Look on the Bright Side: Exploring the Role of Episodic Future Thinking in Anticipatory Anhedonia

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III. List of abbreviations

ACE-III Addenbrookes Cognitive Examination Third Edition

AD Alzheimer's Disease

ANOVA Analysis of Variance

ANCOVA Analysis of Covariance

BDI Beck Depression Inventory

bvFTD Behavioural variant of frontotemporal dementia

CBI-R Cambridge Behavioural Inventory Revised

CI Confidence Interval

DApS Dimensional Apathy Scale

DASS Depression Anxiety and Stress Scale

DSM Diagnostic and Statistical Manual of Mental Disorders

EMM Estimated Marginal Mean

FAS F A S Letter Fluency Task

FRS Frontotemporal Dementia Rating Scale

FTD Frontotemporal Dementia

MDD Major Depressive Disorder

MRI Magnetic Resonance Imaging

RAVLT Rey Auditory Verbal Learning Test

RCF Rey Complex Figure

SD Semantic Dementia

SHAPS Snaith Hamilton Pleasure Scale

SPSS Statistical Package for the Social Sciences

SSRI Selective Serotonin Reuptake Inhibitors

TEPS Temporal Experience of Pleasure Scale

TEPS-A Anticipatory Subscale of the Temporal Experience of Pleasure Scale

TEPS-C Consummatory Subscale of the Temporal Experience of Pleasure Scale

vmPFC Ventromedial prefrontal cortex

VTA Ventral tegmental area

η_p^2 Partial eta-square

χ^2 Chi- square test

IV. List of publications

The following first-author publications form a major part of this thesis. Author contributions are outlined for each publication.

Chapter 2 contains material published as:

Shaw, S. R., Horne, K. S., Piguet, O., Ahmed, R. M., Whitton, A. E., & Irish, M. (2024). Profiles of motivational impairment and their relationship to functional decline in frontotemporal dementia. *Journal of Neurology*, *271*(8), 4963–4971. https://doi.org/10.1007/s00415-024-12430-0

Author contributions: Study design: S.R.S. and M.I.; Data acquisition, S.R.S., O.P., R.M.A. Statistical analysis: S.R.S., A.E.W. and M.I.; Interpretation: S.R.S., A.E.W. and M.I.;

Drafting of manuscript, S.R.S. and M.I.; Editing of manuscript, S.R.S., K.S.H., O.P., R.M.A., A.E.W. and M.I.; Study supervision, M.I and A.E.W.

V. Co-author declaration

We, the undersigned, acknowledge the publication included in this thesis is predominantly the work of Siobhán Shaw and that the information provided regarding co-author contribution is accurate.

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.

Siobhán Shaw

23rd March 2025

Muireann Irish

23rd March 2025

VI. List of presentations and awards

Siobhán R Shaw. Anhedonia in frontotemporal dementia. Paper presented at: Sydney Postgraduate Psychology Conference; 3 December 2021; Virtual. **Winner of the SPPC Neuroscience Research Prize**

Siobhán R Shaw. Uncovering the prevalence and neural substrates of anhedonia in frontotemporal dementia. Paper presented at: Forefront Scientific Meeting; 26th-27th May 2021; Sydney.

Siobhán R Shaw. Anhedonia severity is strongly associated with functional impairment in the behavioural variant of frontotemporal dementia. Poster presented at: Australian Dementia Research Forum; 30-31st May 2022; Virtual

Siobhán R Shaw. Anhedonia in frontotemporal dementia: functional implications and neural correlates. Paper presented at: International Neuropsychological Society; 6-8th July 2022; Barcelona. **Winner of the International Neuropsychological Society Graduate Student Research Award**

Siobhán R Shaw. Anhedonia in frontotemporal dementia: functional implications and neural correlates. Oral presentation at Oxford University, Department of Clinical Neurosciences, 16th July 2022; Oxford, United Kingdom.

Siobhán R Shaw. Anhedonia as an overlooked clinical feature of frontotemporal dementia. Paper presented at: APS Clinical Neuropsychologists Conference. 4-5th November 2022. Sydney.

Siobhán R Shaw. Anhedonia in Frontotemporal Dementia: Neural Substrates and Functional Implications. Paper presented at: Sydney Postgraduate Psychology Conference; 18 November 2022; Sydney. **Winner of the SPPC Best Experimental Presentation Prize**

Siobhán R Shaw. Exploring Anhedonia in Frontotemporal Dementia – From Mechanisms to Management. Poster presented at: Brain and Mind Centre Symposium. 23 November 2023; Sydney

Siobhán R Shaw. Unveiling the interplay between episodic future thinking and anhedonia in dementia. Paper presented at: Special Interest Meeting in Autobiographical Processing and Psychopathology; 27-28 May 2024; Belgium.

Siobhán R Shaw. The interplay between pleasurable event generation and anhedonia and apathy in dementia - A preliminary study. Poster presented at: International Society for Frontotemporal Dementia; 19-22 September 2024; The Netherlands.

Siobhán R Shaw. A look on the bright side: Exploring the role of episodic future thinking in anticipatory anhedonia. Oral presentation at: Social Functioning Modelling Symposium; 15 November 2024; Sydney.

