The Mental Stage: Exploring the Cognitive and Neural Mechanisms of Envisaged Scenes and Social Perception in Neurodegenerative Disorders

Nikki-Anne Wilson

BAppSc (Psych), BSc-Psych (Hons, First)

School of Psychology, Faculty of Science

The University of Sydney

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy.

2021

Table of Contents

Index of Tables

Index of Figures

List of Abbreviations

ACE-III	Addenbrooke's Cognitive Examination-Third Edition
ACE-R	Addenbrooke's Cognitive Examination-Revised
AD	Alzheimer's disease
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
bvFTD	Behavioural variant frontotemporal dementia
CBI-R	Cambridge Behavioural Inventory – Revised
CN	Control
dlPFC	Dorso-lateral prefrontal cortex
DMN	Default mode network
DST	Dewey story test
EI	Experiential index
EP	Entities present
fMRI	Functional magnetic resonance imaging
FSL	Functional MRI of the Brain Software Library
FTD	Frontotemporal dementia
M	Mean
MNI	Montreal Neurological Institute
MTL	Medial temporal lobe
MRI	Magnetic resonance imaging
NPI	Neuropsychiatric inventory

PET	Positron emission tomography
PFC	Prefrontal cortex
RAVLT	Rey Auditory Verbal Learning Test
RCF	Rey Complex Figure
SCI	Spatial coherence index
SD	Standard Deviation
SEN	Sensory descriptions
SNQ	Social norms questionnaire
SPA	Spatial references
SydBat	Sydney Language Battery
TASIT	The Awareness of Social Inference test
TEA	Thoughts, emotions, and actions
TMT	Trail Making Test
ToM	Theory of mind
VBM	Voxel-based morphometry
vmPFC	Ventromedial prefrontal cortex

Dissemination of Findings

The results outlined in this thesis form the basis of the following first-author publications and conference presentations. Author contributions are stated below.

Published Papers

Chapter 3

Wilson, N.-A.,* Ramanan, S*., Roquet, D., Goldberg, Z.-L., Hodges, J. R., Piguet, O & Irish, M. (2020). Scene construction impairments in frontotemporal dementia: Evidence for a primary hippocampal contribution. *Neuropsychologia, 137,* doi:10.1016/j.neuropsychologia.2019.107327. [Impact Factor = 2.9].

*equal contribution. N-AW conducted the critical review of the literature, inter-rater scoring, statistical analysis and interpretation, and completed the pre-processing of the voxel based morphometry. SR completed the voxel based morphometry. MI designed the concept and was primary scorer. All authors contributed to the drafting of the manuscript and critical revision of the final piece.

Chapter 4

Wilson, N.-A., Ahmed, R.M., Hodges, J. R., Piguet, O & Irish, M. (2020). Constructing the social world: Impaired capacity for social simulation in dementia. *Cognition*, *202*, doi:10.1016/j.cognition.2020.104321. [Impact Factor = 3.5]

N-AW designed the study including the task stimuli, conducted pilot testing and a critical review of the literature, completed data scoring, statistical analysis and interpretation, and wrote the paper. MI contributed to study design and drafting of the paper, MI and OP provided input into the interpretation of the results. All authors contributed to the critical revision of the final piece.

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Nikki-Anne Wilson Date 25th Januray, 2021

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor Olivier Piguet Date 27th January 2021

Conference Presentations

Chapter 3

2017. **Wilson, N-A.** *Scene construction performance in behavioural-variant frontotemporal dementia.* Oral presentation at the Scientific Meeting of the Federation of the European Societies of Neuropsychologie, Maastricht, The Netherlands.

2017. **Wilson, N-A.** *Memory reimagined: Scene construction performance in behavioural-variant frontotemporal dementia.* Oral and poster presentation at the Australasian Society for Social and Affective Neuroscience Conference, Melbourne, Australia.

2017. **Wilson, N-A.** *Scene construction in frontotemporal dementia: Exploring underlying* mechanisms. Poster presentation at the ARC Centre of Excellence in Cognition and its Disorders Annual Workshop, Hunter Valley, Australia.

2017. **Wilson, N-A.** *Exploring the neurocognitive mechanisms of impaired capacity for imagination in frontotemporal dementia.* Poster presentation at the Brain and Mind Centre Symposium, The University of Sydney, Sydney, Australia.

2018. **Wilson, N-A.** *Memory reimagined: Scene construction performance in behavioural-variant frontotemporal dementia.* Oral presentation at the International Conference of Prospective Memory, Melbourne, Australia.

2018. **Wilson, N-A.** *Beyond memory: Mental simulation in frontotemporal dementia.* Oral presentation at the ARC Centre of Excellence in Cognition and its Disorders Memory Program Meeting, Manly, Australia.

Chapter 4

2018. **Wilson, N-A.** *Impaired mental simulation in behavioural-variant frontotemporal dementia and impaired social function.* Oral and poster presentation at the 11th International Conference on Frontotemporal Dementias, Sydney, Australia.

2018 **Wilson, N-A.** *Reduced capacity to imagine social scenarios is associated with impaired social knowledge in frontotemporal dementia.* **Awarded best oral (DataBlitz) presentation** at the Sydney Postgraduate Psychology Conference, Sydney, Australia.

2018. **Wilson, N-A.** *Impaired social simulation in the behavioural-variant of frontotemporal dementia: A novel cognitive mechanism underlying social behaviour?* **Awarded best poster presentation** at the Australasian Cognitive Neuroscience Society Conference, Melbourne, Australia.

2018. **Wilson, N-A.** *Social simulation: A novel cognitive mechanism associated with impaired social knowledge in behavioural-variant frontotemporal dementia.* Poster presentation at the Brain and Mind Centre Symposium, The University of Sydney, Sydney, Australia.

2018. **Wilson, N-A.** *Reduced capacity for social simulation is associated with social dysfunction in behavioural-variant frontotemporal dementia.* Poster presentation at the ARC Centre of Excellence in Cognition and its Disorders Annual Workshop, Bowral, Australia.

2019. **Wilson, N-A.** *Reduced social perception is associated with social scene construction deficits in frontotemporal dementia.* Oral presentation at the Australasian Cognitive Neuroscience Society Conference, Launceston, Australia.

2019. **Wilson, N-A.** *Reduced capacity for social simulation is associated with impaired social knowledge in behavioural-variant frontotemporal dementia.* Oral presentation at the Australasian Society for Social and Affective Neuroscience Conference, Newcastle, Australia.

2019. **Wilson, N-A.** *Social simulation: A cognitive mechanism associated with impaired social knowledge in behavioural-variant frontotemporal dementia.* Oral and poster presentation at the Australian Society for the Study of Brain Impairment Conference, Wellington, New Zealand.

Notable Achievements

2016 Australian Postgraduate Award and Research Excellence Scholarship, The University of New South Wales.

2017 The University of Sydney, School of Psychology Stipend and Top-Up Scholarship.

2017 Winner of The University of Sydney Faculty of Science and Brain and Mind Centre Three Minute Thesis competitions, and overall university finalist.

2018 Best oral (DataBlitz) presentation at the Sydney Postgraduate Psychology Conference.

2018 Best poster Presentation at the Australasian Cognitive Neuroscience Society Conference.

2019 The University of Sydney, School of Psychology Publication Prize.

2020 Winner of The University of Sydney Faculty of Science Three Minute Thesis competition, and overall university runner-up, *"Your Life on the Big Screen"*

2020 The University of Sydney, Brain and Mind Centre Award for Excellence and Impact in Research (paper based on Chapter 4).

Statement of Originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes. I certify that the intellectual content of this thesis is the product of my own creation and that all the assistance received in preparing this thesis and sources have been acknowledged.

The research contained within the thesis was conducted under the supervision of Professor Olivier Piguet and Professor Muireann Irish as part of the FRONTIER Frontotemporal Dementia Research Clinic based at the Brain and Mind Centre, The University of Sydney. The standardised neuropsychological assessment battery described in Chapter 2 was predominantly collected by research assistants at FRONTIER. Chapter 3 also contains data largely collected by FRONTIER research assistants and scored by Professor Muireann Irish, though the interpretation, inter-rater scoring, statistical analysis, and neuroimaging pre-processing were all conducted by me.

Data pertaining to all studies were collected through direct contact with participants following written informed consent being obtained from the participant or their Person Responsible. In accordance with the Declaration of Helsinki, ethical approval was obtained from the Human Research Ethics Committee of the South Eastern Sydney Local Health District at the University of New South Wales (HREC 10/126 and HREC 13/177).

Nikki-Anne Wilson Date 25th Januray, 2021

Acknowledgements

The completion of this thesis leaves me humbled by the generosity, guidance, and support I have received from many people, only some of whom it is possible to name here. First and foremost, I would like to thank the participants of the FRONTIER research clinic, without whom this work would not have been possible. The indefatigable commitment to advancing dementia research and the personal good will I have experienced from these patients, and their families, has been one of the highlights of my PhD candidature.

Thanks to my supervisors for contributing profoundly to my intellectual and personal growth throughout this journey. Professor Olivier Piguet, thank you for your mentorship and for creating such a unique and inspiring learning environment. I appreciate your support and guidance to the very end. Professor Muireann Irish, thank you for your insightful intellectual contribution to the development and direction of this thesis, and the opportunities I have received from being a foundational member of the MIND research group.

I am fortunate to have completed my PhD surrounded by a community of colleagues who both generously shared their expertise and encouraged me with their dedication and passion for their work. I particularly thank Mirelle D'Mello, Sherry Chen, Candy Cheung, Zoe-Lee Goldberg, David Foxe, Annu Mothakunnel, and Aurélie Manuel Stocker. Special mention must also go to Cherie Strikwerda-Brown, Tamara Paulin, Emma Johnson, and Marilena DeMayo for everything. It is the only word which comes close and I know I would not be here today without your support. Thanks too to my Honours supervisor, Associate Professor Jenny Batchelor, whose development of, and faith in, my research skills served as the foundation upon which this thesis was built.

I am without words to express my gratitude to Professor Louise Sharpe, Professor Ilona Juraskova, and Susannah Gregory. I wish that I had not needed you quite so much but I am so very, very thankful that you were there.

I also gratefully acknowledge The University of Sydney, School of Psychology for providing funding to support my candidature, as well as additional travel expenses and administrative support. Initial funding of my candidature was also provided by an Australian Government Postgraduate Award and a University of New South Wales Research Excellence scholarship.

More personally, I would like to thank all those, too numerous to mention here, who have helped carry me through some of the most remarkable but challenging years of my life. Special mention to my PhD soul mate, Melissa Brinums, for your friendship, the contagion of your courage, and your unwavering belief in me; as well as my fellow leprechaun, Claire, for changing my life so profoundly for the better and proving that dwelling in the land of Happy Chappy is still the best way to meet the best people. My dear friends, Janna and Sue, thankyou for the generous capacity of your ears and your hearts. Kat, Shu, Tan and Andy, for supporting me largely from afar, and Tas and Sophea for enduring my proximity. Thanks to the considerable assistance from a range of performance enhancing substances, namely prednisone, tea, and Messina milk-chocolate and peanut-butter fudge ice-cream. Yes, and… Improv Theatre Sydney for reminding me that laughter has a never-failing ability to heal and when life is absurd and you don't know what to do, chop carrots. And last, but *most* of all, to my Mum for supporting me and loving me in all the ways that she can.

Dedication

All PhD students feel the weight of the impossibility of this task at some point. As a student with chronic illness, however, who became sick at age 10, entered university with little more than a mid-primary school education, having only ever written a single essay, and completed the majority of her undergraduate degree bedbound/housebound in an often semi-darkened room, for me, this weight was a little heavier than most. The (many) challenges did not end upon the commencement of my PhD candidature. However, as I now stand atop a mountain many suggested I could not climb, I hope my path has cleared the way, just a little, for others like me. My PhD has literally been my passport to the world, and my passion for improving the lives of those living with dementia, my guide.

"It's in the impossible that we find life's greatest adventures and richest rewards. Impossible is good for the soul." Nikki-Anne Wilson

I dedicate this thesis to all those within academia living with a disability whose passion for research drives them to excel not only despite, but often because of, the challenges we face. A rich academic community is only possible within the context of a diverse academic community and we need more diverse voices, of all kinds. It is the insight, ingenuity, empathy, determination, and differing world view from these diverse voices which holds the greatest gift to the discovery of new knowledge. Standing with each other in order to ensure these voices are heard is imperative. As every student with a disability or other point of diversity can attest, our very existence in academic life is testament to our work ethic and problem solving ability. We have so very much to offer, we just need to be given a chance.

Abstract

Imagination has long been proposed to serve an important evolutionary purpose in supporting human cognition. More recently, research investigating the cognitive and neural correlates pertaining to the capacity to envisage mental scenes has revealed extensive associations between mental imagery and a range of everyday cognitive processes. Exploring the role of mental imagery in relation to social cognition, however, is only now gaining momentum. This thesis expands current clinical and theoretical understanding of the cognitive architecture of mental simulation by examining task performance across two dementia syndromes: behavioural variant frontotemporal dementia (bvFTD) which presents as a profound change in personality and behaviour; and Alzheimer's disease (AD), more commonly characterized by severe episodic memory deficits. Results arising from four separate studies demonstrate that the capacity for mental imagery is significantly disrupted across dementia syndromes, appearing to result from divergent cognitive and neural contributions. Importantly, discrete classes of mental simulation emerge, dependent on the sociality and congruency of the scene cues, resulting in disproportionately disrupted task performance largely in the bvFTD group. Specifically, social simulation was particularly impaired in bvFTD and significantly related to broader social perception, knowledge, and behavioural changes in this group. Interestingly, modifying the semantic loading of the scene task appears to increase the capacity for mental construction in bvFTD, at least in some respects. Identification of discrete classes of scene construction expands current conceptions of imagination and further elucidates the clinical profile of dementia syndromes. Furthermore, characterizing the potential cognitive underpinnings of social deficits in bvFTD paves the way for improved diagnosis and behavioural management.

1

General Introduction

"Imagination is more important than knowledge. Knowledge is limited. Imagination encircles the world." Albert Einstein

As adults, we often tend to dismiss imagination as a form of creativity for children which is long outgrown by adulthood. Indeed, the capacity to imagine alternative scenarios has been suggested to play an integral role in learning and development in childhood (Nyhout & Ganea, 2019). Generally defined as the capacity to form mental imagery without immediate sensory input (Crespi et al., 2016), research investigating imagination has historically focused on the philosophical, with the invisible properties of the human mind holding an almost magical appeal to those seeking a larger truth (Nigel, 2020). Recent advances in neuroimaging and cognitive neuroscience, however, have begun to make the magical tangible by identifying the neural networks supporting imagination and how these interact with other cognitive processes (Spreng, Mar, & Kim, 2008). Undeniably, the last two decades have seen a growing understanding of the importance of imagination across the lifespan, including its centrality in many of our everyday experiences. More importantly, elucidating the capacity for mental imagery in neurodegenerative diseases enhances our understanding of how cognition breaks down in these disorders and potentially paves the way for improved clinical diagnosis and management.

Imagination essentially involves the capacity to see that which is not there and although deeply linked to creativity, is viewed as a distinct cognitive process (Pelaprat & Cole, 2011). Whenever

we re-experience a past event or envisage a hypothetical future scenario, it is our imagination which fuels this immersive experience, evoking richly detailed mental imagery which is only differentiated by the intent to move forwards or backwards in time (Mullally & Maguire, 2014). This capacity for mental imagery has long been proposed to support our ability to better understand and adapt to the present. Vygotsky writes that the brain constantly "…combines and creatively reworks elements of… past experience and uses them to generate new propositions and new behaviour…" (1967, translated by Stokes, 2016, p. 9). This extraordinary human ability to consider alternative scenarios has also been suggested to hold an evolutionary advantage (Suddendorf & Redshaw, 2013) particularly in relation to detecting and manage threat (Bulley, Henry, & Suddendorf, 2017). Imagination, therefore, is posited to not only be essential to human thought but to how we perceive experiences across time, our sense of self and personal wellbeing (Smallwood & Andrews-Hanna, 2013), and how we respond to our ever-changing world.

Although much about the ways in which we study the hidden properties of the mind have radically changed with the advent of neuroimaging, the perceived experience of mental processes such as memory, future thinking, and imagination continue to provide new and important insight regarding the richly nuanced, diverse and integrative nature of cognition. Much of the ability to remember and predict relies on the capacity to form a realistic, cohesive mental representation of the world (Spreng et al., 2008). From a neuroscientific perspective, and for the purposes of this thesis, the term mental imagery refers to the ability to mentally envisage three-dimensional, naturalistic scenes, more specifically known as scene construction (Hassabis, Kumaran, Vann, & Maguire, 2007). Scene construction is a multi-faceted process which mirrors the complexity of our day-to-day experiences in the real world. Much can be revealed about the cognitive domains supporting mental construction by examining the richness, salience, and nature of the scene elements

described, and the overall cohesiveness of the scene depiction (Hassabis et al., 2007). While a range of cognitive processes have been implicated in supporting, or being supported by, mental construction (Conti & Irish, in press; Hassabis & Maguire, 2007; Mullally & Maguire, 2014), little research thus far has examined how mental construction may be associated with broader social and behavioural factors. This thesis systematically examines the cognitive architecture of mental construction across neurodegenerative diseases and expands our understanding of the interrelationships between the capacity to simulate social scenarios and broader social function.

1.1 What is Scene Construction?

Scene construction refers to the capacity to mentally generate, and maintain, a richly detailed, naturalistic, three-dimensional scene in one's mind's eye (Hassabis et al., 2007). Originally developed as a method to systematically investigate episodic memory, that is, memory for past experiences (Hassabis et al., 2007), scene construction has evolved into a useful tool to examine the richness and complexities of memory and cognition which traditional neuropsychological measures often fail to capture (Rubin, Deffler, & Umanath, 2019). Scene construction tasks involve imagining and describing aloud an atemporal, everyday scene, for example, a beach, in as much detail as possible and using all senses. Participants are requested to try to imagine a novel scene and avoid simply recounting an existing memory. The resulting scene descriptions can then be scored in accordance with standard protocols and compared across participants, limiting the nuance inherent in recalling unique personal experiences (Hassabis et al., 2007). A schematic representation of the contextual detail comprising an envisaged scene according to the Scene Construction Task scoring protocol (Hassabis et al., 2007) is shown in Figure 1.1.

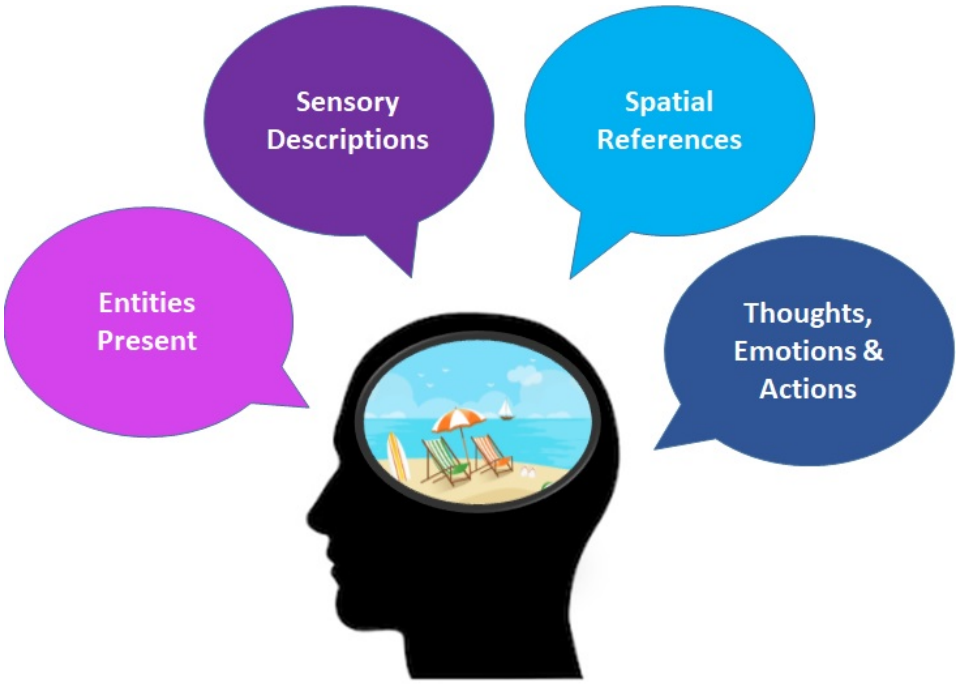

Figure 1.1. Schematic representation of the multi-domain contextual detail captured by the Scene Construction Task scoring protocol (Hassabis et al., 2007).

1.1.1 Neural regions supporting scene construction

As the name suggests, scene construction is a highly integrative process involving multiple domains, including sensory, spatial, and semantic elements (Hassabis & Maguire, 2009). Given this multi-modal complexity, it is unsurprising that an extensive neural network has been identified as supporting scene construction. Functional magnetic resonance imaging (fMRI) studies in healthy individuals have repeatedly identified activation in the brain's Default Mode Network (DMN) as supporting scene construction (Palombo, Hayes, Peterson, Keane, & Verfaellie, 2018; Zeidman, Mullally, & Maguire, 2015). The DMN (Figure 1.2.) is so named as synchronized activation across these different brain regions has been associated with focusing more on mental states driven by internal forces, such as remembering a past experience, and less on external environmental stimuli (Buckner, Andrews-Hanna, & Schacter, 2008). Regions comprising the

DMN include the medial temporal lobes (MTL), particularly the hippocampus, the retrosplenial and posterior cingulate cortices, the temporoparietal junction, and the prefrontal cortex (Palombo et al., 2018; Robin et al., 2015; Summerfield, Hassabis, & Maguire, 2010; Zeidman et al., 2015). Further, it has been demonstrated that different subsets of the DMN may be recruited at various stages of the construction process dependent on the number of scene elements being integrated (Summerfield, Hassabis, & Maguire, 2010). This raises the question of whether the nature of an envisaged scene in addition to the overall integrative load may change the dynamics of scene construction, resulting in class specific task performance in certain populations (explored further in Chapters 4 and 5). In sum, scene construction is a highly dynamic process involving the combination and integration of information from various neural sources (Ciaramelli, De Luca, Monk, McCormick, & Maguire, 2019; Hassabis & Maguire, 2007; Summerfield et al., 2010).

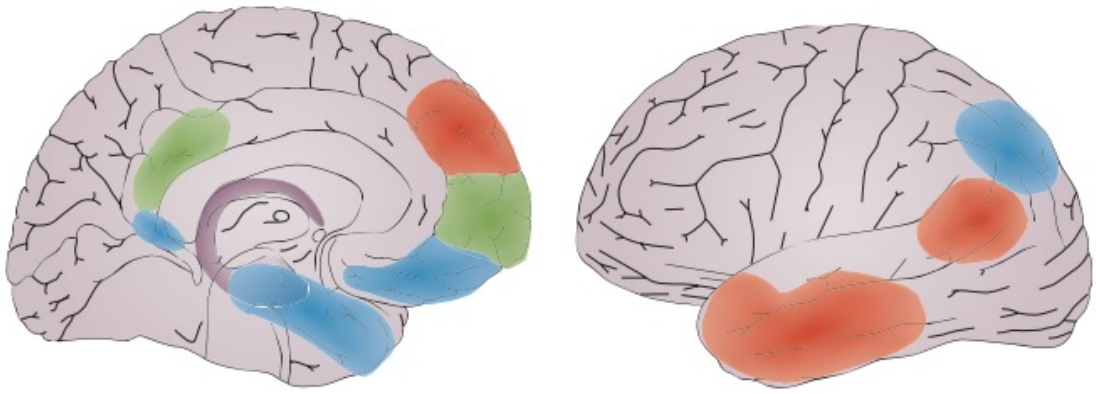

Figure 1.2. Neural regions comprising the default mode network (DMN), including medial temporal lobes (MTL, blue), and dorsomedial prefrontal cortex (dmPFC, red) which converge on the midline core (green). The MTL subsystem is centred on the hippocampus, as well as para-hippocampal, retrosplenial, and ventromedial prefrontal cortices, and the posterior inferior parietal lobule. The dmPFC subsystem includes the temporoparietal junction, lateral temporal cortices and temporal pole. The midline core includes the anterior medial prefrontal cortex, and the posterior cingulate cortex. Adapted from Irish, Piguet, and Hodges, 2012.

1.1.2 Findings from clinical studies

Clinical studies examining patients with selective damage to key regions of the DMN provide further insight into the cognitive and neural underpinnings of scene construction. Possibly the most seminal of these examined patients with hippocampal amnesia, finding significant impairments in recalling the past, imagining the future, and generating richly detailed mental scenes in these patients (Hassabis et al., 2007; Hurley, Maguire, & Vargha-Khadem, 2011; Mullally, Vargha-Khadem, & Maguire, 2014). Posterior parietal damage also appears to impair the richness of an envisaged scene (Ramanan, Alaeddin, et al., 2018), with the angular gyrus particularly proposed to contribute to the contextual integration of the multi-modal detail necessary in the generation of a rich mental image (Ramanan, Piguet, & Irish, 2018). Importantly, the role of prefrontal regions in scene construction remains relatively unexplored. Patients with ventromedial prefrontal cortex (vmPFC) lesions, however, have been shown to be impaired at imagining future and fictitious experiences (Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016). vmPFC patients also demonstrate a reduced ability to extrapolate beyond the immediate sensory environment in response to a scene photograph, known as a boundary extension task (De Luca et al., 2018). Collectively, these findings demonstrate that examining the clinical and cognitive profile of patients with various neurological conditions can reveal much about the interrelationships between mental construction and different cognitive processes.

1.2 Memory, Future Thinking and Scene Construction

To understand the importance of mental imagery in relation to how we interact with and experience the world requires a greater understanding of the cognitive processes previously associated with, and proposed to contribute to, creating an immersive mental experience. Cognitive domains which

have been particularly identified as sharing, or supporting, constructive mental processes include episodic and semantic memory, and future thinking.

1.2.1 Episodic (Autobiographical) Memory

The ability to relive and reminisce over past experiences is the very essence of our life story. Memory is inherently intertwined with our sense of self (Strikwerda-Brown, Grilli, Andrews-Hanna, & Irish, 2019) and sharing memories helps us bond with those close to us. Indeed, remembering together, known as collaborative memory, may potentially improve overall memory performance in older adults (Blumen, Rajaram, & Henkel, 2013). Partly due to the rich and cohesive recollection of past experiences, we tend to think of our memory store as a series of distinct neural representations merely awaiting the neurobiological equivalent of pressing play. It has long been proposed, however, that memory is a reconstructive process (Kolodner, 1983), involving the integration of numerous information sources, including sensory, semantic (knowledge) and emotional (Conway & Pleydell-Pearce, 2000). Due to this highly integrative nature of memory reconstruction, the recollection of past experiences unsurprisingly involves an extensive neural network (Buckner et al., 2008), generally thought to be centred on the hippocampus (Moscovitch, Cabeza, Winocur, & Nadel, 2016). Contributions from neural regions beyond the hippocampus in memory reconstruction are also increasingly being identified, including the prefrontal cortex, posterior cingulate and retrosplenial cortices (Hassabis, Kumaran, & Maguire, 2007; Irish et al., 2018). These findings support the role of the DMN in internally directed cognition and the importance of multi-modal domains in generating richly detailed mental imagery.

The cognitive processes associated with scene construction bear striking similarity to those used in episodic memory, including imagery, autonoetic awareness, that is, a sense of one's own

presence, retrieval of semantic and multi-modal sensory details, and narrative structure (Rubin, Schrauf, & Greenberg, 2003). Further, the spatial layout of a remembered event correlates with the perceived vividness and degree to which an event feels "relived" (Rubin et al., 2019). Clinically, patients with damage to, or dysfunction of, neural regions associated with the DMN exhibit a significantly reduced capacity for recalling richly detailed and immersive previous experiences (Mohan et al., 2016). Impoverished episodic recall has also been shown in patients with major depressive disorder (Söderlund et al., 2014), medial temporal lobe epilepsy (St-Laurent, Moscovitch, Levine, & McAndrews, 2009), schizophrenia (Ricarte, Ros, Latorre, & Watkins, 2017), autism spectrum disorder (Desaunay et al., 2020), and a range of dementia syndromes, including semantic dementia (Irish et al., 2011), frontotemporal dementia (Hornberger, Piguet, & Graham, 2010), and Alzheimer's disease (Irish et al., 2018). While the extent of these deficits varies with the severity of the associated neurological or neurodegenerative syndrome, collectively, these extensive findings demonstrate that disruption within the DMN results in an impoverished capacity to reconstruct richly detailed events from one's past.

1.2.2 Semantic Memory

The distinction between temporally dependent memory for previous experiences and memory supporting our knowledge of the world was first proposed by Tulving (1972). Tulving describes semantic memory as "…organized knowledge a person possesses about words and other verbal symbols, their meaning, and referents, about relations among them…" (Tulving, 1972, p. 386). This dichotomy between memory systems, one a record of our experiences and one knowledge-based, until recently, has continued to underlie much of modern day neuropsychology (Lezak, Howieson, Loring, Hannay, & Fischer, 2004; McAndrews, Cohn, & Gold, 2020). This segregation is becoming increasingly blurred, however, with sematic memory now seen as a dynamic,

constructive, multi-modal system, which is equally responsive to, and essential for, our experience of the world (Duff, Covington, Hilverman, & Cohen, 2020; Renoult, Irish, Moscovitch, & Rugg, 2019). The role of semantic memory is also now emerging in relation to our sense of personal narrative and identity (Strikwerda-Brown, Mothakunnel, Hodges, Piguet, & Irish, 2019) and has been proposed to form the "scaffold" upon which our ability to visualise future or past events depend (Irish, Addis, Hodges, & Piguet, 2012; Irish & Piguet, 2013) Indeed, semantic contributions have also been theorised to heavily support scene construction (Abraham & Bubic, 2015; Irish & Piguet, 2013).

Clinical studies support semantic memory as contributing to a range of cognitive processes. Patients with semantic dementia, a neurodegenerative disease resulting in profound deficits in naming and single word comprehension (Hodges, Patterson, Oxbury, & Funnell, 1992; Warrington & Shallice, 1984) also experience a reduced ability to imagine the future (Irish, Addis, Hodges, & Piguet, 2012) and more impoverished remote autobiographical memories (Irish et al., 2011; Strikwerda-Brown, Mothakunnel, Hodges, Piguet, & Irish, 2018) as well as a decreased capacity to engage in creative problem-solving (Paulin et al. 2020). Further, a range of social-cognitive processes, including theory of mind (ToM) (Bejanin et al., 2017) and apathy, (Ding et al., 2020) have been identified as being disrupted in semantic dementia, particularly as the disease progresses from the left to right hemispheres (Snowden et al., 2001). Overall, increasing evidence supports semantic memory as a dynamic system, forming the framework upon which many of our mental experiences are constructed (Irish & Piguet, 2013).

1.2.3 Prospection or Episodic Future Thinking

The ability to mentally envisage the future, even if that future may be uncertain, has been suggested to hold an evolutionary advantage by helping us detect and manage threat (Bulley, Henry, &

Suddendorf, 2017) and adapt or reassess our present choices in order to achieve the best outcome (Bulley, Henry, & Suddendorf, 2016). Further, specifically instructing older adults to visualise themselves performing a task in the future, in combination with an intent to complete it, increases the likelihood that task will be remembered (Henry et al., 2020). This capacity to simulate future scenarios is known as episodic future thinking, or prospection (Schacter, Addis, & Buckner, 2007). Evidence that patients with amnesia have difficulty imagining the future was first reported over 35 years ago (Tulving, 1985). More recent research, however, has highlighted how the processes involved in remembering our past bear striking similarity to those which help us imagine the future (Schacter et al., 2012). Just as recalling past experiences relies on the ability to combine information from multiple cognitive domains (Schacter & Addis, 2007), so too does the ability to construct a cohesive and realistic representation of how an event might unfold in the future (Wang, Yue, & Huang, 2016).

Neuroimaging studies demonstrate the neural regions involved in prospection heavily overlap with those involved in scene construction (Palombo et al., 2018), including hippocampal, prefrontal and parietal regions associated with the DMN (Buckner et al., 2008; Gilmore, Nelson, Chen, & McDermott, 2018; Spreng et al., 2008). Clinically, individuals with a range of disorders associated with disruption to the DMN have been shown to exhibit deficits in both future thinking and scene construction, including autism spectrum disorder (Lind & Bowler, 2010; Lind & Williams, 2012), schizophrenia (D'Argembeau, Raffard, & Van der Linden, 2008; Raffard, D'Argembeau, Bayard, Boulenger, & Van der Linden, 2010), and a range of dementia syndromes (Irish, Addis, et al., 2012; Irish & Piolino, 2016).

1.2.4 Summary

Collectively, these findings highlight the complexity and interaction of the cognitive processes supporting our ability to remember or prospect, and the importance of mental imagery in sustaining these immersive experiences (Sheldon, Cool, & El-Asmar, 2019; Spreng & Grady, 2010). The interrelationship between our previous experiences, general knowledge, and the ability to envisage the future has provided much insight into how we experience the world, with the capacity to construct richly detailed scenes potentially serving as the hub which binds these processes (Hassabis & Maguire, 2007; Spreng et al., 2008). One domain, however, which has thus far received comparatively little attention in relation to scene construction is social cognition.

1.3 Social Cognition and Social Perception

The ability to engage in social interaction is heavily dependent on our cognitive resources. Forming and maintaining relationships, understanding other's thoughts, feelings and intentions, and coordinating the interface between self and others all involve a range of complex cognitive and neural processes (Adolphs, 2009). The capacity to perceive and interpret social information is broadly referred to as social cognition (Lieberman, 2007). The mechanisms more specifically subtending the ability to perceive social information in order to adapt and update one's behaviour in accordance with the current context, as well as deduce subtle differences in appropriate behaviour between contexts, is variously known as social perception (Dewey, 1991), social understanding (Arioli, Crespi, & Canessa, 2018), social judgement (Nah & Poon, 2011), and social reasoning (Lough et al., 2006). For the purposes of this thesis, the term social perception will be used here on in. Social-cognitive processes are as essential in guiding our everyday experiences as our ability to remember what we did yesterday, and indeed, social cognition is increasingly being shown to work in concert with broader cognition, including memory (Mars et al., 2012).

1.3.1 Neural regions supporting social cognition

Collectively known as "the social brain", the neural processes supporting social cognition include those associated with perceptual, emotional and higher order cognitive functions (Arioli et al., 2018). Of particular note in relation to this thesis, many of the regions which support our ability to empathetically engage with those around us, as well as predict and respond to others behaviour, appear to heavily overlap with those associated with memory, prospection, and the default mode network (Mars et al., 2012; Spreng & Mar, 2012). Medial temporal and parietal regions appear to play an integral role in the processing of social information, including ToM and moral reasoning (Mars et al., 2012; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014; Wen, Mitchell, & Duncan, 2020). The involvement of prefrontal regions, however, is of particular note in relation to social perception. Patients with prefrontal damage display a reduced ability to make appropriate social judgments, often with an associated lack of insight (Kumfor et al., 2017; Lough et al., 2006; Mah, Arnold, & Grafman, 2004).

Given the overlap between regions involved in social cognition and those involved in scene construction (Maguire, Intraub, & Mullally, 2016; Summerfield et al., 2010), these findings invite the speculation that the capacity to envisage mental scenes may contribute to how we navigate the social world. Indeed, hippocampal regions particularly have been proposed to support pro-social behaviour due to their ability to mentally manipulate and flexibly recombine elements into coherent scenarios (Rubin, Watson, Duff, & Cohen, 2014). Further, imagining scenes with and without people appears to result in differential patterns of neural activation, with prefrontal regions preferentially engaged during social, relative to non-social, scenes in healthy individuals (Hassabis et al., 2014).

1.3.2 Social cognition and mental imagery

Increasing attention is being placed on the potential role of mental imagery in social cognition, and even staving off loneliness (Spreng et al., 2020). Previous findings indicate that imagining how an event may unfold can help us determine how to respond to that event, for example, imagining the act of helping is associated with increased prosocial behaviour (Gaesser & Schacter, 2014) and empathic concern (Sawczak, McAndrews, Gaesser, & Moscovitch, 2019) in healthy adults. Envisaging scenes which incorporate personality characteristics have also been suggested to inform our ability to integrate our knowledge of a person into a hypothetical scenario in order to predict others' behaviour (Hassabis et al., 2014).

Clinical findings from a range of neurodevelopmental and psycho-affective conditions support a possible role of mental imagery in social function and behaviour. For example, individuals with autism spectrum disorder (Lind, Bowler, & Raber, 2014), schizophrenia (Raffard et al., 2010), bi-polar disorder (Holmes, Geddes, Colom, & Goodwin, 2008), and depression (Holmes, Blackwell, Burnett Heyes, Renner, & Raes, 2016) have all been shown to exhibit significant disruption in imagining richly detailed mental scenes. Interestingly, both reduced and enhanced mental imagery have been proposed to contribute to maladaptive social behaviour in clinical disorders. Reduced mental imagery in autism spectrum disorder has been suggested to contribute to impaired social understanding and ToM (Lind, Williams, Bowler, & Peel, 2014). Higher self-reported capacity for imagination, however, is associated with increased genetic risk of schizophrenia in males (Crespi, Leach, Dinsdale, Mokkonen, & Hurd, 2016). Vivid mental imagery may amplify prospective based uncertainty and anxiety (Bulley et al., 2017), or increase emotional connections to maladaptive thoughts or memories, as in post-traumatic stress disorder (Hirsch & Holmes, 2007). Collectively, these findings support the role of mental imagery in how we perceive and experience the social

world and highlight the importance of examining how the breakdown, and preservation of, scene construction may contribute to differential social-cognitive presentations across clinical populations.

1.4 Frontotemporal Dementia and Alzheimer's Disease

Dementia is an umbrella term encompassing a group of disorders resulting from degeneration of the brain. The second leading cause of death in Australia, approximately 459,000 Australians live with a dementia diagnosis (Dementia Australia, 2018). In addition to the profound effects on the individual, a dementia diagnosis often results in substantial financial pressures (Boutoleau-Bretonnière, Vercelletto, Volteau, Renou, & Lamy, 2008). These effects on work capacity and family pressures are even more pronounced for those receiving a dementia diagnosis under the age of 65 years, known as younger-onset dementia (Mioshi, Bristow, Cook, & Hodges, 2009). The behavioural variant of frontotemporal dementia (bvFTD) is reported to be the second most common form of younger onset dementia after Alzheimer's disease (AD) (Coyle-Gilchrist et al., 2016; Weder, Aziz, Wilkins, & Tampi, 2007) and is the primary focus of this thesis.

1.4.1 Frontotemporal dementia

As the name indicates, frontotemporal dementia results primarily from progressive degeneration of the frontal and/or anterior temporal lobes (Landin-Romero et al., 2017; Rabinovici et al., 2008). Although not of focus here, in addition to the behavioural presentation, frontotemporal dementia also comprises two language sub-types: semantic dementia, involving deficits in naming and language comprehension (briefly outlined in section 1.2.2); and progressive nonfluent aphasia, characterised by difficulties in speech production (Piguet et al., 2011). In contrast, bvFTD patients predominantly present with a profound change in personality and behaviour, resulting in a

progressive deterioration in social function (Rascovsky et al., 2011). Current bvFTD diagnostic criteria are outlined in Table 1.1. In brief, diagnosis must include profound social and behavioural disinhibition. Emotional blunting or dysregulation, including apathy and loss of empathy, may also occur, along with changes in cognition. Understandably, the characteristic personality changes associated with a diagnosis of bvFTD place a considerable strain on relationships with loved ones and bvFTD is noted as having a greater impact on caregivers than that of other dementia syndromes (Hsieh et al., 2016). Daily life is often severely disrupted by an enhanced need for routine, difficulty adjusting to new situations and compulsive or repetitive behaviours (Chemali, Withall, & Daffner, 2010). Access to appropriate support services may also be challenging due to the nature of the behavioural changes (Etters, Goodall, & Harrison, 2008).

Table 1.1. Condensed diagnostic criteria for possible, probable and definite behavioural variant frontotemporal dementia.

1. Possible: Persistent, recurrent presentation of 3 of the following:
• Behavioural disinhibition • Apathy or inertia • Loss of sympathy or empathy • Perseverative, stereotyped or compulsive/ritualistic behaviour • Hyperorality or dietary changes • Executive deficits with relative sparing of memory and visuospatial functions.
2. Probable: Meets criteria for 1 plus:
• Significant functional decline • Frontal and/or anterior temporal lobe atrophy (MRI/CT) or hypometabolism/hypoperfusion (PET/SPECT)
3. Definite: Meet criteria for 1 or 2 plus:
• Histopathological evidence of frontotemporal lobar degeneration on biopsy or at post-mortem **OR** • Presence of a known pathogenic genetic abnormality, e.g., *C9orf72*

Notes. Adapted from Rascovsky et al. (2011). MRI = magnetic resonance imaging; CT = Computational tomography; PET = Positron-emission tomography; SPECT = Single-photon emission computed tomography.

Upon neuropsychological assessment, significant social-cognitive and cognitive disruption are present in bvFTD. Individuals with bvFTD demonstrate significant difficulties in the ability to identify facial (Hutchings, Palermo, Piguet, & Kumfor, 2017) and emotional expression (Marshall et al., 2019), understand the thoughts and feelings of others (Torralva, Gleichgerrcht, Ardila, Roca, & Manes, 2015), and detect sarcasm (Kipps et al., 2009). Although not the defining feature of the

disease, memory impairments have also been demonstrated in individuals with bvFTD, including substantial deficits in future oriented (Liu et al., 2021) and autobiographical memory which are comparable to those seen in amnestic dementia syndromes such as AD (Irish, Hodges, & Piguet, 2013; McKinnon et al., 2008). The ability for self-projection and future thinking or prospection (Irish, Addis, et al., 2012; Irish & Piolino, 2016) is also significantly compromised in bvFTD. Finally, deficits in executive function are often present in bvFTD patients and form part of the current diagnostic criteria (Rascovsky et al. 2011). A dysexecutive profile may also be evident in other forms of dementia (Ramanan et al., 2017), however, and some bvFTD patients may perform at control levels on executive measures, at least early in the disease course (Ranasinghe et al., 2016). Overall, bvFTD is a highly complex and multifaceted dementia syndrome which significantly impacts the lives of those touched by it.

1.4.2 Alzheimer's disease

Alzheimer's disease (AD) is the most common, and well-known, form of dementia (Dementia Australia, 2018). AD is a progressive, neurodegenerative dementia syndrome resulting primarily from atrophy of the medial temporal, inferior parietal, and posterior cingulate cortices (Landin-Romero et al., 2017; Rabinovici et al., 2008). Characteristically presenting as a profound loss of episodic memory, deficits in language, visuospatial, and executive functions also occur (Table 1.2). Only the amnestic form, however, is included in this thesis and is referred to from here on in.

Table 1.2. Condensed international clinical consensus criteria for Alzheimer's disease (AD).

1. Dementia (All Cause): Cognitive and/or behavioural symptoms which:

- Interfere with function, e.g. at work or usual activities
- Represent a decline from previous level of function
- Are not explained by delirium/other psychiatric disorder
- Are detected/diagnosed via patient history and objective assessment
- Include at least 2 of the following domains:
  - Memory
  - Language
  - Executive function
  - Personality and behaviour
  - Visuospatial function

2. Probable AD: Meet criteria for 1 plus:

- Insidious onset (months to years)
- Clear deterioration in cognition
- Initial and most prominent deficits in one of the following:
  - **Amnestic presentation:** Learning and recall of new information; and cognitive dysfunction in at least one other cognitive domain
  - **Non-amnestic presentations:** Based on the cognitive domain in which the most prominent deficits are evident, and cognitive dysfunction in at least one other cognitive domain.
  - Primary deficits include:
    - *Language*: Word-finding
    - *Visuospatial*: Spatial cognition
    - *Executive*: Reasoning, judgment, & problem-solving

Notes. Adapted from McKhann et al. (2011).

The episodic memory disturbances which are characteristic of AD involve difficulty recalling previous experiences as well as the learning and recall of new information (McKhann et al., 2011). Profound deficits in autobiographical memory also occur and correlate strongly with integrity of posterior midline brain regions including the posterior cingulate cortex (e.g., Irish et al. 2013 Cortex). In contrast, socio-emotional function in AD is generally well preserved, at least in the early stages of the disease (Zhang, Ho, & Fung, 2015). Nonetheless, some socio-emotional

changes have been noted, including reduced cognitive ToM (Synn et al., 2018), and cognitive (but not behavioural) apathy (Kumfor, Zhen, Hodges, Piguet, & Irish, 2018), and cognitive (but not affective) empathy (Dermody et al. 2016; Demichelis, Coundouris, Grainger, & Henry, 2020). Social-cognitive findings are often difficult to interpret, however, within the context of the broader cognitive deficits in this syndrome (Arioli et al., 2018). A reduced capacity to envisage richly detailed mental scenes has also been observed in AD which was uniquely associated with integrity of the posterior cingulate cortex (Irish et al., 2015).

