_diff

REGRESSION /MISSING LISTWISE /STATISTICS COEFF OUTS R ANOVA /CRITERIA=PIN(.05) POUT(.10) /NOORIGIN /DEPENDENT T_pain_diff /METHOD=ENTER Ngroup T distress diff.

Model Summary

a. Predictors: (Constant), T_distress_diff, Ngroup

ANOVA^a

a. Dependent Variable: T_pain_diff

b. Predictors: (Constant), T_distress_diff, Ngroup

Coefficients^a

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a. Dependent Variable: T_pain_diff

Appendix W: SPSS Variable List

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