VII. **List of scholarships**

2022-2025 Research Training Program Stipend Scholarship

2022 and 2024 Postgraduate Research Support Scheme

VIII. **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 work and that all the assistance received in preparing this thesis and sources have been acknowledged.

All studies were caried out during my PhD candidature and were under the supervision of Professor Muireann Irish and Associate Professor Alexis Whitton. The studies contained within this thesis were conducted at FRONTIER, the frontotemporal dementia research clinic, based at the Brain and Mind Centre, the University of Sydney. The data collected from this thesis were collected by me (as a PhD student from September 2022 till current, as an honours student in 2019 and as a research assistant from August 2020-2021), senior neurologists, neuropsychologists, psychologists, occupational therapists, and other experienced research assistants at FRONTIER. All data were collected through direct contact with participants, with written informed consent obtained from all participants or their person responsible.

In accordance with the Declaration of Helsinki, ethical approval for these studies was obtained from the Human Research Ethics Committee (HREC) of the South Eastern Sydney Local Health District as part of the following two projects: “Memory and imagination in ageing” (approval number 2018/479) and “Clinical Assessment for Ageing and Neurodegeneration Research” (approval number 2020/224).

Siobhán Shaw

25th February 2025

IX. Acknowledgements

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Wow, six years. It has absolutely flown by, and I think my little honours student self would never have dreamed of this day. Thank you for replying to that first email back in 2019 and being nothing but supportive and encouraging from that moment onward. You've played such an important part in my life, and I'm so incredibly grateful. Your passion and drive are inspiring, and I feel so fortunate to have learned from you. The way you approach a problem, seeing both the big picture and the smallest details, is unparalleled. The research world is so lucky to have you, and I have no doubt you'll continue to make a profound difference in the lives of researchers, patients, and carers alike. Thank you for teaching me how to think critically, tell a story, and use the data we have to drive meaningful change. It's been an honour to be part of this anhedonia journey with you, one that I will continue to draw from and never forget.

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Thank you also for your continued support and encouragement. The clarity with which you understand an issue and map out a solution is something I can only aspire to. Your thoughtful feedback has always elevated my work, and the depth at which you approach every challenge is truly admirable. I'm incredibly grateful for your guidance and your ability to turn even the most daunting tasks into clear, achievable steps.

To both my supervisors, it has been an absolute privilege to work under and learn from such incredible women. I had no idea how lucky I was back in 2019, and I am so grateful for the unwavering belief you've shown in me ever since. Thank you for everything. I am truly fortunate to have had such inspiring role models.

To my family,

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place, so thank you for that.... You were right, I loved it! The care and consideration the three of you show for others has always been inspirational, driving me to make a difference wherever I can. You've not only pushed me to do my best but, more importantly, made me believe that I can. I have felt nothing short of completely and utterly supported throughout this journey. So, for that, thank you.

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Thank you for all your support. The messages, the thoughtful gifts, and yes, even if I did get a little tired of hearing, "Are you still doing your PhD?"

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Artificial intelligence

During the preparation of this thesis, Otter.ai was used only for the purposes of transcription, the details of which are included within the methodology section for Chapter 4.

X. Abstract

Anhedonia, defined as a diminished capacity to experience pleasure, is a pervasive symptom that profoundly impacts quality of life, reducing motivation, social engagement, and functional independence. While traditionally associated with psychiatric conditions, recent evidence highlights its prevalence in frontotemporal dementia (FTD). Understanding the multidimensional nature of anhedonia and its cognitive underpinnings is crucial for improving diagnosis, clinical management, and patient outcomes.

This thesis comprises four studies that investigate the nature and impact of anhedonia in FTD. Chapter 2 identifies distinct motivational profiles across dementia syndromes: a domain-general motivational impairment in behavioural variant FTD (bvFTD), a predominantly anhedonic profile in semantic dementia (SD), and more pronounced executive and initiation apathy in Alzheimer's disease (AD). Correlation analyses revealed syndrome-specific associations between these motivational symptoms and functional impairment. Chapter 3 further characterises anhedonia from a multidimensional perspective, demonstrating widespread impairments across both anticipatory and consummatory dimensions in bvFTD and SD, while consummatory pleasure appears relatively preserved in AD. Importantly, correlational analyses revealed a novel link between anhedonia and behavioural changes in dementia. Chapter 4 builds on these findings, showing that deficits in episodic future thinking are strongly associated with anticipatory anhedonia in FTD. Specifically, individuals with FTD demonstrate an impaired ability to mentally simulate positive future events, highlighting a potential cognitive mechanism underlying anhedonia in this population. Finally,

Chapter 5 demonstrates that multidimensional anhedonia could serve as a potential diagnostic marker, differentiating bvFTD from mood disorders, with consummatory anhedonia emerging as a key distinguishing feature.

Together, the work presented in this thesis underscores the importance of recognising anhedonia as a core clinical feature of FTD, with significant implications for diagnosis, management, and quality of life. By elucidating the cognitive and behavioural underpinnings of anhedonia, this work paves the way for more targeted interventions aimed at improving patient outcomes and supporting caregivers.