1.5 Summary and Thesis Aims

The capacity to envisage richly detailed scenes is increasingly being identified as an important mental process which supports, and/or is supported by, a range of everyday cognitive domains, including memory (Hebscher, Levine, & Gilboa, 2017), prospection (Palombo et al., 2018), and ToM (Gaesser, 2020). Therefore, it is somewhat surprising that, to date, relatively little research has examined the clinical importance of scene generation across dementia syndromes.

1.5.1 Part 1: Studies 1-3

The first part of this thesis aimed to systematically examine the capacity for mental imagery in bvFTD and AD patients. Following on from previous findings showing individuals with AD demonstrate a significantly reduced ability to form richly detailed mental imagery, Study (1) aimed to examine scene construction in bvFTD, and its neural and cognitive correlates. Previous findings have suggested discrete patterns of neural activity associated with envisaging scenes with and without people (Hassabis et al., 2014). Study (2) expanded the exploration of social imagery by examining social, versus non-social, scene construction in bvFTD, a clinical population known to exhibit profound social deficits (Rascovsky et al., 2011). Lastly, previous research has identified contributions from both semantic and episodic memory in scene generation (Hassabis & Maguire,

2007; Irish et al., 2017), and particularly an interrelationship between the two (Addis, Musicaro, Pan, & Schacter, 2010). Study (3) manipulated the congruency and sociality of envisaged scenes in order to further explore the cognitive architecture of mental imagery by limiting episodic recruitment and increasing semantic load.

1.5.2 Part 2: Study 4

In order to more fully appreciate the potential role of mental imagery in social cognition, and particularly its possible contribution to the characteristic social deficits in bvFTD, social perception in bvFTD and AD were also examined. Deficits in the ability to identify the thoughts, feelings, and intentions of others have already been shown in bvFTD (Bora, Walterfang, & Velakoulis, 2015). Many previously used tasks examining the capacity to identify and appropriately respond to social information in bvFTD, however, tend to conflate the capacity to identify overt social violations with higher-order cognitive abilities, such as ToM (Henry, Phillips, & Von Hippel, 2014; Kipps et al., 2009; Kumfor et al., 2017). Study (4) aimed to address this gap in the literature by more directly examining the extent to which dementia ratings of social violations deviate from control ratings on a social perception task, as well as the nature of deviation. More importantly, this study aimed to explore the interrelationship between social perception and a range of other social-cognitive measures, particularly the capacity to envisage richly detailed social scenes.

1.5.3 Overall Thesis Aims

The identification of overlapping processes supporting memory, prospection and mental construction (Buckner et al., 2008) paves the way for elucidating how seemingly disparate cognitive domains work in concert in support of everyday function. The emerging role of mental construction as a potential hub which binds these processes speaks to the importance of mental

imagery in unifying theories of cognition (Spreng et al., 2008). The role of mental imagery in supporting pro-social behaviour (Gaesser & Schacter, 2014) particularly highlights the importance of examining the profile of scene construction across dementia syndromes which characteristically result in differential social-cognitive presentations (McKhann et al., 2011; Rascovsky et al., 2011). Understanding of the social manifestations of dementia has historically fallen behind that of the memory and cognitive effects, despite the social impact being associated with greater caregiver distress (Hsieh et al., 2016). Nonetheless, scene construction has already been demonstrated as an important variable of interest in other psycho-social conditions, including autism spectrum disorder (Lind et al., 2014), schizophrenia (Raffard et al., 2010), and clinical depression (Holmes et al., 2016). By combining philosophical and theoretical views of the mind with contemporary neuropsychology, cognitive neuroscience, and novel experimental methods, this thesis systematically examines the capacity for mental imagery in bvFTD as a potential unifying framework regarding the cognitive and social difficulties seen in this disorder.

2

General Methods

This chapter provides an overview of the general experimental methods and materials used across studies. Information regarding participant recruitment, ethics, and neuropsychological assessment is also included. Methods and materials specific to each study are presented in the relevant chapters.

2.1 Participants

Study participants were recruited through the FRONTIER dementia clinic based at the Brain and Mind Centre, The University of Sydney, Australia. Although largely focusing on frontotemporal dementia, FRONTIER is a younger onset dementia clinic which conducts research into a range of neurodegenerative disorders. Individuals diagnosed with dementia were community dwelling and attended the clinic accompanied by a support person. Healthy older control participants were friends or family of the patient attending the FRONTIER clinic, or were recruited via the Neuroscience Research Australia (NeuRA) research volunteer panel, or local community groups.

A detailed family history was obtained and a comprehensive cognitive assessment (outlined in section 2.3) was conducted. A diagnosis of dementia was established based on a combination of cognitive profile, multi-disciplinary clinical consensus, and neuroimaging. Specifically, the resulting clinical profile was reviewed by an experienced neurologist in consultation with a neuropsychologist and occupational therapist. This was then considered within the context of any

identified neural atrophy based on magnetic resonance imaging (MRI) and/or associated cerebral hypometabolism identified on positron emission tomography (PET).

2.1.1 Inclusion and exclusion criteria

Inclusion criteria

All dementia patients included in the study conformed to current consensus criteria for the diagnosis of bvFTD (Rascovsky et al., 2011) or AD (McKhann et al., 2011). Clinical presentation of bvFTD patients included progressive behavioural and/or personality changes and social disinhibition, for example, inappropriate behaviour, apathy, reduced empathy, perseverative behaviour and/or executive dysfunction (Rascovsky et al., 2011). Conversely, AD patients typically presented with significant episodic memory, visuospatial, and language (particularly word-finding) difficulties (McKhann et al., 2011), within the context of relatively intact social behaviour.

Exclusion criteria

A screening questionnaire to determine suitability to take part in the study was completed by all participants prior to participation. All participants were required to be proficient in English due to the heavily weighted language component of the neuropsychological and experimental tasks. Vision or hearing loss, a significant psychiatric history, any previously diagnosed neurological condition, or alcohol or substance abuse, also precluded participation in the study.

Healthy control participants were required to score ≥ 88/100 on the Addenbrooke's Cognitive Examination - Revised Edition (ACE-R) (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006), or the updated Addenbrooke's Cognitive Examination - Third Edition (ACE-III) (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013) as a measure of overall cognitive function (See Section 2.3.1).

2.2 Ethics

Permission to undertake the study was granted by the University of New South Wales and South Eastern Sydney Health Service ethics committees (HREC 10/126 and HREC 13/177). Informed consent was obtained from all participants, or their person responsible, prior to study participation in accordance with the Declaration of Helsinki. All participants volunteered their time; however, travel costs were reimbursed where necessary.

2.3 Cognitive Assessment

All participants completed a formal neuropsychological assessment targeting the main cognitive domains, including an overall cognitive screen as a measure of global cognition, as well as specific measures of memory, language, and executive function. Details of the tasks pertaining to each of the cognitive domains are outlined below.

2.3.1 Global cognition

The Australian version of the ACE-R (Mioshi et al., 2006) or ACE-III (Hsieh et al., 2013) was used as a measure of overall cognitive performance. Both versions of the ACE comprise five sub-domains assessing five cognitive domains, including attention and orientation, memory, verbal fluency, language and visuospatial function (outlined within the relevant section more extensively below). The subdomains of the ACE-III significantly correlate with performance on standardised neuropsychological tests (Hsieh et al., 2013). Previous research indicates the ACE-R and ACE-III are reliable and valid cognitive measures which display excellent sensitivity and specificity in discriminating dementia patients from healthy controls (Hsieh et al., 2013; Mioshi et al., 2006; So et al., 2018). Providing a total score out of 100, where higher scores denote better cognitive performance, a clinical cut off score of ≤ 88 is used by both the ACE-R and ACE-III as an indicator of cognitive impairment. Different versions of the ACE have been shown to significantly correlate,

regardless of diagnosis (So et al., 2018). To ensure consistency between study participants when data collection occurred across ACE versions, however, as in Chapter 3, scores on the ACE-III were converted to ACE-R using the methods outlined in So et al (2018) based on the majority of participants in this study completing the older measure. Finally, the ACE is reasonably brief to administer, taking approximately 15-20 minutes, reducing the potential confound of fatigue in clinical populations.

2.3.2 Attention and orientation

Attention and Orientation were measured using the ACE sub-domain of the same name. Three components comprise the attention and orientation subdomain of the ACE-III/R, which together provide a total possible score of 18 points. The orientation component of the task comprises a series of questions pertaining to establishing whether the participant can correctly locate themselves within time (day, date, month, year and season) and space (current location, including building name and floor, suburb, state and country). The attentional component of the task includes repeating a three-word list (which will later be recalled as part of the memory subdomain see section 2.4.3) and serial subtraction (subtracting 7 from 100, and then 7 again from each subsequent number, for a maximum of five subtractions).

The Digit Span Forward subtest from the Wechsler Adult Intelligence Scale-III (Wechsler, 1997) was also used as a measure of attention. Similar to the attentional component of the ACE-III/R, a string of digits of increasing lengths are read aloud by the experimenter and the participant is asked to repeat the numbers in the same order. The string length starts with 2 digits and goes up to 8 (maximum score), with two trials at each length. The task is discontinued if the participant makes more than two errors for the same string length.

2.4.3 Memory

The memory subdomain of the ACE-III/R was used as an overall measure of memory, in addition to more specific measures of verbal episodic and visuospatial memory, outlined below. Four components comprise the ACE-III/R memory sub-domain, resulting in a total possible score of 26 points. First, the participant is asked to recall the three words provided in the attention and orientation section (see section 2.3.2 above). A name and address unfamiliar to the participant is then read aloud by the experimenter and the participant is requested to repeat it back in full. Up to three repetitions are provided where necessary, however, only the third repetition is scored (name, number, street name, street type, suburb, state). Next, a verbal cue asks the participant to name four well-known individuals (for example, the current Prime Minister of Australia). Finally, at the completion of the testing session, the participant is asked to recall as much of the previously given name and address as possible. If the participant fails to recall any details, a recognition component is included.

Verbal Episodic Memory

Verbal episodic memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT, Schmidt, 1996). The RAVLT involves two components. First, a series of 15 unrelated words (List A) is read aloud to the participant across five consecutive trials. At the completion of each trial, the participant is asked to recall as many words as possible. A second list of 15 unrelated words (List B) is then read aloud to the participant and immediate recall is tested, following which, recall for List A is again tested (without repeating the original list). Finally, recall for List A is tested again following a 30-minute delay, resulting in a measure of delayed episodic verbal memory which is the primary variable of interest related to this thesis. The RAVLT has been shown to be

a reliable psychometric instrument which has good internal consistency and adequate divergent and convergent validity (Magalhães, Malloy-Diniz, & Hamdan, 2012).

Visuospatial Memory

Visuospatial episodic memory was assessed using the recall component of the Rey Complex Figure (RCF, Meyers, 1995; Rey, 1941). In this task, participants copy a complex geometric shape as accurately as possible. The RCF comprises two components, the copy (outlined in section 2.3.6) and the recall, completed following a three-minute delay. A total score of 36 is possible, with points allocated for the accurate reproduction and placement of each element. The RCF recall has been shown to be a helpful and valid measure of visuospatial function in the differential diagnosis of dementia (Salimi et al., 2018).

2.3.4 Verbal Fluency

Verbal fluency was measured using the ACE-III/R sub-domain which includes two components with a maximum possible score of 14 points. The sub-domain includes measures of both phonetic (words starting with a particular letter) and category fluency (words belonging to a particular group, for example, animals), with a maximum score of 7, outlined in Figure 2.1. Names of people and places, repeated words (including different sexes of the same animal), and words not belonging to the particular category are not counted toward this score. In the case of animals, however, all types of animal are accepted, including mythical creatures (e.g., unicorn).

Letters:	
≥ 18	7
14-17	6
11-13	5
8-10	4
6-7	3
4-5	2
2-3	1
0-1	0

Animals:	
≥ 22	7
17-21	6
14-16	5
11-13	4
9-10	3
7-8	2
5-6	1
< 5	0

Figure 2.1. Scoring matrix used for the Letters and Animals fluency subdomain of the ACE-III and ACE-R. For each task, the left column represents the raw number of words generated and the right column shows the corresponding scaled score resulting in a range from 0-7 with higher scores denoting better task performance.

2.3.5 Language

The ACE-III/R language (Hsieh et al., 2013; Mioshi et al., 2006) sub-domain and the Sydney Language Battery (SydBat) (Savage et al., 2013) were used as measures of language and semantic processing. Resulting in a maximum total of 26 points, the language subdomain of the ACE-III/R assesses verbal and written comprehension, repetition, naming, semantic knowledge, and pronunciation. Participants are requested to complete a series of tasks including: (i) responding to verbal instructions (in the ACE-III all instructions are said aloud, in the ACE-R some instructions are written) involving interacting with a pencil and paper; (ii) writing two complete sentences on any topic; (iii) repeating a word list; (iv) repeating aloud and stating the meaning of two commonly used proverbs, “All that glitters is not gold” and “A stitch in time saves nine;” (v) verbally identifying a series of 12 objects, for example, harp, crown; (vi) pointing to the object which best pertains to a statement read by the experimenter, for example, “point to the one associated with

the monarchy;" and (vii) reading a list of words aloud which deviate from traditional phonetic structure, for example, sew, pint.

The SydBat (Savage et al., 2013) is a measure of single-word language processing comprising four subtests assessing naming, repetition, comprehension and semantic association of 30 multisyllabic words of increasing difficulty (i.e., from high to low word frequency). For the purposes of this thesis, only naming, comprehension and semantic association were of interest. Similar to the ACE-III/R, the naming task involves a series of visual images being displayed, one at a time, and participants verbally identifying each item. Mispronunciation due to phonemic, phonological or semantic substitutions, as well as any omissions, are counted as an error. The comprehension and semantic association subtests again involve a series of visual cues, however, for these tasks multiple items are displayed at once and the participant is asked to either identify the picture which matches a word provided by the experimenter, or is the most closely associated with a target image. One point is given for each correct item, with each subtest having a maximum of 30 points where higher scores denote better language performance.

2.3.6. Visuospatial Function

A combination of the ACE-III/R visuospatial sub-domain and the RCF copy task were used to assess visuospatial function. The ACE-III/R visuospatial subdomain has a total possible score of 16 points. Participants complete a series of illustrative tasks including copying visual cues (infinity loop, three dimensional cube) and drawing a clock face with numbers (and adding the time). Following this, an image of two squares containing a collection of dots is placed in front of the participant and they are asked to count the dots in each square without pointing. Finally, a series of visually degraded (i.e., partially incomplete) letters are shown to the participants and they are asked to verbally identify each letter.

The RCF copy task was also used as a measure of visuospatial function. As outlined in section 2.4.3, the RCF involves participants reproducing a complex geometric figure as accurately as possible. Points are allocated based on accuracy and placement, resulting in a maximum total of 36. The organisational strategy utilised by the participant to copy the task may also be assessed, however, normative data pertaining to organisation of the copy component have been shown to be limited (Wilson & Batchelor, 2015) and was therefore not included in this thesis.

2.3.7 Executive Function

Various measures of executive function were included to assess set-shifting, response inhibition, and working memory. The Trail Making Test (Tombaugh, 2004) includes two components assessing attention (Part A) and set-shifting (Part B). Part A requires participants to draw a line to connect a series of consecutively numbered dots as quickly as possible. In Part B, the participant is again asked to connect a series of dots, however, this time the participant is required to switch between numbers and letters in consecutive order (e.g. 1-A, 2-B, 3-C… etc.). Time taken to complete each section is recorded (in seconds) and the difference between sections (Part B minus Part A) is calculated as a measure of executive functioning.

The Hayling Sentence Completion Test (Burgess & Shallice, 1997) was used as a measure of response inhibition. The Hayling has been shown to be a reliable and valid test which is sensitive to impaired executive function in clinical populations (Strauss, Sherman & Spreen, 2006). Consisting of two sections, the task involves the examiner reading a series of sentence cues aloud and participants providing a one-word verbal response. Sections 1 and 2 involve participants completing the sentence cue read by the examiner as quickly as possible (e.g., “He posted a letter without a…”). For Section 2, however, participants are instructed to provide a response which does *not* fit the sentence cue. Related, and partly related, words are counted as Category A and

Category B errors respectively. For example, in response to the cue, "The captain wanted to stay with the sinking…", the words "ship" or "helicopter" would be Category A and B errors, respectively. Response latency for Sections 1 and 2, and the total number of errors for Section 2, are scaled and summed to create an overall measure of response inhibition while accounting for response initiation. Lower scores denote poorer performance and the maximum possible score is seven.

2.4 Clinical Assessment

The clinical profile of the two patient groups was assessed using measures of disease duration, severity, and overall behavioural change.

2.4.1 Disease duration

Based on reports from a knowledgeable informant, disease duration was used as an indicator of disease stage, calculated as the years elapsed between the onset of first symptoms and the date of participation in the study.

2.4.2. Disease severity

The Clinical Dementia Rating scale – Frontotemporal Lobar Degeneration (CDR-FTLD) was used to measure disease severity. The CDR-FTLD has been shown to be 27% more sensitive in detecting decline in FTD patients over twelve months than the standard CDR (Knopman, Weintraub, & Pankratz, 2011). Eight domains of everyday function are assessed by the CDR-FTLD including memory, orientation, judgement and problem solving, community affairs, home and hobbies, personal care, behaviour, comportment and personality, and language. This is two more than the standard CDR which does not include the behavioural and personality component. Each domain is rated on a five-point scale (except for personal care which is rated on a four-point

scale) ranging from normal (0) to severely impaired (3). The sum of the ratings for each domain comprise an overall measure of illness severity known as the "Sum of Boxes" resulting in a total possible score of 24, where higher scores denote more severe disease.

2.4.3 Behavioural assessment

The Cambridge Behavioural Inventory Revised (CBI-R; Wear et al., 2008) was used as a measure of overall behavioural change. The CBI-R is a 45-item carer questionnaire designed to assess behavioural and psychiatric symptoms in areas of memory and orientation, everyday skills, self-care, abnormal behaviour, mood, beliefs, eating habits, sleep, stereotypical behaviours, and motivation. A 0-4 point scale is used to denote the frequency of the behaviours and summed to create a total score which is then converted to a percentage scale (maximum score 100). Higher scores denote more substantial behavioural changes. Control participants completed a self-rated version of the questionnaire. The CBI-R has been shown to be a robust, valid instrument for the differentiation of neurodegenerative diseases (Wedderburn et al., 2008).

2.5 Scene Construction Task

The capacity to generate, and maintain, richly detailed mental imagery was assessed using various modifications of the Scene Construction task (Hassabis et al, 2007). More specific details pertaining to methodology can be found in the relevant chapters. Broadly, this task involves the experimenter reading aloud a short verbal cue (a written cue was also placed in front of the participant for the duration of the task) and the participant being asked to imagine, and verbally describe, a series of scenes in as much detail as possible, using all their senses. Prior to commencing the task, participants are instructed to try to create a new scene and avoid simply recounting a memory. Following each scene description, the participant's subjective experience of

the scene is assessed by asking a series of questions pertaining to the perceived vividness, difficulty level of detail, sense of presence within the constructed scene, and the degree to which the imagined scene resembled a memory.

Scene descriptions were recorded, transcribed verbatim, and scored for contextual detail in line with the criteria outlined by Hassabis et al (2007). Briefly, each scene description was segmented into a set of content statements and coded in accordance with four discrete categories: Spatial References (SPA), Entities Present (EP), Sensory Descriptions (SEN), and Thoughts/Emotions/Actions (TEA) (see Chapters 3, 4, and 5 for more specific information pertaining to methodology). To avoid more verbose answers potentially confounding results, in accordance with Hassabis et al, the maximum score for each subcategory was capped at 7 points, resulting in a maximum Total Content score of 28.

2.6 Statistical Analyses

All statistical analyses were conducted using IBM SPSS Version 26. Study specific analyses are outlined in the relevant chapters. Normality of distribution was assessed using Kolmogorov-Smirnov tests and, unless otherwise specified, all statistical assumptions for parametric models were met. Statistical significance was set at $p < .05$ for all analyses and correction for multiple comparisons was applied where appropriate.

3

Setting the Scene: Impaired Scene Construction in bvFTD

This chapter is a modified version of Wilson, N.-A., Ramanan, S., Roquet, D., Hodges, J. R., Piguet, O., & Irish, M. (2020). Scene construction impairments in frontotemporal dementia: Evidence for a primary hippocampal contribution. *Neuropsychologia*, *137*(B 57), 289–300. https://doi.org/10.1016/j.neuropsychologia.2019.107327

The capacity to generate naturalistic three-dimensional and spatially coherent representations of the world is known as scene construction (Mullally & Maguire, 2013). A recently emerging cognitive domain, scene construction has been posited to support a range of complex constructive endeavours, including autobiographical memory and future thinking (Spreng et al., 2008). Significant insights into the neurocognitive architecture of scene construction have been gleaned from functional neuroimaging studies in healthy individuals, with consistent reports of brain activation in a core network anchored on the hippocampus, as well as the vmPFC, parahippocampal, retrosplenial, and posterior parietal regions (Hassabis, Kumaran, & Maguire, 2007; Palombo et al., 2018; Summerfield et al., 2010; Zeidman et al., 2015). Increasing attention is particularly being directed towards the dynamic interplay between the hippocampus and ventromedial prefrontal cortex (vmPFC) in the generation of complex mental scenes.

Clinical populations with selective damage to key nodes of the core construction network have provided important insights in relation to mental construction. Patients with hippocampal amnesia display pervasive impairments in recalling the past, imagining the future, and generating detailed representations of static scenes (Hassabis, Kumaran, Vann, et al., 2007; Race et al., 2011). Collectively, these impairments have been taken as evidence of a primary contribution of the hippocampus to the construction of scene imagery, with far-reaching consequences for any cognitive function where instantiation of scene imagery is beneficial for task performance (McCormick et al., 2018). Patients with hippocampal damage appear unable to extrapolate beyond the immediate boundaries of a scene even when presented with a picture, known as a boundary extension task, producing impoverished narratives which lack spatial references (Mullally, Intraub, & Maguire, 2012). These studies have been instrumental in demonstrating a critical role for the hippocampus in the provision of a spatial context from which past, future, and hypothetical scenarios can be constructed (Mullally & Maguire, 2013).

Complementary findings from patients with selective damage to the vmPFC also warrant consideration. Important commonalities and differences emerge in relation to mental construction between patients with vmPFC lesions and those with hippocampal lesions (McCormick et al., 2018). First, vmPFC patients display impoverished autobiographical retrieval relative to healthy adults, and these deficits extend to the domain of future thinking, resulting in severe difficulties simulating personally and non-personally relevant events (Bertossi et al., 2016; Verfaellie, Wank, Reid, Race, & Keane, 2019). Atemporal forms of scene construction are also deleteriously affected with vmPFC patients displaying deficits in boundary extension, suggesting difficulties akin to those seen in patients with hippocampal damage in extrapolating beyond the immediate stimuli (De Luca et al., 2018). Unlike hippocampal meditated deficits, however, impaired boundary

extension in vmPFC patients appears to be more related to integrating the scene elements rather than generating the spatial context per se (De Luca et al., 2018). Collectively, these findings point towards patients with vmPFC damage showing reduced performance on any task requiring a perceptual decoupling from the external environment and the initiation of endogenous processing to search and curate appropriate content (McCormick et al., 2018).

While accruing evidence points to the importance of medial temporal and prefrontal regions in scene construction, the precise nature of their respective contributions remains unclear. In this light, neurodegenerative populations offer an opportunity to explore how the progressive degeneration of medial temporal and prefrontal structures impacts the capacity for scene construction (Irish & van Kesteren, 2018). A reduced capacity for scene construction has previously been established in AD, driven primarily by atrophy of the posterior cingulate cortex (Irish et al., 2015). Considering episodic memory (Irish, Piguet, Hodges, & Hornberger, 2014) and future thinking (Irish & Piolino, 2016) are profoundly impoverished in AD, associated impairments in the capacity to generate richly detailed atemporal scenes supports broader deficits in constructive dependent cognition in this syndrome.

Despite divergent clinical presentations, considerable overlap exists in the cognitive profile between AD and bvFTD. Previous reports identify a range of impairments across a broad array of constructive endeavours in bvFTD, including autobiographical memory (Matuszewski et al., 2006; McKinnon et al., 2008), and future thinking (Irish & Piolino, 2016). While originally conceptualised as primarily a disorder of social cognition, recent studies converge to reveal marked episodic memory disruption in this syndrome (Bertoux et al., 2014) attributable, in part, to hippocampal dysfunction (Frisch et al., 2013; Irish, Piguet, Hodges, & Hornberger, 2014). Most recently, impaired capacity for mind wandering has been reported in bvFTD, again related to

hippocampal dysfunction in the context of large-scale network anomalies (O'Callaghan, Shine, Hodges, Andrews-Hanna, & Irish, 2019). Importantly, however, a point of divergence between bvFTD and AD patients is that spatial navigation appears to be relatively well preserved in bvFTD, at least in the early stages of this syndrome, in part reflecting the preservation of posterior parietal structures (Tu et al., 2015). This is important as spatial information has been proposed to play a central role in the generation of mental scenes, thought to be largely subtended by the hippocampus (Maguire et al., 2016; Summerfield et al., 2010). The question is raised, therefore, regarding whether comparatively preserved real-world spatial navigation translates to the generation of spatially cohesive mental scenarios within the context of broader constructive deficits.

The evidence to date converges to suggest a primary impairment in constructing contextually detailed representations across past and future contexts in bvFTD, for both personal and non-personal content (Irish, Eyre et al., 2014). It remains unclear, however, whether bvFTD patients are capable of generating detailed descriptions of static atemporal scenes; the putative spatial backdrop for more complex constructive endeavours (Maguire et al., 2016). To this end, the objective of this study was to investigate the capacity for scene construction in bvFTD, and its associated neural correlates. Previous reports point to the vmPFC in supporting the generation of richly detailed mental imagery (Bertossi et al., 2016; De Luca et al., 2018) and temporally anchored hypothetical scenarios (Verfaellie et al., 2019). Given the characteristic prefrontal atrophy identified in bvFTD (Landin-Romero & Piguet, 2017), it was hypothesised that bvFTD patients would exhibit a reduced capacity for scene construction, relative to control participants, subtended primarily by reduced structural integrity of the vmPFC. In contrast, it was hypothesised that scene construction deficits in AD would mirror previous reports (Irish et al., 2015) implicating the posterior cingulate and parietal regions. Finally, given the more severe medial temporal and

posterior atrophy associated with AD, it was hypothesised that AD patients would exhibit more extensive scene construction deficits than bvFTD patients.

3.1 Materials and Methods

3.1.1 Participants

A total of 62 participants were recruited to take part in the study. Nineteen individuals with a diagnosis of clinically probable bvFTD were compared to 18 participants with typical AD, and 25 healthy older control participants. A subset of the data from the AD group have previously been reported in a separate study (Irish et al., 2015) and are included here as a disease control group. Patients underwent comprehensive neurological examination, cognitive assessment, and structural neuroimaging. As outlined in Chapter 2 section 2.1, dementia diagnosis was established via multi-disciplinary clinical consensus and structural neural imaging in accordance with current diagnostic criteria (McKhann et al., 2011; Rascovsky et al., 2011). Study participation was dependent on meeting the inclusion and exclusion criteria (Chapter 2 section 2.1.1) and full consent being obtained.

Healthy control participants were recruited through the Neuroscience Research Australia research volunteer panel and local community groups. Control suitability to take part in the study was based on inclusion and exclusion criteria outlined in Chapter 2 section 2.1.1, and overall cognitive performance. Note, one control participant scored 83 on the ACE-R but was included in the study as there was no evidence of any functional or cognitive decline, or significant atrophy on structural Magnetic Resonance Imaging (MRI).

3.1.2 Neuropsychological assessment

Participants completed a comprehensive battery of neuropsychological tests, outlined in Chapter 2 section 2.3. Of note, given that the majority of participants had completed the ACE-R, ACE-III scores were converted to ACE-R scores using a standardised conversion algorithm (So et al., 2018). Neuropsychological domains of particular relevance to this study include verbal (RAVLT 30 minute, Schmidt, 1996) and nonverbal (RCF, Meyers & Meyers, 1995; Rey, 1941) episodic memory, language ability - naming, comprehension, and semantic association (SydBat; Savage et al., 2013), as well as attention and executive function (Digit Span Forward and Backward; Wechsler, 1997; TMT B-A; Reitan, 1958; Hayling, Burgess & Shallice, 1997).

3.1.3 Assessment of scene construction

As introduced in Chapter 1 section 1.1, the capacity to imagine fictitious scenes was measured using a modified version of the Scene Construction task developed by Hassabis et al. (2007). Participants were instructed to imagine and describe a series of commonplace scenes in as much detail as possible in response to a brief description read aloud by the experimenter. The description was printed on a card and remained visible to participants for the duration of the task. To avoid fatigue in the dementia patients, the task was shortened by excluding three future based scenarios from the original protocol in order to probe seven atemporal scenes (Beach, Museum, Pub, Ship, Market, Forest, Castle) (Irish et al., 2015). Prior to commencing the task, participants were instructed to create a new scene and to avoid recounting a previous memory. Participants spoke extemporaneously and provided their scene descriptions until they reached a natural end to their narrative, following which, general probes were provided to elicit further details.

Participant Ratings and Spatial Coherence

Subsequent to each scene description, participants provided a series of subjective ratings pertaining to their perceived experience of the envisaged scene. Ratings were obtained in relation to the difficulty ("How difficult did you find it to imagine this scene?"), vividness ("How vivid was the scene you imagined in your mind's eye?"), level of perceived detail ("How detailed do you feel your description of the scene was?"), feeling of presence within the imagined scene (i.e., "How much of a sense of being there did you have when imagining?"), and the similarity to a previous experience ("How similar to a memory was your imagined scene?") on a scale of 1-5 with higher scores reflecting greater difficulty, vividness, detail and sense of presence, respectively but *less* similarity to a previous memory (see Hassabis et al., 2007).

Participants also rated the spatial coherence of the scenes by providing a yes/no response in accordance with how accurately a series of 14 statements reflected the spatial properties of their mental constructions, for example, "I could see it as one whole scene in my mind's eye". Testing lasted for approximately 45 minutes. Interviews were digitally recorded for subsequent transcription and scoring.

Scene construction scoring

Transcripts were scored in accordance with the original scoring protocol developed by Hassabis et al. (2007). Each scene description was segmented into a set of content statements, which were then classified into discrete categories: Entities Present, referring to the number of animals, objects or people included in the scene; Sensory Descriptions, statements describing the characteristics of an entity (in any modality, e.g. "the chair is made of wood", "I can smell the food"); Spatial References, referring to the spatial location of entities within the environment (e.g., "to my left…"; "approximately two metres away…"); and Thoughts/Emotions/Actions, including introspective

statements of the participant (e.g., “I feel alone”) as well as thoughts, intentions or actions of other people within the scene (e.g., “he pours a drink”). The maximum score for each subcategory was capped at 7 points, leading to a maximum Total Content score of 28.

The Spatial Coherence Index reflected the degree to which participants subjectively rated their scenes as spatially integrated, ranging from -6 (completely fragmented) to +6 (completely integrated). An objective Quality Judgement rating was assigned by the experimenter as an index of the overall richness of the constructed scene, ranging from 0 (evokes no mental image) to 10 (evokes an extremely vivid mental picture). An independent rater, blind to group membership, scored all scene construction data. A sub-set of scenes from 9 bvFTD, 8 AD, and 8 controls (172 scenes in total) were scored by the candidate, also blind to diagnosis and study hypotheses. Inter-rater reliability revealed excellent consistency between the two raters for Total Content (Cronbach's alpha = .917) and the objective quality judgment (Cronbach's alpha = .853).

Finally, the Experiential Index, reflecting the overall richness of the imagined experience was calculated from the four subcomponents of the task: Total Content, Subjective Ratings of Perceived Salience and Sense of Presence, Spatial Coherence Index, and Objective Quality Judgment (for full scoring details see Hassabis et al., 2007). For each participant, a mean Experiential Index score averaged across all scenes was calculated with the score ranging from 0 (not experienced at all) to 60 (extremely richly experienced).

3.1.4 Statistical analyses

Behavioural data were analysed using SPSS Version 26 (IBM). Group differences on categorical variables (i.e., sex) were examined using Chi-square tests. For continuous variables, normality of data distribution was assessed using a combination of Kolmogorov-Smirnov tests and box-and-

whisker plots. For non-normally distributed data (i.e., disease duration and disease severity), Wilcoxon-Mann-Whitney tests were used to examine group differences. Where data were normally distributed (i.e., neuropsychological assessment and scene construction performance measures), group differences were assessed using Analysis of Variance (ANOVA) with Sidak correction for post hoc comparisons adjusting for small sample sizes. The alpha level to determine statistical significance was set at $p < .05$. Effect sizes for all ANOVA statistics are denoted using partial eta-squared values. Finally, two-tailed Pearson's correlations were administered to examine associations between general neuropsychological performance and Experiential Index scores in bvFTD and AD groups. All correlations were corrected for multiple comparisons using the Benjamini-Hochberg 'false discovery rate' approach (Benjamini & Hochberg, 1995).

Image acquisition

Participants underwent whole-brain T1-weighted imaging using a 3T Philips MRI scanner with standard quadrature head coil (8 channels), using the following sequences: coronal orientation, matrix 256 × 256, 200 slices, 1 mm isotropic voxel resolution, echo time/repetition time = 2.6/5.8 ms, flip angle a = 8°. Structural MRI data were available for 18 bvFTD, 17 AD, and 22 control participants.

Voxel-based morphometry (VBM)

VBM analyses were employed to identify voxelwise changes in grey matter intensity across participant groups using the FSL-VBM toolbox (Ashburner & Friston, 2000) from the FMRIB Software Library package (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/fslvbm/index.html) (Smith et al., 2004). A standard pre-processing pipeline was followed where structural MR images were brain-extracted (using the FSL Brain Extraction Tool or BET; Smith, 2002) followed by tissue segmentation (using FMRIB's Automatic Segmentation Tool or FAST; Zhang, Brady, & Smith,

2001). Following this, the FMRIB non-linear registration approach (FNIRT; Andersson, Jenkinson, & Smith, 2007) was used to align all brain-extracted images to the Montreal Neurological Institute standard space (MNI52), using a b-spline representation of the registration warp field (Rueckert, 1999). From the resulting images, a study-specific template was created to which a nonlinear re-registration of native grey matter images was performed. The registered partial volume maps were then modulated by dividing by the Jacobian of the warp field, to correct for local contraction and expansion. The final modulated segmented images were smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

Unbiased whole-brain general linear models were used to explore grey matter intensity differences between patient and control groups via permutation-based non-parametric testing (Nichols & Holmes, 2001), employing 5000 permutations per contrast. Differences in cortical grey matter intensities in bvFTD, AD, and control groups were examined using regression models with separate directional contrasts (i.e., t-tests). Years of education was included as a nuisance variable in all contrasts in the atrophy analyses. Clusters were then extracted using the Threshold-Free Cluster Enhancement (TFCE) method and corrected for Family-Wise Error (FWE) at a strict threshold of $p < .005$ and cluster extent threshold of 500 contiguous voxels.

To examine associations between scene construction performance and grey matter intensity, three separate correlation-only statistical models were run, each with a positive t-contrast. First, the neural substrates of the Experiential Index were explored, as the primary outcome measure on the task, representing the overall richness of the constructed scenes. Given that this is an aggregate score, the specific regions implicated in detail generation (Total Content) and integration of details (Spatial Coherence) were also examined, as the two main subcomponents on this task (Hassabis et al. 2007). Correlation analyses were performed separately within patient groups (i.e., separate

models for bvFTD and AD patients). Anatomical locations of statistical significance were overlaid on the MNI standard brain with maximum coordinates provided in MNI stereotaxic space. All anatomical labels were determined using the Harvard-Oxford probabilistic atlas. For all VBM correlation analyses, clusters were extracted using a voxelwise approach corrected for False Discovery Rate at a threshold of $p < .05$. All results are reported at a conservative cluster threshold of 200 contiguous voxels.

3.2 Results

3.2.1 Demographic and clinical information

As displayed in Table 3.1, participants did not differ in terms of age, F (2, 59) = 1.5, p = .22; η_p^2 = .04, or sex distribution, χ^2 = 2.9, p = .22. A significant group difference was found for years of education, F (2, 59) = 8.8; p < .001; η_p^2 = .23, with post hoc comparisons indicating this was driven by higher mean education in the control group compared to each of the patient groups (both p values ≤ .005). No significant difference was evident in years of education between patient groups (p = .961). Disease severity was also comparable between patient groups, W = 307.5, p = .795, as was disease duration (years elapsed since onset of symptoms), W = 223.5, p = .11, and carer ratings of functional decline on the CBI-R, W = 277.5, p = .125. Finally, AD and bvFTD groups displayed significant impairments on the cognitive screening tool relative to controls (ACE-R Total), F (2, 59) = 38.4, p < .001; η_p^2 = .56, with no significant differences between patient groups (p = .11).

Table 3.1. Demographics and clinical profile for study groups.

	bvFTD	AD	Controls	Group effect (p value)	Post hoc (direction of effect)
N	19	18	25		
Sex (M:F)	14:5	10:8	12:13	n.s.	-
Age (years)	62.5 (8.3)	66.5 (8.0)	66.1 (7.0)	n.s.	-
Education (years)	11.8 (1.9)	11.5 (2.8)	14.2 (2.3)	$p < .001$	CN > bvFTD, AD
Disease duration (years)	5.7 (2.8)	4.6 (3.6)	-	n.s.	-
Disease Severity (CDR-FTLD Sob)	7.0 (5.1)	5.6 (2.1)	-	n.s.	-
CBI-R Total (%)	34.4 (14.9)	25.3 (11.2)	2.9 (1.6)	$p < .001$	CN < bvFTD, AD
ACE-R Total[a] (100)	81.9 (10.7)	73.7 (8.7)	95.0 (4.1)	$p < .001$	CN > bvFTD, AD

*Note*s. [a]Given that the majority of participants had completed the ACE-R, ACE-III scores were converted to ACE-R scores using a standardised conversion algorithm (So et al., 2018). For all groups, mean and standard deviation reported. bvFTD = behavioural variant frontotemporal dementia; AD = Alzheimer's disease. CN = Controls. n.s. = not significant. CDR-FTLD SoB = Clinical Dementia Rating – Frontotemporal Lobar Degeneration Sum of Boxes; CBI-R = Cambridge Behavioural Inventory – Revised; ACE-R = Addenbrooke's Cognitive Examination - Revised.

3.2.2 Cognitive profiles

Neuropsychological testing revealed significant group effects across cognitive measures which were in keeping with canonical profiles of cognitive impairment in the two patient groups relative to controls (Table 3.2). Looking at attention and executive function, a significant group effect was found for the Digit Span Forwards, F (2, 59) = 19.84; p = .001, η_p^2 = .41, Digit Span Backwards, F (2, 59) = 17.26; p = .001, η_p^2 = .39, the Hayling, F (2, 52) = 14.57; p = .005, η_p^2 = .35, and TMT B-A, F (2, 50) = 8.91; p = .005, η_p^2 = .29. Significant group effects were also evident in verbal, F

(2, 53) = 56.10; $p \leq .0001$, $\eta_p^2 = .63$, and visuospatial, F (2, 56) = 33.95; $p = .001$, $\eta_p^2 = .55$, delayed episodic memory. Finally, group differences emerged in verbal fluency, F (2, 55) = 13.68; $p = .001$, $\eta_p^2 = .35$, semantic association, F (2, 46) = 9.59; $p = .001$, $\eta_p^2 = .29$, comprehension, F (2, 48) = 14.46; $p = .001$, $\eta_p^2 = .38$, and naming, F (2, 51) =18.83; $p = .001$, $\eta_p^2 = .43$.

Post hoc analyses revealed that, relative to controls, bvFTD patients displayed significant impairments in executive function (Hayling, $p \leq .0001$; TMT B-A, $p = .036$), verbal ($p \leq .0001$) and visuospatial ($p = .001$) delayed episodic recall, semantic naming ($p = .004$) and semantic association ($p = .002$), in the context of relatively intact semantic comprehension ($p = .727$). Comparing AD patients with control performance revealed characteristic deficits in verbal ($p \leq .0001$), and visuospatial ($p \leq .0001$) delayed episodic recall, and executive function (Hayling, $p \leq .0001$; TMT B-A, $p \leq .0001$), in the context of global semantic difficulties on naming ($p \leq .0001$), comprehension ($p \leq .0001$), and semantic association ($p = .003$), in the AD group. Direct comparison of the patient groups revealed disproportionately poorer verbal and nonverbal episodic memory and semantic comprehension performance in AD relative to bvFTD (all p values < .01). No other significant differences were evident between the patient groups (all p values ≥ .1).

Table 3.2. Neuropsychological profile of the three groups.

	bvFTD *M(SD)*	AD *M(SD)*	Controls *M(SD)*	Group effect (*F*)	Post hoc (direction of effect)
Episodic memory					
RAVLT 30 minute	4.7 (3.7)	0.9 (0.9)	10.7 (3.0)	56.1***	CN > bvFTD > AD
RCF 3-min recall	11.5 (6.7)	2.8 (2.9)	18.3 (6.1)	33.9**	CN > bvFTD > AD
Language processing					
SydBat Naming	23.6 (2.5)	21.4 (3.7)	27 (2.3)	18.8**	CN > bvFTD, AD
Comprehension	28.5 (1.2)	26 (2.7)	29.1 (1)	14.4**	CN, bvFTD > AD
Semantic Association	26 (2.5)	26.2 (2.4)	28.7 (1)	9.5**	CN > bvFTD, AD
Letter fluency	28.6 (14.9)	28.1 (12.8)	48.6 (14.7)	13.6**	CN > bvFTD, AD
Attention and executive functions					
Digit span forwards	9.2 (2.2)	8 (1.9)	12.1 (2.2)	19.8**	CN > bvFTD, AD
Digit span backwards	5.3 (2.2)	4.3 (1.5)	8.1 (2.4)	17.2**	CN > bvFTD, AD
TMT B-A (seconds)	92.8 (51.4)	143.4 (130.5)	42 (23.5)	8.9**	CN > bvFTD, AD
Hayling Overall Scaled	4.2 (1.9)	3.7 (1.9)	6.4 (.9)	14.5**	CN > bvFTD, AD

Notes. *M* = mean, *SD* = standard deviation. *** = p <.0001, ** = p < .001; bvFTD = behavioural-variant frontotemporal Dementia; AD = Alzheimer's disease; CN = Controls. RAVLT = Rey Auditory Verbal Learning Test; RCF = Rey Complex Figure; SydBat = Sydney Language Battery; TMT B-A = time difference between parts B and A of the Trail Making Test.

3.2.3 Scene construction performance

Experiential Index

The principal result, illustrated in Figure 3.1 and Table 3.3, was a significant main effect of group on the primary outcome measure of the scene construction task (Experiential Index), F (2, 59) = 51.7; p < .001; η_p^2 =.63, with post hoc analyses indicating both bvFTD and AD patient groups demonstrated marked scene construction impairments relative to controls (both p values <.001).

Direct comparison of the patient groups did not reveal any significant differences (Experiential Index, p = .116). To understand the nature of these impairments, the subcomponents of the Experiential Index are considered next.

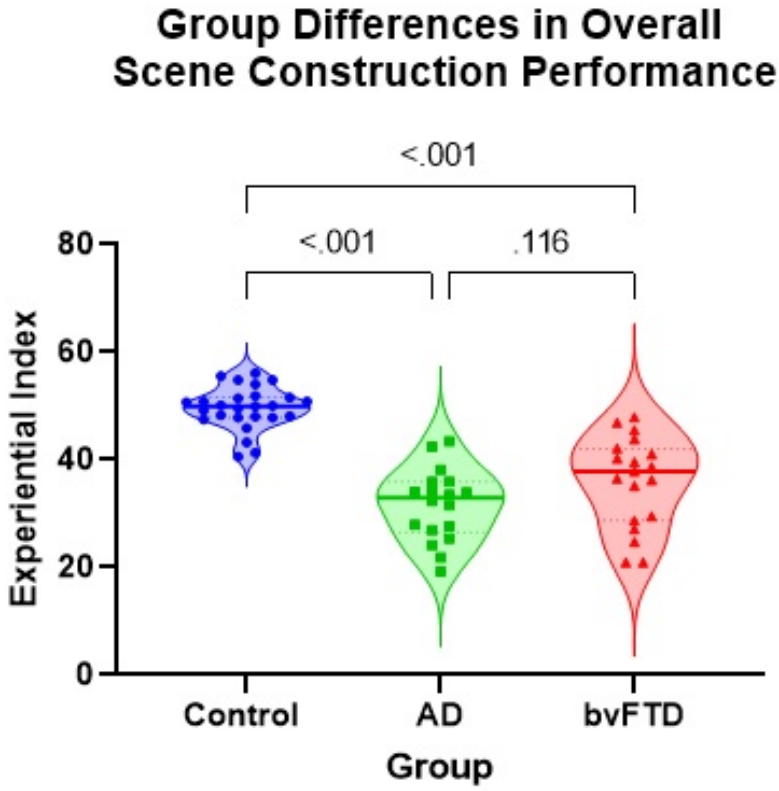

Figure 3.1. Experiential Index based on a composite score comprising Total Content scores, Subjective Ratings of Perceived Salience and Sense of Presence, the Spatial Coherence Index, and Objective Quality Judgment (maximum score 60, see Section 3.1.3). Bolded horizontal lines depict the median and data points represent individual scores. Adjusted pairwise comparisons shown. bvFTD = behavioural variant frontotemporal dementia, AD = Alzheimer's disease.