Pleasure is the structure of society. From childhood until death we are secretly, cunningly or obviously pursuing pleasure. So whatever our form of pleasure is, I think we should be very clear about it because it is going to guide and shape our lives. It is therefore important for each one of us to investigate closely, hesitantly and delicately this question of pleasure, for to find pleasure, and then nourish and sustain it, is a basic demand of life and without it existence becomes dull, stupid, lonely and meaningless.

~ Jiddu Krishnamurti

1.1. The importance of pleasure and the reward system

Pleasure is a fundamental human experience that enhances life by adding meaning and joy. From the warmth felt in the company of friends and family, to the simple delight of savouring a favourite meal, our capacity for pleasure brings richness to daily life. This feeling is universal, a shared capacity that transcends culture and age. However, pleasure is not simply a "feel-good" aspect of life; it serves a deeper, more essential purpose.

Pleasure plays a crucial role in survival by driving behaviours necessary for staying alive and reproducing. From an evolutionary perspective, the experience of pleasure encourages actions like eating and socialising (Kringelbach, 2009). As Charles Darwin suggested, emotional reactions such as pleasure are adaptive responses that have evolved to help organisms navigate their environments and enhance survival (Darwin, 1993). In this way, pleasure and displeasure reactions are prominent affective responses across all mammals, shaped by natural selection and conserved through evolution for their survival value (Je et al., 2001; Kringelbach & Berridge, 2010b). The brain has evolved

specialised circuits to mediate hedonic reactions, rewarding survival-enhancing behaviours such as seeking food and forming social bonds with pleasurable feelings, which, in turn, motivates organisms to repeat these beneficial actions (Kringelbach & Berridge, 2010a; Lewis et al., 2021). Thus, pleasure is more than just an enjoyable feeling—it is a biological tool that ensures humans engage in behaviours critical for survival and reproduction. However, the complexities of how these processes operate across different contexts are still not fully understood.

1.2. Reward system overview

An important starting point for understanding reward processing is recognising that rewards involve three psychological components: *liking* (the hedonic response), *wanting* (the motivation to seek out rewards), and *learning* (the association between cues and outcomes) (Berridge & Kringelbach, 2015). These components are posited to interact dynamically, with 'wanting' driving the anticipatory period, while 'liking' governs the consummatory experience of pleasure, and 'learning' helps reinforce behaviour based on rewards throughout the process (Kringelbach & Berridge, 2017).

Each of these components is driven by a complex network of regions that make up the brain's reward circuit (Figure 1.1). This reward circuit comprises several key brain regions including the ventral tegmental area (VTA), striatum and orbitofrontal cortex, which together process and respond to rewarding stimuli (Berridge & Robinson, 2003; Haber, 2011; Kringelbach & Berridge, 2010b). The VTA is a central hub, projecting dopaminergic pathways to the nucleus accumbens, dorsal striatum (putamen, caudate), orbitofrontal cortex, prefrontal cortex, and subregions of the anterior cingulate cortex (See Figure 1.1, Haber & Knutson, 2010; Knowland & Lim, 2018; Pizzagalli, 2014, 2022).

The core components of the reward system are anatomically connected by the medial forebrain bundle (Haber & Knutson, 2010; Lesage & Stein, 2022) — a white matter tract that plays a critical role in the experience of pleasure and motivated behaviour (Bracht et al., 2015; Coenen et al., 2011; Fenoy et al., 2022).

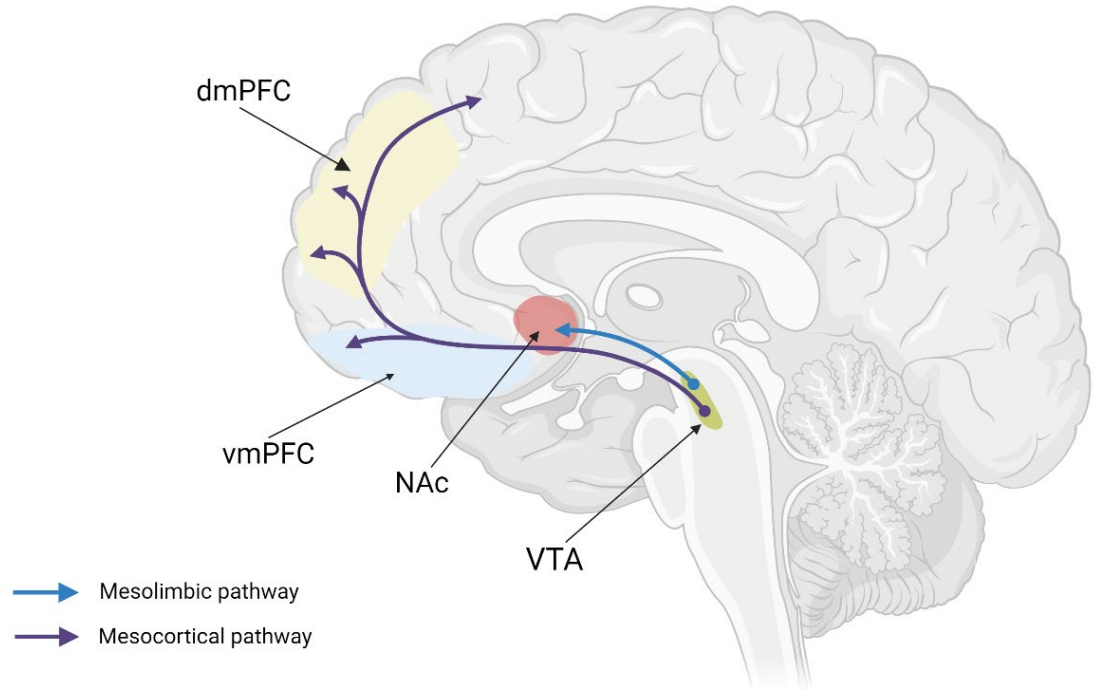


Figure 1.1. The brain's reward circuit

The mesolimbic pathway is one of the major dopaminergic pathways in the brain, crucial for reward processing. It originates in the ventral tegmental area (VTA) and projects to key structures in the limbic system, particularly the nucleus accumbens (NAc). The mesocortical pathway is another major dopaminergic pathway in the brain. This pathway begins in the VTA, like the mesolimbic pathway, but projects primarily to the prefrontal cortex (PFC) and other areas of the cortex. Created in https://BioRender.com.

Each component of reward processing activates specific regions of this circuit to drive motivated behaviour. For example, the sight, smell, or even the thought of your favourite food acts as a cue, triggering the 'wanting' phase as dopamine is released from the VTA into regions such as the striatum, including the nucleus accumbens, via the mesolimbic pathway (See Figure 1.1), sparking a craving and motivating you to seek the food (Lewis et al., 2021). Once you take the first bite, the 'liking' or consummatory phase is triggered, with the orbitofrontal cortex evaluating the taste, the insular cortex processing sensory aspects of flavour, and the ventral pallidum amplifying the pleasurable sensation (Berridge & Dayan, 2021; Haber, 2011; Stark et al., 2022). During this process, 'learning' occurs as the hippocampus links the cue with the pleasure experienced (See Figure 1.2), ensuring that the cue gains incentive salience and motivational value, which drives you to seek it out again (Berridge & Kringelbach, 2015; Nguyen et al., 2021).

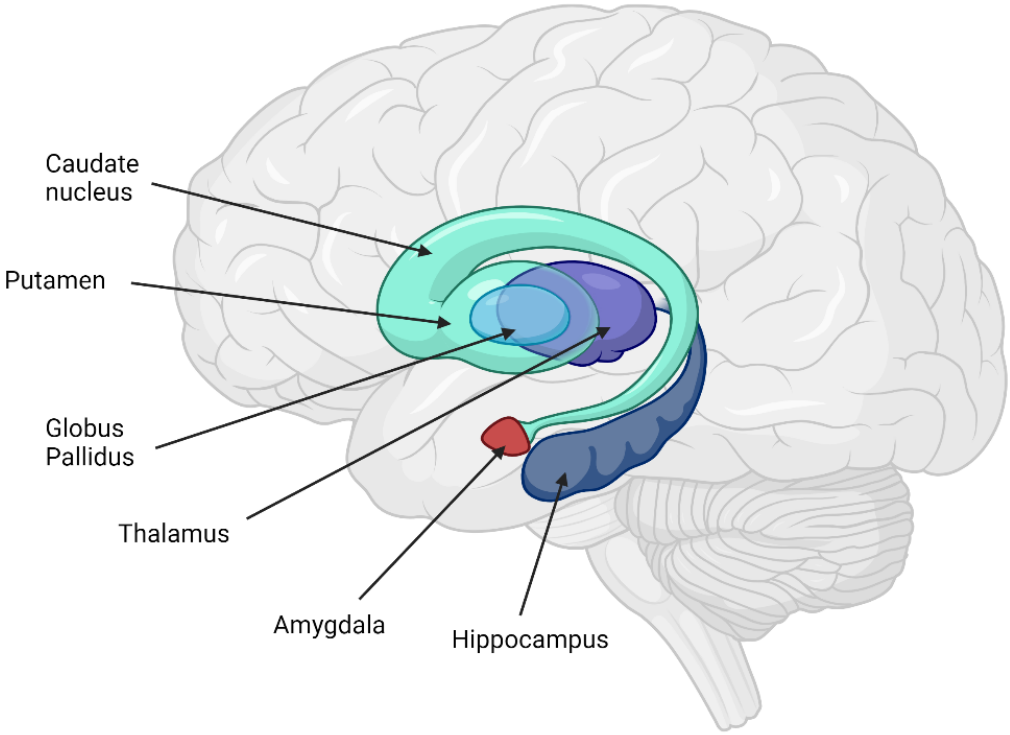


Figure 1. 2. Key subcortical structures of the brain's reward system.

The brain's reward system comprises striatal regions including the putamen, caudate nucleus, hippocampus, amygdala, thalamus and globus pallidus. Created in https://BioRender.com.