Total Content

A significant main effect of group was found for the overall level of contextual detail generated by participants during scene construction, F (2, 59) = 36.2; p < .001; η_p^2 = .55. As illustrated in

Figure 3.2 and Table 3.3, this effect reflected the impoverished level of detail provided by bvFTD and AD patients in relation to controls (both p values < .001).

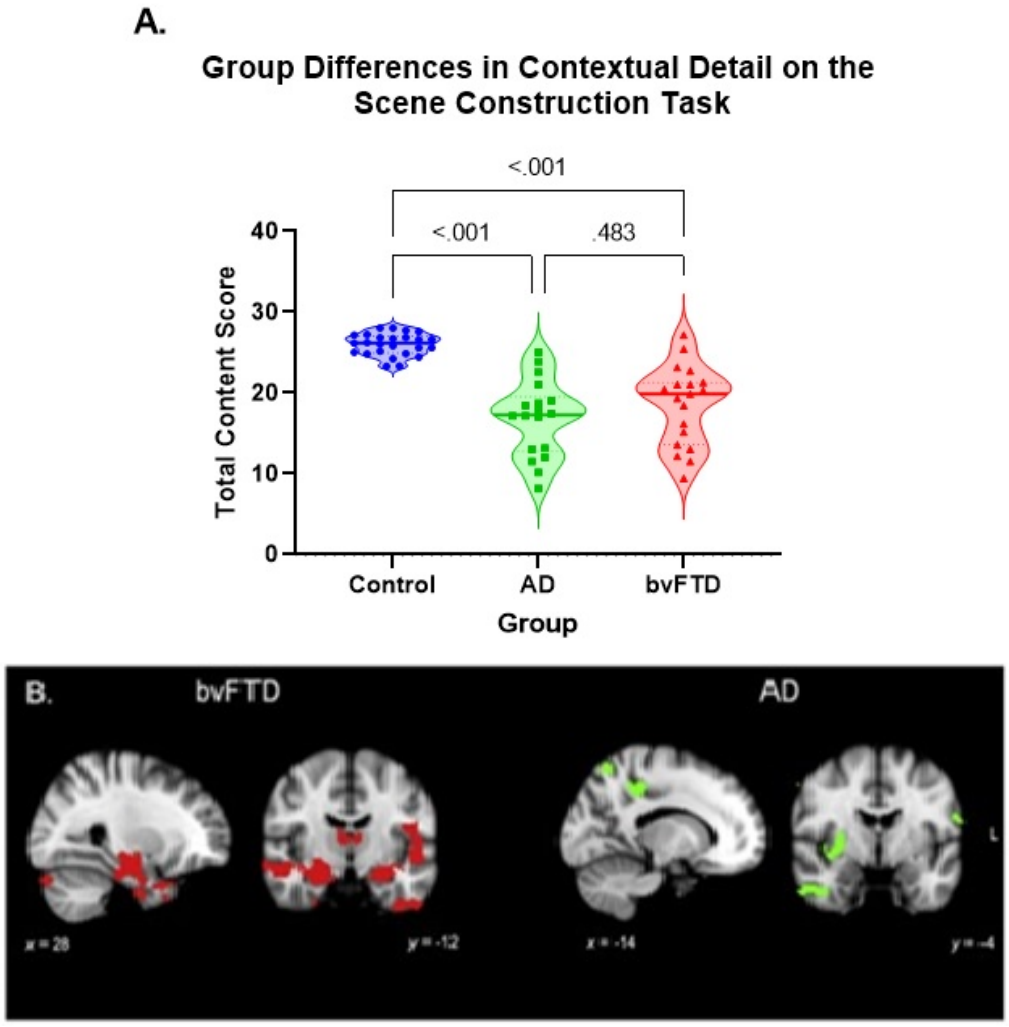

Figure 3.2. Total Content generated on the scene construction task in bvFTD, AD, and Control groups. (A) Behavioural scores (maximum score = 28). Bolded horizontal lines depict the median and data points represent individual scores. Adjusted pairwise comparisons shown. (B) Grey matter regions which correlate significantly with Total Content in bvFTD (red) and AD (green). Coloured voxels indicate regions that emerged as significant in the voxel-based morphometry correlation analyses at $p < .05$ corrected for False Discovery Rate with a cluster threshold of 200 contiguous voxels. All clusters reported at $t \geq 3.1$. Clusters are overlaid on the Montreal Neurological Institute (MNI) standard brain with x and y coordinates reported in MNI standard space. bvFTD = behavioural variant frontotemporal dementia, AD = Alzheimer's disease.

Looking across the Content subcategories, further group differences were evident for Spatial References, F (2, 59) = 49.2; $p < .001$; $\eta_p^2 = .62$, Entities Present, F (2, 59) = 24; $p < .001$; $\eta_p^2 = .44$, Sensory Descriptions, F (2, 59) = 14.5; $p < .001$; $\eta_p^2 = .33$, and Thoughts/Emotions/Actions, F (2, 59) = 21; $p < .001$; $\eta_p^2 = .41$. Post hoc tests revealed that bvFTD patients were significantly impaired relative to control participants in providing Spatial References ($p \leq .0001$), Entities Present ($p \leq .0001$), and Thought/Emotion/Action details ($p \leq .0001$). In the AD group, post hoc comparisons revealed significantly poorer performance relative to controls across all content categories, Spatial References ($p \leq .0001$), Entities Present ($p \leq .0001$), Sensory Descriptions ($p \leq .0001$), and Thought/Emotion/Actions ($p \leq .0001$). Comparison between patient groups revealed similar performance on Spatial References, Entities Present, and Thought/Emotion/Action details (all p values $\geq .1$). A notable exception, however, was the subcategory of Sensory Descriptions, for which bvFTD patients provided a comparable level of details to controls ($p > .644$), as well as outperforming the AD group ($p = .012$, see Table 3.3). To ensure that these differences in Sensory Description content were not attributable to differential cueing across patient groups, the average number of probes provided by the experimenter across trials was examined. No significant differences were evident between AD and bvFTD groups in terms of the number of probes provided during scene construction ($t = -.676$, $p = .503$). Moreover, when the number of probes provided was included as a co-variate, the difference between the patient groups for Sensory Descriptions remained statistically significant ($p = .002$).

Spatial coherence

The Spatial Coherence Index represents the degree to which participants judge their imagined representations as being spatially contiguous. A significant main effect of group was present, F (2,59) = 8.8; $p < .001$; $\eta_p^2 = .23$, with both patient groups rating their constructed scenes as spatially

fragmented, relative to controls (both p values < .01). BvFTD ratings were not found to differ from those provided by the AD group (p > .1), with both patient groups endorsing a comparable reduced level of spatial coherence and a lack of integration in their constructed scenes (Figure 3.3 and Table 3.3).

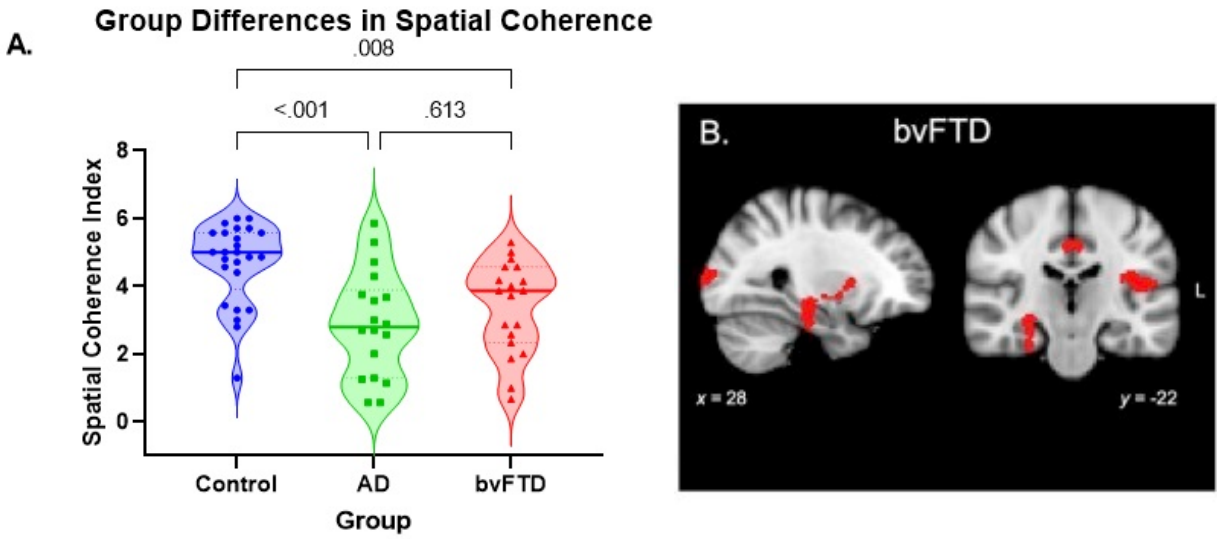

Figure 3.3. Spatial Coherence Index ratings for bvFTD, AD, and Control groups. (A) Behavioural scores for participant groups, ranging from spatially fragmented (0) to highly spatially integrated (6). Bolded horizontal lines depict the median and data points represent individual scores. Adjusted pairwise comparisons shown. (B) Grey matter regions which correlate significantly with Spatial Coherence Index ratings in bvFTD (no significant clusters emerged in the AD group). Coloured voxels indicate regions that emerged as significant in the voxel-based morphometry correlation analyses at p < .05 corrected for False Discovery Rate with a cluster threshold of 200 contiguous voxels. All clusters reported at $t \geq 4.4$. Clusters are overlaid on the Montreal Neurological Institute (MNI) standard brain with x and y coordinates reported in MNI standard space. bvFTD = behavioural variant frontotemporal dementia, AD = Alzheimer's disease.

Quality judgment

A significant group effect was evident in the quality of the scene descriptions, F (2, 59) = 93.1; p = .001; η_p^2 = .75. Post hoc analyses revealed an independent rater, blind to group membership, rated the scene descriptions in both bvFTD (p = .001) and AD ($p \leq .0001$) groups as of lower overall quality relative to controls, approximating highly schematised accounts lacking in rich visual imagery. Interestingly, the scene descriptions provided by bvFTD patients were rated as of better overall quality relative to the AD group (p = .049) evoking a richer mental picture in the mind's eye of the rater (Table 3.3).

Participant ratings

Finally, significant group effects were evident in participant subjective ratings pertaining to the vividness of the envisaged scene, F (2, 59) = 4.3; p = .016; η_p^2 = .12, and the perceived similarity with previous experiences, F (2, 59) = 4.6; p = .013; η_p^2 = .13. Post hoc analyses revealed bvFTD (p = .005) and AD (p = .015) patients rated their imagined scenes as less vivid than control participants, and more similar to existing memories (bvFTD, p = .046, AD, p = .006). This pattern emerged despite the absence of significant group effects in the self-reported level of difficulty in the generation of the scene, F (2, 59) = 2.5; p = .08; η_p^2 = .08, the number of details produced, F (2, 59) = 2.3; p = .1; η_p^2 = .07, and the sense of presence within imagined scenes, F (2, 59) = 2.1; p = .13; η_p^2 = .06. Direct comparisons between patient groups failed to reveal any significant differences on the subjective ratings (all p values ≥ .1).

Table 3.3. Scene construction performance in participant groups.

	bvFTD *M(SD)*	AD *M(SD)*	Controls *M(SD)*	Group effect (*p*)	Post hoc (direction of effect)
Experiential Index (0–60)	35.8 (8.3)	31.4 (6.6)	49.9 (3.5)	<.001	CN > bvFTD, AD
Total Content (0–28)	18.4 (4.9)	16.8 (4.7)	25.9 (1.3)	<.001	CN > bvFTD, AD
Spatial References (0–7)	3.5 (1.3)	2.8 (1.2)	5.9 (0.7)	<.001	CN > bvFTD, AD
Entities Present (0–7)	4.8 (1.8)	4.3 (1.4)	6.9 (0.2)	<.001	CN > bvFTD, AD
Sensory Descriptions (0-7)	6.2 (0.7)	5.1 (1.4)	6.6 (0.4)	<.001	CN, bvFTD > AD
Thoughts, Emotions, Actions (0–7)	4.3 (1.7)	4.5 (1.3)	6.5 (0.5)	<.001	CN > bvFTD, AD
Spatial Coherence Index (0–6)	3.3 (1.3)	2.7 (1.7)	4.5 (1.3)	<.001	CN > bvFTD, AD
Quality Judgment (0–18)	4.7 (1.2)	3.1 (.9)	7.3 (.7)	<.001	CN > bvFTD > AD
Participant ratings (0–5)					
Difficulty	2.2 (0.6)	2.4 (0.4)	2.0 (0.6)	n.s.	-
Vividness	3.5 (0.5)	3.5 (0.5)	4.0 (0.5)	.016	CN > bvFTD, AD
Level of Detail	3.0 (0.5)	2.9 (.5)	3.2 (0.4)	n.s.	-
Sense of Presence	3.7 (0.5)	3.5 (.7)	3.9 (0.6)	n.s.	-
Similar to Memories	2.6 (0.9)	2.3 (0.4)	3.0 (0.6)	.013	CN < bvFTD, AD

Notes. Minimum to maximum score for each metric shown in brackets. *M* = mean, *SD* = standard deviation. In keeping with Hassabis et al. (2007), Spatial Coherence Index ratings were normalised around 0 with negative values reported as 0, and Quality ratings (range 0–10) were multiplied by 1.8 for inclusion in the Experiential Index score. n.s. = not significant. bvFTD = behavioural variant frontotemporal dementia; AD = Alzheimer's disease, CN = Controls.

Associations between scene construction performance and cognitive tasks

Exploratory two-tailed Pearson's correlations between Experiential Index scores and neuropsychological test performance were run to explore possible cognitive mechanisms

contributing to scene construction performance (Table 3.4). For bvFTD, *r* values point to controlled word generation and retrieval abilities (Letter fluency task, $p = .049$) and executive function (Hayling Overall Scaled Score, $p = .05$) as potential correlates with Experiential Index Scores, however, significance values were marginal. No significant correlations emerged in the AD group (all *p* values ≥ .48).

Table 3.4. Pearson's correlations between Experiential Index and neuropsychological test performance in bvFTD and AD groups

Neuropsychological tests	Experiential Index	
	bvFTD	AD
Episodic memory		
RAVLT 30 minute	.48	.12
RCF 3-minute delayed recall	.17	.22
Language processing		
SydBat Naming	.25	.29
Comprehension	.38	.16
Semantic association	.52	.14
Letter Fluency (F, A, S)	**.61***	.46
Attention and executive functions		
Digit span forwards	-.14	.13
Digit span backwards	-.07	.30
TMT B-A	.14	-.22
Hayling Overall Scaled Score	**.58***	.30

Notes. Pearson *r* values reported (adjusted for multiple comparisons using 'false discovery rate' approach). * = $p < .05$. bvFTD = behavioural-variant frontotemporal dementia; AD = Alzheimer's disease; SydBat = Sydney Language Battery; RAVLT = Rey Auditory Verbal Learning Test; RCF = Rey Complex Figure; TMT B-A = time difference between parts B and A of the Trail Making Test.

Finally, the extent to which Total Content and the Spatial Coherence Index were related in each patient group was considered. In bvFTD, the provision of contextual details (Total Content) was strongly associated with the spatial integration of the constructed scenes (Spatial Coherence: r = .61; p = .005). A similar association was observed in the AD group (r = .47; p = .045).

Voxel-based morphometry analyses

Group differences in grey matter intensity were consistent with previously published reports in bvFTD (Rosen et al., 2002) and AD (Karas et al., 2004), see Table 3.5. Relative to controls, the bvFTD group displayed grey matter intensity reduction predominantly in bilateral prefrontal regions, including ventromedial prefrontal and inferior frontal gyri, frontal poles, orbitofrontal and insular cortices. This cluster extended medially towards the anterior cingulate cortices and subcortical regions such as the bilateral putamen and caudate nuclei. Atrophy extended into lateral temporal and posterior parietal regions including the bilateral angular and supramarginal gyri, and lateral occipital cortices.

Conversely, in AD atrophy was centred primarily on the bilateral posterior parietal cortices including the supramarginal and angular gyri, extending into lateral and medial temporal regions including the right posterior hippocampus, and left anterior hippocampus. The bilateral frontal poles and medial prefrontal cortices were also affected in AD.

Table 3.5. Voxel-based morphometry results showing regions of significant grey matter intensity decrease in bvFTD and AD patient groups compared to controls.

Contrast	Regions	Side	Number of voxels	Peak MNI coordinates			*t*-value
				x	*y*	*z*	
bvFTD vs. controls	Right frontal pole extending bilaterally to include orbitofrontal cortex, anterior cingulate cortex, paracingulate gyrus, ventromedial medial prefrontal cortex, caudate, putamen, inferior/middle/superior frontal gyrus, insular cortex, right temporal pole, bilateral temporal cortices, extending posteriorly angular and supramarginal gyri, and lateral occipital cortices	B	32,647	10	62	-22	3.9
AD vs. controls	Parietal operculum cortex, supramarginal gyrus, angular gyrus, lateral occipital cortex, superior/middle/inferior temporal gyrus, central operculum cortex, temporal pole, insular cortex, inferior frontal gyrus, frontal pole, orbitofrontal cortex, medial prefrontal cortex extending into right ventromedial prefrontal cortex, right frontal pole	L	16,689	-62	-36	18	3.9
	Lateral occipital cortex, supramarginal gyrus, angular gyrus, superior/middle temporal gyrus	R	4,907	52	-60	-8	3.7
	Temporal pole, parahippocampal gyrus, hippocampus (anterior)	L	900	-40	-2	-50	3.1
	Hippocampus (posterior), thalamus, posterior cingulate cortex	R	604	22	-38	-2	3.3
	Middle temporal gyrus, superior temporal gyrus, inferior temporal gyrus	R	549	60	-18	-10	3.1

Notes. MRI scans unavailable for 1 AD, 1 bvFTD, and 3 controls. Years in education included as a nuisance variable in all contrasts. MNI coordinates represent the peak of the maximal difference between groups. All clusters reported using the threshold free cluster enhancement method (TFCE) and corrected for Family Wise Error (FWE) at $p < .005$ at a cluster threshold of 500 contiguous voxels. L = Left; R = Right; B = Bilateral; MNI = Montreal Neurological Institute.

3.2.4 Grey matter correlates of scene construction performance

Neural substrates of the Experiential Index

Overall scene construction performance in bvFTD, as captured by the Experiential Index, was found to correlate with grey matter intensity in predominantly prefrontal and temporal regions. Lateral and medial prefrontal regions including the right frontal pole, right orbitofrontal cortex, right anterior cingulate and paracingulate, and bilateral insular cortices were implicated, as well as lateral temporal regions including the bilateral superior temporal gyrus, left temporal pole, and right middle temporal gyrus. Further, medial temporal regions including the bilateral hippocampi and amygdala, and right parahippocampal gyrus correlated with the Experiential Index, as did bilateral posterior parietal (supramarginal gyrus) and cerebellar cortices. Subcortical regions, including the bilateral thalami, were further implicated.

In contrast, scene construction performance in the AD group correlated exclusively with grey matter intensity of posterior parietal regions including the bilateral inferior parietal lobule (supramarginal gyrus) and left superior parietal lobule, extending medially into the left posterior cingulate cortex and precuneus. The right putamen was also implicated.

Neural bases of Total Content scores

Total Content scores were also examined as the key indicator of the amount of details generated within imagined scenes (Figure 3.2). In bvFTD, Total Content scores were associated with grey matter intensity decrease of bilateral hippocampi and amygdala and the right thalamus extending towards lateral temporal lobe structures (right middle temporal gyrus and left superior temporal gyrus) and towards ventral posterior regions such as the left temporal fusiform cortex and right cerebellar cortices.

In AD, on the other hand, Total Content scores were associated with grey matter intensity decrease of posterior parietal regions such as bilateral postcentral, left posterior cingulate, and left superior parietal and lateral occipital cortices. In addition, right inferior parietal (supramarginal gyrus), inferior temporal and temporal pole cortices, as well as subcortical regions such as the right thalamus emerged.

Neural substrates of Spatial Coherence Index scores

Finally, the neural bases associated with the ability to generate spatially contiguous scenes via the Spatial Coherence Index was explored (Figure 3.3). In bvFTD, Spatial Coherence Index scores were associated with grey matter intensity decrease of the right mid-cingulate gyrus, the right hippocampus (predominantly head & body) extending into the putamen, a portion of the right anterior and posterior parahippocampal gyrus, the right occipital pole, and the left central opercular cortex extending into the left insular cortex. Spatial coherence in AD, by contrast was not associated with any significant clusters at the 200 contiguous cluster threshold.

3.3 Discussion

Contemporary theories of episodic memory emphasise the centrality of the hippocampus in supporting a range of (re)constructive endeavours previously shown to be disrupted in bvFTD, including remembering the past and envisaging the future (Frisch et al., 2013; Irish, Piguet, et al., 2014). Supporting the hypothesis that the construction of atemporal scenes would also be deleteriously affected in this population, this study revealed bvFTD patients exhibit a significantly reduced capacity for scene construction relative to control participants. Interestingly, the magnitude of scene construction deficits in bvFTD was comparable to that observed in AD, diverging from expectations that bvFTD patients would outperform their AD counterparts and

pointing to scene construction as an important variable of interest across diverse clinical populations. Neuroimaging analyses supported the prediction that scene construction deficits would be mediated by divergent neural substrates across bvFTD and AD groups, however, the hippocampus (not the vmPFC) emerged as the primary neural correlate across all task metrics in the bvFTD group. Posterior neural regions once again emerged as subtending scene construction deficits in AD (Irish et al., 2015). These findings establish a fundamentally reduced capacity to construct temporally independent mental scenes in bvFTD, adding to existing reports of impaired performance on a broad array of constructive endeavours in this syndrome. While the majority of this discussion will focus on the novel findings in bvFTD, comparisons between patient groups are also considered.

3.3.1 Overall scene construction performance in bvFTD

The chief finding from this study was a fundamental impairment in the construction of spatially coherent scene imagery in bvFTD, resulting in impoverished scene descriptions that were self-rated as spatially fragmented. The current findings complement previous reports of marked disturbances in past-oriented autobiographical memory and episodic future thinking in bvFTD (Irish & Piolino, 2016; Irish et al., 2013; McKinnon et al., 2008) and suggest that these impairments extend to static scenes which lack a specific temporal context. Using the Experiential Index as the main outcome measure on the scene construction task, significant associations were found between bilateral hippocampal and right parahippocampal grey matter intensity decrease and scene construction performance in bvFTD. This finding is in keeping with prominent theoretical accounts which ascribe a central role to the hippocampus in the generation and maintenance of spatially integrated scenes (Maguire and Mullally, 2013). Diverging from expectations, the vmPFC did not emerge as a primary neural correlate in relation to scene

construction task performance in bvFTD. Scene construction impairments in bvFTD were, however, associated with grey matter intensity decrease across medial and lateral prefrontal cortices which have been shown to be important for cognitive control (Koechlin, Ody, & Kouneiher, 2003). Posterior parietal regions, which are thought to house and integrate sensory-perceptual representations aiding episodic memory retrieval (Ramanan, Alaeddin, et al., 2018; Shimamura, 2011) and scene construction (Summerfield et al., 2010) were also implicated, as were lateral temporal regions known to support semantic processing during future simulation (Irish et al., 2012, Irish & Piguet, 2013). As such, these findings suggest that the overall richness of constructed scenes relies on the integrity of prefrontal, posterior parietal and lateral temporal cortical regions, anchored on the medial temporal lobes.

3.3.2 Contextual detail and spatial coherence in bvFTD

Next, the neural substrates of the Total Content and Spatial Coherence subcomponents in each patient group were explored. The impaired generation of contextual detail in bvFTD was associated with grey matter intensity decrease of the bilateral hippocampi, amygdala, and the right thalamus extending towards lateral temporal and ventral posterior temporal cortices. For Spatial Coherence ratings in bvFTD, the right hippocampus and cortical midline regions such as the right mid-cingulate, as well as the left insular cortex were implicated. Thus, across these independent analyses, the right hippocampus (predominantly head and body) emerged as one of the few regions associated with the impaired provision of contextual details and the spatial integration of the scene in bvFTD. Increasing attention is being paid to functional subdivisions across the long axis of the hippocampus in supporting memory processes (Sekeres, Winocur, & Moscovitch, 2018) with the proposal that the anterior hippocampus may make a unique contribution to forming internal representations of spatially coherent scenes (Zeidman & Maguire, 2016). The observation of a core

contribution of the right anterior hippocampus in this context is noteworthy as it dovetails with previous findings of a critical role for this region in episodic future thinking capacity in independent samples of bvFTD patients (Irish et al., 2013, 2016). As such these findings sit well with current theoretical models endorsing the right anterior hippocampus as a potential hub for scene-base cognition (Zeidman & Maguire, 2016).

3.3.3 Neural regions beyond the hippocampus and scene construction in bvFTD

Looking beyond the hippocampus, regions from the frontoparietal control network, such as the anterior cingulate and inferior parietal cortices, were also implicated in scene construction performance impairments in bvFTD. It may be that degeneration of regions within the frontoparietal control network disrupts fundamental aspects of cognitive control, essential for goal-directed task performance (Spreng et al., 2010). Importantly, the anterior cingulate and insular cortices form critical nodes of the Salience Network of the brain, a large scale network involved in processing the perceived importance of incoming stimuli (Menon, 2015; Seeley et al., 2007). Degeneration of the Salience Network is an early feature of bvFTD (Zhou et al., 2010) and has been implicated in disrupting the capacity to toggle efficiently between attention-grabbing stimuli from the external environment and internal forms of mentation in this syndrome (O'Callaghan et al., 2019). These findings underscore the importance of considering how regional atrophy patterns relate to broader disruption of large-scale functional brain networks; a critical avenue for future research.

3.3.4 The vmPFC and scene construction in bvFTD?

Despite predictions regarding the potential contribution of the vmPFC to scene imagery in bvFTD, no significant associations between vmPFC grey matter intensity decrease and the three outcome measures of interest emerged on the scene construction task. It has been suggested that the vmPFC

interacts with neocortical sites to initiate the activation and retrieval of schematic elements, prior to engaging in scene construction (Ciaramelli et al., 2019). Put forward by Ciaramelli et al (2019), these elements may then be supplied to the hippocampus, via fronto-hippocampal structural connections, for integration into a spatially coherent 'static' scene. Once a spatially coherent mental scene has been constructed, the vmPFC and hippocampus are posited to interact with the temporoparietal cortices to facilitate the temporal unfolding of the static scene into a dynamic event (Ciaramelli et al., 2019). In this way, the vmPFC is suggested to aid in the selection of context-specific elements relevant to goal-directed scene construction, rather than directly supporting integration of spatiotemporal elements to form coherent scenes per se (Barry, Barnes, Clark, & Maguire, 2018; Ciaramelli et al., 2019; McCormick et al., 2018)

In line with previous reports (Bertossi et al., 2016) and the study hypothesis, focal vmPFC damage would be expected to produce a reduction in the number of contextual elements embedded into constructed scenes, possibly reflecting a difficulty in activating schematic elements for repurposing during mental simulation. One possible explanation for the lack of emergence of the vmPFC in the current study is the reduced voxel-level variance of this region in the bvFTD group. As correlational methods such as VBM depend on continuous distribution of data, floor effects of grey matter intensity in the vmPFC region, due to its early and marked degeneration in bvFTD, may have precluded this region from emerging as a significant neural correlate of scene construction performance. It may also be that where vmPFC and hippocampal atrophy co-occur, the more subtle vmPFC impairments are overshadowed by the more overt hippocampally-mediated difficulties. This proposal requires formal empirical investigation, potentially by differentially taxing processes subserved by the vmPFC (e.g., affective, social content) versus the hippocampus (e.g., novelty).

3.3.5 Scene construction performance in AD – the role of posterior regions

As previously reported (Irish et al., 2015), AD patients demonstrated profound deficits in scene construction, the neural substrates of which predominantly reflected posterior parietal dysfunction. Supporting the hypothesis that divergent neural regions would subtend scene construction performance in bvFTD and AD, regions including the posterior cingulate cortex and supramarginal gyrus in the inferior parietal cortex were found to correlate with the amount of contextual detail produced (Total Content) and the overall richness of the constructed scene (Experiential Index) in the AD group. No significant neural correlates in AD emerged, however, with Spatial Coherence ratings. Results showing that scene construction impairments are primarily mediated by posterior parietal, rather than medial temporal, degeneration resonate well with current theoretical accounts of episodic memory in which posterior regions are proposed to particularly subtend simulation aspects of recollection (Ranganath & Ritchey, 2012). By such accounts, lateral and medial parietal regions are purported to support the integration and reinstatement of spatiotemporal and perceptual elements, contributing the requisite contextual details for the mental construction of vivid scenes in the mind's eye (Ramanan et al., 2018).

3.3.6 Scene construction across dementia syndromes

This study revealed that the capacity to construct richly detailed mental scenes is comparably disrupted across dementia syndromes, contradicting expectations based on the cognitive and neural profile of these patient groups. Despite divergent clinical presentations, previous studies in AD and bvFTD have revealed comparable performance on autobiographical memory (Matuszewski et al., 2006; McKinnon et al., 2008; Irish et al., 2011), and future thinking (Irish et al., 2016; Irish, Hodges, Piguet, 2013) tasks in these syndromes. Therefore, similar profiles of scene construction performance are possibly not surprising. Whether more subtle differences exist in the profile of

mental imagery between dementia syndromes, however, and how these may relate to the clinical presentation of bvFTD and AD, remains a question for future study. Interestingly, bvFTD and AD patients also provided comparable levels of spatial details in the current study, despite previous reports establishing more extensive deficits in spatial processing in AD, relative to bvFTD (Tu et al., 2015). This is important as it implies that the profile of real-world spatial ability may not translate to the envisaged world, and conversely, speaks to the need to investigate how the capacity to envisage scenes may support real-world navigation.

3.3.7 Summary and implications

This study establishes a fundamental deficit in the ability to generate richly detailed, spatially cohesive mental scenes in bvFTD which are devoid of temporal context, adding to a growing body of literature identifying a reduced capacity for a range of mental constructive endeavours in bvFTD (Irish, Hodges & Piguet, 2013; Irish, Piguet, et al., 2014). Neuroimaging findings point to a critical role for the right hippocampus in the construction of spatially integrated and contextually rich scenes in this syndrome. While the emergence of the hippocampus as the primary neural region mediating scene construction performance in bvFTD diverged from predictions, in line with current literature (Ciaramelli et al., 2019), future studies are required to determine when and how the vmPFC may work in concert with the hippocampus in this process. Given the proposed integrative role of the vmPFC in the generation of mental imagery, and schema-related organisation (Bertossi et al., 2016; McCormick et al., 2018; Spalding, Jones, Duff, Tranel, & Warren, 2015), of particular importance will be establishing whether the nature of an envisaged scene may moderate task performance across clinical populations. Chapters 4 and 5 begin this work by examining how scene cues targeting the integration of socio-emotional detail (Wilson et al., 2020b) and which increase the reliance on conceptual knowledge result in differential task

performance across dementia syndromes. In sum, this chapter establishes the capacity for scene construction as being significantly disrupted in bvFTD and provides an important impetus to explore the nature of these deficits across various constructive contexts.

4

Constructing the Social World: Social simulation in bvFTD

This chapter is a modified version of Wilson, N.-A., Ahmed, R. M., Hodges, J. R., Piguet, O., & Irish, M. (2020). Constructing the social world: Impaired capacity for social simulation in dementia. *Cognition*, *202*(May), 104321. https://doi.org/10.1016/j.cognition.2020.104321

Increasing attention is being directed towards determining the cognitive and neural mechanisms which support the capacity for scene construction (Mullally & Maguire, 2013), with a view to informing how we mentally construct and interact with the world around us. Chapter 3 identified a fundamentally reduced capacity for mental construction in bvFTD which is comparable to that seen in AD patients (Irish et al., 2015; Wilson et al., 2020a). Given the divergent neural profile subtending scene construction deficits across these dementia syndromes, the question is raised whether the nature of an envisaged scene may moderate task performance in these clinically distinct populations. Expanding findings from Chapter 3 (Wilson et al., 2020a), here, the capacity to incorporate rich socio-emotional detail within an envisaged scene is explored.

As reviewed in Chapter 3, the complexity of scene construction is reflected on the neural level with fMRI studies providing compelling evidence for the involvement of a core construction network centred on the hippocampus (Hassabis, Kumaran, & Maguire, 2007; Mullally, Hassabis, & Maguire, 2012; Zeidman & Maguire, 2016). Importantly, for the purposes of this study, regions

within the prefrontal cortex have also been implicated in mental construction (Barry, Barnes, Clark, & Maguire, 2018; Bertossi et al., 2016; McCormick et al., 2018).

Associations between the vmPFC and a wide variety of complex cognitive processes have previously been identified, including the formation and instantiation of schemas; superordinate knowledge structures which extract commonalities across events and experiences (Gilboa & Marlatte, 2017). Schemas have been suggested to support mental construction by providing the necessary scaffold (Irish & Piguet, 2013) or framework from which a single scene snapshot can be created (Ciaramelli, De Luca, Monk, McCormick, & Maguire, 2019. The vmPFC also has a well-established role in the computation of socio-emotional and subjective value (Kable & Glimcher, 2007) and has been implicated in supporting an array of socio-emotional processes. Our social knowledge, the ability to perceive and interpret social situations, as well as make appropriate social decisions (Arioli et al., 2018; Dang, Mattan, Kubota, & Cloutier, 2019; Rudebeck, Bannerman, & Rushworth, 2008) have all been suggested to be supported, at least in part, by the vmPFC.

Notably, activity in the vmPFC has been demonstrated to scale linearly in relation to the tuning of one's personal preferences to adjust to the potential preferences of others, suggesting an important role in calibrating and refining social inferences based on social context (Tamir & Mitchell, 2010). Where mental construction is concerned, increased vmPFC activation has been observed when healthy individuals imagine scenes containing people, relative to empty scenes (Hassabis et al., 2014). This resonates with findings from a separate fMRI study documenting vmPFC activation during the integration of socio-emotional knowledge to convey the emergent affective quality of a constructed episode (Benoit, Szpunar, & Schacter, 2014).

In this sense, the construction of scenes with social elements may contain an additional layer of complexity, requiring the individual to not only generate the spatial framework for the scene, but also to integrate relevant social information. Constructing social scenes, therefore, likely involves perspective taking via ToM, social knowledge, and integration of schematic information related to the specific social context. Understanding the underlying cognitive processes which support the capacity for scene construction has proven particularly important for explicating how we remember the past, imagine the future, and navigate in the world around us (Clark & Maguire, 2016). How social forms of construction are impacted by different profiles of neurodegeneration, and the possible mechanisms driving these changes, offers the opportunity to build on previous work by exploring the cognitive architecture of simulating the social world.

The differential clinical profile of bvFTD and AD, within the context of comparable scene construction deficits (Chapter 3, Wilson et al., 2020a), offers a unique opportunity to investigate the possibility of discrete classes of scene construction dependent on the nature of the stimuli. BvFTD patients display marked frontoinsular cortical degeneration, including but not limited to the vmPFC (Irish & van Kesteren, 2018) and substantial socio-emotional disturbances (Henry, Phillips, & Hippel, 2014; Hutchings, Hodges, Piguet, & Kumfor, 2015; Kumfor & Piguet, 2012). It remains unclear, however, whether the predominant prefrontal atrophy and socio-emotional deficits characteristic of bvFTD are associated with a reduced capacity to simulate the social world. Here, it was hypothesised that bvFTD patients would show disproportionate impairments in the construction of social, relative to non-social, scenes, on a modified scene construction task which would not be apparent in the AD group. The potential cognitive mechanisms associated with social and non-social mental imagery were also explored in order to gain new insights into the mental processes by which humans mentally construct and represent real-world social scenarios.

4.1 Materials and Methods

4.1.1 Participants

A total of 54 participants were recruited through the FRONTIER frontotemporal dementia research group, based at the Brain and Mind Centre, The University of Sydney. Twenty individuals with a clinical diagnosis of probable bvFTD and 14 individuals with typical Alzheimer's disease (AD) were contrasted with 20 healthy older control participants. A comprehensive neuropsychological assessment was conducted and dementia diagnosis was established in accordance with the criteria outlined in Chapter 2 sections 2.3 and 2.1 respectively. Healthy controls were recruited through the FRONTIER volunteer registry and local community groups and conformed to inclusion and exclusion criteria (Chapter 2 section 2.1.1).

4.1.2 Cognitive assessment

Participants completed a comprehensive neuropsychological test battery covering the main cognitive domains, see Chapter 2 section 2.3. General cognitive functioning was measured using the Addenbrooke's Cognitive Examination – Third Edition (ACE-III; Hsieh et al., 2013; So et al., 2018). Cognitive variables of particular relevance to this study included, delayed verbal (RAVLT; Schmidt, 1996) and visuospatial (RCF 3 minute; Meyers & Meyers, 1995; Rey, 1941) episodic memory, and response inhibition (Hayling; Burgess & Shallice, 1997).

4.1.3 Social norms questionnaire

A subset of participants completed the Social Norms Questionnaire (Possin et al., 2013) (bvFTD = 15; AD = 12, control, 17). This questionnaire is a 22-item ‘‘yes’’ or ‘‘no’’ self-report measure to detect inappropriate social behaviour in hypothetical scenarios. Three scores are obtained from the measure. The SNQ Total score has a maximum score of 22 with higher scores indicating

greater knowledge of social norms. Two subscales may also be obtained with higher scores representing *poorer* social knowledge. The "Over-adhere" score (range 0-10) represents social rigidity and refers to endorsement of a socially *appropriate* behaviour (i.e., wearing the same shirt twice in 2 weeks) as *inappropriate*. The "Break" score (range 0-12) refers to endorsement of a socially *inappropriate* behaviour (i.e., eating pasta with your fingers) as *appropriate*. The SNQ has been established as a valid measure of social knowledge in bvFTD (Panchal et al., 2015).

4.1.3 Social simulation task

The ability to construct spatially coherent social and non-social scenes was measured using a modified version of the Scene Construction task developed by Hassabis et al. (2007). In keeping with the original study protocol, participants were instructed to imagine, and describe aloud, atemporal scenes in as much detail as possible, using all their senses. Informed by previous research on this topic (Hassabis et al., 2014), "social scenes" were operationally defined as scenes constructed in relation to cues which evoke a sense of being surrounded by people. Pilot testing in 10 healthy young adults (mean age: 34.4 years) was conducted to determine which cues from a pool of 18 evoked the strongest sense of being surrounded by people. The strongest ratings of "feeling surrounded by people" (i.e., social) were provided for the *Crowded Train* (M = 6.2 SD = 1.0) and *Busy Restaurant* (M = 5.80, SD = 1.1) cues, while the strongest "feeling of being alone" was elicited by the *Abandoned Warehouse* (M = 6.00, SD = 1.2), and *Forest* (M = 6.1, SD = 1.0) cues. The task therefore contained two conditions with two trials per condition; Social ("Busy Restaurant", "Crowded Train") and Non-Social ("Forest", "Abandoned Warehouse"), with each participant generating a total of four descriptions. To minimise cognitive demand in patients, Social and Non-Social trials were completed in a blocked design, with order of Social/Non-Social blocks counterbalanced across participants, and the Spatial Coherence Index was not included.

Participants were requested to imagine and describe in detail a number of scenes in response to cues. They were instructed to create a new scene and to not simply recount a related experience from memory. Cues were read aloud and presented on a sheet of paper which remained in front of participants for the duration of the trial to minimise working memory demands. Unlike the standard Hassabis et al. (2007) task, participants were told at the beginning of the task that some of the scenes would include people and some would not include people, and this direction was included in the scene cue. Instructions for non-social scenes (Abandoned Warehouse, Forest) proceeded as follows, "There are NO other people around you. I want you to describe the experience and the surroundings in as much detail as possible, using all your senses." For the two social scenes (Busy Restaurant, Crowded Train) the instruction was as follows, "There ARE people all around you. I want you to describe the experience and the surroundings in as much detail as possible, including what the people are doing and feeling and using all your senses." Prior to commencing the task, in line with Hassabis et al. 2007, a representative scene example ("Crowded Beach") was provided by the test administrator who pretended to imagine and describe the scene in vivid detail.

Participants were encouraged to speak freely and to provide as much detail as possible for each scene. Trials were limited to a total of two minutes, to minimise fatigue. General prompts were provided to encourage elaboration or if the participant failed to speak for approximately 20-30 seconds. Unlike the original Hassabis et al. (2007) protocol, which allows for repeated prompting to elicit detail, a maximum of two prompts were given to each participant to standardise the test administration. Importantly, these prompts were non-directive and merely served to encourage the participant to provide additional details, for example, "Can you tell me any more details about that scene?" or "Thinking about that scene in the busy restaurant, are there any other details that you

can tell me?" The entire test session lasted approximately 25-30 minutes and was digitally recorded for subsequent transcription and scoring.

Subjective ratings

In accordance with the study protocol developed by Hassabis et al (2007) and outlined in Chapter 3 section 3.1.3, following each scene description, participants were asked to subjectively rate the perceived difficulty, vividness, level of detail, feeling of presence within the imagined scene, and the similarity to a previous experience on a scale of 1-5 with higher scores reflecting greater difficulty, vividness, detail and sense of presence, respectively but *less* similarity to a previous memory (see Hassabis et al., 2007). An additional rating was also included to capture the degree of social integration/immersion the participant felt during construction, as follows, "How much did you feel a sense of being alone in the scene?", rated on a scale from 1-5 with higher ratings indicating a stronger sense of being surrounded by people.

Scoring

A modified version of the scene construction scoring protocol outlined by Hassabis et al. (2007) and described in Chapter 3, section 3.1.3 was used to score the scene transcripts. Scene descriptions were subdivided into content statements and assigned to one of four content categories: Entities Present, Sensory Descriptions, Spatial References, and Thoughts/Emotions/Actions. In keeping with the original scoring protocol (Hassabis et al., 2007), the maximum number of details for each subcategory was capped at 7 points leading to a maximum Total Content Score of 28. All transcripts were scored blind to group membership. Due to the Spatial Coherence Index (see Chapter 3 section 3.1.3) being excluded from the study protocol in order to limit testing demand in a clinical population, the full Experiential Index could not be calculated, therefore, Total Content scores are used as the primary measure of scene construction performance.

4.1.4 Statistical analyses

Data were analysed using IBM SPSS (Version 26). Group differences on categorical variables (i.e., sex) were examined using Chi-squared tests. For continuous variables, normality of distributions was examined using Kolmogorov-Smirnov tests. Where data were normally distributed (i.e., age at assessment, years of education) group differences were assessed using univariate ANOVAs. For non-normally distributed variables (i.e., participant ratings) non-parametric Wilcoxon signed-rank tests for related samples were used. Group differences on the social simulation task were assessed via repeated measures mixed ANOVAs with Bonferroni correction for post hoc comparisons. The alpha level to determine statistical significance was set at $p < .05$. Partial eta-squared values (η_p^2) were included as a measure of effect size for all ANOVA statistics. One-tailed Spearman correlations were run to explore associations between disease severity and total content on the social construction condition. All correlations were corrected for multiple comparisons using Bonferroni adjustment. Finally, Analyses of Covariance (ANCOVA) were run, controlling for cognitive domains of interest, to further explore the potential mechanisms underlying social versus non-social scene construction.

4.2 Results

4.2.1 Demographic and clinical information

No significant difference in age at assessment, F (2, 50) = 2.48; p = .094, η_p^2 = .09, or sex distribution, χ^2 = 2.97; p = .226, was found between groups (Table 4.1). A significant group difference was observed for years of education, F (2,50) = 6.43, p = .003; η_p^2 = .21, with post hoc tests indicating that this was driven by higher levels of education in controls relative to bvFTD (p = .002). No significant differences were observed in years of education between patient groups (p = .318), or between AD patients and healthy controls (p =.262). Controlling for years of education

in the main analyses did not change the overall pattern of results and therefore education was not considered further. No other significant group differences in demographics were evident (all *p* values >.2).