Importantly, this cue also engages 'learning' processes through the generation of a reward prediction error, which occurs when there is a discrepancy between the expected and actual outcomes (Deng et al., 2023; Kumar et al., 2018; Rescorla, 1972). If the food is more enjoyable than anticipated, the positive reward prediction error enhances dopaminergic activity, reinforcing the value of the cue and encouraging future pursuit of similar rewards (Schultz, 2016, 2024). Conversely, if the food is less pleasurable than expected, a negative reward prediction error adjusts expectations and reduces the motivational salience of the cue (Schultz, 2024).

Thus, the brain's reward circuitry is widespread, encompassing both cortical and subcortical structures (Berridge & Kringelbach, 2015). These key regions operate as a coordinated system, ensuring that the processes of 'wanting', 'liking', and 'learning' work together to motivate individuals to seek rewards and reinforce adaptive behaviours essential for survival and well-being. Ongoing research and technological developments continue to reveal new insights into the complexity and functions of this system. However, despite significant progress, critical questions remain about how disruptions to these processes manifest across different clinical conditions, highlighting the need for further exploration.

1.3. What happens when there is a breakdown in the reward system?

Given that the reward system plays a critical role in motivating behaviours and promoting survival, disruptions to this system can have severe consequences, which are consistently highlighted in neuropsychiatric disorders. One of the most well-

documented disorders associated with reward system dysfunction is Major Depressive Disorder (MDD). MDD is characterised by persistent low mood, fatigue, and impaired cognitive function (American Psychiatric Association, 2022). Importantly, a hallmark feature of MDD is diminished interest or pleasure in almost all activities, otherwise known as *anhedonia* (Serretti, 2023).

1.4. Anhedonia

First defined by Théodule-Armand Ribot in 1896 as a reduced ability to experience pleasure, anhedonia originally referred to a simple inability to derive enjoyment from sensory stimuli like sweet tastes or pleasant smells (Ribot, 1896). Over time, however, the term has evolved to address more complex psychological processes, especially where it relates to clinical disorders like MDD (Shankman et al., 2014). Modern re-conceptualizations of anhedonia recognise the independent but interconnected roles of deficits in 'wanting' and 'liking', commonly referred to as anticipatory and consummatory anhedonia, respectively (Shankman et al., 2014). Anticipatory anhedonia involves impairments in the ability to anticipate or feel motivated by the prospect of future rewards, reflecting a breakdown in the motivational (or incentive salience) component of reward processing (Gard et al., 2006, 2007). Consummatory anhedonia, on the other hand, refers to difficulties in deriving pleasure from consuming or engaging with a reward in-the-moment (Gard et al., 2006, 2007). This expanded definition better captures the multifaceted nature of anhedonia, encompassing not just deficits in experiencing pleasure but also in the motivation to seek and engage with rewarding experiences.

Anhedonia is not limited to MDD; it is observed across a diverse range of disorders, suggesting that it may represent a transdiagnostic phenomenon, potentially underpinned by shared neural mechanisms. This perspective has driven significant

research into the importance of reward system dysfunction in clinical disorders ranging from depression to schizophrenia and post-traumatic stress disorder (PTSD; Guineau et al., 2023; Schaub et al., 2021; Trøstheim et al., 2020). However, emerging evidence also indicates that the neural underpinnings of anhedonia may not be entirely consistent across these disorders, with variations reflecting disorder-specific mechanisms (Hamilton et al., 2015; G. Li et al., 2021; Liang et al., 2022). This distinction raises critical questions about the extent to which anhedonia is truly transdiagnostic or whether its manifestation is shaped by the unique neurobiological and clinical profiles of each disorder.

To explore these complexities, this section critically examines the existing literature on anhedonia across psychiatric disorders, highlighting both commonalities and discrepancies in its neural correlates. This review provides a foundation for understanding how these findings may, or may not, translate to neurodegenerative disorders like frontotemporal dementia (FTD), where the study of anhedonia remains comparatively underdeveloped (Husain & Roiser, 2018).

1.5. Anhedonia in major depressive disorder

Extensive research has been dedicated to uncovering the neurobiological mechanisms underlying reward deficits in depression. Anhedonia in MDD reflects a breakdown in the reward system processes, with reduced activity in several key brain regions. Central to this dysfunction is the ventral striatum, particularly the nucleus accumbens, which shows diminished activation during both the anticipation and consumption of rewards in people with MDD (Keren et al., 2018; Pizzagalli, 2014). Reduced activation in the ventral striatum in MDD during reward anticipation has also

been linked to the severity of anhedonia and depression symptoms (Hägele et al., 2015; Takamura et al., 2017). This blunted striatal response, often associated with a dampened dopaminergic system, helps explain why previously pleasurable activities, such as spending time with friends or family, no longer elicits the same emotional responses in individuals with MDD (Craske et al., 2024). The orbitofrontal cortex also plays a significant role in this dysfunction. Structural MRI studies have revealed decreased grey matter volume in the orbitofrontal cortex, along with the caudate nucleus, in individuals with depression (Enneking et al., 2019; Ward et al., 2019). Additionally, individuals with depression display frontostriatal hypoactivation, particularly in the orbitofrontal cortex and ventral striatum, when presented with unexpected rewards (Segarra et al., 2016). Hypoactivation in the orbitofrontal cortex likely impairs the ability to evaluate and assign value to rewards (Borsini et al., 2020). This diminished function may contribute to a reduced sensitivity to rewarding stimuli, underpinning the lack of motivation and pleasure that characterises anhedonia in MDD.