A significant group effect emerged in overall cognitive performance (ACE-III), F (2,51) = 66.76; $p \leq .0001$, $\eta_p^2 = .72$, with post hoc tests indicating both patient groups displayed significantly lower cognitive performance relative to controls (both *p* values <.05). No significant difference was evident between the two patient groups (p =.067). Disease duration, as measured by years elapsed since symptom onset, did not significantly differ between bvFTD and AD, t (29) = 0.20 p = .841, d =.07. Clinical severity on the CDR-FTLD SoB score was also comparable between patient groups, t (30) = 0.39, p = .699, d =.14.

Table 4.1. Demographics and clinical characteristics of study participants.

	bvFTD *M(SD)*	AD *M(SD)*	Controls *M(SD)*	Group effect (*F* value)	Post hoc (direction of effect)
N	20	14	20		
Sex (M:F)	16:4	10:4	11:9	3.0[a]	-
Age (years)	61.2 (7.5)	65.4 (8.1)	65.1 (4.2)	2.3	-
Education (years)	11.8 (2.1)	13.4 (2.9)	15.1 (3.3)	**6.4****	CN > bvFTD
Disease duration (years)	6.5 (3.3)	6.2 (5.5)	-	-.202[b]	-
Disease severity (CDR-FTLD SoB)	7.0(4.4)	6.5 (3.4)	-	-.390[b]	-
Behavioural Changes (CBI-R Total)	37. 3 (17.8)	29.3 (16.2)	4.8(3.8)	**22.3*****	CN < bvFTD, AD
ACE-III Total (100)	75.6 (7.8)	70.1 (9.0)	94.9 (2.5)	**66.8*****	CN > bvFTD, AD
RAVLT 30 min (15)	4.2 (3.0)	1.2 (1.3)	10.5 (1.6)	**67.9*****	CN > bvFTD > AD
RCF 3 min (36)	11.4 (7.3)	3.0 (2.1)	16.3 (4.6)	**21.1*****	CN > bvFTD > AD
Hayling Overall (7)	4.4 (2.1)	3.8 (1.1)	6.0 (1.0)	**8.4****	CN > bvFTD, AD
TMT B-A (seconds)	123.1(115.8)	137.9 (58.3)	45.4 (14.2)	**6.1****	CN < bvFTD, AD
SydBat (30)					
Naming	23.0 (2.7)	21.4 (4.4)	27.0 (2.4)	**13.4*****	CN > bvFTD, AD
Semantic association	27.0 (2.2)	25.6 (2.2)	28.6 (1.1)	**11.0*****	CN > AD
SNQ Total (22)	17.6 (2.2)	19.3 (1.3)	19.7 (1.5)	**6.3****	CN > bvFTD
Break (12)	1.9 (1.6)	0.8 (1.1)	0.8 (1.0)	**5.1***	CN > bvFTD
Over-adhere (10)	2.7 (1.6)	2.0 (1.1)	1.5 (1.5)	2.7	-

Notes. [a]Pearson Chi-Square. [b]Independent samples *t*-test. Maximum scores for all variables shown in brackets where appropriate. *M* = Mean; *SD* = standard deviation. * = $p < .05$; ** = $p < .01$; *** = $p < .0001$. bvFTD = behavioural-variant frontotemporal dementia; AD = Alzheimer's disease; CN = Controls; CDR-FTLD SoB = Clinical Dementia Rating – Frontotemporal Lobar Degeneration Sum of Boxes; CBI-R = Cambridge Behavioural Inventory – Revised; ACE-III = Addenbrooke's Cognitive Examination – Third Edition; RAVLT – Rey Auditory Verbal Learning Test; RCF – Rey Complex Figure; SydBat = Sydney Language Battery; SNQ = Social Norms Questionnaire. Data unavailable across the following tests - CDR-FTLD: 1 AD, 1 bvFTD; CBI-R: 3 CN; RAVLT: 2 CN, 3 AD; RCF 3 minute: 2 CN, 2 AD; Hayling: 2 CN, 3 AD, 2 bvFTD; TMT B-A: 2 CN, 6 AD, 4 bvFTD; SydBat: 2 CN, 6 bvFTD; SNQ: 3 CN, 2 AD, 5 bvFTD.

4.2.2 Cognitive profiles

Significant group differences emerged in cognition which were in keeping with the clinical profile of the two dementia syndromes (Table 4.1). Looking at executive function, a significant group effect was found for both the Hayling, F (2, 44) = 8.44; p = .001, η_p^2 = .28, and TMT B-A, F (2, 39) = 6.09; p = .005, η_p^2 = .24. Significant group effects were also evident in verbal, F (2, 46) = 67.87; $p \leq .0001$, η_p^2 = .75, and visuospatial, F (2, 47) = 21.12; $p \leq .0001$, η_p^2 = .47, delayed episodic memory. Finally, significant group effects emerged in semantic naming, F (2, 43) = 13.39; $p \leq .0001$, η_p^2 = .38, and association, F (2, 43) = 11.03; $p \leq .0001$, η_p^2 = .34. Post hoc comparisons revealed, relative to control participants, bvFTD and AD patients displayed significant impairments in executive function (Hayling, bvFTD, p = .010; AD, p = .001; TMT B-A, bvFTD, p = .016; AD, p = .021), verbal and visuospatial delayed episodic memory retrieval (RAVLT, both p values <.0001; RCF, bvFTD, p = .025; AD, $p \leq .0001$), and semantic naming (SydBat, bvFTD, p = .003; AD, $p \leq .0001$). AD patients also performed significantly worse than control participants in semantic association ($p \leq .0001$), with a trend towards a deficit in the bvFTD group (p = .056). Comparison of the patient groups revealed disproportionate episodic memory deficits across verbal (p =.003) and visuospatial ($p \leq .0001$) measures in AD relative to bvFTD. No other significant differences were evident between the patient groups (all p values ≥ .1).

4.2.3 Social knowledge questionnaire

A significant group difference was observed on the social knowledge task overall (SNQ Total), F (2, 41) = 6.28; p = .004, η_p^2 = .24, and the SNQ Break score, F (2, 41) = 5.05; p = .011, η_p^2 = .20. Post hoc pairwise comparisons revealed bvFTD patients demonstrated reduced social knowledge compared to controls (SNQ Total, p = .004), with a trend towards the AD group also outperforming the bvFTD group (p = .054). No significant differences emerged between AD patients and controls

(p = .867). bvFTD patients were also significantly less likely to successfully identify social norm violations compared to controls (SNQ Break, p = .025) and AD patients (p = .029). No significant group effect was found for the SNQ over-adherence sub-score, F (2, 41) = 2.73; p = .077, η_p^2 = .12.

4.2.4 Scene construction performance

Content of social versus non-social scenes

A mixed ANOVA with group (control, bvFTD, AD) as the between subjects factor and condition (social, non-social) as the within subjects factor revealed a significant main effect for group, F (2, 51) = 19.20; $p \leq .0001$, η_p^2 = .43. Post hoc analysis indicated this was driven by higher overall task performance in controls relative to patients (both p values ≤ .0001). No significant difference in overall task performance was evident between bvFTD and AD groups (p = .987). No main effect of condition was observed, F (1, 51) = 1.24; p = .271; η_p^2 = .02; however, the group by condition interaction was significant, F (2, 51) = 3.86; p = .028; η_p^2 = .13. Post hoc tests indicated that this was driven by disproportionately poorer performance in the social, relative to non-social, condition exclusively in the bvFTD group (p = .006). In contrast, controls (p = .322) and AD patients (p = .865) displayed comparable performance across social and non-social conditions, see Figure 4.1.

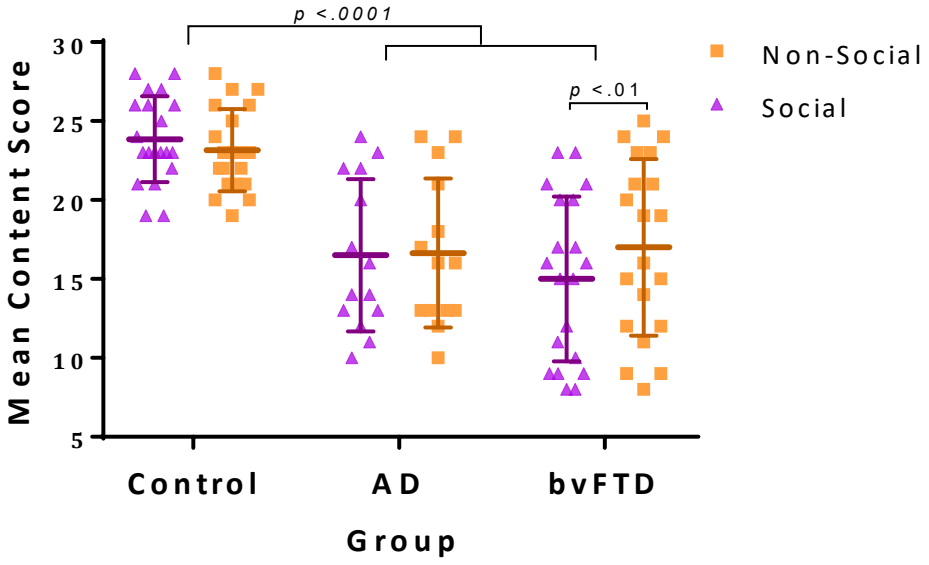

Figure 4.1. Group performance on the scene construction task across social and non-social conditions. Scores represent average social and non-social content scores (maximum score = 28). Horizontal lines depict the mean group performance and whiskers depict the standard deviation. bvFTD = behavioural-variant frontotemporal dementia; AD = Alzheimer's disease.

Post hoc comparisons across the three groups for each condition separately revealed that bvFTD and AD patients performed significantly worse than controls in the non-social condition (all p values < .0001), with no significant difference between the patient groups (p = .985). A similar pattern emerged in the social condition, with both patient groups generating significantly less detail than control participants (all p values <.0001), with no significant difference between patient groups (p = .750).

To explore potential associations between disease severity and task performance in the bvFTD and AD groups, Spearman rank correlations were run in each group separately. A significant association was observed between disease severity (CDR-FTLD SoB) and social construction (Total Content score) in the AD (r_s = -.576, p = .020) and bvFTD groups (r_s = -.393, p = .048),

however, no significant difference was found between the magnitude of these relationships, Fisher's $z = 0.6$, $p = .274$. No significant relationship was observed between disease severity and non-social construction in either patient group (AD, $r_s = -.278$, $p = .179$; bvFTD $r_s = -.386$, $p = .051$).

Contextual details profiles

Looking at the type of detail generated on the scene construction task, a significant main effect for group was observed, $F(2, 51) = 22.33$, $p \leq .0001$; $\eta_p^2 = .47$, and content category, $F(3, 51) = 11.91$, $p \leq .0001$, $\eta_p^2 = .19$, but not for condition, $F(1, 51) = 1.94$; $p = .170$, $\eta_p^2 = .04$. Due to unequal group sizes and highly correlated content scores (all r values $\geq .4$) (Field, 2009), Roy's largest root was used to assess the interaction between group (bvFTD, AD, controls), condition (Social, Non-Social), and contextual detail (SEN, SPA, EP, TEA). The mixed ANOVA revealed a significant three-way interaction, $\Theta = 0.20$, $F(3, 50) = 3.30$; $p = .028$, $\eta_p^2 = .17$, $\beta = .72$, indicating the effect of condition on the content scores differed across the three groups.

Investigating the three-way interaction further, in the social condition, adjusted post hoc comparisons revealed that bvFTD patients provided significantly fewer contextual details across all subcategories relative to controls (all p values <.0001, Figure 4.2). By contrast, AD patients provided comparable Thoughts/Emotions/Actions details to controls ($p = .351$), in the context of significantly impoverished contextual details for the other subcategories (all p values < .0001). Comparison of the two patient groups revealed AD patients provided significantly more details pertaining to Thoughts/Emotions/Actions than the bvFTD group ($p \leq .0001$). No other significant differences were evident between the patient groups across the remaining categories (all p values $\geq .9$).

In the non-social condition, bvFTD patients provided fewer details across all subcategories relative to controls (all p values < .02), with the exception of Entities Present (p = .167). In contrast, AD patients provided fewer contextual details relative to controls for all subcategories (all p values < .01) with the exception of Thoughts/Emotions/Actions (p = .144, Figure 4.2). No significant differences were found between patient groups in any of the detail categories (all p values ≥ .2).

Finally, within-group comparisons revealed that bvFTD patients provided significantly fewer Sensory Descriptions ($p \leq .0001$), Spatial References (p = .026), and Entities Present (p = .002) in social, relative to non-social, scenes. No difference emerged in the bvFTD group between social and non-social conditions in the Thoughts/Emotions/Actions category (p =.359). In contrast, AD patients provided significantly more Thoughts/Emotions/Actions ($p \leq .0001$), as well as fewer Sensory Descriptions (p = .025) and spatial references (p = .002) in social, relative to non-social, scenes. No difference was found between social and non-social scenes in the number of entities included in the AD group (p = .926). Controls also provided significantly more Thoughts/Emotions/Actions in the social, relative to non-social, condition (p < .0001; See Figure 4.2). No other comparisons were significant (all $p \geq .06$).

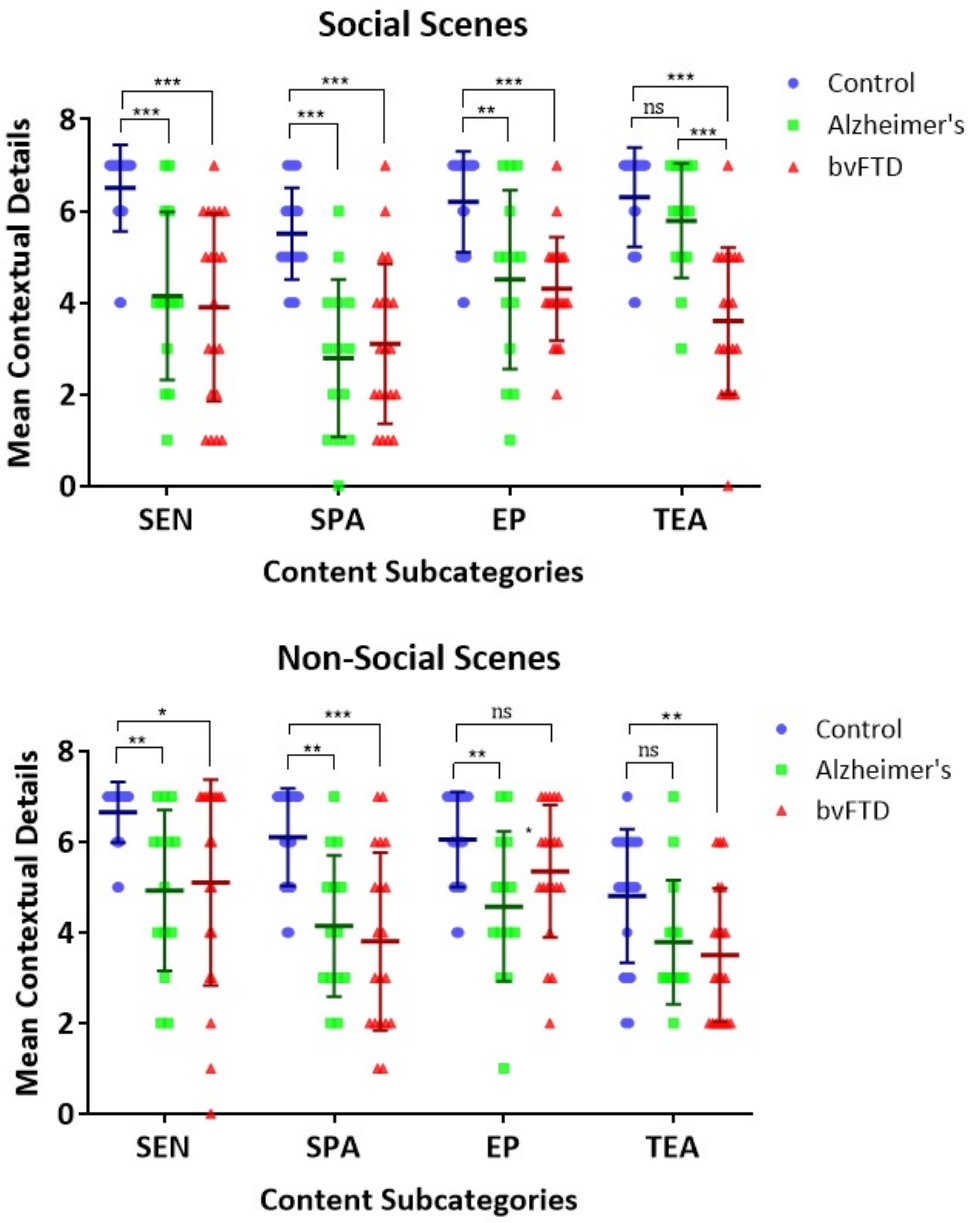

Figure 4.2. Social (top) and non-social (bottom) content subcategory scores on the scene construction task for each group (maximum score per subcategory = 7). Horizontal lines depict the mean and whiskers the standard deviation. SEN = Sensory Descriptions, SPA=Spatial References, EP = Entities Present, TEA = Thoughts/Emotions/Actions. bvFTD = behavioural-variant frontotemporal dementia. * = p <.05. ** = p <.01; *** = p <.0001, ns = non-significant.

Participant Subjective Ratings

Wilcoxon signed-rank tests were used to explore differences in subjective ratings within each group across conditions. All groups rated the non-social scenes as eliciting a greater sense of being alone than the social scenes, (bvFTD, T =170.5, p =.002; AD, T = 89.5, p =.002; control, T = 210.0, p < .0001), see Table 4.2. In addition, for AD and controls, social scenes were rated as *more* similar to a previous memory (AD, T = 14.0, p =.026; control, T = 6.0, p <.0001), but *less* difficult than non-social scenes, (AD, T = 0.0, p =.007; control, T = 22.5, p = .028). Finally, the AD group rated the social scenes as eliciting a greater level of detail than the non-social scenes (T = 26.0, p =.041). BvFTD patients did not rate their social constructions as any more vivid (p = .244), more detailed (p = .295), more difficult (p =.849), as evoking a greater sense of presence (p = .490), or as more similar to a previous memory (p = .062) than their non-social constructions.

Table 4.2. Mean and standard deviation of subjective ratings in social and non-social conditions

		bvFTD *M(SD)*	AD *M(SD)*	Controls *M(SD)*
Difficulty (1-5)	Non-Social	2.6 (1.2)	2.5 (0.6)	2.0 (0.8)
	Social	2.6 (1.1)	1.9 (0.7)	1.7 (0.8)
Vividness (1-5)	Non-Social	3.3 (0.9)	3.5 (0.5)	3.8 (0.9)
	Social	3.0 (0.72)	3.6 (0.8)	3.8 (1.0)
Level of Detail (1-5)	Non-Social	3.1 (0.7)	2.8 (0.6)	3.4 (0.6)
	Social	3.3 (0.8)	3.2 (0.9)	3.3 (0.9)
Sense of Presence (1-5)	Non-Social	3.4 (0.9)	3.7 (0.8)	4.0 (0.8)
	Social	3.6 (0.9)	3.9 (0.7)	4.0 (0.8)
Sense of being Alone (1-5)	Non-Social	1.8 (0.9)	1.9 (0.8)	1.4 (0.4)
	Social	3.3 (1.3)	4.2 (1.0)	4.1 (1.1)
Similar to Memory (0-5)	Non-Social	3.0 (1.1)	2.9 (1.2)	3.2 (1.0)
	Social	2.5 (0.9)	2.1 (0.5)	2.3 (0.8)

Notes. M = mean, *SD* = standard deviation. For all ratings higher scores = stronger perceived experience, i.e., greater difficulty; more vividness; richer detail; stronger sense of presence; with the exception of similarity to memory where *lower* scores = *more* similar to a previous memory.

4.2.5 Controlling for cognitive processes

Separate mixed ANCOVAs were performed to examine whether group differences in social construction persisted when controlling for response inhibition (Hayling test), executive function (TMT B-A), verbal episodic memory (RAVLT 30 minute), and social knowledge (SNQ Total). The significant group by condition interaction persisted when controlling for response inhibition, F (2, 43) = 3.54, p = .038, η_p^2 = .14, and social knowledge, F (2, 40) = 3.65, p = .035, η_p^2 = .15, but not when controlling for executive function, F (2, 38) = 2.97, p = .063, η_p^2 = .14, or verbal episodic memory, F (2, 45) = 1.45, p = .246, η_p^2 = .06. Bonferroni adjusted post hoc comparisons revealed

that the significant interaction when controlling for response inhibition was driven by the bvFTD group performing significantly worse than controls, irrespective of condition (p = .005), with disproportionately poor social, relative to non-social, performance (p = .004). When response inhibition was controlled, however, AD patients performed similarly to healthy controls on the construction task, irrespective of condition (p = .310), and again showed no significant difference between social and non-social scenes (p = .710). In contrast, the social knowledge interaction appeared to be driven by both patient groups performing significantly worse than control participants, irrespective of condition (AD p = .002; bvFTD p = .003), however, only the bvFTD group performed significantly worse on social, compared to non-social, constructions (bvFTD = p =.004, AD p = .904, controls, p = .436). No other group differences were significant (all $p \geq .05$).

4.3 Discussion

This study investigated the capacity for social versus non-social forms of mental construction in bvFTD, a degenerative disorder of the brain characterised by prominent changes in personality and socio-emotional function, attributable to early degeneration of the vmPFC. By manipulating the social content of the to-be-constructed scenes, a disproportionate deficit in social, relative to non-social, scene construction in bvFTD was revealed, supporting the hypothesis. This deficit persisted when controlling for response inhibition and social knowledge, yet was ameliorated when executive function and episodic memory were covaried in the analyses. These findings reveal social simulation as a potentially unique class of mental construction. Here, the implications from these findings in relation to the clinical profile of bvFTD and theoretical models of mental construction are considered.

4.3.1 Reduced social construction in bvFTD

The most striking finding of this study is the marked deficit in social, compared to non-social, scene construction in bvFTD, in line with the hypothesis and previous reports of impairments on a range of social tasks in this population (Henry, Phillips, & Hippel, 2014; Kumfor et al., 2014; Strikwerda-Brown et al., 2019; Marshall et al., 2019). Relative to controls, bvFTD patients generated impoverished social scenes, with significant impairments across all content subcategories. Within-group comparisons revealed that compared to non-social construction, bvFTD patients provided significantly fewer sensory descriptions, spatial references and unique entities in the social condition. This paucity of contextual details for social scenes occurred despite explicitly prompting participants to include details of what the people in the scene "may be doing or feeling", pointing to social cues reducing the salience of contextual detail in bvFTD. Interestingly, bvFTD patients provided comparable levels of entities present to controls during non-social construction, potentially reflecting an intact capacity to recruit relevant non-social information from semantic memory. Despite this capacity to populate non-social scenes with the appropriate elements (e.g., inanimate objects, animals), bvFTD patients were unable to harness the appropriate schema or conceptual knowledge when the cue was social in nature. The disproportionate impairment on social, relative to non-social, trials in bvFTD expands previous findings identifying fundamental deficits in scene generation in bvFTD (Chapter 3, Wilson et al., 2020a). Deficits in social construction in bvFTD appear to directly relate to the social nature of the to-be-simulated scene, complementing the impaired social function which is characteristic of this syndrome.

The process of social construction requires the curation, selection, and integration of additional social elements (i.e., people) into the spatial array. Moreover, some consideration of the thoughts,

feelings, and actions of those people is required, potentially requiring social inference or ToM. Given these additional demands, whether the social condition is inherently more demanding relative to non-social construction becomes an important question to address. Despite marked performance deficits in the social construction condition, bvFTD patients subjectively rated the vividness, level of detail, sense of presence, and level of difficulty comparably across conditions. Moreover, social scenes were self-reported by bvFTD patients as eliciting a stronger sense of being surrounded by people than the non-social scenes. These ratings suggest that on the subjective level, at least, bvFTD patients did not find the social condition more difficult than the non-social condition and successfully perceived the differences in social quality between the two cues. This indicates that the bvFTD group derived some sense of the need for social integration in the social construction trials, albeit demonstrating a reduced capacity to incorporate this increased social demand, relative to controls, within their scene descriptions.

4.3.2 Relatively preserved social construction in AD

Considering next the AD group, while overall performance on the scene construction task was impaired relative to controls, the provision of total contextual details was not found to differ across social and non-social scenes. Given previous findings of markedly compromised scene construction in AD (Irish et al., 2015; Wilson et al., 2020a), the comparable deficits across social and non-social conditions suggest a fundamental breakdown in the capacity to construct the foundational spatial array, irrespective of the nature of the scene contents. Despite this generic breakdown in scene construction, AD patients provided significantly more socio-emotional details in the social versus non-social condition, mirroring the control profile, albeit at a lower performance level. This suggests that in spite of a core impairment in the basic process of scene construction, AD patients adhered to the task instructions on social trials, and incorporated the

thoughts, emotions and actions of others in the scene. These findings resonate with a large body of work suggesting that socio-emotional processes including ToM, emotion recognition, and empathic concern remain relatively intact in AD until late into the disease course (Dermody et al., 2016; Irish, Hodges, & Piguet, 2014; Kumfor et al., 2014).

4.3.3 Cognitive mechanisms associated with social construction

Possible underlying mechanisms driving social construction impairments in bvFTD were also explored. Four cognitive domains previously implicated in social-cognitive processes were examined; executive dysfunction, response inhibition, social knowledge, and episodic memory (Ibanez & Manes, 2012; Laillier et al., 2019; Ramanan et al., 2017; Spreng & Mar, 2012). Previous research indicates bvFTD patients may have a specific difficulty in directing attention away from the external environment to initiate endogenous forms of spontaneous cognition (O'Callaghan, Shine, Hodges, Andrews-Hanna, & Irish, 2019). A reduced capacity to inhibit one's own perspective to consider the thoughts, emotions, and actions of individuals within social contexts has also been demonstrated in the context of ToM impairments (Le Bouc et al., 2012). Impaired response inhibition has further been proposed to contribute to reduced social knowledge in bvFTD (Baez, Garcia, & Ibanez, 2016; Ibanez & Manes, 2012). Controlling for response inhibition in the main analyses, however, did not ameliorate social construction deficits in the bvFTD group. Similarly, despite a large body of evidence pointing to marked social knowledge impairments in bvFTD, controlling for social knowledge on the SNQ did not ameliorate their social construction impairments.

In contrast, the group by condition interaction disappeared after controlling for executive function and verbal episodic memory. These findings, while preliminary, suggest that engaging in certain forms of social construction requires additional executive and episodic memory resources,

however, the precise nature of these contributions requires further concerted study. Of particular interest in this context is the observation that both AD and controls rated the social scenes as being more similar to a previous memory than non-social scenes. Speculatively, on social trials participants may defer to previous autobiographical experiences, extracting relevant social and affective details required to elevate a basic scene description to a socially-laden scenario. Within the context of comparable autobiographical memory deficits across dementia syndromes (Hornberger, Piguet, Graham et al., 2010), a reduced ability to delineate socially relevant information from past experiences in bvFTD may contribute to the construction of socio-emotionally impoverished scenes.

4.3.4 Social construction and broader social cognition

The identified association with episodic memory resonates well with recent studies suggesting a foundational role for episodic memory in prosocial intentions (Gaesser & Schacter, 2014) and socially-oriented behaviour in general (Spreng & Mar, 2012). By this view, the extraction of relevant information from personal experiences has been posited to facilitate the abstraction of social conceptual knowledge, which in turn, informs strategic social behaviour (Spreng & Mar, 2012). In this sense, predicting the best way to behave in a given situation likely involves extracting relevant information from past experiences, alongside person- and context-specific information, and applying this to the current situation. It is interesting therefore, that bvFTD patients did not report this increased reliance on autobiographical memory during social compared to non-social construction. Whether this reflects the well-documented impairments in autobiographical memory (Irish et al., 2011), or the canonical disruption to the self in this syndrome (Strikwerda-Brown, Grilli, et al., 2019; Wong et al., 2017) remains unclear and will be important to clarify in future studies.

4.3.5 Limitations and methodological considerations

A number of methodological issues warrant consideration in the current context. Social construction is inherently multifaceted, and, due to time constraints and the risk of fatigue in a clinical population, it was not possible to explore the potential relationship between social construction and related processes including ToM and schematic knowledge. The traditional lab-based memory task may also fail to capture the contextually rich and dynamic nature of episodic memory as related to scene construction. Finally, it remains unclear whether bvFTD patients experience additional difficulties in the explicit recovery and description of their constructed scenes, and it will be important to disentangle the role of narrative construction in this regard (Race et al., 2011).

4.3.6 Summary and implications for future studies

This study expands previous findings demonstrating a reduced capacity for scene construction in bvFTD (Chapter 3, Wilson et al., 2020a), revealing a disproportionate deficit in constructing socio-emotionally laden scenes, relative to non-social scenes. Considering the extensive role of the vmPFC in social processing, and the suggested importance of hippocampal-prefrontal networks in mental construction (Lieberman, Straccia, Meyer, Du, & Tan, 2019; McCormick et al., 2018; Verfaellie et al., 2019), future work examining the neural architecture of social construction will elucidate how the capacity to envisage social scenes may align with broader social-cognitive processes. Given that social simulation has been suggested to facilitate many aspects of human behaviour (Gaesser, Keeler, & Young, 2018), clinically, this study adds to current understanding of bvFTD and identifies social simulation as a potential variable of interest in relation to the profound social deficits seen in this syndrome (further explored in Chapter 6). Placed within the broader literature, these findings also provide an important development in understanding the

cognitive architecture of mental construction, and the cognitive processes subtending it, and give rise to the possibility of further classes of scene construction dependent on the nature of the stimuli, for example, familiarity. The reliance on past experiences in populating hypothetical scenarios (Schacter et al., 2007), particularly when envisaging social scenes, raises the question whether less familiar scene cues may evoke differential task performance across dementia syndromes, explored further in Chapter 5.

5

Putting the Pieces Together: Incongruent Scene Construction

Previous Chapters revealed bvFTD patients demonstrate a reduced capacity to envisage richly detailed atemporal everyday scenes (Chapter 3, Wilson et al., 2020a), which is disproportionately disrupted in the construction of social, versus non-social scenes (Chapter 4, Wilson et al., 2020b). These findings converge with previously identified deficits in a range of constructive endeavours in bvFTD and AD (Irish, Hodges, Piguet, 2013; Irish & Piolino, 2016) and highlight the need to further explore the complex cognitive architecture of mental imagery across these dementia syndromes. Given the strong association between episodic memory and scene construction previously identified (Hassabis & Maguire, 2007; Maguire et al., 2016), particularly in regards to social construction (Chapter 4, Wilson et al., 2020b), this chapter investigates how different scene cues modulate the recruitment of past experiences and increase semantic load.

As previously reviewed (Chapter 1), extensive evidence now supports the capacity to envisage richly detailed, spatially cohesive mental scenarios as being associated with a range of multifaceted cognitive processes, including autobiographical memory (Hebscher et al., 2017), future thinking (Palombo et al., 2018), navigation (Lind, Williams, Raber, Peel, & Bowler, 2013), and ToM (Gaesser, 2020). The complexity of generating and maintaining this spatially cohesive scene is reflected in neuroimaging studies demonstrating a distributed core construction network centred on the hippocampus (Hassabis, Kumaran, Vann, et al., 2007; Mullally, Hassabis, et al., 2012; Zeidman & Maguire, 2016), with right hippocampal contributions particularly identified as

subtending scene construction deficits in bvFTD (Chapter 3, Wilson et. al., 2020a). Posterior parietal regions, including the retrosplenial cortex (Auger, Zeidman, & Maguire, 2017; Dalton & Maguire, 2017), angular gyrus (Ramanan, Piguet, & Irish, 2018; Summerfield, Hassabis, & Maguire, 2010), and lateral temporal cortices (Benoit & Schacter, 2015) have also been identified in supporting the generation of mental scenes.

Following on from Chapter 4, clinical and neuroimaging studies also reveal considerable prefrontal contributions to mental construction, including deficits found in patients with prefrontal lesions, thereby reflecting the prominence of these regions for mental constructive processes (Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016; McCormick, Ciaramelli, De Luca, & Maguire, 2018). Importantly, for the purposes of this Chapter, the neural underpinnings of imagery-based aspects of scene generation appear to particularly involve the ventromedial prefrontal cortex (vmPFC), suggested to be due to its connectivity with the hippocampus (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). However, the integrative aspects of mental construction, in other words, the incorporation of multiple scene elements, have been reported to more heavily recruit the dorsolateral prefrontal cortex (dlPFC) (Summerfield et al., 2010). This is consistent with dlPFC activity being particularly involved in relational processing, in other words, forming associations between items (Blumenfeld, Parks, Yonelinas, & Ranganath, 2011), and executive control (Seeley et al., 2007). Hippocampal contributions to semantic relational processing, that is, identifying common meaning between elements, even when unrelated, also point to the importance of relational processing in the integration of discrete stimuli (Keane, Bousquet, Wank, & Verfaellie, 2020). Relational processing has been proposed to complement the generation of complex mental imagery by incorporating inter-item relationships within a spatial context (Eichenbaum & Cohen, 2014). These findings support scene construction as a highly dynamic process requiring both

generation and maintenance and speak to the importance of interacting and integrative aspects of cognition in constructing hypothetical scenarios.

The multifaceted nature of scene generation is also reflected in the interrelationship between semantic and episodic processes in autobiographical memory. Previous reports demonstrate a significant negative relationship between the number of non-specific or general details (semantic or "external" details) and the number of details specifically linked to the episode being recalled (episodic or "internal" details) (Devitt, Addis, & Schacter, 2017). In this sense, episodic information may be used more as a way of enriching scenarios which inherently support drawing upon previous experience, rather than serving as the foundational structure upon which the scene is constructed (Devitt et al., 2017). Indeed, decreasing the ease with which episodic experiences can be recruited results in a greater reliance on semantic detail. Addis et al (2010) demonstrated this by asking healthy older adults to recombine multiple previous experiences into a single hypothetical scenario, with greater recombination leading to reduced episodic and increased semantic detail. The interplay between episodic and semantic processes is supported by evidence from clinical populations. Individuals with semantic dementia, a neurodegenerative disease affecting the medial temporal lobes resulting in profound semantic deficits yet relatively preserved episodic memory, display a reduced capacity for constructing future scenarios comparable to that seen in Alzheimer's disease (Irish, Addis, et al., 2012a,b). This indicates that both semantic and episodic processes appear to be necessary in the generation of rich mental imagery. Nonetheless, how the nature of the envisaged scene may influence the relative contributions from each of these cognitive processes remains relatively unexplored.

In what way information is perceived and processed depends on the extent to which that information conforms to pre-existing knowledge. Rather than existing in isolation, the information

we garner from our experiences in the world is organised into overriding knowledge structures drawn from the commonalities of past events, known as schemas (Ghosh & Gilboa, 2014). These knowledge structures provide a cognitive framework, influencing how we perceive and interpret incoming information (Gilboa & Marlatte, 2017). The neurobiology of schema networks heavily overlaps with regions associated with scene construction, centred largely on the vmPFC and the hippocampus (Spalding et al., 2015). Indeed, schemas have been suggested to play a pivotal role in mental construction, providing the necessary framework from which a scene can be created (Ciaramelli, De Luca, Monk, McCormick, & Maguire, 2019; Irish & Piguet, 2013). The integration of new information which is congruent with existing knowledge appears to rely heavily on the vmPFC, while information which is novel or incongruent appears to be primarily processed by medial temporal regions of the brain (Van Kesteren, Ruiter, Fernández, & Henson, 2012).

The capacity to integrate social information is also central to scene processing, with vmPFC regions previously shown to exhibit increased activation in response to scenes containing people, relative to empty scenes (Hassabis et al., 2014). This is consistent with the vmPFC being extensively associated with an array of socio-emotional processes, including social knowledge, social perception, and decision making (for an overview see Adolphs, 2009), in addition to playing an important role in autobiographical memory and self-referential processing (Lin, Horner, & Burgess, 2016). As demonstrated by the previous study (see Chapter 4), the integration of social information into constructed scenes may serve as an additional layer of cognitive complexity which is disproportionately impacted by the deterioration of prefrontal regions (Wilson et al., 2020b).

bvFTD provides a unique opportunity to unpack the integrative aspects of scene construction due to the characteristic profile of primarily prefrontal - principally medial prefrontal early on - and

anterior temporal lobe atrophy (Landin-Romero et al., 2017; Rosen et al., 2002) in the context of associated hippocampal driven scene construcion deficits (Chapter 3, Wilson et al., 2020a). Patients with bvFTD also exhibit significant disturbances in the capacity to appropriately integrate contextual information, particularly social information (Ibanez & Manes, 2012), and reduced cognitive flexibility (Eslinger et al., 2007; Kumfor, Ibañez, et al., 2018; Paulin et al., 2020). Findings from the previous studies (see Chapters 3 and 4) revealed significant impairments in the fundamental process of scene construction (Wilson et al., 2020a) and social construction (Wilson et al., 2020b) in bvFTD. It remains unclear, however, how the cognitive and neurobiological profiles characteristic to this disorder affect the construction of incongruent scenes which inherently increase the integrative load of the construction.

The objectives of this study were to explore the capacity for incongruent scene construction, that is, scenes comprising elements which typically do not go together, across dementia syndromes in order to further elucidate episodic and semantic contributions to the generation of mental scenes. Following on from previous findings indicating differential task performance in bvFTD across social and non-social construction (Wilson et al., 2020b), two conditions were manipulated - sociality and congruence. Consistent with previous findings indicating increased integrative load results in more impoverished autobiographical memory descriptions (Addis et al., 2010), it was hypothesised that incongruent scenes would evoke less contextually rich scene descriptions than congruent scenes in the two patient groups relative to controls. Further, due to the increased socio-emotional complexity in the generation of social scenes, it was hypothesised that bvFTD, but not AD or controls, would produce more impoverished social scene descriptions relative to non-social scenes, complementing previous findings (Chapter 4). Finally, given both incongruent and social construction may potentially rely more heavily on the vmPFC due to its contribution to both

knowledge integration (Spalding et al., 2015) and social processing (Adolphs, 2009), it was hypothesised that bvFTD patients would demonstrate the greatest impairment in the construction of incongruent social scenes relative to all other conditions.

5.1 Materials and Methods

5.1.1 Participants

A total of 50 participants were recruited through FRONTIER, the frontotemporal dementia research group based at the Brain and Mind Centre, The University of Sydney. Fifteen individuals with a clinical diagnosis of probable bvFTD and 11 individuals with typical Alzheimer's disease (AD) were contrasted with 16 healthy older control participants. Four bvFTD patients were excluded due to achieving an ACE-III score greater than 88 (see Chapter 2 section 2.1), one due to language difficulties, and one due to the task being discontinued. Two AD patients were excluded, one due to soring an ACE-III of 90 and one due to becoming confused during the assessment. Further details regarding participant recruitment, inclusion and exclusion criteria and clinical criteria used to establish dementia diagnosis are outlined in Chapter 2 section 2.1.

5.1.2 Cognitive assessment

Following the procedures outlined in Chapter 2 section 2.3, participants completed a comprehensive neuropsychological battery assessing the main cognitive domains. The primary variables of interest in the current study included measures of verbal (RAVLT 30 minute, Schmidt, 1996) and visuospatial (RCF 3 minute, Meyers & Meyers, 1995; Rey, 1941) episodic memory, semantic association and naming (SydBat, Savage et al., 2013), and response inhibition (Hayling sentence completion task, Burgess & Shallice, 1997).

5.1.3 Scene construction task

Following on from the scene construction task (Hassabis et al., 2007) outlined in the general method section (Chapter 2 section 2.5) and the previous two chapters, the scene construction task was again modified to include an additional Congruent/Incongruent condition. Scenes were selected following pilot testing where 10 healthy adults rated various combinations of scene-object and scene-person elements on a seven-point scale according to, "How much do these two things go together?" Higher scores reflected greater congruence and lower scores greater incongruence. The two pairs with the highest and lowest scores were selected for the congruent scenes (Hospital and Doctor; Classroom and Books, both $M = 7.00$, $SD = 0.00$) and incongruent scenes (Funeral and Clown; Beach and Ice-Skates, both $M = 1.00$, $SD = 0.00$).

In keeping with the original scene construction protocol (Hassabis et al, 2007) and the social construction procedure (Wilson et al, 2020b) outlined in Chapters 3 and 4, participants were instructed to imagine and describe aloud atemporal scenes in as much detail as possible, avoiding restating a memory. Participants were informed that each scene cue would contain a background setting and a person or object. These instructions differed from the original scene construction task in the use of a more succinct cue which was standardised in syntactic structure, unlike the original cues which set the scene through more extensive narrative descriptions (Chapter 3 section 3.1.3). Scene cues contained two parts, a background setting and a person or object and participants were instructed to make sure to include both elements into the scene description, "Even if the two things don't feel like they belong together at all, I want you to try really hard to create as believable a scenario as possible including both the background setting and the person or object." All scene cues followed the same syntax structure, for example, "You're at a funeral. There is a clown there. Make sure to include the clown into the funeral scene you describe." An example incongruent

scene was then provided (Office Boardroom and Hairdryer) whereby the experimenter confirmed with the participant that the two example elements did not go together but then pretended to complete the task while reciting a standardised scene description (an example of a scene and prompting instructions are presented in Appendix A). Cues were read aloud and presented on a sheet of paper (with the two scene elements in bold text) which remained in front of participants for the duration of the trial to minimise working memory demands.

A total of four scenes were included and each scene trial was limited to two minutes to reduce the potential confound of fatigue in people with dementia. To minimise cognitive demand in patients, Congruent and Incongruent trials were completed in a blocked design, with order of Congruent/Incongruent blocks counterbalanced across participants. General prompts were provided to encourage elaboration or if the participant failed to include the two scene elements. Importantly, these prompts were non-directive, limited to two prompts per scene and merely served to encourage the participant to provide additional details, for example, "Remembering to include both the X and the Y in the scenario that you're describing, are there any other details you can tell me?" The entire test session lasted approximately 25-30 minutes and was digitally recorded for subsequent transcription and scoring.

Subjective ratings

In keeping with the original Hassabis et al (2007) protocol and Chapters 3 and 4, following each scene description, participants were asked to rate each scene in accordance with their perceived experience in relation to the difficulty, vividness, level of detail, sense of presence, and similarity to a previous memory (see Chapter 2 section 2.5). An additional rating was included to capture the degree to which the two elements were realistically integrated into a coherence scene, "How

realistic did the scene feel to you?", rated on a scale from 1-5 with higher ratings indicating a stronger sense of realism.

Scoring

A modified version of the scene construction scoring protocol outlined by Hassabis et al. (2007) and introduced in Chapters 3 and 4 was used to score the scene transcripts in accordance with four types of contextual detail: (i) Entities Present (ii) Sensory Descriptions (iii) Spatial References, and (iv) Thoughts/Emotions/Actions. The maximum number of details for each subcategory was capped at 7 points leading to a maximum Total Content Score of 28, in keeping with the original scoring protocol (Hassabis et al., 2007). Due to the Spatial Coherence Index (see Chapter 3 section 3.1.3) being excluded from the study protocol, the full Experiential Index could not be calculated, therefore, Total Content scores are used as the primary measure of scene construction performance.

For incongruent scenes, an integration and immersion score was created to measure the degree to which the two elements were successfully incorporated *into the scene*. A three-point scale was used whereby (0) denoted little or no integration of the two elements, (1) the two items were integrated in the narrative but lacked a sense of immersion *within the overall scene*, and (2) the two elements were richly integrated both within the narrative *and* the overall envisaged scene, in other words, integration *and* immersion. A subset of the data (n = 12 scenes) scored by an independent rater blind to study hypotheses demonstrated high inter-rater reliability (Cronbach's alpha = .85). All transcripts were scored blind to group membership.

5.1.4 Statistical analyses

Data were analysed using IBM SPSS version 26. For continuous variables, normality of distributions was examined using Kolmogorov-Smirnov tests. Group differences for normally

distributed continuous variables (e.g., age at assessment, years of education) were assessed using univariate ANOVAs. Group differences on categorical variables (e.g., sex) were examined using Chi-squared tests. Where limited cognitive data resulted in small and uneven sample sizes, or data were non-normally distributed (e.g., participant subjective ratings, TEA subcomponents, integration and immersion scores) non-parametric Kruskal-Wallis tests for independent samples and Wilcoxon signed-rank tests for related samples were used. Group differences on the scene construction task were assessed via a mixed 3 x 2 x 2 ANOVA with group (control, AD, bvFTD) as the between-subjects factor, and sociality (social, non-social) and congruency (congruent, incongruent) as the within-subjects factors. For ease of interpretation, and due to no main effect of congruency being found, two mixed 3 x 2 x 4 ANOVAs were then performed in the incongruent and congruent conditions separately with group as the between-subjects factor, sociality and contextual detail category (Entities Present, Sensory Descriptions, Spatial References and Thoughts/Emotions/Actions) as the within-subjects factors. To further break down the Thoughts/Emotions/Actions category, the number of thoughts, emotions and actions was summed for each scene and divided by the individual's total raw TEA score before being multiplied by 100 to create a percentage score. Post hoc comparisons were adjusted using Bonferroni correction where appropriate, however, due to the exploratory nature of the study, where extensive comparisons would have resulted in overly conservative Bonferroni correction (e.g. subjective ratings, correlations with cognitive variables) uncorrected values are reported. The alpha level to determine statistical significance was set at $p < .05$. Partial eta-squared values (η_p^2) were assessed as a measure of effect size for ANOVA statistics.