The mesolimbic reward system is further implicated in MDD through abnormal structural and functional connectivity. Diffusion tensor imaging studies have shown that disrupted structural connections within the reward network in MDD are associated with anhedonia (Bracht et al., 2014; Yang et al., 2017). Specifically, microstructural alterations in the medial forebrain bundle, which links the VTA to the medial orbitofrontal cortex, have been associated with anhedonia and depression severity in MDD (Bracht et al., 2014). Task-based fMRI research in MDD further highlights that abnormal connectivity between the posterior ventromedial prefrontal cortex (vmPFC) and the mesolimbic reward system when encountering pleasurable stimuli is negatively correlated with anhedonia (Young et al., 2016).

These findings highlight that anhedonia in MDD is underpinned by disruptions across multiple nodes of the reward system, encompassing both structural and functional impairments. The reduced activation in the ventral striatum and orbitofrontal cortex, coupled with disrupted connectivity in the mesolimbic reward pathway, suggests that MDD impairs the ability to anticipate, evaluate, and respond to rewarding stimuli. This multifaceted breakdown not only diminishes the emotional salience of rewards but also impacts motivation and goal-directed behaviour, providing a neurobiological basis for the pervasive lack of pleasure and engagement observed in MDD.

1.6. Anhedonia in schizophrenia

Beyond depression, anhedonia is present in other psychiatric disorders, including schizophrenia (Haslam, 1809; Meehl, 1990), eating disorders (Davis & Woodside, 2002) and PTSD (Nawijn et al., 2015). In schizophrenia, anhedonia is considered one of the core negative symptoms and is linked to significant abnormalities in reward processing that impact both social engagement and daily activities (Pelizza & Ferrari, 2009). Motivational deficits in schizophrenia are thought to stem from an impaired ability to differentiate between potential rewards and loss-avoidance signals, involving dysfunction in the frontostriatal pathway, including the vmPFC, anterior cingulate cortex, insula, and ventral striatum (Waltz et al., 2018). Research into the neural underpinnings of anhedonia in schizophrenia has identified dysregulation within similar reward-related circuits as found in MDD, including the frontostriatal, mesocortical, and mesolimbic pathways (Brugger et al., 2020; Liang et al., 2022; Segarra et al., 2016; Waltz et al., 2018). Specifically, reduced activity in the orbitofrontal cortex and the ventral striatum during reward anticipation is associated with greater anhedonia and more severe depressive symptoms in schizophrenia (Arrondo et al., 2015; Harvey et al., 2010). Additionally, severity of self-

reported anhedonia in schizophrenia is negatively correlated with activity in the orbitofrontal cortex and vmPFC, indicating that reduced activity in these regions may underlie the diminished capacity for pleasure (Harvey et al., 2010). Furthermore, reduced activation of the anterior cingulate cortex and vmPFC in response to receiving unexpected rewards has been shown to predict task-related motivation in individuals with schizophrenia, linking these regions to the severity of anhedonia (Segarra et al., 2016).

1.7. Anhedonia in post-traumatic stress disorder

Anhedonia is also prevalent in PTSD, contributing to significant impairments in psychosocial functioning, heightened psychiatric comorbidities, and the chronicity of PTSD symptoms (for review see Vinograd et al., 2022). Research suggests that anhedonia in PTSD arises from dysregulated reward processing and has been linked to reduced functional connectivity between the ventral pallidum and regions within the brain's default mode network (G. Li et al., 2021; Vinograd et al., 2022). Similarly, in eating disorders, individuals with anorexia nervosa exhibit deficits in 'wanting' or incentive salience (Haynos et al., 2021). Despite recognising the pleasantness of typically rewarding stimuli, such as food, they report lower motivation to pursue them (reviewed by Dolan, Khindri, et al., 2022). In contrast, individuals with binge-eating disorder and bulimia nervosa show mixed findings, with both heightened and reduced activation in reward-related brain regions like the ventral striatum and anterior cingulate cortex in response to food cues, suggesting variability in reward sensitivity (Lee et al., 2017; Schienle et al., 2009).

These clinical disorders collectively reveal that anhedonia stems from widespread disruptions across key nodes of the brain's reward circuitry, including the ventral striatum, orbitofrontal cortex, and broader mesocorticolimbic networks. Importantly, these findings highlight the intricate interplay between motivational, cognitive, and affective processes that underlie the experience of pleasure and engagement with rewards. While much progress has been made in understanding anhedonia in psychiatric disorders, far less attention has been given to its manifestation in neurodegenerative disorders, such as frontotemporal dementia.

1.8. Anhedonia in neurodegeneration

1.8.1. Frontotemporal dementia (FTD)

FTD refers to a group of early-onset dementia syndromes that typically affect individuals under the age of 65 (Onyike & Diehl-Schmid, 2013). FTD accounts for 12-20% of all dementia cases and affects approximately 15-22 out of every 100,000 people (Khan & Jesus, 2023). It causes progressive cognitive, emotional, and behavioural decline, ultimately leading to loss of function and death. Alongside Alzheimer's disease (AD), FTD is a major subtype of dementia, with similar prevalence rates to AD in individuals under 60 (Zamboni et al., 2024). Both syndromes create significant emotional and financial stress for caregivers and families (Neil & Bowie, 2008). Although dementia is usually associated with memory and cognitive issues, younger-onset dementias like FTD often present with notable neuropsychiatric symptoms and motivational disturbances (Lyketsos et al., 2002). This thesis specifically examines two subtypes of FTD—behavioural variant frontotemporal dementia (bvFTD) and semantic dementia (SD).

1.8.2. Behavioural variant frontotemporal dementia

BvFTD is characterised by significant personality and behavioural changes, occurring alongside executive dysfunction (Piguet et al., 2017). Patients typically exhibit a spectrum of behavioural symptoms, including altered reward responsiveness, disinhibition, apathy, and compulsive behaviours such as overeating and impulsivity (Ahmed, Irish, Henning, et al., 2016; Galimberti et al., 2015; Perry et al., 2017; Wei et al., 2020). At the neural level, brain atrophy in bvFTD initially affects the frontoinsular cortices, anterior cingulate cortex, and medial prefrontal cortex, spreading to nearby medial and lateral prefrontal regions (Seeley et al., 2008). Over time, atrophy extends to the anterior temporal regions and continues to spread to more posterior temporal and subcortical areas, including the caudate and ventral striatum - key regions involved in reward processing (see Figure 1.3; Haber, 2011; Landin-Romero et al., 2017). The behavioural symptoms observed in bvFTD are increasingly recognised as manifestations of reward system dysfunction. Indeed, multiple studies have implicated disruptions in reward processing in altered eating and sexual behaviours in bvFTD (Ahmed, Irish, Henning, et al., 2016; Ahmed et al., 2018).

While disinhibition and impulsivity are hallmark features of bvFTD, apathy and loss of motivation are equally pervasive, often contributing significantly to functional impairment (Merrilees et al., 2013; Salech et al., 2021). Notably, apathy is one of the earliest and most defining symptoms of bvFTD, forming a core diagnostic criterion (Radakovic et al., 2021; Rascovsky et al., 2011). Clinically, apathy manifests as a striking reduction in goal-directed behaviour, diminished emotional engagement, and an overall decline in initiative (Wei et al., 2020; Wong et al., 2023). This motivational dysfunction,

particularly in the context of reward system atrophy, suggests that hedonic processing deficits may be a critical but underexplored feature of bvFTD.