5.2 Results

5.2.1 Demographic and clinical information

Age at assessment, F (2, 39) = 1.0; p = .393; η_p^2 = .05, and sex distribution, χ^2 (2, 42) = 5.15; p = .076, did not significantly differ across control, AD and bvFTD groups (Table 5.1). A significant group effect was shown for years of education, F (2, 38) = 8.03; p = .001; η_p^2 = .30. Post hoc tests indicated this reflected the higher levels of education in controls relative to the two dementia syndromes (both p values ≤ .038), however, the two patient groups were comparable (p =.707). Controlling for years of education in the main analysis failed to alter the findings therefore, education was not considered further. Disease severity, as measured by the CDR-FTLD Sum of Boxes score, t (24) = 0.67, p = .509, and disease duration (years from symptom onset), t (21) = 1.57, p = .131, were also similar between the two patient groups. Finally, a significant group effect was evident regarding overall behavioural change (CBI-R), F (2, 36) = 21.32; $p \leq .0001$; η_p^2 = .54. Post hoc comparisons indicated ratings between patient groups were similar (p = .517); however, the two patient groups demonstrated substantial behavioural changes in comparison to control participants (both p values ≤ .0001). Examining the abnormal behaviour sub-test of the CBI-R revealed a significant group effect, F (2, 36) = 14.23; $p \leq .0001$; η_p^2 = .44, with post hoc tests showing both patient groups were again rated as exhibiting significantly greater abnormal behaviour than controls (both p values ≤ .022). More substantial abnormal behaviour was also found in the bvFTD, relative to AD, group (p = .046).

Table 5.1. Demographics and clinical characteristics of study participants

	bvFTD *M(SD)*	AD *M(SD)*	Controls *M(SD)*	Group Effect (*F* value)	Post hoc (direction of effect)
N	15	11	16	-	-
Sex (M:F)	13:2	6:5	8:8	5.15 [a]	-
Age (years)	61.40 (9.1)	64.73 (8.4)	64.69 (4.4)	0.96	-
Education (years)	11.72 (2.1)	12.59 (2.6)	14.93 (2.2)	8.03**	CN > AD, bvFTD
Disease duration (years)	6.71 (3.5)	4.56 (2.8)	-	0.67 [b]	-
Disease severity (CDR-FTLD SoB)	6.33 (3.8)	6.77 (3.3)	-	1.57[b]	-
Behavioural change (CBI-R Total)	38.48 (16.7)	30.86 (17.1)	4.96 (4.0)	21.32***	CN < AD, bvFTD
Abnormal Behaviour (CBI-R Sub-scale)	40.56 (22.2)	20.83 (22.7)	3.21 (4.2)	14.23***	CN < AD < bvFTD

Notes. [a]Chi-square value. [b]Independent samples *t*-test. *M* = mean, *SD* = standard deviation. Corrected post hoc comparisons are reported. ** = $p < .01$, *** = $p < .0001$. bvFTD = behavioural-variant frontotemporal dementia; AD = Alzheimer's disease CN = Controls; CDR-FTLD SoB = Clinical Dementia Rating – Frontotemporal Lobar Degeneration Sum of Boxes; CBI-R = Cambridge Behavioural Inventory – Revised. Years of Education data unavailable for 1 control.

5.2.2 Cognitive profiles

Relative to control participants, bvFTD and AD patients displayed characteristic cognitive deficits largely in keeping with their clinical diagnoses (Table 5.2). Significant group effects emerged in attention and executive function, Digit Span Forwards, H (2) = 18.60, p = .007, Digit Span Backwards, H (2) = 14.12, p = .001, Hayling, H (2) = 9.83, $p \leq .0001$, and TMT B-A, H (2) = 11.37, p = .003. Examining verbal H (2) = 26.90, $p \leq .0001$ and visuospatial, H (2) = 18.53, $p \leq .0001$, delayed episodic memory also revealed significant group effects; as did overall language, H (2) = 18.14, $p \leq .0001$, semantic association, H (2) = 18.80, $p \leq .0001$, and naming H (2) = 15.98,

$p \leq .0001$. Verbal fluency also significantly differed between the three groups, $H(2) = 19.01$, $p \leq .0001$.

Post hoc comparisons revealed, bvFTD and AD patients exhibited deficits in executive function (Hayling, bvFTD, $p = .013$, AD, $p \leq .0001$; Digit Span Backwards, bvFTD, $p = .039$, AD, $p = .001$), verbal episodic memory (RAVLT 30 minute, bvFTD, $p = .001$, AD, $p = <.0001$), and verbal fluency (bvFTD, $p = .001$, AD, $p \leq .0001$). The AD, but not bvFTD, group also demonstrated marked visuospatial episodic memory dysfunction (RCF 3 minute, bvFTD, $p = .504$, AD, $p = <.0001$), significantly reduced capacity for attention (Digit Span Forwards, bvFTD, $p = .089$, AD, $p = .007$) and divided attention (TMT B-A, bvFTD, $p = .159$, AD, $p = .003$), relative to control participants. Both patient groups showed significant deficits in overall language ability relative to controls (ACE Language, bvFTD, $p = .006$, AD, $p \leq .0001$). A significantly reduced capacity for semantic association (bvFTD, $p = .243$, AD, $p = <.0001$) and naming (bvFTD, $p = .145$, AD, $p = <.0001$) in comparison to controls, however, were only evident in the AD group following correction for multiple comparisons. Disproportionate deficits in visuospatial episodic memory were found in the AD group, relative to the bvFTD group (p .005) and a trend towards a significant difference in semantic association which failed to survive correction ($p = .078$). No other significant differences were evident between the patient groups (all p values $\geq .10$), likely due to small sample sizes and the cognitively demanding nature of the task possibly resulting in a relatively high-functioning patient population despite adhering to diagnostic criteria.

Table 5.2. Descriptive statistics and group differences in cognitive profile

	bvFTD *M(SD)*	AD *M(SD)*	Controls *M(SD)*	Group Effect (*H*)	Post hoc (direction of effect)
ACE-III Total (100)	77.7 (6.5)	64.8 (9.8)	95.3 (2.5)	32.80**	CN > AD, bvFTD
RAVLT 30-mins (15)	5.2 (2.8)	1.1 (1.7)	10.8 (1.7)	26.90**	CN > AD, bvFTD
RCF 3-mins (36)	13.2 (6.7)	2.4 (2.0)	16.6 (4.2)	18.53**	CN > AD; bvFTD > AD
Hayling overall (7)	4.9 (1.3)	3.6 (0.8)	6.3 (0.7)	18.60**	CN > AD, bvFTD
Digit Span Forwards	8.9 (2.3)	7.9 (0.7)	11.3 (2.8)	9.83*	CN > AD
Digit Span Backwards	5.1 (2.0)	3.7 (1.8)	8.3 (3.0)	14.12*	CN > AD, bvFTD
TMT B-A (seconds)	82.3 (56.7)	142.2 (74.2)	45.7 (14.9)	11.37*	CN < AD
SydBat Naming (30)	24.1 (2.3)	19.6 (4.9)	27.1 (2.3)	15.98**	CN > AD
SydBat Semantic (30)	27.0 (2.0)	24.3 (2.3)	28.6 (1.0)	18.80**	CN > AD
ACE-Language (26)	23.3 (2.5)	21.7 (2.8)	25.5 (0.8)	18.14**	CN > AD, bvFTD
ACE-Fluency (14)	8.6 (2.3)	8.0 (2.6)	11.9 (1.6)	19.01**	CN > AD, bvFTD

Notes. Maximum test scores shown in brackets where appropriate. *M* = mean. *SD* = standard deviation. Corrected post hoc comparisons shown. * = p <.01, ** = p <.0001. bvFTD = behavioural-variant frontotemporal dementia; AD = Alzheimer's disease, CN = Controls; ACE-III = Addenbrooke's Cognitive Examination – Third Edition; RAVLT = Rey Auditory Verbal Learning Test; RCF = Rey Complex Figure; Hayling overall scaled score; TMT B-A = Trail Making Test - Time B minus Time A; SydBat = Sydney Language Battery. Data unavailable for the following tests: RAVLT: 2 CN, 4 AD; RCF: 2 CN, 3 AD; Hayling: 2 CN, 4 AD, 1 bvFTD; TMT B-A: 2 CN, 6 AD, 2 bvFTD.

5.2.3 Scene construction performance

A significant group effect was evident on the scene construction task, F (2, 39) = 53.04, $p \leq .0001$, η_p^2 = .73. Post hoc comparisons revealed the two patient groups performed significantly worse than control participants (both $p \leq .0001$); however, bvFTD and AD groups demonstrated similar performance (p =.481). A main effect of sociality, F (1, 39) = 18.58, $p \leq .0001$, η_p^2 = .32, was also present, with participants overall performing more poorly on social, relative to non-social, scenes ($p \leq .0001$). No main effect of congruence was found, F (1, 39) = 2.53, p = .120, η_p^2 = .06.

Pillai's trace revealed a significant three-way interaction, F (2, 39) = 3.52; p = .039, η_p^2 = .15, (Figure 5.1) showing the effect of sociality differed in incongruent and congruent conditions across the three groups. Post hoc comparisons for each level of congruency and sociality are reported. In the incongruent condition, both patient groups performed significantly better in the non-social, relative to social, condition (AD p = .002; bvFTD $p \leq .0001$). In the congruent condition, all three groups showed similar performance on social and non-social scenes (all p values ≥ .2). In the social and non-social conditions, the two patient groups performed significantly worse than controls at each level of congruency (all $p \leq .002$). Post hoc tests demonstrated group performance was similar between patient groups in the social congruent, non-social congruent and social incongruent conditions (all $p \geq .4$) but there was a trend towards the bvFTD group outperforming their AD counterparts in the non-social incongruent condition (p = .067).

A significant two-way group by sociality interaction, F (2, 39) = 9.00; p = .001; η_p^2 = .32, was also demonstrated. Post hoc tests showed bvFTD patients (but not AD patients or controls, both p values ≥.1) constructed significantly more detailed non-social, relative to social, scenes ($p \leq$ .0001). Finally, a significant sociality by congruence interaction was found, F (1, 39) = 23.03; $p \leq$ .0001, η_p^2 = .37, with post hoc comparisons indicating participants performed significantly better in the non-social, relative to the social, condition irrespective of group membership ($p \leq .0001$). No significant group by congruence interaction was found, F (2, 39) = 0.14; p = .870; η_p^2 = .01.

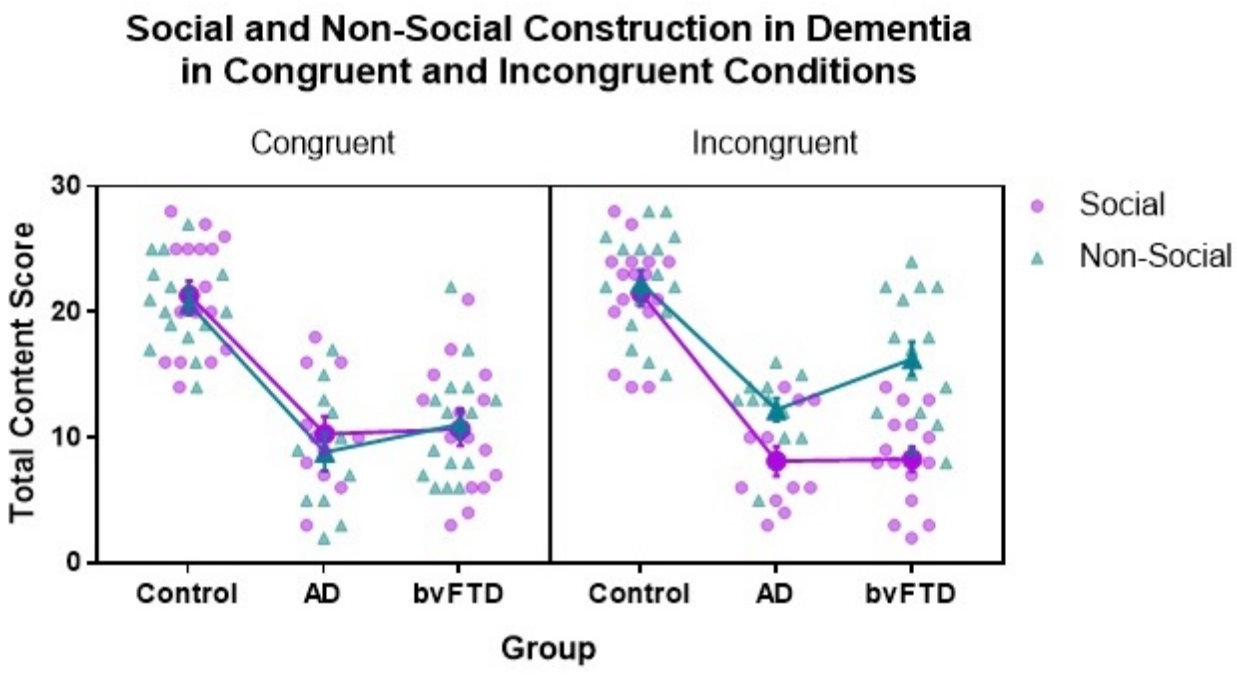

Figure 5.1. Group performance on social and non-social scene construction in congruent and incongruent conditions. Interaction based on estimated marginal means of average content score (max 28) with whiskers representing standard error of measurement. Data points show individual scores. AD = Alzheimer's disease. bvFTD = behavioural-variant frontotemporal dementia.

Contextual detail profile

For ease of interpretation, and given the group differences in performance across conditions identified above, two mixed 2 x 4 x 3 ANOVAs were performed in incongruent and congruent conditions separately to examine differences in contextual detail in social and non-social conditions across the three groups. Main effects, interactions and post hoc comparisons are reported for incongruent and congruent analyses.

In the incongruent condition, a significant group effect was found, F (2, 39) = 42.68; $p \leq .0001$, η_p^2 = .69. Both patient groups performed significantly worse on the scene construction task than control participants (both $p \leq .0001$), however, performance was similar between patient groups

(p = .358). A significant main effect for sociality was also evident, F (1, 39) = 46.46; $p \leq .0001$; η_p^2 = .54, where participants produced significantly more detail in non-social, relative to social, scenes ($p \leq .0001$), irrespective of content category and group membership. Finally, a significant main effect for content detail was found, F (3, 37) = 4.54; p = .008; η_p^2 = .27. Relative to the other content categories, participants produced significantly more unique entities than sensory details (p =.022) and spatial references (p =.016).

No significant three-way interaction was found in the incongruent condition, F (6, 76) = 1.58; p =.166; η_p^2 = .11. However, due to a relatively low observed power (β = .55), post hoc comparisons were included but should therefore be interpreted with caution. The bvFTD group performed significantly better in the non-social, relative to social, condition across all four content categories (all p values ≤ .001). AD and control groups produced significantly more spatial references in the non-social, relative to social, condition (AD, $p \leq .0001$, control, p = .049). In the entities present category, controls produced significantly more entities in the social, relative to non-social condition (p =.007) but no difference emerged in the AD group (p = .368). No other post hoc comparisons were significant (all p values ≥ .2). Two significant two-way interactions were also revealed. A significant sociality by group interaction, F (2, 39) = 12.67; $p \leq .0001$, η_p^2 = .39, showed that, irrespective of content category, both patient groups performed significantly better in the non-social, relative to social, condition (AD, p = .002; bvFTD, $p \leq .0001$; Figure 5.2), whereas no significant difference emerged in the control group (p = .419). Finally, a sociality by content detail interaction, F (3, 37) = 6.75; p =.001; η_p^2 = .35, demonstrated more sensory descriptions, spatial references and thoughts, emotions and actions (but not entities present, p = .271) were provided in the non-social, relative to social, conditions irrespective of group membership (all p values ≤ .004).

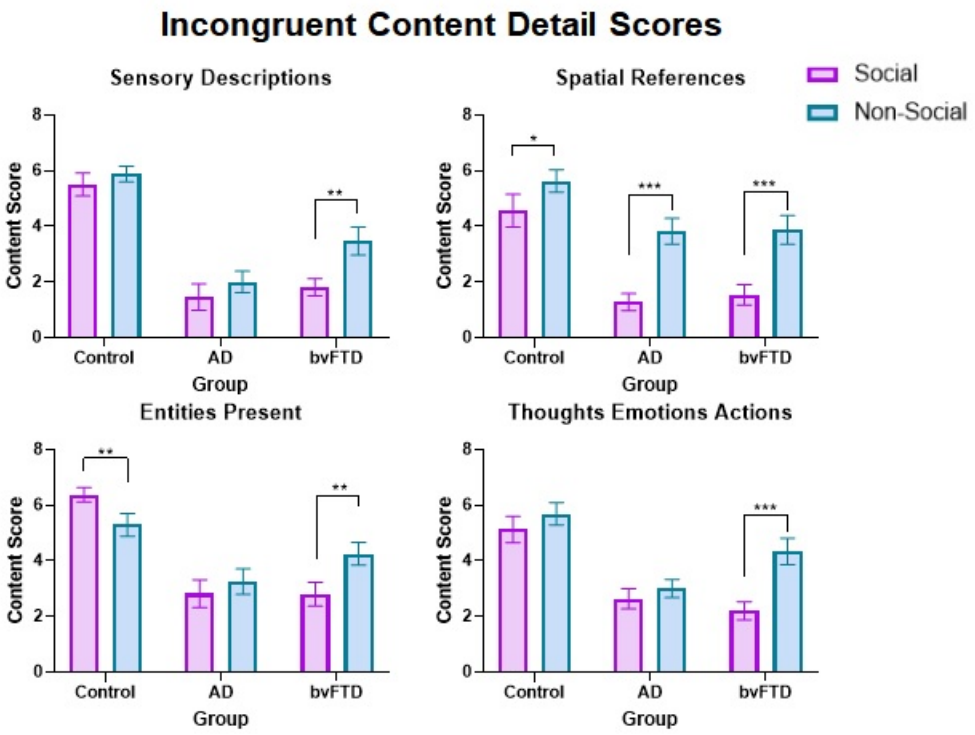

Figure 5.2. Mean social and non-social scene construction contextual detail scores in the incongruent condition. Whiskers represent standard error of measurement. Post hoc significant tests should be interpreted with caution due to the failure to find a significant three way interaction (see section 5.2.3). AD = Alzheimer's disease. bvFTD = behavioural variant of frontotemporal dementia. * = p <.05, ** = p <.01 *** = $p \leq .0001$.

In the congruent condition, a significant group effect was demonstrated, F (2, 39) = 36.19; $p \leq .0001$; η_p^2 = .65. Both patient groups performed significantly worse than control participants on the scene construction task (both p values ≤ .0001), while performance between patient groups was comparable (p = .799). No significant main effect for sociality emerged, F (1, 39) = 0.67; p = .417; η_p^2 = .02; however, a significant main effect for content detail was found, F (3, 37) = 9.92; $p \leq .0001$; η_p^2 = .45. Post hoc comparisons showed that, relative to the other content categories,

participants produced significantly more sensory details than spatial references (p = .024) or thoughts emotions and actions (p =.007), and more unique entities than spatial references (p =.008).

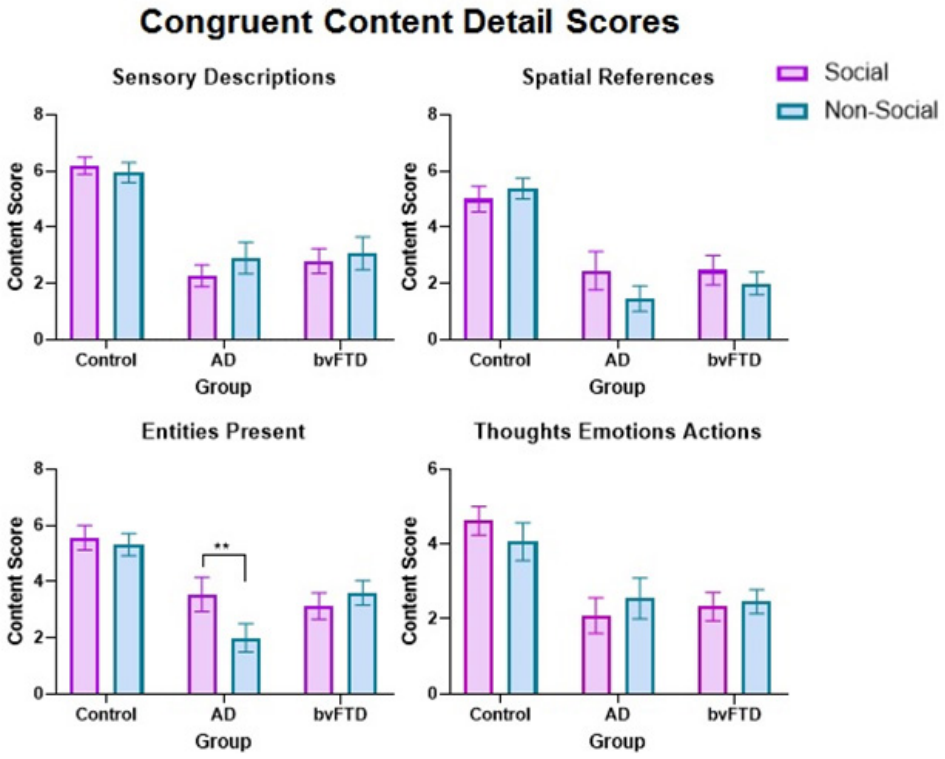

Figure 5.3. Mean social and non-social scene construction contextual detail scores in the congruent condition. Whiskers represent standard error of measurement. AD = Alzheimer's disease. bvFTD = behavioural variant of frontotemporal dementia. ** = p <.01.

A significant three-way interaction was found in the congruent condition, F (6, 76) = 2.63; p = .023; η_p^2 = .17, β =.83. Post hoc tests showed AD patients provided significantly fewer entities present in the non-social, relative to the social, condition (p = .009), in addition to a trend towards a significant difference in the spatial references category (p = .055, Figure 5.3). No other

significant differences in content scores were present between social and non-social conditions in any of the groups (all *p* values ≥ .2). None of the two-way interactions were significant: sociality by group, F (2, 39) = 0.55; p = .579; η_p^2 = .03, sociality by content detail, F (3, 37) = 1.09; p = .364; η_p^2 = .08, content detail by group, F (6, 76) = 1.39; p = .230; η_p^2 = .10.

Differences in thoughts, emotions, and actions sub-components

To further examine the characteristics which may be driving the identified contextual detail interaction effects, the Thoughts, Emotions and Actions category was further broken down into its subcomponents (Table 5.3). Independent sample Kruskal-Wallis tests revealed a significant group effect in the percentage of thoughts provided in the non-social, H (2) = 7.04, p = .030, and social, H (2) = 9.11, p = .011, congruent conditions, as well as the percentage of emotions in the social incongruent condition, H (2) = 6.05, p = .049. A significant group effect also emerged in the action category of the non-social incongruent condition, H (2) = 6.84, p = .033. No other significant group effects emerged (all p values ≥ .16).

Bonferroni adjusted comparisons revealed fewer thought based references were evident in the AD group, relative to controls, in the non-social congruent scene (p =.042). Conversely, in the social congruent scene, fewer thought based references were provided by the bvFTD group, relative to controls (p = .004). Examining the emotional content of the scenes, bvFTD patients provided fewer emotional references compared to controls in the incongruent social scene (p = .045). Despite a trend in mean scores, no significant difference in emotion was found in AD relative to bvFTD (p =.425) or controls (p = 1.00). bvFTD patients also provided significantly more action based references than control participants in the non-social incongruent scene (p = .030). Mean percentage scores also pointed towards a slight numerical trend in increased action references in

the AD group relative to controls, however, this failed to reach significance (p =.356) as did the difference between patient groups (p = 1.00). No other significant between group differences emerged (all p values ≥ .07).

Considering next the within group differences, Wilcoxon Signed Rank tests revealed control participants provided significantly more thought-based references in the non-social, relative to social, incongruent condition (p =.05). No other significant group differences were found in the percentage of thoughts between social and non-social scenes (all $p \geq .1$). Significantly less emotional context was provided by all three groups in the non-social, relative to social, incongruent condition (all p values ≤ .03), but not the congruent condition (all $p \geq .07$). Finally, bvFTD (p = .001), AD (p = .049), and control participants ($p \leq .0001$) all provided a significantly greater proportion of action details in the incongruent non-social, relative to social, condition. No difference in action content was found in the congruent condition (all p values ≥ .2).

Table 5.3. Mean percentage of thoughts, emotions and actions for each scene

			bvFTD % Score	AD % Score	Controls % Score
Congruent	Social	Thoughts	.00	.02	.12
		Emotions	.18	.17	.18
		Actions	.82	.81	.70
	Non-Social	Thoughts	.13	.00	.17
		Emotions	.09	.18	.09
		Actions	.78	.82	.74
Incongruent	Social	Thoughts	.22	.00	.03
		Emotions	.33	.49	.56
		Actions	.45	.51	.41
	Non-Social	Thoughts	.01	.04	.08
		Emotions	.02	.10	.10
		Actions	.97	.86	.82

Notes. Percentage score calculated as the number of thoughts, emotions and actions divided by the total raw TEA score for each scene * 100. bvFTD = behavioural-variant frontotemporal dementia; AD = Alzheimer‘s disease.

Integration and Immersion Score

Independent samples Kruskal-Wallis tests revealed significant differences were found across the three groups in the capacity to cohesively integrate and immerse the two elements into the envisaged scene in the social, H (2) = 16.73, $p \leq .0001$, and non-social, H (2) = 13.12, $p = .001$, conditions. In the social condition, Bonferroni adjusted post hoc comparisons revealed both bvFTD ($M = 1.07$, $SD = 0.70$, $p = .043$) and AD ($M = 0.45$, $SD = 0.69$, $p \leq .0001$) groups were significantly poorer at integrating the scene elements relative to control participants ($M = 1.75$, $SD = 0.58$). Similarly, in the non-social condition, bvFTD ($M = 1.00$, $SD = 0.84$, $p = .044$) and AD ($M = 0.55$, $SD = 0.82$, $p = .001$) patients produced scenes which comparatively lacked integration

compared to controls (M = 1.75, SD = 0.58). Wilcoxon Signed Rank tests failed to reveal any within group differences in integration between the social and non-social conditions (all p values = .7).

Participant subjective ratings

Two sets of Wilcoxon signed-rank tests were used to examine differences in subjective ratings across conditions within each group separately (Table 5.4). Due to the exploratory nature of the analysis, and the large number of comparisons, uncorrected values are reported. In the congruent condition, bvFTD patients rated the non-social congruent task as more difficult than the social congruent task (Z = -2.05, p = .040). In the incongruent condition, all groups reported comparable subjective experiences across social and non-social conditions (all p values ≥ .06), however, a trend towards greater self-reported detail in the non-social, relative to social, incongruent condition was evident in the bvFTD group (Z = -1.90, p = .058). Looking at differences across congruence, in the social condition, bvFTD (Z =-2.52, p = .012) and AD patients (Z = -2.23, p = .026) rated the congruent scenes as significantly more similar to a previous memory than the incongruent scenes. The bvFTD group also rated the incongruent task as more difficult than the congruent task (Z = -2.23, p = .026). In the non-social condition, all three groups rated the congruent scenes as significantly more similar to a previous memory than the incongruent scenes (bvFTD, Z = - 2.70, p = .007; AD, Z = - 2.23, p = .026, control, Z = - 2.72, p = .006). No other comparisons were significant (all p values ≥ .07).

Independent samples Kruskal-Wallis tests failed to reveal any significant differences between the three groups across average difficulty, vividness, level of detail, sense of presence, perceived realism of the scene or similarity to previous memory (all p values ≥ .19).

Table 5.4. Subjective ratings for each condition in participant groups.

			bvFTD *M(SD)*	AD *M(SD)*	Control *M(SD)*
Difficulty	Congruent	Social	2.1 (0.9)	2.5 (0.9)	2.2 (1.1)
		Non-Social	2.9 (1.1)	2.6 (1.1)	2.3 (0.9)
	Incongruent	Social	3.0 (1.1)	2.7 (1.0)	2.4 (1.0)
		Non-Social	2.7 (1.2)	3.4 (1.1)	2.6 (1.3)
Vividness	Congruent	Social	3.2 (0.9)	3.6 (0.7)	3.7 (0.8)
		Non-Social	3.1 (1.0)	3.5 (0.7)	3.6 (1.0)
	Incongruent	Social	3.1 (1.1)	3.1 (0.9)	3.6 (1.0)
		Non-Social	3.3 (1.0)	3.6 (0.9)	3.3 (1.1)
Level of Detail	Congruent	Social	3.3 (0.9)	2.9 (0.8)	3.4 (0.8)
		Non-Social	3.1 (1.0)	2.7 (0.8)	3.4 (0.8)
	Incongruent	Social	3.0 (1.1)	2.7 (0.6)	3.3 (0.8)
		Non-Social	3.4 (1.0)	2.9 (0.9)	3.0 (0.9)
Sense of Presence	Congruent	Social	3.5 (0.9)	4.0 (0.6)	3.9 (1.0)
		Non-Social	3.2 (1.1)	3.5 (0.8)	3.6 (1.1)
	Incongruent	Social	3.1 (1.1)	3.4 (0.9)	3.5 (1.1)
		Non-Social	3.3 (1.2)	3.9 (0.9)	3.4 (1.1)
Realism	Congruent	Social	3.1 (1.0)	3.1 (0.6)	3.3 (1.1)
		Non-Social	2.9 (0.9)	3.3 (0.9)	3.4 (1.0)
	Incongruent	Social	3.1 (1.1)	3.4 (0.9)	3.5 (1.1)
		Non-Social	3.3 (1.2)	3.9 (0.9)	3.4 (1.1)
Similar to Memory	Congruent	Social	2.8 (1.1)	2.6 (1.5)	3.3 (1.0)
		Non-Social	3.1 (1.3)	2.4 (0.8)	3.1 (1.1)
	Incongruent	Social	4.0 (1.0)	4.0 (1.1)	3.9 (1.4)
		Non-Social	4.3 (0.8)	3.8 (1.1)	4.1 (1.4)

Notes. M = mean. *SD* = standard deviation. For all ratings higher scores = stronger perceived experience, i.e. greater difficulty; more vividness; richer detail; more realistic; with the exception of similarity to memory where *lower* scores = *more* similar to a previous memory. bvFTD = behavioural variant frontotemporal dementia. AD = Alzheimer's disease.

5.2.4 Correlations between scene construction and selected cognitive variables

One-tailed Pearson correlations were run to explore potential associations between Total Content generated for each condition and poorer performance on selected measures of cognitive function. Due to small sample sizes, patient groups were combined. Given the exploratory nature of the analysis, uncorrected correlation coefficients are reported (see Table 5.5). Delayed visuospatial episodic memory and semantic ability emerged as being moderately associated with the capacity to construct non-social, congruent scenes; whereas congruent social scenes appeared to be most strongly associated with response inhibition. Semantic association and visuospatial episodic memory were strongly associated with the contextual richness of incongruent construction; while the cohesiveness of incongruent scenes (i.e., integration and immersion scores) was heavily related to verbal and visuospatial episodic memory, response inhibition, and semantic association, particularly in the social condition.

Table 5.5. Pearson correlation coefficients exploring associations between scene construction performance and cognitive variables in the two patient groups combined.

	Total Content Scores				Integration and Immersion Scores	
	Congruent		Incongruent			
	Social	Non-Social	Social	Non-Social	Social	Non-Social
SydBat						
Semantic Association (20)	.237	**.391***	.005	**.483***	**.427***	.011
Naming (20)	-.181	**.427***	.014	.331	.359	.243
RCF 3 minute (23)	.347	**.411***	.214	**.528****	**.600****	**.414***
Hayling Overall Scaled (20)	**.393***	.275	.129	.333	**.606****	.326
RAVLT 30 minute (22)	-143	.090	.261	.177	**.364***	.349

Notes. Integration and Immersion Scores (incongruent scenes only). Uncorrected one-tailed Pearson correlation coefficients. * = $p < .05$ ** = $p \leq .01$. Overall number of participants reported in parentheses. Patient numbers within each test: SydBat = Sydney Language Battery, AD = 11, bvFTD = 9; RCF= Rey Complex Figure, AD = 8, bvFTD= 15; Hayling, AD = 6, bvFTD = 14; RAVLT = Rey Auditory Verbal Learning Test, AD = 7, bvFTD = 15.

5.3 Discussion

This study revealed differential effects of congruency on the capacity for social versus non-social construction in the two patient groups. The use of incongruent scene cues resulted in bvFTD and AD patients producing significantly more detailed scene descriptions in non-social, relative to social, incongruent scenes, contrary to expectations. The relatively increased level of contextual detail in the construction of non-social incongruent scenes, however, was not reflected in the overall cohesiveness of the scene, that is, the level to which the elements were integrated and immersed within the scene. Indeed, no significant differences in integration and immersion were evident between incongruent social and non-social scenes in either patient group. Irrespective of congruency, bvFTD patients constructed significantly more impoverished social, compared to non-social, scenes; supporting the hypothesis and previous findings (Chapter 4, Wilson et al., 2020b). Exploratory analyses primarily point to visuospatial episodic memory, response inhibition, and semantic association as being important correlates with the capacity for incongruent mental construction in dementia syndromes, particularly regarding the degree to which the elements were immersed within the social incongruent scene. These findings speak to the complexities and nuances of scene generation and provide greater insight regarding how the nature of envisaged stimuli impacts scene construction task performance.

5.3.1 Overall patient performance

This study is the first to explore the effects of sociality and congruency on the capacity to generate richly detailed, atemporal scenes. Overall, both patient groups performed significantly worse on the scene construction task than control participants. Although no main effect of congruency was found, results showed that non-social incongruent scene cues improved patient performance on the construction task, relative to social incongruent cues. Given previous work demonstrating higher

integrative load is associated with significantly reduced episodic detail in older adults when recombining previously experienced events (Addis et al., 2010), the current findings did not support the hypothesis that incongruent scene cues would decrease task performance. Previous findings, however, also note that scene based imagery gives rise to greater perceptual detail than event descriptions (Sheldon et al., 2019), and reduced capacity to recruit episodic detail has previously been reported to increase reliance on semantic information (Devitt et al., 2017). Given incongruent scene cues inherently reduce the capacity for episodic recall, and memory-based descriptions are more strongly evoked by social constructions (Wilson et al., 2020b), the use of non-social incongruent cues potentially compounds an already greater reliance on semantic content in non-social construction. Speculatively therefore, this "semantic enrichment" evoked by the generation of non-social incongruent scenes may account for the relatively enhanced task performance by the two patient groups in this condition. Indeed, semantic association performance on an independent task was strongly related to the level of contextual detail provided in the non-social incongruent condition in both patient groups. The trend towards the bvFTD group outperforming the AD group in the non-social incongruent condition is also consistent with more extensive semantic processing deficits in AD patients (Karantzoulis & Galvin, 2011) potentially reducing the capacity for semantic compensation in this group.

5.3.2 Spatial integration

Spatial elements particularly emerged as appearing to contribute to the generation of non-social incongruent scenes. All three groups provided more spatial references in the incongruent non-social, compared to social, condition. This supports previous findings showing reduced spatial references in the construction of social, relative to non-social, scenes in bvFTD and AD patients (Chapter 4, Wilson et al., 2020b). Further, cues with greater spatial context (i.e., locations) have

been shown to generate more richly detailed memories than people cues (Robin, Wynn, & Moscovitch, 2016). Although differences in the level of spatial details were not apparent in the congruent condition, this highlights the importance of a spatial framework in which to unify incongruent elements when social context may be unavailable. Additionally, posterior-medial brain regions have been particularly reported as contributing to spatial context in scene generation (Robin et al., 2016). Therefore, social and congruent scenes may be less dependent on spatial context due to the more extensive recruitment of prefrontal regions, particularly the vmPFC, owing to their involvement in social and schema consistent informational processing (Hassabis et al., 2014; Spalding et al., 2015).

5.3.3 Thoughts, emotions, and actions

More extensive investigation of the contextual composition of the scene descriptions, and particularly the thoughts, emotions, and actions category, revealed all three groups provided significantly more action-based contextual detail in their non-social incongruent scenes relative to the social incongruent condition. Interestingly, this action-based content was shown to particularly enrich the bvFTD non-social incongruent scenes relative to control participants, with mean scores identifying a slight trend of the same nature in the AD group. It is plausible that even within the context of overall impoverished mental imagery, the inclusion of more actions in non-social incongruent scenes may result from a greater reliance on semantic relational processing and functional inter-item associations (see Figure 5.4). Previous findings indicate visual scenes may be categorised based on the functional opportunities they represent, in other words, the relative actions a scene evokes; however, categorisation based on social functionality is more nebulous (Greene, Baldassano, Esteva, Beck, & Fei-Fei, 2016). Similar to spatial based scaffolding previously described (Robin et al., 2016), it is proposed that within the context of non-social

incongruent scenes, action-based references may provide an anchor in the generation of novel scene descriptions which may not be yielded by social incongruent cues. Finally, the inclusion of more unique entities and sensory descriptions by bvFTD patients in the incongruent non-social, relative to social, condition is consistent with the observation of social cues generally evoking less contextually rich mental scenes in bvFTD (Chapter 4, Wilson et al., 2020b). Conversely, the significantly greater number of unique entities provided by AD patients in the congruent social, relative to non-social, condition is consistent with social context providing an additional support structure from which to populate a scene which may not be as salient in bvFTD.

bvFTD

Kids playing [TEA-Action], balls being thrown [TEA-Action], sandcastles being built [TEA-Action]. People riding the waves [TEA-Action], getting dumped [TEA- Action], getting up again and riding the waves. But to the right of me, I see a woman with ice-skates on, ice-skates, ice-skates, she walks into the water with the ice-skates on. I thought, what a wonderful idea. This will help her stand up, she won't get knocked over in the water [TEA-Action]. She's not going to skate on the sand, what a silly thought I had. No, she's going to skate through the water [TEA-Action], she's going to dig her heels in so to speak and stand her ground against the incoming waves.

AD

Well I wandered [TEA-Action] down to the beach and it was exceedingly hot. And I nearly tripped over [TEA –Action] some ice-skates and so I thought I might try them on [TEA-Action]. Which I did. But it took me several times to sort of stand up straight and get my balance [TEA-Action]. And um, so I sort of staggered along [TEA-Action] the beach with the ice-skates on. I think that's about it. So I decided then that they were just too heavy and I took them off [TEA-Action]. [giggles] Having ice-skates at the beach.

Control

So I put my ice-skates on and I head off [TEA-Action] into the lake and, on to the lake sorry. I'm whizzing around [TEA-Action] because I'm actually quite an accomplished ice-skater and represented Uzbekistan in the last Olympics. But I look back on to the shore and somebody is waving [TEA-Action] at me and I wonder why and then I hear a horrible creaking noise.

Figure 5.4. Example scene excerpts from non-social incongruent scenes (Beach and Ice-Skates) highlighting the inclusion of action-based descriptions in each of the participant groups.

5.3.4 Integration and immersion

Next, the reduced capacity to integrate and immerse the scene elements within the envisaged scene was considered. Although performance between social and non-social conditions was comparable, the two patient groups produced significantly less integrated scene descriptions relative to controls. Considering the better task performance in the non-social, compared to social, incongruent condition demonstrated by both patient groups, recent evidence supports the capacity to generate detail without necessarily evoking richly integrated mental imagery. Patients experiencing amnesia due to medial temporal lobe damage exhibit difficulty creating scene-based scripts, for example, buying groceries, despite generating the same number of overall steps (Lynch, Keane, & Verfaellie, 2020). Speculatively, this suggests that although action- and semantic- based content may provide an anchor upon which to create a detailed incongruent scene, particularly in the non-social condition, an overall impoverished immersive experience appears to remain across dementia syndromes.

5.3.5 Neural regions supporting incongruent scene construction

The neural regions supporting the construction of commonplace scenes have been extensively reported (Mullally & Maguire, 2014), particularly hippocampal contributions to the formation of a cohesive spatial context (Hassabis, Kumaran, Vann, et al., 2007). The contribution of prefrontal regions, however, is proposed to be complementary, potentially likely to be dependent on the nature of the task, for example, familiarity (Robin, Garzon, & Moscovitch, 2019; Van Kesteren et al., 2012) and socio-emotional content (Adolphs, 2009). In this context, the vmPFC has been proposed to support mental imagery (Andrews-Hanna et al., 2010), albeit within an extensive neural network supporting this dynamic constructive process. The narrative integration of incongruent scene stimuli, however, may be associated with an increased reliance on the dlPFC

(Blumenfeld et al., 2011; Ranganath, 2010) and hippocampus (Keane et al., 2020), due to their involvement in relational processing. Associations and distinctions between relational processing and scene construction have been much debated (e.g., Roberts, Schacter, & Addis, 2018). Generally, these processes have been suggested to work in concert in the generation of complex mental scenes by forming inter-object relationships within an overall spatial context (Eichenbaum & Cohen, 2014). Although the neural substrates of incongruent scene construction were not the focus of this study, one proposal is that the construction of incongruent scenes may particularly require relational processing, regardless of the resulting level of immersion within the scene. To date, no studies have examined the neural correlates of incongruent scene generation. Potential candidate regions of interest include the vmPFC, dlPFC and hippocampus due to their previously reported role in relational processing and cognitive flexibility (Blumenfeld et al., 2011; Keane et al., 2020, Paulin et al., 2020, Ranganath, 2010).

5.3.6 Cognitive mechanisms

Finally, the nature of the scene cues appeared to considerably influence the cognitive mechanisms associated with mental construction. Speaking to the potentially more complex involvement of multiple cognitive domains in creating richly immersive social constructions (Wilson et al., 2020b), the capacity to cohesively integrate and immerse incongruent social elements was strongly associated with executive function in the patient groups combined. This resonates with recent studies suggesting a foundational role for episodic memory and response inhibition in social behaviour (Baez et al., 2016; Gaesser & Schacter, 2014). Visuospatial episodic memory also emerged as strongly associated with mental construction across conditions. A moderate to strong relationship between semantic association and task performance in the non-social incongruent condition speaks to the suggested increased reliance on semantic relational processing when

episodic and social content is less salient. Overall, these exploratory findings indicate diverse cognitive mechanisms subtending the generation of richly detailed mental imagery dependent on the nature of the envisaged scene.

5.3.7 Limitations and methodological considerations

Of course, the current study is not without its limitations. To avoid the potential confound of excessive fatigue in a clinical population, the study was limited to one trial per condition. A more comprehensive investigation of the effects of incongruent scene cues utilising both multiple scene cues and larger samples is warranted; particularly in relation to action based semantic associations which in this study may have been influenced by the nature of the scene cue (i.e., ice-skates may inherently evoke more action based associations). Further, a significant three-way interaction in the incongruent condition was not found, however, mean scores, two-way interaction effect sizes, and strongly significant post hoc comparisons point to limited power possibly confounding this result. In addition, while bvFTD patients provided fewer contextual details within social, relative to non-social, scenes irrespective of congruency, this was not evident in the congruent condition alone, conflicting with previous findings (Chapter 4, Wilson et al., 2020b). This may stem from the hospital-doctor scene potentially being overly familiar within this population and therefore more semanticised, increasing task performance in the social condition. Finally, some characteristics of the sample are of note. The bvFTD group in this study performed at control level on some executive (TMT B-A) and semantic (SydBat) measures, potentially indicating a relatively high-performing sample. Nonetheless, the current findings provide important foundations from which to further investigate the influence of incongruent stimuli in the generation of atemporal mental scenes.

5.3.8 Summary and implications for future studies

Extending the findings from Chapter 4 investigating social construction (Wilson et al., 2020b), this study provides further evidence that the processes subtending mental construction are heavily influenced by the nature of the scene cue. Incongruent non-social scene cues evoked significantly more detailed constructions in the bvFTD and AD groups, relative to incongruent social cues. This increased level of detail, however, was not reflected in the level of integration and immersion of the elements within the scene in either patient group. Further analysis revealed non-social incongruent scenes appeared to particularly draw upon spatial scaffolding and evoke more action based contextual detail across all three groups. These findings sit well within the context of the current literature identifying the capacity to generate richly detailed and cohesive mental scenes as a highly complex and nuanced process which appears to be heavily influenced by the nature of the to-be-constructed scene.

6

Social Perception, Social Knowledge, and Social Construction

Given the evidence presented in Chapters 3 and 5 that bvFTD patients exhibit significant disruption in the capacity for mental construction, and particularly, findings from Chapter 4 showing reduced social simulation in bvFTD, an important next step involves exploring the clinical correlates of these deficits. The characteristic social deficits associated with bvFTD have been shown to have the most substantial impact on caregivers (Chemali et al., 2010; Mioshi et al., 2013). Current understanding of why these behavioural changes occur is considerably lacking, however, particularly in relation to how bvFTD patients interpret overt social norm violations. Considering the emerging role of mental simulation in a range of cognitive processes (Hassabis & Maguire, 2009), this chapter examines how a reduced capacity for social simulation may sit within broader social processing deficits in bvFTD.

The capacity to perceive and interpret social information, known as social cognition, is essential in navigating our everyday lives. Social cognition guides our ability to form and maintain relationships, understand the thoughts, feelings and intentions of others, and to behave appropriately in response (Adolphs, 2009). Importantly, part of the complexity of social interaction involves the ability to adapt and update one's behaviour in accordance with the current context, as well as deduce subtle differences in appropriate behaviour between contexts (Arioli et al., 2018). Although variously referred to as social understanding (Arioli et al., 2018), social judgement (Nah & Poon, 2011), and social reasoning (Lough et al., 2006), the ability to interpret social context is

generally considered to fall under social perception (Dewey, 1991; Zebrowitz, 1990). Social perception is deeply integrated with more basic perceptual processes (Zebrowitz, 1990), such as identifying facial expression and emotion (McDonald, Flanagan, Rollins, & Kinch, 2003), as well as social knowledge (Shany-Ur, Rankin, Badalà, Nouri-mahdavi, & Raoof, 2010). Disruption to social perception results in a reduced ability to make judgements regarding social situations and respond accordingly (Addington, Saeedi, & Addington, 2006), tending to manifest in behaviour which may erroneously be interpreted by others as rudeness or a lack of manners.

As outlined in Chapter 1, bvFTD is a severe, progressive neurodegenerative brain disease which is characterised by a profound breakdown in social cognition (Rascovsky et al., 2011; Strikwerda-Brown et al. 2019 ToM review). Individuals with bvFTD demonstrate significant difficulties across multiple social-cognitive processes, including the ability to identify facial (Hutchings et al., 2017) and emotional expression (Marshall et al., 2019), ToM (Henry, Phillips, & Von Hippel, 2014), and sarcasm detection (Kipps et al., 2009). Due to the multifaceted nature of social cognition, it is often difficult to determine specific processes which may be contributing to altered social behaviour. Although social-cognitive deficits have been shown to be significantly more pronounced in bvFTD, poor performance on social-cognitive tasks is also evident in other forms of dementia, including Alzheimer's disease (Bora et al., 2015; Reul, Lohmann, Wiendl, Duning, & Johnen, 2017). Considering social dysfunction is not a defining characteristic of Alzheimer's disease (McKhann et al., 2011), at least in the early stages, this suggests that factors contributing to poor performance on social-cognitive measures may be multifaceted.

Integrating social information in order to determine what may, or may not, be appropriate behaviour in a given situation involves a complex understanding of social rules and the ability to understand how the application of these rules may shift dependent on the context (Arioli et al.,

2018; Zebrowitz, 1990). For example, what may be appropriate behaviour amongst family or friends may not be amongst acquaintances. Given the inherent context of social situations is often dependent on our relationships with, and the emotions of, others, many social perception measures tend to conflate social perception and ToM (Arioli et al., 2018). One of the most commonly used measures of identifying social violations is the faux pas recognition test (Baron-Cohen, 2002) involving a series of written vignettes whereby one of the protagonists commits a social misdeed, for example, revealing plans for a surprise party to the intended recipient prior to the event. Understanding the inappropriateness of this behaviour, however, requires, first, an awareness of the impact of the misdeed upon each of the characters knowledge of the event, as well as the resulting emotions. Due to this additional cognitive complexity, the faux pas recognition test is generally used to measure ToM integrity rather than social perception (Henry, Phillips, & Von Hippel, 2014; Kipps et al., 2009) and lacks robust specificity in differentiating bvFTD from other neurological diseases (Delbeuck, Pollet, Pasquier, Bombois, & Moroni, 2020). The Awareness of Social Inference Test (TASIT, McDonald et al., 2003) which utilises short videos is also of note regarding the assessment of social perception. Although a useful diagnostic measure in bvFTD (Kumfor et al., 2017), this test focuses more on emotional evaluation and sarcasm detection rather than inappropriate behaviour per se. Videoed vignettes have also been shown to invoke differential age-related patterns of performance, with older participants showing a reduced capacity to identify inappropriate behaviours in comparison to younger participants (Halberstadt, Ruffman, Murray, Taumoepeau, & Ryan, 2011). The Dewey Story Test (DST, Dewey, 1991), however, was developed as a specific measure of social perception for children with autism spectrum disorder and involves identifying (written) overt behavioural transgressions. Previous findings indicate

bvFTD patients show a reduced ability to identify social norm violations on this measure (Lough et al., 2006), however, performance across dementia syndromes remains unclear.

Difficulties identifying overt social norm violations have been reported as important contributors to the social-cognitive deficits associated with a range of clinical disorders, including autism spectrum disorder (Nah & Poon, 2011), and schizophrenia (Fukuhara et al., 2017). Disruption of prefrontal regions has been proposed to significantly contribute to these deficits (Pinkham, Hopfinger, Pelphrey, Piven, & Penn, 2008). These findings complement those identifying the ventromedial prefrontal cortex (vmPFC) as an important contributor to a range of social-cognitive processes (Hiser & Koenigs, 2018), including social decision making (Rudebeck et al., 2008) and social perception or understanding (Arioli et al., 2018). Together with the role of the temporoparietal junction in ToM (Schuwerk, Schurz, Müller, Rupprecht, & Sommer, 2017), and the amygdala in emotion (Phelps, 2006), the vmPFC forms part of what is generally known as "the social brain" (Adolphs, 2009). Regions of the social brain considerably overlap with the patterns of atrophy observed in bvFTD (Strikwerda-Brown, Ramanan, & Irish, 2019). Considerable interplay has been identified between the social brain and other neural networks, for example, the default mode network, involved in inwardly directed thought (Mars et al., 2012), and particularly memory (Amodio, 2019). Hippocampal regions appear to markedly support this interplay between social cognition and memory due to their involvement in flexible cognition and social behaviour (Rubin, Watson, Duff, & Cohen, 2014). These findings suggest memory systems, at least in part, appear to subtend our ability to integrate social information in order to interpret, modify, and respond to the current context (Amodio, 2019).

Given the emerging importance of understanding the contribution from memory systems to social behaviour, one emerging domain thus far receiving little attention in relation to social cognition is

scene construction, or the capacity to envisage richly detailed, naturalistic, three-dimensional scenes (Hassabis, Kumaran, Vann, & Maguire, 2007). Scene construction is heavily associated with both autobiographical and semantic memory (Irish & Piguet, 2013) and the capacity to construct social scenes has been potentially identified as a special class of mental construction (Wilson et al., 2020b). bvFTD patients display a significantly reduced capacity for constructing social, relative to non-social, scenes and poorer social simulation in bvFTD is significantly associated with a reduced ability to identify social norms (Wilson et al., 2020b). Processing social situations requires the multifaceted integration of a range of spatial, temporal, evaluative, and social aspects which may be particularly amenable to, and supported by, the integrative mechanisms associated with scene construction (Lieberman et al., 2019). Indeed, the role of the vmPFC in mental imagery (Bertossi et al., 2016) has been suggested to particularly subtend this socially integrative aspect of situational processing (Lieberman et al., 2019). Given the inherent ambiguity of social interaction, the capacity to envisage, and perhaps even mentally role play, social situations may support one's ability to successfully navigate this ambiguity.

This study examines the capacity for social perception in bvFTD and Alzheimer's disease using a modified social perception task (Dewey, 1991) describing overt behavioural transgressions. Previous findings indicate bvFTD patients are significantly less likely to identify overt social norm violations than controls (Lough et al., 2006). How bvFTD patients differ in rating behavioural transgressions in comparison to other dementia syndromes, however, and the extent to which difficulties with social perception relate to other social-cognitive deficits in this syndrome, remains unanswered. It was hypothesised that bvFTD patient ratings of the behavioural transgressions would significantly diverge from both the Alzheimer's group and control ratings. Secondly, given the characteristic social disinhibition associated with a diagnosis of bvFTD (Rascovsky et al.,

2011), it was hypothesised that bvFTD patients would rate the social violations as less socially inappropriate than controls. Further, the interrelationship between social perception and other measures of social-cognition and behaviour, including social knowledge, social simulation, and neuro-psychiatric symptoms was explored. It was hypothesised that more substantial difficulties in social perception would be associated with poorer social knowledge, a reduced ability to envisage richly detailed social scenarios, and greater overall behavioural and neuropsychiatric symptoms.

6.1 Materials and Methods

6.1.1 Participants

All participants were recruited through FRONTIER, the frontotemporal dementia research group based at the Brain and Mind Centre, The University of Sydney. The performance of 25 individuals with a clinical diagnosis of probable bvFTD, 18 individuals with typical Alzheimer's disease (AD), and 17 healthy older control participants was compared. Three bvFTD patients were excluded due to achieving an ACE-III score greater than 88 (see exclusion criteria in Chapter 2 section 2.1.1), one due to language difficulties, and three due to becoming confused or the task being incomplete. Five AD patients were excluded - four due to becoming confused during the assessment, and one due to soring an ACE-III of 90. This resulted in a final sample of 18 bvFTD, 13 AD, and 17 controls. Further details regarding participant recruitment, inclusion and exclusion criteria and clinical criteria used to establish dementia diagnoses are outlined in Chapter 2.

6.1.2 Cognitive Assessment

Consistent with previous studies, participants completed a comprehensive neuropsychological battery assessing the main cognitive domains (see Chapter 2 section 2.3). In the current study, the

primary variables of interest included overall cognitive capacity (ACE-III, Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013), measures of delayed verbal (RAVLT 30 minute, Schmidt, 1996) and visuospatial (RCF 3 minute, Meyers & Meyers, 1995; Rey, 1941) episodic memory, response inhibition (Hayling sentence completion task, Burgess & Shallice, 1997), attention and working memory (Digit Span Forwards and Backwards, Weschler, 1997).

6.1.3 Behavioural Measures

The Cambridge Behavioural Inventory Revised (CBI-R; Wear et al., 2008) was used as a measure of overall behavioural change. As outlined in Chapter 2 section 2.4.3, the CBI-R is a 45-item carer questionnaire designed to assess behavioural and psychiatric changes in areas of memory and orientation, everyday skills, self-care, abnormal behaviour, mood, beliefs, eating habits, sleep, stereotypical behaviours, and motivation. A 0-4 point scale is used to denote the frequency of the behaviours and summed to create a total score which is then converted to a percentage scale (maximum score 100). Higher scores denote more substantial behavioural changes. Control participants completed a self-rated version of the questionnaire. The CBI-R has been shown to be a reliable, valid and clinically useful tool in the differentiation of neurodegenerative disorders (Wedderburn et al., 2008).

The Neuropsychiatric Inventory (NPI, Cummings et al., 1994) is a 12 item scale assessing the frequency and severity of behavioural and psychiatric symptoms including: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, sleep and appetite. Frequency and severity scores are multiplied to create a Total NPI score with a maximum of 144 where higher scores reflect more severe neuropsychiatric disturbance.

6.1.4 Social Norms Questionnaire

The Social Norms Questionnaire (SNQ) (Possin et al., 2013) was used as a measure of social knowledge. The SNQ is a 22-item ‘‘yes’’ or ‘‘no’’ self-report scale measuring the capacity to identify appropriate social behaviour in the presence of an acquaintance. Scoring of the appropriateness of social norms is in accordance with mainstream culture of the United States of America. Three scores are obtained from the measure. The SNQ Total score has a maximum score of 22 with higher scores indicating *greater* knowledge of social norms. Two sub-scales may also be obtained on which higher sub-scores represent *poorer* performance. The “Over-adhere” score (range 0-10) represents social rigidity and refers to endorsement of a socially appropriate behaviour (e.g., wearing the same shirt twice in 2 weeks) as inappropriate. The “Break” score (range 0-12) refers to endorsement of a socially inappropriate behaviour (e.g., eating pasta with your fingers) as appropriate. The SNQ has been established as a valid measure of social knowledge which distinguishes bvFTD and AD patients and significantly correlates with frontal executive deficits (Panchal et al., 2015).

6.1.5 Social construction task

The ability to construct spatially coherent social (and non-social) scenes was measured using a modified version of the Scene Construction task (Hassabis et al., 2007), outlined in Chapter 4 section 4.1.3. Participants imagined and described aloud atemporal scenes in as much detail as possible, using all their senses. To minimise fatigue, scene descriptions were capped at two minutes and a total of four scenes were included, two social scenes (Busy Restaurant, Crowded Train) and two non-social scenes (Forest, Abandoned Warehouse). In keeping with the original study protocol (Hassabis et al., 2007), scene descriptions were transcribed verbatim and scored for contextual detail according to four content categories, Entities Present, referring to the number of

animals, objects or people included in the scene; Sensory Descriptions, statements describing the characteristics of an entity (in any modality, e.g., "the chair is made of wood", "I can smell the food"); Spatial References, referring to the spatial location of entities within the environment (e.g., "to my left…"; "approximately two metres away…"); and Thoughts/Emotions/Actions, including introspective statements of the participant (e.g., "I feel alone") as well as thoughts, intentions or actions of other people within the scene (e.g., "he pours a drink"). The maximum number of details for each subcategory was capped at seven points leading to a maximum Total Content Score of 28.

6.1.6 Social Perception Task

A series of vignettes based on the Dewey Story Test (Dewey, 1991) were used to assess the capacity to identify overt behavioural transgressions. Choice of vignettes was based on the behaviours described violating Australian cultural norms and contained simple narratives which were constrained to no more than 150 words, limiting the possibility of fatigue. A total of seven vignettes were included in the study, two from the original Dewey Story Test, one from Nah and Poon (2011), and four written for the purposes of this study (see Appendix B for an example scene). Pilot testing was conducted in a small sample of healthy young adults (n = 7). Inter-item analysis based on total raw scores for each of the vignettes revealed reasonably comparable inter-item consistency across scenarios (Cronbach's alpha =.571) and that the behaviours described violated social norms (Grand M = 4.13, SD = 1.77). Each story comprised a series of statements relating to the behaviour of the protagonist which the participant was instructed to rate according to how they thought "most people would judge that behaviour if they witnessed it". Participants were informed that, "Some of the things described in the story may seem strange", and that, "We use the word 'strange' to describe something that most people wouldn't do." Stories were read aloud by the experimenter in full; following which, each statement was repeated, one at a time,

and ratings obtained. Ratings were provided on a four-point scale, 0 = 'fairly normal', 1 = 'rather strange', 2 = 'very eccentric', 3 = 'shocking'. Story order was randomised across participants and a practice story was provided (practice story and rating scale included in Appendix B). Participants were assured that the task was not about memory to alleviate anxiety and stories were printed and placed in front of the participant for the duration of the task.

Scoring

In line with previous studies (Lough et al., 2006; Nah & Poon, 2011), scoring was based on deviation from control ratings. To determine the extent to which the two patient groups deviated from controls, each item was first examined and the most common response given by control participants (determined by ≥ 30% of controls endorsing the rating) was assigned a score of 0. For items where more than one response was endorsed by ≥ 30% of control participants both responses were given a rating of 0 (Callenmark et al., 2014). A Total Social Perception Deviation Score was derived from the extent to which patient ratings deviated from control responses; in other words, if the majority of controls rated an item as 'very eccentric' (score of 2), and a patient rated that item as 'rather strange' (score of 1), or 'shocking' (score of 3), a deviation score of 1 was applied, regardless of the direction of the deviation. Higher scores represent greater deviation. Control responses and deviation scores applying to each item are included in Appendix B. In order to examine the direction of deviation and constrast patient performance with scenes which evoked more ambiguous social ratings from the majority of control participants, a Social Perception Directional Score was created based only on summed deviation scores for items on which control participants endorsed mid-range values and therefore represented over or under rating relative to control responses (see Appendix B).

6.1.7 Statistical analyses

Data were analysed using IBM SPSS version 26. For continuous variables, normality of distributions was examined using Kolmogorov-Smirnov tests. Group differences for normally distributed continuous variables (e.g., age at assessment, years of education) were assessed using univariate ANOVAs. Group differences on categorical variables (i.e., sex) were examined using Chi-squared tests. Where data were non-normally distributed (e.g., cognitive variables) or a sub-set of scores resulted in small and unequal samples sizes, non-parametric Kruskal-Wallis tests for independent samples and Wilcoxon signed-rank tests for related samples were used. Group differences on the social construction task were assessed using a two-way mixed ANOVA with group (control, AD, bvFTD) as the between-subjects variable, and sociality (social, non-social) as the within-subjects variable. Group differences on the social perception task and social norms task were assessed via a one-way ANOVA. One-tailed, partial Pearson correlations were used to assess the relationship between poorer performance on the social tasks and the cognitive variables of interest while controlling for overall cognitive deficits. Bonferroni correction was applied to post hoc comparisons where appropriate. Due to the exploratory nature of the study, where extensive comparisons would have resulted in overly conservative correction (e.g., correlations with cognitive variables) uncorrected values are reported. The alpha level to determine statistical significance was set at $p < .05$. Partial eta-squared values (η_p^2) were used as a measure of effect size for ANOVA statistics.

6.2 Results

6.2.1 Demographic and clinical information

Age at assessment, F (2, 45) = 2.19; p = .124; η_p^2 = .09, and sex distribution (Fisher's Exact Test, p =.077) did not differ significantly across control, AD and bvFTD groups (Table 6.1). Years of education significantly differed between groups, F (2, 45) = 3.78; p = .030; η_p^2 = .14, with post hoc comparisons revealing that this was driven by significantly fewer years of education in the bvFTD group relative to controls (p = .034). Disease severity, as measured by the CDR-FTLD SoB score, t (27) = 0.96, p = .344, and disease duration (years from symptom onset), U = 92.50, p = .261, were comparable between patient groups. Finally, a significant group effect was evident regarding overall behavioural change on the CBI, H (2) = 25.48; p <.0001. Post hoc comparisons demonstrated both patient groups exhibited greater behavioural changes in comparison to control participants (both p values ≤ .002); however, performance between patient groups was similar (p = .994). Looking at the abnormal behaviour sub-score of the CBI also revealed a significant group effect, H (2) = 18.52; p < .0001, with post hoc tests showing the bvFTD group exhibited significantly more abnormal behaviour than controls (p ≤ .0001). Mean scores also revealed higher levels of abnormal behaviour in the bvFTD group, relative to AD patients, however, this and all remaining comparisons failed to reach significance (all p values ≥ .089).

Table 6.1. Demographics and clinical characteristics of study participants.

	bvFTD	AD	Controls	Group Effect (*p* value)	Post hoc (direction of effect)
N	18	13	17	-	-
Sex (M:F)	15:3	8:5	8:9	.077[a]	-
Age (years)	61.4 (7.6)	66.0 (7.1)	64.8 (4.4)	.124	-
Education (years)	12.1 (2.1)	13.8 (3.2)	14.4 (2.3)	.030	CN > bvFTD
Disease duration (years)	6.8 (3.3)	6.4 (6.5)	-	.261	-
Disease severity (CDR-FTLD SoB)	7.4 (4.2)	6.0 (3.3)	-	.344	-
Behavioural change: Overall (CBI-R Total)	40.5 (20.6)	28.1 (18.4)	4.3 (3.3)	<.0001	CN < bvFTD, AD
Abnormal behaviour (CBI-R Abnormal Sub-Scale)	38.2 (23.4)	20.8 (23.8)	3.9 (4.8)	<.0001	CN < bvFTD

Notes. [a] Fisher's Exact Test. Participant scores reported as means with standard deviations shown in parentheses. Bonferroni corrected comparisons are shown. bvFTD = behavioural-variant frontotemporal dementia; AD = Alzheimer's disease, CN = Controls. CDR-FTLD SoB = Clinical Dementia Rating – Frontotemporal Lobar Degeneration Sum of Boxes; CBI-R = Cambridge Behavioural Inventory – Revised.

6.2.2 Cognitive profiles

Relative to controls, bvFTD and AD patients displayed characteristic cognitive deficits which were largely in keeping with their clinical diagnoses (Table 6.2). Significant group effects emerged in attention and executive function, Digit Span Forwards, H (2) = 7.37, p = .025, Digit Span Backwards, H (2) = 15.63, p = ≤ .0001, Hayling, H (2) = 15.92, p ≤ .0001, and TMT B-A, H (2) = 12.58, p = .002. Examining verbal, H (2) = 28.91, p ≤ .0001, and visuospatial, H (2) = 18.14, p ≤ .0001, delayed episodic memory also revealed significant group effects; as did overall language, H (2) = 15.78, p ≤ .0001, semantic association, H (2) = 10.98, p = 004, and naming H (2) = 14.51,

p = 001. Verbal fluency also significantly differed between the three groups, H (2) = 22.35, $p \leq$ .0001.

Post hoc tests revealed, relative to controls, both patient groups exhibited deficits in overall cognition (bvFTD: $p \leq .0001$, AD: $p \leq .0001$), delayed verbal episodic memory (bvFTD $p \leq .0001$, AD, $p \leq .0001$), executive function (Hayling, bvFTD p =.008, AD, p =.001; Digit Span Backwards, bvFTD p =.004, AD, p =.001; TMT B-A, bvFTD p =.016, AD, p =.008), language (ACE Language, bvFTD p = .006; AD p = .001, SydBat naming, bvFTD p = .008, AD p = .002), and verbal fluency (bvFTD $p \leq .0001$, AD, $p \leq .0001$). The bvFTD and control groups performed similarly in visuospatial episodic memory (p =.346), attention (p =.247), and semantic association (p =.383). Significant deficits on these measures, however, were found in the AD group relative to controls, visuospatial episodic memory ($p \leq .0001$), attention (p =.022), semantic association (p =.003). Comparison of the patient groups revealed disproportionate deficits in the AD relative to bvFTD group in visuospatial episodic memory (p = .008). No other significant differences between patient groups emerged (all p values $\geq .10$).

Table 6.2. Descriptive statistics and group differences in cognitive profile.

	bvFTD *M(SD)*	AD *M(SD)*	Controls *M(SD)*	Group Effect (*H* value)	Post hoc (direction of effect)
ACE-III Total (100)	75.4 (8.2)	64.5 (2.4)	95.1 (2.7)	34.98***	CN > bvFTD, AD
RAVLT 30-mins (15)	4.0 (3.1)	1.4 (1.5)	10.7 (1.7)	28.91***	CN > bvFTD, AD
RCF 3-minutes (36)	12.3 (7.7)	3.3 (2.3)	16.3 (5.0)	18.14***	CN > AD; bvFTD > AD
Hayling overall (7)	4.4 (2.2)	3.8 (0.7)	6.1 (0.9)	15.92***	CN > bvFTD, AD
Digit Span Forwards	9.2 (2.3)	7.9 (1.3)	10.9 (2.8)	7.37*	CN > AD
Digit Span Backwards	4.8 (1.8)	4.0 (1.7)	8.2 (2.9)	15.63***	CN > bvFTD, AD
TMT B-A (seconds)	103.7 (73.7)	104.2 (22.6)	45.7 (14.6)	12.58**	CN < bvFTD, AD
SydBat Naming (30)	23.0 (3.0)	21.0 (5.0)	27.1 (2.3)	14.51**	CN > bvFTD, AD
SydBat Semantic (30)	27.0 (2.2)	25.2 (2.6)	28.5 (1.0)	10.98**	CN > AD
ACE-Language (26)	23.0 (2.4)	21.2 (4.3)	25.2 (1.0)	15.78***	CN > bvFTD, AD
ACE-Fluency (14)	7.3 (3.2)	7.3 (2.8)	11.9 (1.7)	22.35***	CN > bvFTD, AD

Notes. Maximum test scores shown in brackets where appropriate. *M* = mean, *SD* = standard deviation. Bonferroni corrected comparisons shown. *** = $p \leq .0001$, ** = $p < .01$, * = $p < .05$. bvFTD = behavioural-variant frontotemporal dementia; AD = Alzheimer's disease, CN = Controls. ACE-III = Addenbrooke's Cognitive Examination – Third Edition; RAVLT = Rey Auditory Verbal Learning Test; RCF = Rey Complex Figure. Hayling overall scaled score; TMT B-A = Trail Making Test Time B minus Time A; SydBat = Sydney Language Battery – Naming and Semantic Association. Data unavailable across the following tests: RAVLT: 2 CN, 5 AD; RCF: 2 CN, 3 AD; Hayling: 2 CN, 5 AD, 2 bvFTD; Digit Span: 4 CN, 2 AD; TMT B-A: 2 CN, 8 AD, 4 bvFTD; SydBat Naming/Semantic Association : 2 CN, 3 AD, 6 bvFTD.

6.2.3 Social perception task

Total deviation scores (irrespective of direction) revealed social perception significantly differed between the three groups, F (2, 45) = 5.98; p = .005; η_p^2 =.21. Post hoc comparisons (Figure 6.1, left) showed this was driven by the two patient groups significantly deviating from control scores (bvFTD, p =.007; AD, p =.037). Performance between patient groups was similar (p =.977).

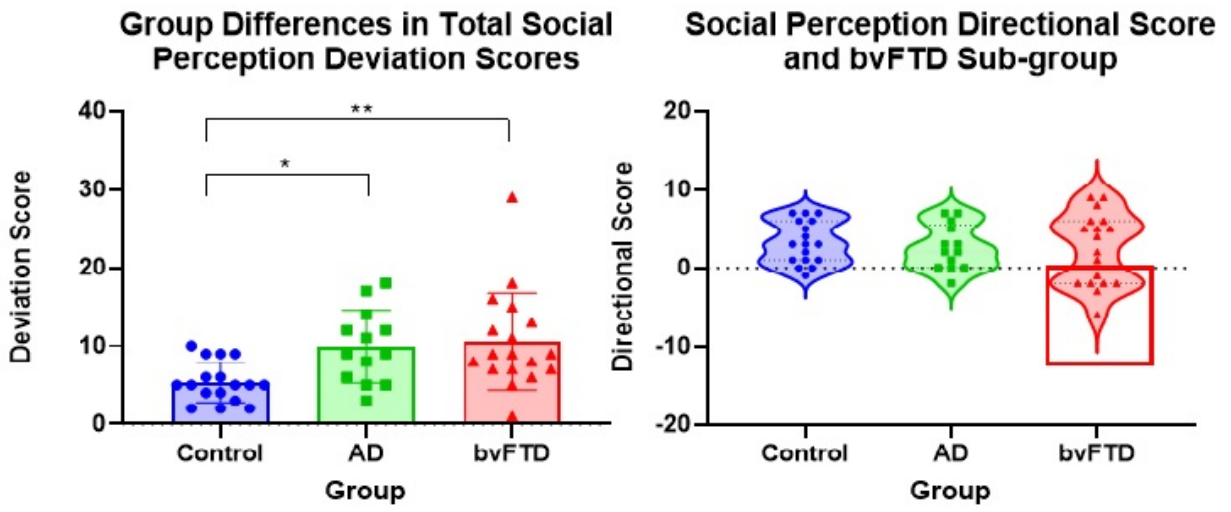

Figure 6.1. (Left) Group differences in the extent to which participant ratings deviate from the most commonly endorsed control responses (≥30%, Callenmark et al., 2014), irrespective of direction, on the social perception task. Data points represent individual scores. Bonferroni corrected comparisons. * = p <.05 ** = p <.01. (**Right**) Direction of deviation based on (10) items for which control participants endorsed mid-range values, that is, patient ratings could *positively* or *negatively* deviate from controls (see Appendix B). Box indicates negatively deviating bvFTD sub-group (7 bvFTD patients). AD = Alzheimer's disease. bvFTD = behavioural-variant frontotemporal dementia.

Examining the social perception directional score revealed significant variability in the bvFTD group (Figure 6.1, right). Based on a total of 10 items where control participants endorsed mid-range values (Appendix B), 7 bvFTD patients were identified whose scores negatively deviated from control ratings. A subgroup of bvFTD patients with positive deviation scores was also identified but was not examined further due to the small sample size (n = 3) as well as mean scores being comparable between the positively deviating sub-group and the mid-range bvFTD sub-group (p = .125). One AD patient also negatively deviated from controls but inclusion of this participant in the sub-group analysis failed to alter the results, therefore, only the bvFTD sub-groups are considered further. Differences in demographic profile between the low rating bvFTD sub-group

and the mid-high rating bvFTD group were examined (Table 6.3). A significant difference in age at assessment revealed the bvFTD low sub-group was older than the bvFTD mid/high group (M = 66.86, SD = 5.70 vs. M = 57.91, SD = 6.73, p = .008). No other significant differences in demographics (sex, years of education) or clinical severity (illness duration, CDR-FTLD SoB) were found (all p values ≥ .18). Cognitive and behavioural profile, and performance on the social tasks, were also comparable between bvFTD sub-groups (all p values ≥ .17).

Table 6.3. Means and standard deviations of bvFTD sub-groups on cognitive and social measures.

	bvFTD low sub-group (n = 7)	bvFTD mid/high sub-group (n = 11)	Group Effect (U value)
Cognitive Profile			
ACE-III Total	78.6 (5.0)	73.4 (9.4)	24.5
Fluency	6.3 (3.2)	7.9 (3.2)	30.0
Language	22.9 (2.8)	23.1 (2.2)	39.5
RAVLT 30-minutes	5.0 (2.5)	3.4 (3.3)	26.5
RCF 3-minutes	13.7 (5.9)	11.5 (8.8)	31.5
Hayling overall scaled score	3.4 (1.8)	4.8 (2.2)	15.5
Digit Span Forwards	8.6 (2.5)	9.6 (2.2)	26.5
Digit Span Backwards	4.4 (1.4)	5.0 (2.1)	31.0
Social and Behavioural Measures			
SNQ Total	17.0 (1.9)	17.7 (2.6)	24.5
Break	1.2 (1.2)	1.7 (1.6)	24.5
Over-adhere	3.8 (2.0)	2.6 (1.7)	18.0
Scene Construction			
Social	16.8 (2.5)	14.5 (5.6)	19.5
Non-Social	16.6 (2.7)	18.3 (6.2)	18.5
CBI-R Total	43.0 (29.4)	38.8 (13.9)	25.5
Abnormal Behaviour	33.9 (30.3)	41.0 (18.8)	33.5
NPI Total	25.5 (15.2)	28.4 (13.2)	17.5

Notes. bvFTD = behavioural-variant frontotemporal dementia; ACE-III = Addenbrooke's Cognitive Examination – Third Edition; RAVLT = Rey Auditory Verbal Learning Test; RCF = Rey Complex Figure; Hayling overall scaled score; SNQ = Social Norms Questionnaire; CBI-R = Cambridge Behavioural Inventory – Revised; NPI = Neuro-psychiatric Inventory.

Social norms task

A significant group effect was revealed for SNQ Total scores, F (2, 37) = 7.22; p = .002; η_p^2 = .28, and SNQ Over-adherence scores, F (2, 37) = 3.63; p = .037; η_p^2 = .16. A trend towards a significant group difference was also found in SNQ break scores, F (2, 37) = 3.18; p = .053; η_p^2 = .15. Post hoc comparisons revealed the bvFTD group performed significantly worse than control participants on all three measures of social norms (SNQ Total, p = .002; SNQ Over-adherence, p = .033; SNQ Break, p = .048). No other group differences in SNQ scores were present (all p values ≥ .18).

6.2.4 Social construction task

A significant group effect emerged on the construction task, F (2, 39) = 14.93; $p \leq .0001$; η_p^2 = .43. Post hoc comparisons revealed both patient groups performed significantly worse on the construction task relative to control participants (bvFTD, $p \leq .0001$; AD, p = .001). No difference between patient groups was observed (p =.848). No main effect of sociality was found, F (1, 39) = 0.03; p = .876; η_p^2 = .00. A significant two-way interaction revealed the effect of sociality varied by group, F (2, 39) = 6.69; p = .003; η_p^2 = .26. Post hoc comparisons showed the bvFTD group provided significantly more detailed scene descriptions in the non-social, relative to social, scenes (p =.003). No other post hoc comparisons were significant (all p values ≥ .18).

6.2.5 Correlations between social measures

Pearson correlations were used to explore the relationship between social perception and other social experimental tasks. Due to limited data, only correlations on the social perception task irrespective of the direction of deviation were examined. Uncorrected one-tailed r values are reported (Table 6.4). In the bvFTD group, social perception was strongly associated with social

construction (p =.003), and moderately associated with non-social construction, however, this failed to reach significance even when uncorrected (p = .052). Moderate associations also emerged in the bvFTD group between social perception and knowledge of social norms (SNQ Total, p = .047, SNQ Over-adhere, p = .05). Greater deviation on the social perception task related to more impoverished social scene descriptions, poorer knowledge of social norms and greater social rigidity. More substantial overall behavioural change (p =.032) and neuropsychiatric symptoms (p = .034) were also associated with greater deviation in social perception scores in the bvFTD group; however, no association was evident with abnormal behaviour (p = .311). No significant correlations were observed between the social measures and social perception in the AD group (all p values ≥.1). An association between the capacity for non-social mental construction and social perception emerged in the control group (p = .022).

Table 6.4. Correlations between social perception total deviation scores and other social measures.

	bvFTD	AD	Controls
Social Norms Questionnaire (SNQ)			
Total	-.**433***	-.163	-.046
Break	.151	.378	.132
Over-adhere	**.427***	-.069	-.003
Scene Construction			
Social	-.**666****	-.065	.150
Non-Social	-.436	-.131	-.**496***
Behaviour (CBI-R)			
Total	.**489***	.149	-.199
Abnormal Behaviour	.125	.231	-.348
Neuropsychiatric Inventory (NPI)			
Total	.**500***	-	-

Notes. Uncorrected one-tailed Pearson correlation coefficients reported. Deviation scores represent the extent to which participant ratings deviate from the most commonly endorsed control responses (endorsed by ≥30% of control participants, Callenmark et al., 2014). * = $p < .05$, ** = $p < .01$. bvFTD = behavioural-variant frontotemporal dementia; AD = Alzheimer's disease. SNQ = Social Norms Questionnaire; CBI-R = Cambridge Behavioural Inventory - Revised; NPI = Neuro-psychiatric Inventory.

6.2.6 Partial correlations with cognitive variables

Pearson partial correlations were used to explore the relationship between reduced social perception (irrespective of the direction of deviation) and selected measures of cognition, while controlling for overall cognition. Uncorrected one-tailed Pearson *r* values are reported (Table 6.5). In the bvFTD group, the extent to which social perception deviated from control scores was significantly associated with executive function (working memory, $p = .045$). A trend also emerged between reduced social perception and delayed verbal recall ($p = .055$). In the AD group, more

pronounced deviation in social perception was strongly associated with poorer verbal fluency (p = .022). Finally, in the control group, controls showing greater social perception variability performed more poorly on visuospatial episodic memory (p = 004).

Table 6.5. Partial correlations between social perception total deviation scores and selected measures of cognition while controlling for overall cognitive function.

	bvFTD	AD	Controls
RAVLT 30-minutes	-.401	-.064	-.360
RCF 3-minutes	-.239	.360	**-.683****
Hayling overall	-.111	-.295	-.253
Digit Span Backwards	**-.454***	.022	. 150
ACE-III Fluency	-.206	**-.589***	.010

Notes. Uncorrected one-tailed partial Pearson correlation coefficients controlling for ACE-III Total score. * = p <.05, ** = p <.01. bvFTD = behavioural-variant frontotemporal dementia; AD = Alzheimer's disease. RAVLT = Rey Auditory Verbal Learning Test; RCF = Rey Complex Figure; Hayling overall scaled score; ACE-III = Addenbrooke's Cognitive Examination – Third Edition. Data unavailable across the following tests: RAVLT: 2 CN, 5 AD; RCF: 2 CN, 3 AD; Hayling: 2 CN, 5 AD; Digit Span Backwards, 2 CN, 3 AD, 2 bvFTD.

6.3 Discussion

This study demonstrated a reduced capacity for social perception in bvFTD and AD patients. Irrespective of the direction of deviation, patient ratings of the social vignettes significantly deviated from control ratings, consistent with the hypothesis. Ratings between patient groups, however, were similar, contradicting the expected findings. Examining the nature of deviation from control ratings revealed a sub-set of bvFTD, but largely not AD, patients rated the scenes as less shocking than controls, consistent with the second hypothesis. Finally, the extent to which bvFTD patients diverged from control ratings was significantly associated with broader social-cognitive measures, including social construction, social knowledge, and level of behavioural and

neuropsychiatric changes, supporting the proposed relationship between social simulation and broader social and behavioural measures in this group. These findings indicate reduced social perception may be an important contributor to the extensive social difficulties which are characteristic of bvFTD and speak to the multifaceted and interacting nature of social-cognitive processes.

6.3.1 Social perception in bvFTD and AD

Difficulties in identifying overt social norm violations significantly contribute to the social-cognitive deficits associated with a range of clinical disorders, including autism spectrum disorder (Nah & Poon, 2011), and schizophrenia (Fukuhara et al., 2017). The nature and extent of social perception deficits in bvFTD, however, as well as how these compare to other dementia syndromes, has remained relatively unexplored. This study found bvFTD and AD patient ratings (irrespective of the direction of deviation) significantly deviated from control ratings on the social perception task. While overall deviation scores were similar between patient groups, examining the direction of deviation revealed the tendency to rate social norm violations as less shocking than controls was largely only apparent in the bvFTD group. These results support previous work reporting a reduced ability to identify social violations in bvFTD on vignette based tasks (Lough et al., 2006) and indicate that the nature of deviation from control ratings may prove useful in differentiating dementia syndromes. Nevertheless, considerable variability was evident within the bvFTD group and the failure to find a significant difference between patient groups on overall deviation scores speaks to the inherent difficulties in interpreting social-cognitive measures within the context of multifaceted cognitive deficits (Dodich, Crespi, Santi, Cappa, & Cerami, 2020). These findings highlight social perception as potentially contributing to a reduced capacity to appropriately interpret, and respond to, the behaviour of others in some bvFTD patients.

6.3.2 Social perception and mental construction

The multifaceted nature of social interaction inherently requires the incorporation of a range of cognitive and social information, recruiting multiple neural regions (Amodio, 2019; Mars et al., 2012). The hippocampus has been particularly highlighted as a potential hub in which social cognition and memory systems may work in concert in order to integrate and interpret social situations (Rubin et al., 2014), particularly due to their role in mental imagery (Lieberman et al., 2019; Wilson et al., 2020b). This study highlights the capacity to envisage richly detailed social scenes as potentially supporting social perception in bvFTD, with poorer social construction strongly associated with greater deviation from control ratings on the social perception task. These findings are consistent with previous reports indicating disproportionate deficits in social, relative to non-social, construction in bvFTD which are associated with poorer social knowledge (Wilson et al., 2020b). This study, therefore, provides further evidence that the ability to identify appropriate and inappropriate behaviour may be supported by the generation of richly detailed social scenes, potentially aiding one's ability to navigate the inherent ambiguity of social interaction. Further, consistent with previous reports of reduced social perception significantly contributing to social-cognitive deficits in other clinical disorders (Fukuhara et al., 2017; Nah & Poon, 2011), reduced social perception was significantly associated with more profound behavioural and neuropsychiatric symptoms in the bvFTD group. Collectively, these results provide an important overview regarding how a reduced capacity for social perception may, in combination with other social measures, contribute to the characteristic social-cognitive deficits associated with bvFTD.

6.3.3 Cognitive processes associated with social perception

Given the ability to interpret and respond to the social environment is an inherently complex and multifaceted process, so too are the cognitive mechanisms proposed to sustain this ability. Previous findings have indicated the neural regions making up the "social brain" heavily overlap with regions involved in memory (Arioli et al., 2018; Hiser & Koenigs, 2018; Rubin et al., 2014). Indeed, investigating the role of memory in our ability to interpret, modify, and appropriately respond to the current context has recently gained momentum (Amodio, 2019). A trend towards a significant relationship between social perception and delayed verbal episodic recall points to memory's potential complementary role in social perception in the bvFTD group. Previous studies have also identified the importance of higher order cognition in integrating social cues and updating one's behaviour accordingly (Baez et al., 2019). This study found social perception was moderately associated with working memory in the bvFTD group, supporting previous findings indicating executive control may contribute to a reduced capacity to interpret social information in bvFTD (Baez et al., 2019; Lough et al., 2006). The failure to find significant differences in cognitive profile between the low rating bvFTD sub-group and the mid-high rating bvFTD sub-group warrants further investigation. A significant difference in age between the two sub-groups was revealed and is consistent with previous findings suggesting certain aspects of social cognition decrease with age, including ToM (Bottiroli, Cavallini, Ceccato, Vecchi, & Lecce, 2016). Given illness duration and severity were similar across the two bvFTD sub-groups, however, indicates the driving mechanisms underlying such profound heterogeneity in the bvFTD group remain largely elusive.

Visuospatial memory also emerged as significantly supporting social perception in the control group, with less robust visuospatial memory associated with greater social perception variability.

Speculatively, even within the context of intact social perception and cognitive function, individual differences in visuospatial memory, and in turn, potentially mental imagery, may influence the interpretation of social norm violations. Previous reports propose spatial processing as heavily contributing to navigating the social world, even in healthy people (Laurita & Spreng, 2017; Montagrin, Saiote, & Schiller, 2018), including our ability to perceive the perspectives of others (Proulx, Todorov, Aiken, & de Sousa, 2016). Indeed, just as spatial processing has been proposed to enhance memory for events (Robin et al., 2016) and provide a scaffold upon which a mental scene is generated (Irish, Addis, et al., 2012; Robin, 2018, also Chapter 5), better visuospatial memory may enhance the capacity to envisage and interpret the nuance of social situations (Lieberman et al., 2019). Finally, the finding that reduced social perception is associated with poorer verbal fluency in AD patients is consistent with verbal processing deficits being a large contributor to the deterioration of social cognition in AD as the disease progresses (Dos Santos et al., 2020).

6.3.4 Limitations and methodological considerations

Findings from this study serve as the foundation for further work exploring the potential relationship between a broad range of social-cognitive processes and mental construction. Nonetheless, some important limitations are of note. First, the small sample size substantially impacted the ability to examine sub-groups, and therefore, further elucidate the potential characteristics differentiating under- and over-rating bvFTD patients. The small sample size also limits the robustness of the correlational analyses and should be considered when interpreting the findings. Second, the reliance on Western cultural interpretations (Dewey, 1991; Possin et al., 2013) of what constitutes appropriate social behaviour limits the generalisability of these findings and speaks to the importance of cultural diversity in social-cognitive research (Miller, Wice, &

Goyal, 2018). Third, findings pertaining to the performance of healthy participants based on social perception tasks designed for clinical populations need to be interpreted with caution due to healthy participants often perceiving these tasks as whimsical and amusing (Dewey, 1991), possibly influencing task performance and engagement. Nonetheless, the current findings provide important evidence pertaining to the cognitive processes which may contribute to individual differences in social perception in control participants, highlighting the need for further exploration of both healthy and clinical populations in this area.

6.3.5 Summary and implications

Some level of ambiguity - and therefore variability - in interpreting appropriate behaviour is inherent within social perception, even for healthy people, despite sharing a common overall social perspective (Dewey, 1991). Difficulties in perceiving social information, however, have been shown to significantly contribute to the challenges in identifying appropriate and inappropriate behaviour in a range of clinical disorders (Fukuhara et al., 2017; Nah & Poon, 2011). This study extends previous findings pertaining to reduced social perception in bvFTD (Lough et al., 2006) by identifying significant deviations from control ratings across dementia syndromes. Importantly, however, the tendency to underrate social violations was largely only apparent in the bvFTD group, suggesting reduced social perception may contribute to the characteristic social disinhibition in this disorder, at least in some patients. These findings also proffer the potential clinical utility of the nature of social perception deficits in aiding the differential diagnosis of dementia syndromes.

By further elucidating the possible cognitive mechanisms supporting social perception in healthy and clinical populations, this study complements previous work pertaining to social simulation (Chapter 4, Wilson et al., 2020b) as a potential mediator in social behaviour. Further, within the

context of the broader literature identifying an emerging role of hippocampal contributions to social cognition (Montagrin et al., 2018), the current findings provide the foundation for future work investigating how processes known to be subtended by the hippocampus, including mental construction (Chapter 3, Hassabis et al., 2007), may aid the flexible recombination of previous experiences in order to simulate an often socially ambiguous world. The identification of a relationship between a reduced ability to identify appropriate behaviour and mental construction in bvFTD begins the process of determining how these processes sit within broader social deficits in bvFTD. These results also complement extant clinical findings pertaining to mental construction and social behaviour in autism spectrum disorder (Lind & Williams, 2012) and schizophrenia (Raffard et al., 2010). Given the profound impact from the social deficits seen in bvFTD on caregivers (Spreadbury & Kipps, 2016), most notably, this study paves the way for greater understanding regarding the potential mechanisms driving behavioural changes in bvFTD.

7

Summary and General Discussion

The objectives of this thesis were to (i) systematically examine the capacity for mental simulation in dementia syndromes as well as its associated cognitive and neural mechanisms and, (ii) explore the relationship between mental construction and broader social processing, including social perception, social knowledge, and behaviour. Collectively, Chapters 3-5 identified a profound disruption in the capacity for mental simulation in bvFTD and AD which was particularly associated with episodic memory, semantic processing, and executive function. Importantly, differential performance on the scene construction task across dementia syndromes and task modifications points to distinct classes of mental construction dependent on the nature of the stimuli. Chapter 6 extended the clinical utility of these findings by presenting novel evidence regarding the interrelationship between mental imagery, broader social cognition, and behaviour in bvFTD. How these findings inform our overall view of the cognitive and neural mechanisms supporting mental imagery, and their clinical implications, are discussed below.

7.1 Mental Construction and the Default Mode Network in bvFTD and AD

The generation of a richly detailed mental scene is a highly complex process requiring multi-modal integration which has been shown to heavily rely on the extensive neural network known as the default mode network (Hassabis & Maguire, 2009). Medial temporal regions, including the hippocampus, have been particularly identified as supporting mental construction (Summerfield et al., 2010) and the findings from Chapter 3 are consistent with hippocampal atrophy disrupting

the capacity for richly detailed mental imagery in bvFTD. Evidence from clinical populations, however, has placed increasing attention on the potential contribution from prefrontal regions in the generation of mental scenes, particularly the vmPFC (Barry et al., 2018; Bertossi et al., 2016; McCormick et al., 2018). Findings from Chapter 3 surprisingly failed to reveal a significant association between integrity of the vmPFC and the capacity for fundamental scene construction in bvFTD, despite previous reports highlighting the importance of this region in mental imagery due to its considerable hippocampal connectivity (Andrews-Hanna et al., 2010). Previous findings also suggest divergent neural regions may support different aspects of mental construction depending on task demands (Hassabis et al., 2014; Summerfield et al., 2010). Chapters 4 and 5 revealed manipulating the nature of envisaged scenes, particularly the social content, results in differential task performance. Therefore, further investigation of potential prefrontal contributions in the generation of more diverse classes of mental imagery may elucidate potential higher-order contributions from these regions. Indeed, given socio-emotional (Kable & Glimcher, 2007) and relational processing (Blumenfeld et al., 2011) both, in part, rely on prefrontal regions, further exploration of more extensive neural contributions to scene generation may be particularly important for social and incongruent construction. Nonetheless, the hippocampal mediated scene construction deficits identified in bvFTD point to the centrality of hippocampal contributions in subtending a reduced capacity for mental imagery across different neurological populations (Hassabis, Kumaran, Vann, et al., 2007; Mullally et al., 2014; Race et al., 2011).

Considering these findings in relation to previously identified scene construction deficits in AD (Irish et al., 2015), Chapter 3 revealed the reduced capacity for mental imagery in bvFTD patients was comparable to that seen in AD. Nonetheless, neuroimaging analyses suggested that these impairments were mediated by divergent neural substrates, with disrupted scene processing in AD

associated primarily with atrophy in posterior parietal regions and the posterior cingulate cortex. Interestingly, extant reports support parietal regions as particularly contributing to the contextual richness of an imagined scene (Ramanan, Piguet, et al., 2018). Findings from Chapter 3 demonstrated AD patients produced scenes of significantly less quality than bvFTD patients, within the context of similar overall content deficits. The differential neural networks subtending mental imagery in bvFTD and AD patients also complement the findings from Chapter 4 which revealed manipulating the sociality of the envisaged cue resulted in distinct profiles of task performance across dementia syndromes. Findings from Chapter 5 also support the nature of envisaged scenes recruiting cognitive processes known to be supported by different neural structures, for example, semantic and episodic contributions. Greater task complexity also resulted in subtle differences between dementia syndromes, however, greater exploration of these differences within the context of broader cognitive deficits is required. Collectively, these findings converge well with previous reports that the generation of richly detailed mental imagery is supported by the capacity for complex, multi-modal integration (Hassabis & Maguire, 2007; Summerfield et al., 2010; Zeidman et al., 2015) with the relative input from various neural regions possibly dependent upon the nature of the stimuli.

7.2 Evidence for Discrete Classes of Mental Construction

The need for multi-modal integration in scene construction has been previously reported (Hassabis & Maguire, 2007; Summerfield et al., 2010; Zeidman et al., 2015). The extent to which manipulating the nature of the imagined scene modifies the relative contribution from various cognitive domains, however, and in turn task performance, has remained relatively unexplored. Findings from this thesis considerably add to the existing literature regarding the cognitive

architecture of mental imagery by identifying social construction as a potentially discrete class of mental construction which further moderates task performance dependent on congruency.

7.2.1 Social construction

Chapter 3 revealed the capacity for mental construction in bvFTD and AD was comparably reduced relative to healthy controls. Findings from Chapter 4, however, revealed disproportionate deficits in social, relative to non-social, construction in bvFTD. The failure to identify a similar effect in AD is consistent with the differential social-cognitive profile displayed by these dementia syndromes (McKhann et al., 2011; Rascovsky et al., 2011). Importantly, the social scenes appeared to elicit a significant increase in socio-emotional details, relative to non-social scenes, in both AD and control groups which was not evident in bvFTD patients. Due to the inherent complexity of social situations (Lieberman et al., 2019), the integration of social information into a constructed scene likely requires additional cognitive resources to appropriately populate the scene with the relevant socio-emotional detail. Given the decreased salience of socio-emotional context (Ibanez & Manes, 2012) and profound social deficits which characterise bvFTD (Rascovsky et al., 2011), this reduced socio-emotional richness may stem from a broader decline in social-cognitive reserve in this syndrome. More importantly, differential task performance in bvFTD and AD groups – despite equivalent deficits on a standard scene construction task in Chapter 3 - point to the mental simulation of social scenes forming a discrete class of mental construction which is supported by the integration of additional socio-emotional contextual detail.

7.2.2 Sociality and incongruent construction

The capacity for mental construction is intricately associated with both our previous experiences and knowledge of the world (Mullally & Maguire, 2014). The relative contribution of, and interplay between, episodic and semantic processes in generating richly detailed mental scenarios

has been widely reported (Addis et al., 2010; Devitt et al., 2017; Irish & Piguet, 2013). Semantic knowledge has been particularly identified as providing an essential framework upon which many of our mental experiences are formed, including future thinking and scene construction (Irish et al., 2017; Renoult, Irish, Moscovitch, Rugg, 2019). Although manipulating task congruency alone failed to reveal significant differences in performance (Chapter 5), limiting the recruitment of episodic contributions, and in turn, increasing semantic engagement, resulted in differential performance in both patient groups across social conditions. Relative to social incongruent cues, non-social incongruent cues evoked more richly detailed scene descriptions from both bvFTD and AD patients. This suggests the potential increased semantic load associated with non-social incongruent scene elements may modify task performance due to being driven by differential cognitive and neural mechanisms relative to more commonplace scene generation. Nevertheless, the increased contextual detail in non-social incongruent scenes was not reflected in the level to which the elements were integrated and immersed *within the scene*, supporting previous findings in medial temporal amnesia regarding the capacity to generate detail without necessarily evoking richly integrated, cohesive mental imagery (Lynch et al., 2020). Finally, given the increased reliance on spatial elements in constructing incongruent non-social scenes identified across both patient and control groups, these findings collectively highlight semantic and spatial scaffolding in potentially supporting mental construction when episodic and social resources are limited.

7.3 Mental Simulation and Social Perception

The multifaceted nature of social interaction has been suggested to inherently require the incorporation of a range of cognitive and social information, recruiting multiple neural regions (Amodio, 2019; Mars et al., 2012). The theoretical need for an integrative hub in which to support this multi-modal input is therefore apparent. The contribution from hippocampal (Rubin et al.,

2014) and prefrontal regions (Eisenreich, Akaishi, & Hayden, 2017) to cognitive flexibility and executive control, as well as their role in mental imagery (Bertossi et al., 2016; Hassabis, Kumaran, Vann, et al., 2007; Wilson et al., 2020a) points to these regions as potentially working in concert to provide this hub. Impaired executive control has previously been implicated in the profound social deficits seen in bvFTD (Baez et al., 2019; Eslinger et al., 2007; Lough et al., 2006) and interestingly even in AD (Ramanan et al., 2017). The role of the vmPFC in mental imagery has particularly been identified as potentially supporting integrative facets of situational processing (Lieberman et al., 2019), as well as providing dynamic input into the generation and maintenance of envisaged scenes (McCormick et al., 2018). The importance of the hippocampus is also emerging in subtending a range of complex social endeavours, particularly thought to be due to its connectivity with prefrontal regions (Rubin et al., 2014).

The novel findings from Chapter 6 revealed the capacity for mental simulation, and particularly social simulation, was strongly associated with the degree to which bvFTD patient ratings diverged from control participants on a social perception task. These findings complement those from Chapter 4 suggesting a reduced capacity for social construction in bvFTD may contribute to the broader social deficits in this syndrome. Considering these findings within the context of the current literature, this adds to existing studies identifying reduced mental imagery in other neuro-psychiatric and developmental disorders associated with social deficits (Crespi et al., 2016; Lind, Williams, et al., 2014; Raffard et al., 2010). Importantly, these results also extend previous propositions regarding potential hippocampal contributions to social function via supporting flexible mental representations (Rubin et al., 2014). Speculatively, a reduced capacity for mental simulation in bvFTD appears to result in a disrupted ability to mentally integrate and manipulate

social information in order to simulate social scenarios, and therefore, make appropriate social contextual judgments.

7.4 Memory as the Foundation for Broader Cognitive and Social Functions

Memory plays an essential role in how we integrate our experiences across time in order to create the unique personal narrative which forms our sense of self (Strikwerda-Brown, Grilli, et al., 2019). Recent advances in memory research, however, point to a much broader role for how the structures supporting memory may help us interact with the world. The human capacity for inwardly directed thought drives much of our everyday cognitive experience (Buckner et al., 2008) and this is increasingly being attributed to the role of the default mode network, particularly the hippocampus, in generating richly detailed mental simulations (Maguire et al., 2016; Maguire & Mullally, 2013; Schacter et al., 2012). The relative contribution from mental imagery, and the memory systems which support it, to pro-social behaviour, however, has only recently gained momentum (Gaesser, 2020). This thesis considerably expands previous findings by highlighting the powerhouse of activity provided by the default mode network in supporting our ability to envisage, and ultimately interact with, the world and its people. Both episodic and semantic memory appear to particularly support the capacity to simulate the world, with the relative contribution from each of these cognitive domains highly dependent on the nature of the envisaged scene. The inherent emotional richness imbued in recalling social experiences outlined in Chapter 4, and the reliance on semantic knowledge in the generation of mental scenes when previous experiences are less salient (Chapter 5) speak to the dynamic interplay between episodic and semantic processes in supporting a broad range of cognitive and social-cognitive processes. Although further examination is necessary, in sum, hippocampal mediated deficits in scene imagery identified in bvFTD, support the role of this structure in a number of complex social

constructive processes beyond the domain of memory, albeit within the context of broader neural contributions.

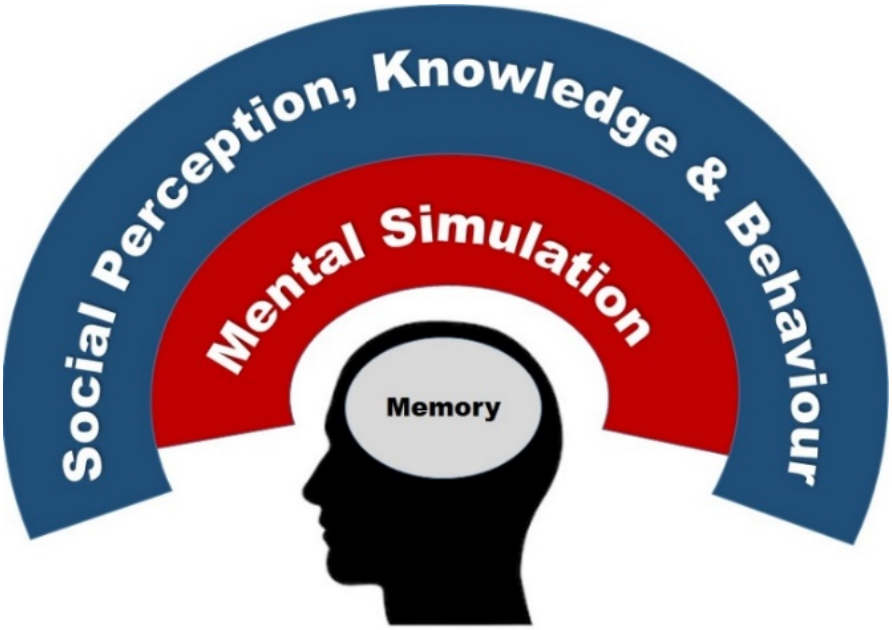

Figure 7.1. Schematic representation of the interrelationship between cognitive systems supporting memory, mental simulation, and broader social function. Largely supported by the default mode network (DMN), the capacity to envisage richly detailed mental scenes is associated with a range of cognitive immersive experiences, including autobiographical memory and future thinking. This thesis extends these findings by demonstrating the role of mental simulation in relation to broader social function in dementia syndromes.

7.5 Clinical Insights

The behavioural changes associated with bvFTD have been reported to cause the most substantial impact on carers and result in significant difficulties in accessing appropriate services (Etters et al., 2008; Hsieh et al., 2016). Considerable stigma also still exists, particularly in relation to some of the more sensitive behavioural characteristics which may be observed in bvFTD, such as sexual disinhibition and invading others' personal space (Mendez & Shapira, 2013), tending to make

going out in public increasingly problematic. Although the extent of these social difficulties has been well characterised in bvFTD, the mechanisms driving these behavioural changes remain relatively elusive. Expanding Vygotsky's (1967) view of imagination as a platform which allows for the creative recombination of previous experiences in order to facilitate new behaviour, the capacity for social simulation particularly could be conceived as a mental stage supporting the hypothetical enactment of scenarios in order to make appropriate social judgements. When this capacity breaks down, as in bvFTD, it may be harder to appropriately integrate this information and modify behaviour accordingly. The identification of a reduced capacity for mental imagery in bvFTD as a potential unifying mechanism supporting, or at least associated with, the social-cognitive deficits in this syndrome paves the way for future clinical interventions potentially targeting these processes.

The current findings also offer substantial implications in the differential diagnosis of dementia syndromes. Although social function is relatively preserved in AD, at least in the early stages (McKhann et al., 2011), differentiating AD and bvFTD on social-cognitive measures remains difficult due to many of these tasks being conflated with higher order cognitive processes, such as executive dysfunction, which may be disrupted across dementia syndromes (Bora et al., 2015; Reul et al., 2017; Shany-Ur et al., 2010). The current findings offer the pattern of deficits in relation to discrete classes of mental imagery as a potential diagnostic tool in the differentiation of bvFTD from AD. Although further work is needed to apply these outcomes to the bedside, the identification of differential profiles of mental imagery across dementia syndromes goes some way to elucidating the potential clinical utility of scene construction tasks which has, thus far, been lacking. Social simulation may provide the potential for more sensitive discrimination between

dementia syndromes due to its ability to capture aspects of diruspted social processing not measured on exisiting social-cogntive tasks.

7.6 Methodological Considerations

By its very definition, imagination refers to the capacity to perceive that which is not there (Nigel, 2020). Therefore, the systematic study of imagination is inherently difficult and not without its limitations. Of most importance in relation to this thesis is the unavoidable reliance on self-report measures, which although consistent with seminal cognitive neuroscience methodology within this domain (Hassabis et al., 2007), must be considered within the context of the limitations of subjective reports (Miloyan, & McFarlane, 2019). Of course, studying the subjective experience of a clinical population such as bvFTD which is characterised by a profound lack of personal insight (Mendez & Shapira, 2011) merely adds to this caveat. Nevertheless, the scene construction methods on which this thesis is largely based have been extensively used in clinical populations and serve as an exemplar of the ways in which memory research can be both standardised and modified to examine this emerging cognitive domain (Hassabis & Maguire, 2007). Indeed, given the inherent subjectivity of mental simulation research, relating findings within this area to real world applications is paramount and highlights the importance of the findings from Chapter 6 in the potential clinical utility of these tasks.

A second limitation of particular importance is the inherent reliance on verbal expression and fluency in the investigation of mental scenes, potentially conflating language ability with task performance. Although previous reports have suggested narrative ability is dissociated from constructive performance (Race et al., 2011), this limitation was pre-empted prior to conducting these clinical studies by conducting pilot testing utilising a picture description task containing a

farmyard scene. Although group comparisons, $H\ (2) = 17.72$, $p \leq .0001$, on a subset of participants showed the patient groups did produce descriptions containing significantly fewer words than controls (both $p \leq .007$, control $n = 19$, $M = 241.89$, $SD = 43.52$), no significant difference between bvFTD and AD patients was revealed ($p = .678$; bvFTD, $n = 15$, $M = 132.60$, $SD = 61.54$; AD, $n = 4$, $M = 112.25$, $SD = 30.10$). While failing to address the potential for narrative deficits in dementia syndromes to confound scene construction performance, these results impart some confidence that the differential task performance across dementia syndromes in this thesis was not due to differences in narrative ability. In addition, statistical comparison of the two patient groups on verbal fluency was performed for all studies. Nonetheless, the heavy reliance on verbal measures, although unavoidable, should be within mind when considering the findings.

Potential confounding differences in the nature of the scene cues must also be considered. Similar to the challenges associated with visual perceptual tasks, such as figure ground organisation (Wagemans et al., 2012), comparing across scenes inherently opens the possibility for differences in scene complexity. The many different sources of richly detailed information and emotional associations contained in real-world visual scenes is enormously difficult to control across task conditions. It cannot be said that findings from this thesis fully account for these differences, nor was it the aim of this thesis to do so. By manipulating scene conditions in order to more fully examine the nature of mental construction, however, these findings serve as the foundation for further research unpacking the potentially extensive variables supporting the complexities of mental imagery.

7.7 Summary and Final Remarks

The premise that imagination may serve as a hub through which everyday experiences are integrated and interpreted is not new. Theories pertaining to the essential role of imagination in human cognition stretch as far back as Aristotle and his musings "On The Soul" (*De Anima*; 350 BC, as cited in Nigel, 2020). Indeed, the capacity to perceive that which is not there, and conceive alternatives to what is, has been suggested to hold an important human evolutionary advantage (Suddendorf & Redshaw, 2013). This thesis traced the emergence of the cognitive domain of imagination from its philosophical beginnings, to its neural architecture and the increasing identification of its role in everyday cognition, and particularly social cognition. Evidence supporting the clinical importance of mental simulation continues to mount. The novel findings from this thesis pertaining to possibly discrete classes of mental construction expand current conceptions of the cognitive architecture of mental simulation in neurodegenerative disorders. More importantly, by demonstrating profound, and clinically distinct, deficits in the capacity for mental simulation across dementia syndromes, these findings pave the way for improved dementia diagnosis and management. In conclusion, the breakdown of mental simulation in neurodegenerative disease outlined in this thesis offers a small glimpse into life without a mental stage and raises the curtain on future work unpacking the common and discrete elements of this historically revered human ability.

References

Abraham, A., & Bubic, A. (2015). Semantic memory as the root of imagination. *Frontiers in Psychology, 6*, 1–5. https://doi.org/10.3389/fpsyg.2015.00325

Addington, J., Saeedi, H., & Addington, D. (2006). Influence of social perception on cognitive and social functioning in psychosis. *British Journal of Psychiatry, 189*, 373–378.

Addis, D. R. (2018). Are episodic memories special? On the sameness of remembered and imagined event simulation. *Journal of the Royal Society of New Zealand, 48*(2–3), 64–88. https://doi.org/10.1080/03036758.2018.1439071

Addis, D. R., Musicaro, R., Pan, L., & Schacter, D. (2010). Episodic simulation of past and future events in older adults: Evidence from an experimental recombination task. *Psychology and Aging, 25*(2), 369–376. https://doi.org/10.1037/a0017280.Episodic

Adolphs, R. (2009). The social brain: Neural basis of social knowledge. *Annual Review of Psychology, 60*(60), 693–716. https://doi.org/10.1146/annurev.psych.60.110707.163514.The

Amodio, D. M. (2019). Social Cognition 2.0: An interactive memory systems account. *Trends in Cognitive Sciences, 23*(1), 21–33. https://doi.org/10.1016/j.tics.2018.10.002

Andersson, J. L. R., Jenkinson, M., & Smith, S. (2007). Non-linear optimisation. FMRIB Technical Report (Vol. TR07JA1). Oxford.

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-anatomic fractionation of the brain's default network. *Neuron, 65*(4), 550–562. https://doi.org/10.1016/j.neuron.2010.02.005

Arioli, M., Crespi, C., & Canessa, N. (2018). Social cognition through the lens of cognitive and clinical neuroscience. *BioMed Research International*, 2018. https://doi.org/10.1155/2018/4283427

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry - The methods. *NeuroImage, 11*(6 I), 805–821. https://doi.org/10.1006/nimg.2000.0582

Auger, S. D., Zeidman, P., & Maguire, E. A. (2017). Efficacy of navigation may be influenced by retrosplenial cortex-mediated learning of landmark stability. *Neuropsychologia, 104*(April), 102–112. https://doi.org/10.1016/j.neuropsychologia.2017.08.012

Baez, S., Garcia, A. M., & Ibanez, A. (2016). The social context model of psychiatric and neurological diseases. In W. M. & S. Krach (Eds.), *Social Behaviour from Rodents to Humans: Current Topics in Behavioural Neuroscience (Vol. 30).* Springer, Cham.

Baez, Sandra, Pinasco, C., Roca, M., Ferrari, J., Couto, B., García-Cordero, I., … Torralva, T. (2019). Brain structural correlates of executive and social cognition profiles in behavioural variant frontotemporal dementia and elderly bipolar disorder. *Neuropsychologia, 126*, 159-169. https://doi.org/10.1016/j.neuropsychologia.2017.02.012

Baron-Cohen, S. (2002). *Faux Pas Recognition Test* (Adult Version), 1–47.

Barry, D. N., Barnes, G. R., Clark, I. A., & Maguire, E. A. (2018). The neural dynamics of novel scene imagery. BioRxiv, 39(22), 4375–4386. https://doi.org/10.1101/429274

Bejanin, A., Chételat, G., Laisney, M., Pélerin, A., Landeau, B., Merck, C., … Desgranges, B. (2017). Distinct neural substrates of affective and cognitive theory of mind impairment in

semantic dementia. Social Neuroscience, 12(3), 287–302. https://doi.org/10.1080/17470919.2016.1168314

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological), 57*(1), 289-300.

Benoit, R. G., & Schacter, D. L. (2015). Specifying the core network supporting episodic simulation and episodic memory by activation likelihood estimation. *Neuropsychologia, 75*(8), 450–457. https://doi.org/10.1016/j.bbamem.2015.02.010.Cationic

Benoit, R. G., Szpunar, K. K., & Schacter, D. L. (2014). Ventromedial prefrontal cortex supports affective future simulation by integrating distributed knowledge. *Proceedings of the National Academy of Sciences, 111*(46), 16550–16555. https://doi.org/10.1073/pnas.1419274111

Bertossi, E., Aleo, F., Braghittoni, D., & Ciaramelli, E. (2016). Stuck in the here and now: Construction of fictitious and future experiences following ventromedial prefrontal damage. *Neuropsychologia, 81*, 107–116. https://doi.org/10.1016/j.neuropsychologia.2015.12.015

Bertoux, M., De Souza, L. C., Corlier, F., Lamari, F., Bottlaender, M., Dubois, B., & Sarazin, M. (2014). Two distinct amnesic profiles in behavioural variant frontotemporal dementia. *Biological Psychiatry, 75*(7), 582–588. https://doi.org/10.1016/j.biopsych.2013.08.017

Blumen, H. M., Rajaram, S., & Henkel, L. (2013). The applied value of collaborative memory research in aging: Behavioral and neural considerations. *Journal of Applied Research in Memory and Cognition, 2*(2), 107–117. https://doi.org/10.1016/j.jarmac.2013.03.003

Blumenfeld, R. S., Parks, C. M., Yonelinas, A. P., & Ranganath, C. (2011). Putting the pieces together: The role of dorsolateral prefrontal cortex in relational memory encoding. *Journal of Cognitive Neuroscience, 23*(1), 257–265. https://doi.org/10.1162/jocn.2010.21459.Putting

Bora, E., Walterfang, M., & Velakoulis, D. (2015). Theory of mind in behavioural-variant frontotemporal dementia and Alzheimer's disease: A meta-analysis. *Journal of Neurology, Neurosurgery and Psychiatry, 86*(7), 714–719. https://doi.org/10.1136/jnnp-2014-309445

Bottiroli, S., Cavallini, E., Ceccato, I., Vecchi, T., & Lecce, S. (2016). Theory of Mind in aging: Comparing cognitive and affective components in the faux pas test. *Archives of Gerontology and Geriatrics, 62*, 152–162. https://doi.org/10.1016/j.archger.2015.09.009

Boutoleau-Bretonnière, C., Vercelletto, M., Volteau, C., Renou, P., & Lamy, E. (2008). Zarit burden inventory and activities of daily living in the behavioural variant of frontotemporal dementia. *Dementia and Geriatric Cognitive Disorders, 25*(3), 272–277. https://doi.org/10.1159/000117394

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences, 1124*(1), 1–38. https://doi.org/10.1196/annals.1440.011

Bulley, A., Henry, J. D., & Suddendorf, T. (2017). Thinking about threats: Memory and prospection in human threat management. *Consciousness and Cognition, 49*, 53–69. https://doi.org/10.1016/j.concog.2017.01.005

Bulley, A., Henry, J., & Suddendorf, T. (2016). Prospection and the present moment: The role of episodic foresight in intertemporal choices between immediate and delayed rewards. *Review of General Psychology, 20*(1), 29–47. https://doi.org/10.1037/gpr0000061

Burgess, P. W., & Shallice, T. (1997). *The Hayling and Brixton Tests*. Bury St Edmunds, UK: Thames Valley Test Company.

Callenmark, B., Kjellin, L., Rönnqvist, L., & Bölte, S. (2014). Explicit versus implicit social cognition testing in autism spectrum disorder. *Autism: The International Journal of Research and Practice, 18*(6), 684–693. https://doi.org/10.1177/1362361313492393

Chemali, Z., Withall, A., & Daffner, K. R. (2010). The plight of caring for young patients with frontotemporal dementia. *American Journal of Alzheimer's Disease and Other Dementias, 25*(2), 109–115. https://doi.org/10.1177/1533317509352335

Ciaramelli, E., Luca, F. De, Monk, A. M., Mccormick, C., & Maguire, E. A. (2019). What "wins" in vmPFC: Scenes, situations, or schema? *Neuroscience and Biobehavioral Reviews, 100*(April), 208–210. https://doi.org/10.1016/j.neubiorev.2019.03.001

Clark, I. A., & Maguire, E. A. (2016). Remembering preservation in hippocampal amnesia. Annual Review of Psychology, 67, 51–82. https://doi.org/10.1146/annurev-psych-122414-033739

Conti, F., & Irish, M. (in press). Harnessing visual imagery and oculomotor behaviour to understand prospection. *Trends in Cognitive Sciences*.

Conway, M. A., & Pleydell-Pearce, C. W. (2000). The construction of autobiographical memories in the Self-Memory System. *Psychological Review, 107*(2), 261–288.

Coyle-Gilchrist, I. T. S., Dick, K. M., Patterson, K., Rodríquez, P. V., Wehmann, E., Wilcox, A., … Rowe, J. B. (2016). Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. *Neurology, 86*(18), 1736–1743. https://doi.org/10.1212/WNL.0000000000002638

Crespi, B., Leach, E., Dinsdale, N., Mokkonen, M., & Hurd, P. (2016). Imagination in human social cognition, autism, and psychotic-affective conditions. *Cognition, 150*, 181–199. https://doi.org/10.1016/j.cognition.2016.02.001

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The neuropsychiatric inventory: Comprehensive assessment of psychopathology in dementia. *Neurology, 44*(12), 2308–2314. https://doi.org/10.1212/wnl.44.12.2308

D'Argembeau, A., Raffard, S., & Van der Linden, M. (2008). Remembering the past and imagining the future in schizophrenia. *Journal of Abnormal Psychology, 117*(1), 247–251. https://doi.org/10.1037/0021-843X.117.1.247

Dalton, M. A., & Maguire, E. A. (2017). The pre/parasubiculum: A hippocampal hub for scene-based cognition? *Current Opinion in Behavioural Sciences, 17*, 34–40. https://doi.org/10.1016/j.cobeha.2017.06.001

Dang, T. P., Mattan, B. D., Kubota, J. T., & Cloutier, J. (2019). The ventromedial prefrontal cortex is particularly responsive to social evaluations requiring the use of person-knowledge. *Scientific Reports, 9*(1), 1–11. https://doi.org/10.1038/s41598-019-41544-z

De Luca, F., McCormick, C., Mullally, S. L., Intraub, H., Maguire, E. A., & Ciaramelli, E. (2018). Boundary extension is attenuated in patients with ventromedial prefrontal cortex damage. *Cortex, 108*, 1–12. https://doi.org/10.1016/j.cortex.2018.07.002

Delbeuck, X., Pollet, M., Pasquier, F., Bombois, S., & Moroni, C. (2020). The clinical value of the Faux Pas Test for diagnosing behavioural-variant frontotemporal dementia. *Journal of Geriatric Psychiatry and Neurology*, 089198872096425. https://doi.org/10.1177/0891988720964253

Dementia Australia. (2018). *Dementia Prevalence Data 2018-2058*. Retrieved from https://www.dementia.org.au/information/statistics/prevalence-data

Demichelis, O. P., Coundouris, S. P., Grainger, S. A., & Henry, J. D. (2020). Empathy and Theory of Mind in Alzheimer's Disease: A meta-analysis. *Journal of the International Neuropsychological Society, 26*(10), 963–977. https://doi.org/10.1017/S1355617720000478

Dermody, N., Wong, S., Ahmed, R., Piguet, O., Hodges, J. R., & Irish, M. (2016). Uncovering the neural bases of cognitive and affective empathy deficits in Alzheimer's disease and the behavioral-variant of frontotemporal dementia. Journal of Alzheimer's Disease, 53(3), 801–816.

Desaunay, P., Briant, A. R., Bowler, D. M., Ring, M., Gérardin, P., Baleyte, J. M., … Guillery-Girard, B. (2020). Memory in autism spectrum disorder: A meta-analysis of experimental studies. *Psychological Bulletin, 146*(5), 377–410. https://doi.org/10.1037/bul0000225

Devitt, A. L., Addis, D. R., & Schacter, D. L. (2017). Episodic and semantic content of memory and imagination : A multilevel analysis. *Memory and Cognition, 45*(7), 1078–1094. https://doi.org/10.3758/s13421-017-0716-1

Dewey, M. (1991). Living with Asperger's syndrome. In F. Uta (Ed.), *Autism and Asperger Syndrome* (pp. 184–206). London, UK: Cambridge University Press. https://doi.org/10.1177/1362361309353616

Ding, J., Chen, K., Liu, H., Huang, L., Chen, Y., Lv, Y., … Lambon Ralph, M. A. (2020). A unified neurocognitive model of semantics language social behaviour and face recognition in semantic dementia. *Nature Communications, 11*(1), 1–14. https://doi.org/10.1038/s41467-020-16089-9

Dodich, A., Crespi, C., Santi, G. C., Cappa, S. F., & Cerami, C. (2020). Evaluation of discriminative detection abilities of social cognition measures for the diagnosis of the behavioural variant of frontotemporal dementia: A systematic review. *Neuropsychology Review*. https://doi.org/10.1007/s11065-020-09457-1

Dos Santos, T. T., de Carvalho, R. L., Nogueira, M., Baptista, M. A., Kimura, N., Lacerda, I. B., &, & Dourado, M. C. (2020). The relationship between social cognition and executive functions in Alzheimer's disease: A systematic review. *Current Alzheimer's Research, 17*(5), 487–497.

Duff, M. C., Covington, N. V., Hilverman, C., & Cohen, N. J. (2020). Semantic memory and the hippocampus: Revisiting, reaffirming, and extending the reach of their critical relationship. *Frontiers in Human Neuroscience, 13*(Jan), 1–17. https://doi.org/10.3389/fnhum.2019.00471

Eichenbaum, H., & Cohen, N. J. (2014). Can we reconcile the declarative memory and spatial navigation views on hippocampal function? *Neuron, 83*(4), 764–770. https://doi.org/10.1016/j.neuron.2014.07.032

Eisenreich, B. R., Akaishi, R., & Hayden, B. Y. (2017). Control without controllers: Toward a distributed neuroscience of executive control. *Journal of Cognitive Neuroscience, 29*(10), 1684–1698. https://doi.org/doi:10.1162/jocn_a_01139

Eslinger, P. J., Moore, P., Troiani, V., Antani, S., Cross, K., Kwok, S., & Grossman, M. (2007). Oops! Resolving social dilemmas in frontotemporal dementia. *Journal of Neurology, Neurosurgery and Psychiatry, 78*(5), 457–460. https://doi.org/10.1136/jnnp.2006.098228

Etters, L., Goodall, D., & Harrison, B. E. (2008). Caregiver burden among dementia patient caregivers: A review of the literature. *Journal of the American Academy of Nurse Practitioners, 20*(8), 423–428. https://doi.org/10.1111/j.1745-7599.2008.00342.x

Field, A. (2009). *Discovering Statistics Using SPSS*. Sage Publication (Vol. 58). https://doi.org/10.1234/12345678

Frisch, S., Dukart, J., Vogt, B., Horstmann, A., Becker, G., Villringer, A., … Schroeter, M. L. (2013). Dissociating memory networks in early Alzheimer's disease and frontotemporal lobar degeneration: A combined study of hypometabolism and atrophy. *PLoS ONE, 8*(2). https://doi.org/10.1371/journal.pone.0055251

Fukuhara, K., Ogawa, Y., Tanaka, H., Nagata, Y., Nishida, S., Haga, D., & Nishikawa, T. (2017). Impaired interpretation of others' behaviour is associated with difficulties in recognizing pragmatic language in patients with schizophrenia. *Journal of Psycholinguistic Research, 46*(5), 3–7. https://doi.org/10.1007/s10936-017-9497-8

Gaesser, B. (2020). Episodic mindreading: Mentalizing guided by scene construction of imagined and remembered events. *Cognition, 203*(May), 104325. https://doi.org/10.1016/j.cognition.2020.104325

Gaesser, B., Keeler, K., & Young, L. (2018). Moral imagination: Facilitating prosocial decision-making through scene imagery and theory of mind. *Cognition, 171*, 180–193. https://doi.org/10.1016/j.cognition.2017.11.004

Gaesser, B., & Schacter, D. L. (2014). Episodic simulation and episodic memory can increase intentions to help others. *Proceedings of the National Academy of Sciences, 111*(12), 4415–4420. https://doi.org/10.1073/pnas.1402461111

Ghosh, V. E., & Gilboa, A. (2014). What is a memory schema? A historical perspective on current neuroscience literature. *Neuropsychologia, 53*(1), 104–114. https://doi.org/10.1016/j.neuropsychologia.2013.11.010

Gilboa, A., & Marlatte, H. (2017). Neurobiology of schemas and schema-mediated memory. *Trends in Cognitive Sciences, 21*(8), 618–631. https://doi.org/10.1016/j.tics.2017.04.013

Gilmore, A. W., Nelson, S. M., Chen, H.-Y. Y., & McDermott, K. B. (2018). Task-related and resting-state fMRI identify distinct networks that preferentially support remembering the past and imagining the future. *Neuropsychologia, 110*, 180–189. https://doi.org/10.1016/j.neuropsychologia.2017.06.016

Greene, M. R., Baldassano, C., Esteva, A., Beck, D. M., & Fei-Fei, L. (2016). Visual scenes are categorized by function. *Journal of Experimental Psychology: General, 145*(1), 82–94. https://doi.org/10.1037/xge0000129

Halberstadt, J., Ruffman, T., Murray, J., Taumoepeau, M., & Ryan, M. (2011). Emotion perception explains age-related differences in the perception of social gaffes. *Psychology and Aging, 26*(1), 133–136. https://doi.org/10.1037/a0021366

Hassabis, D., Kumaran, D., & Maguire, E. A. (2007). Using imagination to understand the neural basis of episodic memory. *Journal of Neuroscience, 27*(52), 14365–14374. https://doi.org/10.1523/jneurosci.4549-07.2007

Hassabis, D., Kumaran, D., Vann, S. D., & Maguire, E. A. (2007). Patients with hippocampal amnesia cannot imagine new experiences. *Proceedings of the National Academy of Sciences, 104*(5), 1726–1731. https://doi.org/10.1073/pnas.0610561104

Hassabis, D., & Maguire, E. A. (2007). Deconstructing episodic memory with construction. *Trends in Cognitive Sciences, 11*(7), 299–306. https://doi.org/10.1016/j.tics.2007.05.001

Hassabis, D., & Maguire, E. A. (2009). The construction system of the brain. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 364*, 1263–1271. https://doi.org/10.1093/acprof:oso/9780195395518.003.0026

Hassabis, D., Spreng, R. N., Rusu, A. A., Robbins, C. A., Mar, R. A., & Schacter, D. L. (2014). Imagine all the people: How the brain creates and uses personality models to predict behaviour. *Cerebral Cortex, 24*(8), 1979–1987. https://doi.org/10.1093/cercor/bht042

Hebscher, M., Levine, B., & Gilboa, A. (2017). The precuneus and hippocampus contribute to individual differences in the unfolding of spatial representations during episodic autobiographical memory. *Neuropsychologia*, *110*, 123-133. https://doi.org/10.1016/j.neuropsychologia.2017.03.029

Henry, J. D., Phillips, L. H., & Von Hippel, C. (2014). A meta-analytic review of theory of mind difficulties in behavioural-variant frontotemporal dementia. *Neuropsychologia, 56*(1), 53–62. https://doi.org/10.1016/j.neuropsychologia.2013.12.024

Henry, J. D., Terrett, G., Grainger, S. A., Rose, N. S., Kliegel, M., Bugge, M., … Rendell, P. G. (2020). Implementation Intentions and Prospective Memory Function in Late Adulthood. *Psychology and Aging*, *35*(8), 1105–1114. https://doi.org/10.1037/pag0000563

Hirsch, C. R., & Holmes, E. A. (2007). Mental imagery in anxiety disorders. *Psychiatry*, *6*(4) 161-165.

Hiser, J., & Koenigs, M. (2018). The multifaceted role of ventromedial prefrontal cortex in emotion, decision-making, social cognition, and psychopathology. Biological Psychiatry, *83*(8), 638–647. https://doi.org/10.1016/j.biopsych.2017.10.030.The

Hodges, J. R., Patterson, K., Oxbury, S., & Funnell, E. (1992). Semantic dementia: Progressive fluent aphasia with temporal lobe atrophy. *Brain, 115*, 1783–1806.

Holmes, E. A., Blackwell, S. E., Burnett Heyes, S., Renner, F., & Raes, F. (2016). Mental imagery in depression: Phenomenology, potential mechanisms, and treatment implications. *Annual Review of Clinical Psychology, 12*, 249–280. https://doi.org/10.1146/annurev-clinpsy-021815-092925

Holmes, E. A., Geddes, J. R., Colom, F., & Goodwin, G. M. (2008). Mental imagery as an emotional amplifier: Application to bipolar disorder. *Behaviour Research and Therapy, 46*(12), 1251–1258. https://doi.org/10.1016/j.brat.2008.09.005

Hornberger, M., Piguet, O., Graham, A. J., Nestor, P. J., & Hodges, J. R. (2010). How preserved is episodic memory in behavioral variant frontotemporal dementia? *Neurology, 74*(6), 472–479. https://doi.org/10.1212/WNL.0b013e3181cef85d

Hsieh, S., Leyton, C. E., Caga, J., Flanagan, E., Kaizik, C., O'Connor, C. M., … Mioshi, E. (2016). The evolution of caregiver burden in frontotemporal dementia with and without amyotrophic lateral sclerosis. *Journal of Alzheimer's Disease, 49*(3), 875–885. https://doi.org/10.3233/JAD-150475

Hsieh, S., Schubert, S., Hoon, C., Mioshi, E., & Hodges, J. R. (2013). Validation of the Addenbrooke's Cognitive Examination III in frontotemporal dementia and Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 36*(3–4), 242–250. https://doi.org/10.1159/000351671

Hurley, N. C., Maguire, E. A., & Vargha-khadem, F. (2011). Patient HC with developmental amnesia can construct future scenarios. *Neuropsychologia, 49*(13), 3620–3628. https://doi.org/10.1016/j.neuropsychologia.2011.09.015

Hutchings, R., Hodges, J. R., Piguet, O., & Kumfor, F. (2015). Why should I care? Dimensions of socio-emotional cognition in younger-onset dementia. *Journal of Alzheimer's Disease, 48*(1), 135–147. https://doi.org/10.3233/JAD-150245

Hutchings, R., Palermo, R., Piguet, O., & Kumfor, F. (2017). Disrupted face processing in frontotemporal dementia: A review of the clinical and neuroanatomical evidence. *Neuropsychology Review, 27*(1), 18–30. https://doi.org/10.1007/s11065-016-9340-2

Ibáñez, A. (2018). Brain oscillations, inhibition and social inappropriateness in frontotemporal degeneration. *Brain, 141*(10), 1–3. https://doi.org/10.1093/brain/awy233

Ibanez, A., & Manes, F. (2012). Contextual social cognition and the behavioural variant of frontotemporal dementia. *Neurology, 78*(17), 1354–1362. https://doi.org/10.1212/WNL.0b013e3182518375

Irish, M., Addis, D. R., Hodges, J. R., & Piguet, O. (2012). Considering the role of semantic memory in episodic future thinking: Evidence from semantic dementia. *Brain, 135*(7), 2178–2191. https://doi.org/10.1093/brain/aws119

Irish, M., Eyre, N., Dermody, N., O'Callaghan, C., Hodges, J. R., Hornberger, M., … Piguet, O. (2016). Neural substrates of semantic prospection: Evidence from the dementias. *Frontiers in Behavioural Neuroscience, 10*(Nov), 96. https://doi.org/10.3389/fnbeh.2016.00096

Irish, M., Halena, S., Kamminga, J., Tu, S., Hornberger, M., & Hodges, J. R. (2015). Scene construction impairments in Alzheimer's disease: A unique role for the posterior cingulate cortex. *Cortex*, 73, 10–23. https://doi.org/10.1016/j.cortex.2015.08.004

Irish, M., Hodges, J. R., & Piguet, O. (2014). Right anterior temporal lobe dysfunction underlies theory of mind impairments in semantic dementia. *Brain, 137*(4), 1241–1253. https://doi.org/10.1093/brain/awu003

Irish, M., Mothakunnel, A., Dermody, N., Wilson, N.-A., Hodges, J. R., & Piguet, O. (2017). Damage to right medial temporal structures disrupts the capacity for scene construction: A case study. *Hippocampus, 27*(6). https://doi.org/10.1002/hipo.22722

Irish, M., & Piguet, O. (2013). The pivotal role of semantic memory in remembering the past and imagining the future. *Frontiers in Behavioural Neuroscience, 7*(Apr), 27. https://doi.org/10.3389/fnbeh.2013.00027

Irish, M., Piguet, O., Hodges, J. R., & Hornberger, M. (2014). Common and unique grey matter correlates of episodic memory dysfunction in frontotemporal dementia and Alzheimer's disease. *Human Brain Mapping*, *35*(4), 1422–1435. https://doi.org/10.1002/hbm.22263

Irish, M., & Piolino, P. (2016). Impaired capacity for prospection in the dementias - Theoretical and clinical implications. *British Journal of Clinical Psychology*, *55*(1), 49–68. https://doi.org/10.1111/bjc.12090

Irish, M, Hornberger, M., Lah, S., Miller, L., Pengas, G., Nestor, P. J., … Piguet, O. (2011). Profiles of recent autobiographical memory retrieval in semantic dementia, behavioural-variant frontotemporal dementia, and Alzheimer's disease. *Neuropsychologia*, *49*(9), 2694–2702. https://doi.org/10.1016/j.neuropsychologia.2011.05.017

Irish, M., Hodges, J. R., & Piguet, O. (2013). Episodic future thinking is impaired in the behavioural variant of frontotemporal dementia. *Cortex*, *49*(9), 2377–2388. https://doi.org/10.1016/j.cortex.2013.03.002

Irish, M., Landin-Romero, R., Mothakunnel, A., Ramanan, S. S., Hsieh, S., Hodges, J. R., & Piguet, O. (2018). Evolution of autobiographical memory impairments in Alzheimer's disease and frontotemporal dementia – A longitudinal neuroimaging study. *Neuropsychologia*, *110*(Mar), 14–25. https://doi.org/10.1016/j.neuropsychologia.2017.03.014

Irish, M., & van Kesteren, M. T. R. (2018). New perspectives on the brain lesion approach: Implications for theoretical models of human memory. *Neuroscience, 374*, 319–322. https://doi.org/10.1016/j.neuroscience.2017.10.049

Kable, J. W., & Glimcher, P. W. (2007). The neural correlates of subjective value during intertemporal choice. *Nature Neuroscience, 10*(12), 1625+. https://doi.org/10.1038/nn2007.The

Karantzoulis, S., & Galvin, J. E. (2011). Distinguishing Alzheimer's disease from other major forms of dementia. *Expert Review of Neurotherapeutics*, *11*(11), 1579–1591. https://doi.org/10.1586/ern.11.155

Karas, G. B., Scheltens, P., Rombouts, S. A. R. B., Visser, P. J., Van Schijndel, R. A., Fox, N. C., & Barkhof, F. (2004). Global and local grey matter loss in mild cognitive impairment and Alzheimer's disease. *NeuroImage*, *23*(2), 708–716. https://doi.org/10.1016/j.neuroimage.2004.07.006

Keane, M. M., Bousquet, K., Wank, A., & Verfaellie, M. (2020). Relational processing in the semantic domain is impaired in medial temporal lobe amnesia. *Journal of Neuropsychology, 14*(3), 416–430. https://doi.org/10.1111/jnp.12196

Kipps, C. M., Nestor, P. J., Arnold, R., Hodges, J. R., Acosta-Cabronero, J., Arnold, R., & Hodges, J. R. (2009). Understanding social dysfunction in the behavioural variant of frontotemporal dementia: The role of emotion and sarcasm processing. *Brain, 132*(3), 592–603. https://doi.org/10.1093/brain/awn314

Knopman, D. S., Weintraub, S., & Pankratz, V. S. (2011). Language and behaviour domains enhance the value of the clinical dementia rating scale. *Alzheimer's and Dementia, 7*(3), 293–299. https://doi.org/10.1016/j.jalz.2010.12.006

Koechlin, E., Ody, C., & Kouneiher, F. (2003). The architecture of cognitive control in the human prefrontal cortex. *Science*, *302*(5648), 1181–1185. https://doi.org/10.1126/science.1088545

Kolodner, J. (1983). Reconstructive memory: A computer model. *Cognitive Science*, 281328(7), 281–328.

Kumfor, F., Honan, C., McDonald, S., Hazelton, J. L., Hodges, J. R., & Piguet, O. (2017). Assessing the "social brain" in dementia: Applying TASIT-S. *Cortex*, *93*, 166–177. https://doi.org/10.1016/j.cortex.2017.05.022

Kumfor, F., Ibañez, A., Hutchings, R., Hazelton, J. L., Hodges, J. R., & Piguet, O. (2018). Beyond the face: How context modulates emotion processing in frontotemporal dementia subtypes. *Brain*, *141*(4), 1172–1185. https://doi.org/10.1093/brain/awy002

Kumfor, F., Irish, M., Leyton, C., Miller, L., Lah, S., Devenney, E., … Piguet, O. (2014). Tracking the progression of social cognition in neurodegenerative disorders. *Journal of Neurology*, Neurosurgery and Psychiatry*, 85*(10), 1076–1083. https://doi.org/10.1136/jnnp-2013-307098

Kumfor, F., & Piguet, O. (2012). Disturbance of emotion processing in frontotemporal dementia: A synthesis of cognitive and neuroimaging findings. *Neuropsychology Review, 22*(3), 280–297. https://doi.org/10.1007/s11065-012-9201-6

Kumfor, F., Zhen, A., Hodges, J. R., Piguet, O., & Irish, M. (2018). Apathy in Alzheimer's disease and frontotemporal dementia: Distinct clinical profiles and neural correlates. *Cortex*, *103*, 350–359. https://doi.org/10.1016/j.cortex.2018.03.019

Laillier, R., Viard, A., Caillaud, M., Duclos, H., Bejanin, A., de La Sayette, V., … Laisney, M. (2019). Neurocognitive determinants of theory of mind across the adult lifespan. *Brain and Cognition*, 136(July), 103588. https://doi.org/10.1016/j.bandc.2019.103588

Landin-Romero, R., Kumfor, F., Leyton, C. E., Irish, M., Hodges, J. R., & Piguet, O. (2017). Disease-specific patterns of cortical and subcortical degeneration in a longitudinal study

of Alzheimer's disease and behavioural-variant frontotemporal dementia. *NeuroImage*, *151*(Sep), 72–80. https://doi.org/10.1016/j.neuroimage.2016.03.032

Landin-Romero, R., & Piguet, O. (2017). Recent advances in longitudinal structural neuroimaging of younger-onset dementias. *Neurodegenerative Disease Management*, *7*(6), 349–352. https://doi.org/10.2217/nmt-2017-0057

Laurita, A. C., & Spreng, R. N. (2017). The hippocampus and social cognition. In D. E. Hannula & M. C. Duff (Eds.), *The Hippocampus from Cells to Systems: Structure, connectivity, and functional contributions to memory and flexible cognition* (pp. 537–558). Springer International Publishing AG. https://psycnet.apa.org/doi/10.1007/978-3-319-50406-3_17

Le Bouc, R., Lenfant, P., Delbeuck, X., Ravasi, L., Lebert, F., Semah, F., & Pasquier, F. (2012). My belief or yours? Differential theory of mind deficits in frontotemporal dementia and Alzheimer's disease. *Brain*, *135*(10), 3026–3038. https://doi.org/10.1093/brain/aws237

Lezak, M. D., Howieson, D. B., Loring, D. W., Hannay, J. J., & Fischer, J. S. (2004). *Neuropsychological Assessment* (Fourth). New York: Oxford University Press.

Lieberman, M. D. (2007). Social cognitive neuroscience: a review of core processes. *Annual Review of Psychology*, 58, 259–289. https://doi.org/10.1146/annurev.psych.58.110405.085654

Lieberman, M. D., Straccia, M. A., Meyer, M. L., Du, M., & Tan, K. M. (2019). Social, self, (situational), and affective processes in medial prefrontal cortex (MPFC): Causal, multivariate, and reverse inference evidence. *Neuroscience and Biobehavioural Reviews*, *99*, 311–328. https://doi.org/10.1016/j.neubiorev.2018.12.021

Lin, W. J., Horner, A. J., & Burgess, N. (2016). Ventromedial prefrontal cortex, adding value to autobiographical memories. *Scientific Reports*, *6*(Mar), 1–10. https://doi.org/10.1038/srep28630

Lind, S. E., & Bowler, D. M. (2010). Episodic memory and episodic future thinking in adults with autism. *Journal of Abnormal Psychology*, *119*(4), 896–905. https://doi.org/10.1037/a0020631

Lind, S. E., Bowler, D. M., & Raber, J. (2014). Spatial navigation, episodic memory, episodic future thinking, and theory of mind in children with autism spectrum disorder: Evidence for impairments in mental simulation? *Frontiers in Psychology*, *5*(Dec), 1–20. https://doi.org/10.3389/fpsyg.2014.01411

Lind, S. E., & Williams, D. M. (2012). The association between past and future oriented thinking: Evidence from autism spectrum disorder. *Learning and Motivation*, *43*(4), 231–240. https://doi.org/10.1016/j.lmot.2012.05.004

Lind, S. E., Williams, D. M., Bowler, D. M., & Peel, A. (2014). Episodic memory and episodic future thinking impairments in high-functioning autism spectrum disorder: An underlying difficulty with scene construction or self-projection? *Neuropsychology*, *28*(1), 55–67. https://doi.org/10.1037/neu0000005

Lind, S. E., Williams, D. M., Raber, J., Peel, A., & Bowler, D. M. (2013). Spatial navigation impairments among intellectually high-functioning adults with autism spectrum disorder: Exploring relations with theory of mind, episodic memory, and episodic future thinking. *Journal of Abnormal Psychology*, *122*(4), 1189.

Liu, L., Roquet, D., Ahmed, R. M., Hodges, J. R., Piguet, O., & Irish, M. (2021). Examining prefrontal contributions to past- and future-oriented memory disturbances in daily life in dementia. *Cortex*, *134*, 307–319. https://doi.org/10.1016/j.cortex.2020.11.003

Lough, S., Kipps, C. M., Treise, C., Watson, P., Blair, J. R., & Hodges, J. R. (2006). Social reasoning, emotion and empathy in frontotemporal dementia. *Neuropsychologia*, *44*(6), 950–958. https://doi.org/10.1016/j.neuropsychologia.2005.08.009

Lynch, K., Keane, M. M., & Verfaellie, M. (2020). The status of semantic memory in medial temporal lobe amnesia varies with demands on scene construction. *Cortex*, *131*, 114–122. https://doi.org/10.1016/j.cortex.2020.07.005

Magalhães, S. de S., Malloy-Diniz, L. F., & Hamdan, A. C. (2012). Validity convergent and reliability test-retest of the Rey Auditory Verbal Learning Test. *Clinical Neuropsychiatry*, 9(3), 129–137.

Maguire, E., Intraub, H., & Mullally, S. (2016). Scenes, spaces, and memory traces: What does the hippocampus do? *Neuroscientist*, *22*(5), 10.1177/1073858415600389. https://doi.org/10.1177/1073858415600389

Maguire, E., & Mullally, S. (2013). The hippocampus: A manifesto for change. *Journal of Experimental Psychology: General*, *142*(4), 1180–1189. https://doi.org/10.1037/a0033650

Mah, L., Arnold, M. C., & Grafman, J. (2004). Impairment of social perception associated with lesions of the prefrontal cortex. *American Journal of Psychiatry, 161(*7), 1247–1255. https://doi.org/10.1176/appi.ajp.161.7.1247

Mars, R. B., Neubert, F.-X., Noonan, M. P., Sallet, J., Toni, I., & Rushworth, M. F. S. (2012). On the relationship between the "default mode network" and the "social brain." *Frontiers in Human Neuroscience*, *6*(Jun), 1–9. https://doi.org/10.3389/fnhum.2012.00189

Marshall, C. R., Hardy, C. J. D., Russell, L. L., Bond, R. L., Sivasathiaseelan, H., Greaves, C., … Warren, J. D. (2019). The functional neuroanatomy of emotion processing in frontotemporal dementias. *Brain*, *142*(9), 2873–2887. https://doi.org/10.1093/brain/awz204

Matuszewski, V., Piolino, P., de la Sayette, V., Lalevée, C., Pélerin, A., Dupuy, B., … Desgranges, B. (2006). Retrieval mechanisms for autobiographical memories: Insights from the frontal variant of frontotemporal dementia. *Neuropsychologia, 44*(12), 2386–2397. https://doi.org/10.1016/j.neuropsychologia.2006.04.031

McAndrews, M. P., Cohn, M., & Gold, D. A. (2020). Infusing cognitive neuroscience into the clinical neuropsychology of memory. *Current Opinion in Behavioural Sciences*, *32*, 94–101. https://doi.org/10.1016/j.cobeha.2020.01.011

McCormick, C., Ciaramelli, E., De Luca, F., Maguire, E. A., Luca, F. De, Maguire, E. A., … Maguire, E. A. (2018). Comparing and contrasting the cognitive effects of hippocampal and ventromedial prefrontal cortex damage: A review of human lesion studies. *Neuroscience, 374*, 295–318. https://doi.org/10.1016/j.neuroscience.2017.07.066

McDonald, S., Flanagan, S., Rollins, J., & Kinch, J. (2003). A new clinical tool for assessing social perception after traumatic brain injury. *Journal of Head Trauma Rehabilitation*, *18*(3), 219–238. https://doi.org/10.1097/00001199-200305000-00001

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., … Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia*, *7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005

McKinnon, M. C., Nica, E., Sengdy, P., Kovacevic, N., Moscovitch, M., M., F., … Levine, B. (2008). Autobiographical memory and patterns of brain atrophy in frontotemporal lobar degeneration. *Journal of Cognitive Neuroscience*, *20*(10), 1839–1853. https://doi.org/https://doi.org/10.1162/jocn.2008.20126

Mendez, M. F., & Shapira, J. S. (2011). Loss of emotional insight in behavioural variant frontotemporal dementia or "frontal anosodiaphoria". *Consciousness and Cognition*, *20*(4), 1690–1696. https://doi.org/10.1016/j.concog.2011.09.005

Mendez, M. F., & Shapira, J. S. (2013). Hypersexual behaviour in frontotemporal dementia: A comparison with early-onset Alzheimer's disease. *Archives of Sexual Behaviour*, *42*(3), 501–509. https://doi.org/10.1007/s10508-012-0042-4

Menon, V. (2015). *Salience Network. Brain Mapping: An Encyclopaedic Reference* (Vol. 2). Elsevier Inc. https://doi.org/10.1016/B978-0-12-397025-1.00052-X

Meyers, J., & Meyers, K. (1995). *The Meyers Scoring System for the Rey Complex Figure and Recogntion Trial: Professional manual*. Odessa, FL: Psychological Assessment Resources.

Miller, J. G., Wice, M., & Goyal, N. (2018). Contributions and challenges of cultural research on the development of social cognition. *Developmental Review*, *50*(March), 65–76. https://doi.org/10.1016/j.dr.2018.03.003

Miloyan, B., & McFarlane, K. A. (2019). The measurement of episodic foresight: A systematic review of assessment instruments. *Cortex, 117*, 351-370.

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges, J. R. (2006). The Addenbrooke's Cognitive Examination Revised (ACE-R): A brief cognitive test battery for dementia screening. *International Journal of Geriatric Psychiatry*, 21, 1078–1085.

Mioshi, E., Bristow, M., Cook, R., & Hodges, J. R. (2009). Factors underlying caregiver stress in frontotemporal dementia and Alzheimer's disease. *Dementia & Geriatric Cognitive Disorders*, *27*(1), 76-81 6p. https://doi.org/10.1159/000193626

Mioshi, E., Foxe, D., Leslie, F., Savage, S., Hsieh, S., Miller, L., … Piguet, O. (2013). The Impact of Dementia Severity on Caregiver Burden in Frontotemporal Dementia and Alzheimer Disease. *Alzheimer Disease & Associated Disorders*, *27*(1), 68–73. https://doi.org/10.1097/WAD.0b013e318247a0bc

Mohan, A., Roberto, A. J., Mohan, A., Lorenzo, A., Jones, K., Carney, M. J., … Lapidus, K. A. B. (2016). The significance of the Default Mode Network (DMN) in neurological and neuropsychiatric disorders: A review. *Yale Journal of Biology and Medicine*, *89*(1), 49–57.

Montagrin, A., Saiote, C., & Schiller, D. (2018). The social hippocampus. *Hippocampus*, *28*(9), 672–679. https://doi.org/10.1002/hipo.22797

Moscovitch, M., Cabeza, R., Winocur, G., & Nadel, L. (2016). Episodic memory and beyond: The hippocampus and neocortex in transformation. *Annual Review of Psychology*, 67(1), 105–134. https://doi.org/10.1146/annurev-psych-113011-143733

Mullally, S., Hassabis, D., & Maguire, E. A. (2012). Scene construction in amnesia: An fMRI study. *The Journal of Neuroscience*, *32*(16), 5646–5653. https://doi.org/10.1016/j.neuropsychologia.2013.11.001

Mullally, S., Intraub, H., & Maguire, E. (2012). Attenuated boundary extension produces a paradoxical memory advantage in amnesic patients. *Current Biology*, *22*(4), 261–268. https://doi.org/10.1016/j.cub.2012.01.001

Mullally, S., Vargha-khadem, F., & Maguire, E. A. (2014). Scene construction in developmental amnesia: An fMRI study. *Neuropsychologia*, *52*(1), 1–10. https://doi.org/10.1016/j.neuropsychologia.2013.11.001

Mullally, S., & Maguire, E. (2013). Exploring the role of space-defining objects in constructing and maintaining imagined scenes. *Brain and Cognition*, *82*(1), 100–107. https://doi.org/10.1016/j.bandc.2013.02.013

Mullally, S., & Maguire, E. (2014). Memory, imagination, and predicting the future: A common brain mechanism? *Neuroscientist*, *20*(3), 220–234. https://doi.org/10.1177/1073858413495091

Nah, Y.-H., & Poon, K. K. (2011). The perception of social situations by children with autism spectrum disorders. *Autism : The International Journal of Research and Practice*, *15*(2), 185–203. https://doi.org/10.1177/1362361309353616

Nichols, T. E., & Holmes, A. P. (2001). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Human Brain Mapping, 15,* 1–25.

Nigel, T. (2020). Mental Imagery. In E. Zalta (Ed.), *The Stanford Encyclopaedia of Philosophy* (Fall). Retrieved from https://plato.stanford.edu/archives/fall2020/entries/mental-imagery/

Nyhout, A., & Ganea, P. A. (2019). The Development of the Counterfactual Imagination. *Child Development Perspectives*, *13*(4), 254–259. https://doi.org/10.1111/cdep.12348

O'Callaghan, C., Shine, J. M., Hodges, J. R., Andrews-hanna, J. R., & Irish, M. (2019). Hippocampal atrophy and intrinsic brain network dysfunction relate to alterations in mind wandering in neurodegeneration. *Proceedings of the National Academy of Sciences*, *116*(8), 3316–3321. https://doi.org/10.1073/pnas.1818523116

Palombo, D. J., Hayes, S. M., Peterson, K. M., Keane, M. M., & Verfaellie, M. (2018). Medial Temporal Lobe Contributions to Episodic Future Thinking: Scene Construction or Future Projection? *Cerebral Cortex*, *28*(Feb), 447–458. https://doi.org/10.1093/cercor/bhw381

Panchal, H., Paholpak, P., Lee, G., Carr, A., Barsuglia, J. P., Mather, M., … Mendez, M. F. (2015). Neuropsychological and neuroanatomical correlates of the Social Norms Questionnaire in frontotemporal dementia versus Alzheimer's disease. *American Journal of Alzheimer's Disease and Other Dementias*, *31*(4), 326–332. https://doi.org/10.1177/1533317515617722

Paulin, T., Roquet, D., Kenett, Y. N., Savage, G., & Irish, M. (2020). The effect of semantic memory degeneration on creative thinking: A voxel-based morphometry analysis. *NeuroImage*, *220*, 117073.

Pelaprat, E., & Cole, M. (2011). “Minding the gap”: Imagination, creativity and human cognition. *Integrative Psychological and Behavioural Science*, *45*(4), 397–418. https://doi.org/10.1007/s12124-011-9176-5

Phelps, E. A. (2006). Emotion and Cognition: Insights from Studies of the Human Amygdala. *Annual Review of Psychology*, *57*(1), 27–53. https://doi.org/10.1146/annurev.psych.56.091103.070234

Piguet, O., Kumfor, F., & Hodges, J. (2017). Diagnosing, monitoring and managing behavioural variant frontotemporal dementia. *Medical Journal of Australia*, *207*(7), 303–308. https://doi.org/10.5694/mja16.01458

Pinkham, A. E., Hopfinger, J. B., Pelphrey, K. A., Piven, J., & Penn, D. L. (2008). Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. *Schizophrenia Research*, *99*(1–3), 164–175. https://doi.org/10.1016/j.schres.2007.10.024

Possin, K. L., Feigenbaum, D., Rankin, K. P., Smith, G. E., Boxer, A. L., Wood, K., … Kramer, J. H. (2013). Dissociable executive functions in behavioural variant frontotemporal and Alzheimer dementias. *Neurology*, *80*(24), 2180–2185. https://doi.org/10.1212/WNL.0b013e318296e940

Proulx, M. J., Todorov, O. S., Aiken, A. T., & de Sousa, A. A. (2016). Where am I? Who am I? The relation between spatial cognition, social cognition and individual differences in the built environment. *Frontiers in Psychology*, *7*(Feb), 1–23. https://doi.org/10.3389/fpsyg.2016.00064

Rabinovici, G. D., Seeley, W. W., Kim, E. J., Gorno-Tempini, M. L., Rascovsky, K., Pagliaro, T. A., … Rosen, H. J. (2008). Distinct MRI atrophy patterns in autopsy-proven Alzheimer’s

disease and frontotemporal lobar degeneration. *American Journal of Alzheimer's Disease and Other Dementias*, *22*(6), 474–488. https://doi.org/10.1177/1533317507308779

Race, E., Keane, M. M., Verfaellie, M., Race, K. & V., Race, E., Keane, M. M., & Verfaellie, M. (2011). Medial temporal lobe damage causes deficits in episodic memory and episodic future thinking not attributable to deficits in narrative construction. *Journal of Neuroscience, 31*(28), 10262–10269. https://doi.org/10.1523/JNEUROSCI.1145-11.2011

Raffard, S., D'Argembeau, A., Bayard, S., Boulenger, J.-P., & Van der Linden, M. (2010). Scene construction in schizophrenia. *Neuropsychology*, *24*(5), 608–615. https://doi.org/10.1037/a0019113

Ramanan, S., Alaeddin, S., Goldberg, Z. lee, Strikwerda-Brown, C., Hodges, J. R., & Irish, M. (2018). Exploring the contribution of visual imagery to scene construction: Evidence from Posterior Cortical Atrophy. *Cortex, 106*, 261–274. https://doi.org/10.1016/j.cortex.2018.06.016

Ramanan, S., de Souza, L. C., Moreau, N., Sarazin, M., Teixeira, A. L., Allen, Z., … Bertoux, M. (2017). Determinants of theory of mind performance in Alzheimer's disease: A data-mining study. *Cortex*, *88*, 8–18. https://doi.org/10.1016/j.cortex.2016.11.014

Ramanan, S., Piguet, O., & Irish, M. (2018). Rethinking the role of the angular gyrus in remembering the past and imagining the future: The contextual integration model. *Neuroscientist*, *24*(4), 342–352. https://doi.org/10.1177/1073858417735514

Ramanan, S., Bertoux, M., Flanagan, E., Irish, M., Piguet, O., Hodges, J. R., & Hornberger, M. (2017). Longitudinal executive function and episodic memory profiles in behavioral-

variant frontotemporal dementia and Alzheimer's disease. *Journal of the International Neuropsychological Society, 23*(1), 34–43. https://doi.org/10.1017/S1355617716000837

Ranasinghe, K. G., Rankin, K. P., Lobach, I. V., Kramer, J. H., Sturm, V. E., Bettcher, B. M., ... & Miller, B. L. (2016). Cognition and neuropsychiatry in behavioral variant frontotemporal dementia by disease stage. *Neurology, 86*(7), 600-610.

Ranganath, C. (2010). Binding items and contexts: The cognitive neuroscience of episodic memory. *Current Directions in Psychological Science*, *19*(3), 131–137. https://doi.org/10.1177/0963721410368805

Ranganath, C., & Ritchey, M. (2012). Two cortical systems for memory-guided behaviour. *Nature Reviews Neuroscience*, *13*(10), 713–726. https://doi.org/10.1038/nrn3338

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., … Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*, *134*(9), 2456–2477. https://doi.org/10.1093/brain/awr179

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills*, 8(3), 271-276.

Renoult, L., Irish, M., Moscovitch, M., & Rugg, M. D. (2019). From knowing to remembering: the semantic–episodic distinction. *Trends in Cognitive Sciences*, *23*(12), 1041-1057.

Reul, S., Lohmann, H., Wiendl, H., Duning, T., & Johnen, A. (2017). Can cognitive assessment really discriminate early stages of Alzheimer's and behavioural variant frontotemporal

dementia at initial clinical presentation? *Alzheimer's Research and Therapy*, *9*(1), 1–12. https://doi.org/10.1186/s13195-017-0287-1

Rey, A. (1941). L'examen psychologique dans les cas d'encephalopathie traumatique. *Archives de Psychologie*, 28, 286–340.

Ricarte, J. J., Ros, L., Latorre, J. M., & Watkins, E. (2017). Mapping autobiographical memory in schizophrenia: Clinical implications. *Clinical Psychology Review*, *51*, 96–108. https://doi.org/10.1016/j.cpr.2016.11.004

Roberts, R. P., Schacter, D. L., & Addis, D. R. (2018). Scene construction and relational processing: Separable constructs? *Cerebral Cortex*, *28*(5), 1729-1732. https://doi.org/10.1093/cercor/bhx081

Robin, J. (2018). Spatial scaffold effects in event memory and imagination. *Wiley Interdisciplinary Reviews: Cognitive Science*, *9*(4), 1–15. https://doi.org/10.1002/wcs.1462

Robin, J., Garzon, L., & Moscovitch, M. (2019). Spontaneous memory retrieval varies based on familiarity with a spatial context. *Cognition*, *190*(April), 81–92. https://doi.org/10.1016/j.cognition.2019.04.018

Robin, J., & Moscovitch, M. (2017). Details, gist and schema: hippocampal–neocortical interactions underlying recent and remote episodic and spatial memory. *Current Opinion in Behavioural Sciences, 17,* 114-123. https://doi.org/10.1016/j.cobeha.2017.07.016

Robin, J., Wynn, J., & Moscovitch, M. (2016). The spatial scaffold: The effects of spatial context on memory for events. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *42*(2), 308–315. https://doi.org/10.1037/xlm0000167

Rosen, H. J., Gorno-Tempini, M. L., Goldman, W. P., Perry, R. J., Schuff, N., Weiner, M., … Miller, B. L. (2002). Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology*, *58*(2), 198–208. https://doi.org/10.1212/WNL.58.2.198

Rubin, D. C., Deffler, S. A., & Umanath, S. (2019). Scenes enable a sense of reliving: Implications for autobiographical memory. *Cognition*, *18*3, 44–56. https://doi.org/10.1016/j.cognition.2018.10.024

Rubin, D. C., Schrauf, R. W., & Greenberg, D. L. (2003). Belief and recollection of autobiographical memories. *Memory and Cognition*, *31*(6), 887–901. https://doi.org/10.3758/BF03196443

Rubin, R. D., Watson, P. D., Duff, M. C., & Cohen, N. J. (2014). The role of the hippocampus in flexible cognition and social behaviour. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2014.00742

Rudebeck, P. H., Bannerman, D. M., & Rushworth, M. F. S. (2008). The contribution of distinct subregions of the ventromedial frontal cortex to emotion, social behaviour, and decision making. *Cognitive, Affective and Behavioural Neuroscience*, *8*(4), 485–497. https://doi.org/10.3758/CABN.8.4.485

Rueckert, D. (1999). Nonrigid registration using free-form deformations: Application to breast MR images. *IEEE Transactions on Medical Imaging*, *18*(8), 712–721. https://doi.org/10.1109/42.796284

Salimi, S., Irish, M., Foxe, D., Hodges, J. R., Piguet, O., & Burrell, J. R. (2018). Can visuospatial measures improve the diagnosis of Alzheimer's disease? *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring*, *10,* 66–74. https://doi.org/10.1016/j.dadm.2017.10.004

Savage, S., Hsieh, S., Piguet, O., Hodges, J. R., Leslie, F., Foxe, D., … Foxe, D. (2013). Distinguishing subtypes in primary progressive aphasia: Application of the Sydney Language Battery. *Dementia and Geriatric Cognitive Disorders*, *35*(3–4), 208–218. https://doi.org/10.1159/000346389

Sawczak, C., McAndrews, M. P., Gaesser, B., & Moscovitch, M. (2019). Episodic simulation and empathy in older adults and patients with unilateral medial temporal lobe excisions. *Neuropsychologia*, *135*(Nov),107243, https://doi.org/10.1016/j.neuropsychologia.2019.107243

Schacter, D. L., & Addis, D. R. (2007). The cognitive neuroscience of constructive memory: Remembering the past and imagining the future. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *362*(1481), 773–786. https://doi.org/10.1098/rstb.2007.2087

Schacter, D. L., Addis, D. R., & Buckner, R. L. (2007). Remembering the past to imagine the future: The prospective brain. *Nature Reviews Neuroscience*, *8*(9), 657–661. https://doi.org/10.1038/nrn2213

Schacter, D. L., Addis, D. R., Hassabis, D., Martin, V. C., Spreng, R. N., & Szpunar, K. K. (2012). The future of memory: Remembering, imagining, and the brain. *Neuron*, *76*(4), 677–694. https://doi.org/10.1016/j.neuron.2012.11.001

Schmidt, M. (1996). *Rey Auditory Verbal Learning Test: A Handbook*. Los Angeles, CA: Western Psychological Services.

Schurz, M., Radua, J., Aichhorn, M., Richlan, F., & Perner, J. (2014). Fractionating theory of mind: A meta-analysis of functional brain imaging studies. *Neuroscience and Biobehavioural Reviews*, *42*, 9–34. https://doi.org/10.1016/j.neubiorev.2014.01.009

Schuwerk, T., Schurz, M., Müller, F., Rupprecht, R., & Sommer, M. (2017). The rTPJ's overarching cognitive function in networks for attention and theory of mind. *Social Cognitive and Affective Neuroscience*, *12*(1), 157–168. https://doi.org/10.1093/scan/nsw163

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., … Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience*, *27*(9), 2349–2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Sekeres, M. J., Winocur, G., & Moscovitch, M. (2018). The hippocampus and related neocortical structures in memory transformation. *Neuroscience Letters*, *680*(May), 39–53. https://doi.org/10.1016/j.neulet.2018.05.006

Shany-Ur, T., Rankin, K. P., Badalà, F., Nouri-mahdavi, K., & Raoof, D. A. (2010). Personality and social cognition in neurodegenerative disease. *Current Opinion in Neurology*, *24*(6). https://doi.org/10.2217/FON.09.6.Dendritic

Sheldon, S., Cool, K., & El-Asmar, N. (2019). The processes involved in mentally constructing event- and scene-based autobiographical representations. *Journal of Cognitive Psychology*, *31*(3), 261–275. https://doi.org/10.1080/20445911.2019.1614004

Shimamura, A. P. (2011). Episodic retrieval and the cortical binding of relational activity. *Cognitive, Affective and Behavioural Neuroscience*, *11*(3), 277–291. https://doi.org/10.3758/s13415-011-0031-4

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. https://doi.org/10.1002/hbm.10062

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*(SUPPL. 1), 208–220. https://doi.org/10.1016/j.neuroimage.2004.07.051

Snowden, J. S., Bathgate, D., Varma, A., Blackshaw, A., Gibbons, Z. C., & Neary, D. (2001). Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *Journal of Neurology Neurosurgery and Psychiatry*, 70(3), 323–332. https://doi.org/10.1136/jnnp.70.3.323

So, M., Foxe, D., Kumfor, F., Murray, C., Hsieh, S., Savage, G., … Piguet, O. (2018). Addenbrooke's Cognitive Examination III: Psychometric characteristics and relations to functional ability in dementia. *Journal of the International Neuropsychological Society*, *24*(8), 854–863. https://doi.org/10.1017/S1355617718000541

Söderlund, H., Moscovitch, M., Kumar, N., Daskalakis, Z. J., Flint, A., Herrmann, N., & Levine, B. (2014). Autobiographical episodic memory in major depressive disorder. *Journal of Abnormal Psychology*, *123*(1), 51–60. https://doi.org/10.1037/a0035610

Spalding, K. N., Jones, S. H., Duff, M. C., Tranel, D., & Warren, D. E. (2015). Investigating the neural correlates of cchemas: Ventromedial prefrontal cortex is necessary for normal

schematic influence on memory. *The Journal of Neuroscience*, *35*(47), 15746–15751. https://doi.org/10.1523/JNEUROSCI.2767-15.2015

Spreadbury, J., & Kipps, C. (2016). Measuring younger onset dementia: A comprehensive review of the quantitative and qualitative psychosocial research. *Alzheimer's and Dementia*, *12*(7), P1012. https://doi.org/10.1177/1471301216661427

Spreng, N., Mar, R. A., & Kim, A. S. N. (2008). The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: A quantitative meta-analysis. *Journal of Cognitive Neuroscience*, *21*(3), 489–510. https://doi.org/10.1162/jocn.2008.21029

Spreng, R. N., Dimas, E., Mwilambwe-Tshilobo, L., Dagher, A., Koellinger, P., Nave, G., … Bzdok, D. (2020). The default network of the human brain is associated with perceived social isolation. *Nature Communications*, 11(1), 1–11. https://doi.org/10.1038/s41467-020-20039-w

Spreng, R. N., & Grady, C. L. (2010). Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *Journal of Cognitive Neuroscience*, *22(*6), 1112–1123. https://doi.org/10.1162/jocn.2009.21282

Spreng, R. N. N., & Mar, R. A. R. A. (2012). I remember you: A role for memory in social cognition and the functional neuroanatomy of their interaction. *Brain Research*, *1428,* 43–50. https://doi.org/10.1016/j.brainres.2010.12.024

St-Laurent, M., Moscovitch, M., Levine, B., & McAndrews, M. P. (2009). Determinants of autobiographical memory in patients with unilateral temporal lobe epilepsy or excisions.

Neuropsychologia, *47*(11), 2211–2221. https://doi.org/10.1016/j.neuropsychologia.2009.01.032

Stokes, D. (2016). *Imagination and creativity. The Routledge Handbook of Philosophy of Imagination*, *42*(1), 247–261. https://doi.org/10.4324/9781315657905

Strikwerda-Brown, C., Ramanan, S., & Irish, M. (2019). Neurocognitive mechanisms of theory of mind impairment in neurodegeneration: A transdiagnostic approach. *Neuropsychiatric Disease and Treatment, 15*, 557.

Strikwerda-Brown, C., Grilli, M. D., Andrews-Hanna, J., & Irish, M. (2019). "All is not lost"—Rethinking the nature of memory and the self in dementia. *Ageing Research Reviews, 54*(June). https://doi.org/10.1016/j.arr.2019.100932

Strikwerda-Brown, C., Mothakunnel, A., Hodges, J. R., Piguet, O., & Irish, M. (2018). External details revisited: A new taxonomy for coding 'non-episodic' content during autobiographical memory retrieval. *Journal of Neuropsychology*, *13*(3), 371-397. https://doi.org/10.1111/jnp.12160

Strikwerda-Brown, C., Mothakunnel, A., Hodges, J. R., Piguet, O., & Irish, M. (2019). External details revisited: A new taxonomy for coding 'non-episodic' content during autobiographical memory retrieval. *Journal of Neuropsychology*, *13*(3), 371–397. https://doi.org/10.1111/jnp.12160

Suddendorf, T., & Redshaw, J. (2013). The development of mental scenario building and episodic foresight. *Annals of the New York Academy of Sciences*, *1296*(1), 135–153. https://doi.org/10.1111/nyas.12189

Summerfield, J. J., Hassabis, D., & Maguire, E. A. (2010). Differential engagement of brain regions within a "core" network during scene construction. *Neuropsychologia*, *48*(5), 1501–1509. https://doi.org/10.1016/j.neuropsychologia.2010.01.022

Synn, A., Mothakunnel, A., Kumfor, F., Chen, Y., Piguet, O., Hodges, J. R., & Irish, M. (2018). Mental states in moving shapes: distinct cortical and subcortical contributions to theory of mind impairments in dementia. *Journal of Alzheimer's Disease, 61*(2), 521-535.

Tamir, D. I., & Mitchell, J. P. (2010). Neural correlates of anchoring-and-adjustment during mentalizing. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(24), 10827–10832. https://doi.org/10.1073/pnas.1003242107

Torralva, T., Gleichgerrcht, E., Ardila, M. J. T., Roca, M., & Manes, F. F. (2015). Differential cognitive and affective theory of mind abilities at mild and moderate stages of behavioural variant frontotemporal dementia. *Cognitive and Behavioural Neurology*, *28*(2), 63–70. https://doi.org/10.1097/WNN.0000000000000053

Tu, S., Wong, S., Hodges, J. R., Irish, M., Piguet, O., & Hornberger, M. (2015). Lost in spatial translation: A novel tool to objectively assess spatial disorientation in Alzheimer's disease and frontotemporal dementia. *Cortex, 67,* 83–94. https://doi.org/10.1016/j.cortex.2015.03.016

Tulving, E. (1972). *Episodic and semantic memory*. Organization of Memory, *1*, 381–403.

Tulving, E. (1985). *Memory and consciousness*. Canadian Psychology, *26*(1), 1–11.

Van Kesteren, M. T. R., Ruiter, D. J., Fernández, G., & Henson, R. N. (2012). How schema and novelty augment memory formation. *Trends in Neurosciences*, *35*(4), 211–219. https://doi.org/10.1016/j.tins.2012.02.001

Verfaellie, M., Wank, A. A., Reid, A. G., Race, E., & Keane, M. M. (2019). Self-related processing and future thinking: Distinct contributions of ventromedial prefrontal cortex and the medial temporal lobes. *Cortex*, *115,* 159–171. https://doi.org/10.1016/j.cortex.2019.01.028

Wagemans, J., Elder, J. H., Kubovy, M., Palmer, S. E., Peterson, M. A., Singh, M., & von der Heydt, R. (2012). A century of Gestalt psychology in visual perception: I. Perceptual grouping and figure-ground organization. *Psychological Bulletin*, *138*(6), 1172–1217. https://doi.org/10.1037/a0029333

Wang, T., Yue, T., & Huang, X. T. (2016). Episodic and semantic memory contribute to familiar and novel episodic future thinking. *Frontiers in Psychology*, *7*(Nov), 1–9. https://doi.org/10.3389/fpsyg.2016.01746

Warrington, E. K., & Shallice, T. (1984). Category specific naming impairments. *Brain*, *107,* 829–853.

Wear, H. J., Wedderburn, C. J., Mioshi, E., Williams-Gray, C. H., Mason, S. L., Barker, R. A., & Hodges, J. R. (2008). The Cambridge Behavioural Inventory revised. *Dementia & Neuropsychologia*, *2*(2), 102–107. https://doi.org/10.1590/S1980-57642009DN20200005

Wedderburn, C., Wear, H., Brown, J., Mason, S. J., Barker, R. A., Hodges, J., & Williams-Gray, C. (2008). The utility of the Cambridge Behavioural Inventory in neurodegenerative

disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *79*(5), 500–503. https://doi.org/10.1136/jnnp.2007.122028

Weder, N. D., Aziz, R., Wilkins, K., & Tampi, R. R. (2007). Frontotemporal dementias: A review. *Annals of General Psychiatry*, *6*(1), 15. https://doi.org/10.1186/1744-859X-6-15

Wen, T., Mitchell, D. J., & Duncan, J. (2020). The functional convergence and heterogeneity of social, episodic, and self-referential thought in the default mode network. *Cerebral Cortex*, *30*(11), 5915–5929. https://doi.org/10.1093/cercor/bhaa166

Weschler, D. (1997). *WAIS-III Administration and Scoring Manual*. San Antonio, Texas: Psychological Cooperation.

Wilson, N.-A., & Batchelor, J. (2015). Examining Rey Complex Figure Test organization in healthy adults. *Journal of Clinical and Experimental Neuropsychology*, *37*(10), 1052–1061. https://doi.org/10.1080/13803395.2015.1075473

Wilson, N.-A., Ramanan, S., Roquet, D., Hodges, J. R., Piguet, O., & Irish, M. (2020). Scene construction impairments in frontotemporal dementia: Evidence for a primary hippocampal contribution. *Neuropsychologia*, *137*(B 57), 289–300. https://doi.org/10.1016/j.neuropsychologia.2019.107327

Wilson, N. A., Ahmed, R. M., Hodges, J. R., Piguet, O., & Irish, M. (2020). Constructing the social world: Impaired capacity for social simulation in dementia. *Cognition*, *202*(May), 104321. https://doi.org/10.1016/j.cognition.2020.104321

Wong, S., Irish, M., Leshikar, E. D., Duarte, A., Bertoux, M., Savage, G., … Hornberger, M. (2017). The self-reference effect in dementia: Differential involvement of cortical

midline structures in Alzheimer's disease and behavioural-variant frontotemporal dementia. *Cortex, 91,* 169–185. https://doi.org/10.1016/j.cortex.2016.09.013

Zebrowitz, L. A. (1990). *Social perception*. Thomson Brooks/Cole Publishing Co.

Zeidman, P., & Maguire, E. A. (2016). Anterior hippocampus: the anatomy of perception, imagination and episodic memory. *Nature Reviews Neuroscience*, *17*(3), 173–182. https://doi.org/10.1038/nrn.2015.24

Zeidman, P., Mullally, S., & Maguire, E. (2015). Constructing, perceiving, and maintaining scenes: Hippocampal activity and connectivity. *Cerebral Cortex*, *25*(10), 3836–3855. https://doi.org/10.1093/cercor/bhu266

Zhang, F., Ho, Y. W., & Fung, H. H. (2015). Learning from normal aging: Preserved emotional functioning facilitates adaptation among early Alzheimer's disease patients. *Aging and Disease*, *6*(3), 208–215. https://doi.org/10.14336/AD.2014.0620

Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging*, *20*(1), 45–57. https://doi.org/10.1109/42.906424

Zhou, J., Greicius, M. D., Gennatas, E. D., Growdon, M. E., Jang, J. Y., Rabinovici, G. D., … Seeley, W. (2010). Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain*, *133*(5), 1352–1367.

Appendix A

Chapter 5

Example scene

I'm going to give you an example with two things that don't feel like they belong together. "You're in a boardroom. There is a hairdryer there". So I could say:

> *"I'm standing in an impressive office boardroom in a city skyscraper. Out the window I can see the whole city! I'm excited as I'm here to launch a national advertising campaign for my new hairdryer. The room smells of coffee – I'm already on to my third cup and now I'm not sure if its nerves or caffeine I can feel! They've told me that they've secured a big celebrity for the launch – I can hear voices approaching from outside now – I can't wait to see who it is!"*

See how I included the hairdryer into the boardroom scene, even though those aren't two things which would normally belong together? I'm going to give you 2 minutes to describe each scene and it's really important that you try to keep talking for the whole 2 minutes.

Prompting instructions

If they are stuck and fail to say anything for more than 15-30 seconds OR if they are only including ONE of the cue elements encourage in a general way:

Prompt 1: 'Remembering to include both the X and the Y in the scenario that you're describing, are there any other details you can tell me?

If still nothing after another 15-30 seconds prompt again:

Prompt 2: 'As you picture the scenario with the X and the Y, is there anything else you can describe to me?'

If still nothing, end task and note time. Do not continue to prompt.

Appendix B

Chapter 6

Example Dewey Story Test (Dewey, 1991)

Keith worked in the city and would eat his lunch on a bench in the park. Keith often scattered some of his sandwich on the ground for the pigeons ( ). One day a baby's pram was parked beside the bench where he eats his lunch. Keith noticed that a woman was pushing an older child on the swings nearby. The baby in the pram began to cry but the lady did not hear this because the swing was squeaking. Keith knew when his nephew cried sometimes this meant a pin in his nappy had opened. Rather than bother the mother, Keith quickly checked the baby's nappy to see whether he could feel an open pin ( ).

Rating Scale

Fairly normal behaviour in that situation (0)

Rather strange behaviour in that situation (1)

Very eccentric behaviour in that situation (2)

Shocking behaviour in that situation (3)

Table B6.1 Percentage of most endorsed control responses and assigned deviation scores for each item.

	Social Perception Raw Rating			
	0	1	2	3
Cake 1	0.95	1	2	3
Cake 2	1.0	1	2	3
Cake 3	0.60	0.40	1	2
Cake 4	-3	-2	-1	0.75
Dog 1	1.00	1	2	3
Dog 2	-1	0.55	0.40	1
Dog 3	-1	0.40	0.60	1
Dog 4	0.90	1	2	3
Window 1	0.90	1	2	3
Window 2	-1	0.65	0.30	1
Window 3	-1	0.40	0.50	1
Window 4	-3	-2	-1	0.90
Ice-Cream 1	0.80	1	2	3
Ice-Cream 2	1	0.40	0.40	1
Ice-Cream 3	0.50	0.30	1	2
Ice-Cream 4	-3	-2	-1	0.80
Itchy 1	1.0	1	2	3
Itchy 2	-1	0.50	1	2
Itchy 3	0.90	1	2	3
Itchy 4	-1	0.70	1	2
Sleep 1	0.75	1	2	3
Sleep 2	0.80	1	2	3
Sleep 3	0.65	0.30	1	2
Sleep 4	-1	0.65	1	2
Sleep 5	-1	0.30	0.40	1
Hair 1	1.00	1	2	3
Hair 2	-1	0.50	0.35	1

Notes. Items shown in yellow represent responses endorsed by ≥ 30% of control participants and therefore given a deviation score of 0. Ratings on mid-range items were summed to create the Social Perception directional score.