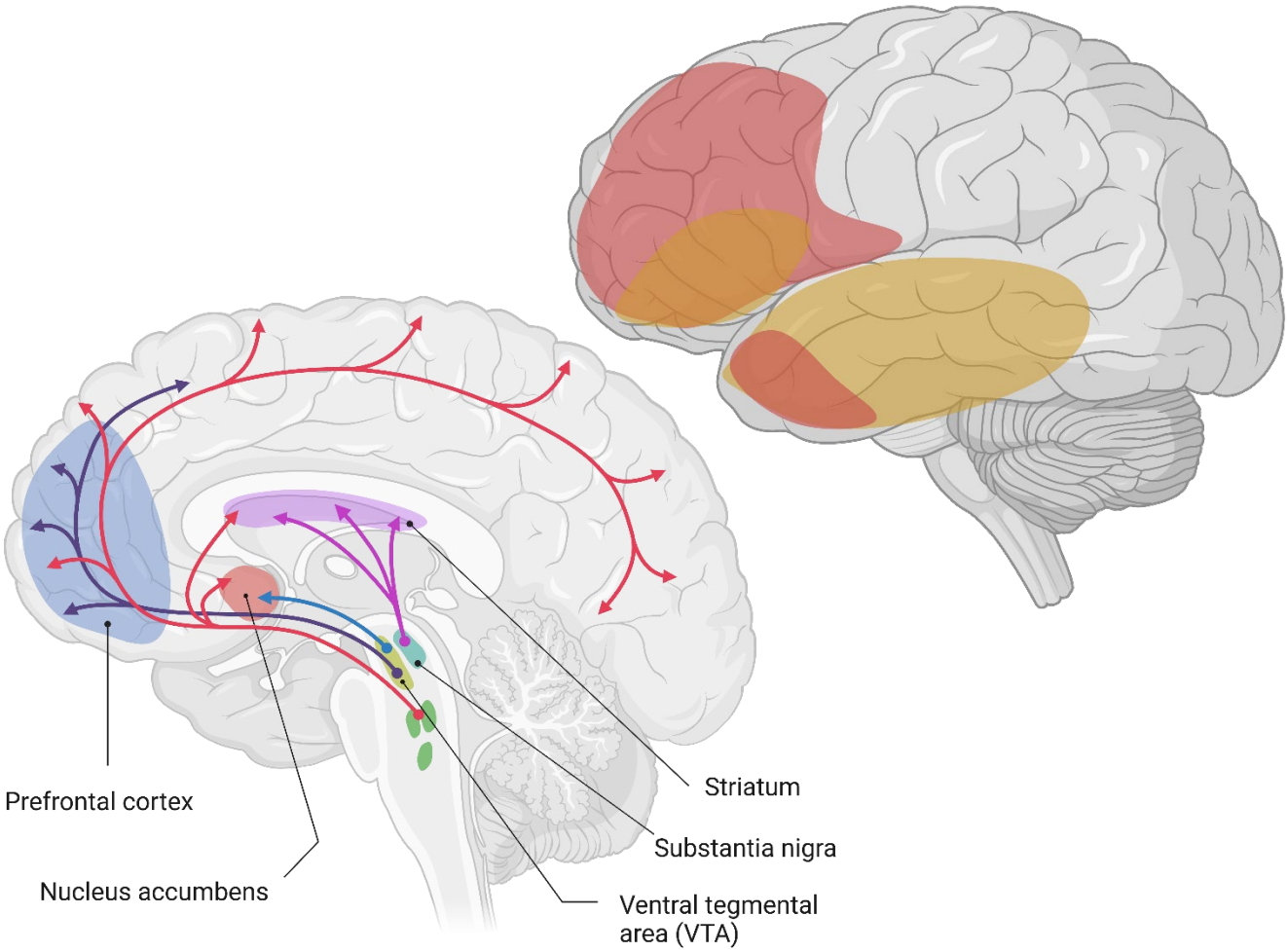


Figure 1.3. Overlap between the brain's reward circuit and patterns of atrophy in FTD.

Overlap between key regions of brain's reward circuit including the prefrontal cortex and striatum and patterns of atrophy in FTD. In bvFTD (red), atrophy initially affects the frontoinsular cortices, anterior cingulate cortex, and medial prefrontal cortex, spreading to lateral prefrontal regions and subcortical structures, including the caudate and ventral striatum. In contrast, SD (yellow) is characterised by asymmetric atrophy, predominantly affecting the anterior temporal lobes and temporal pole, including the hippocampus and amygdala, with progression extending into the insula and orbitofrontal cortices. Approximate anatomical boundaries are indicated. Created in https://BioRender.com.

1.8.3. Semantic dementia

In contrast to bvFTD, SD is primarily a language disorder, characterised by the progressive deterioration of semantic knowledge (Gorno-Tempini et al., 2011). Individuals with SD exhibit marked impairments in understanding the meaning of words and/or identifying objects (Hodges & Patterson, 2007). However, as the disease progresses, individuals with SD often develop behavioural and motivational changes, including loss of empathy, impaired theory of mind, and increased behavioural rigidity (Horne et al., 2024; Irish et al., 2014; Wong et al., 2023). Other cognitive functions, such as visuospatial processing and episodic memory, tend to remain relatively intact in the early stages (Irish & Piolino, 2016). Atrophy in SD is predominantly localised to the anterior temporal lobes, with a characteristic left-lateralised pattern, progressively extending into the insula and orbitofrontal cortices—regions implicated in reward processing (see Figure 1.3; Landin-Romero et al., 2016; Lewis et al., 2021). While language deficits are the defining feature of SD, emerging evidence suggests that motivational impairments are a critical but under recognised aspect of the syndrome.

Recent research has highlighted that apathy in SD is more prevalent than previously appreciated, with symptoms such as social withdrawal, diminished engagement in daily activities, and reduced initiative becoming more pronounced in later disease stages (Radakovic et al., 2021; Wong et al., 2020). These findings suggest that SD, like bvFTD, involves significant disruptions to reward-related motivation, warranting further investigation into its role in hedonic processing deficits.

1.9. Anhedonia in FTD

Although apathy has been widely studied in bvFTD and emerging evidence suggests motivational impairments in SD, anhedonia remains largely overlooked in the FTD literature. This gap is particularly striking given that atrophy in FTD prominently affects key structures of the reward system, including the orbitofrontal cortex, ventral striatum, and anterior cingulate cortex - regions fundamentally involved in the experience of pleasure (Bertoux et al., 2015; Chu et al., 2024; Landin-Romero et al., 2017).

Recent studies have begun to address this gap, demonstrating the presence of marked anhedonia in bvFTD and SD (Shaw, El-Omar, Ramanan, et al., 2021; Shaw, El-Omar, Roquet, et al., 2021; Shaw et al., 2024). Notably, this loss of hedonic tone represented a significant departure from patients' premorbid disposition, indicating an emergent clinical feature rather than an underlying trait of these individuals (Shaw, El-Omar, Roquet, et al., 2021). Given the substantial overlap between regions of atrophy in FTD and core reward circuits (see Figure 1.3) , these findings suggest that anhedonia may be a critical but under-recognised feature of FTD, warranting further investigation into its neural and behavioural manifestations.

1.9.1. Neural correlates of anhedonia in FTD

Using a transdiagnostic approach, one previous study reported that anhedonia in FTD is associated with grey matter loss in bilateral orbitofrontal, medial prefrontal, and paracingulate cortices, as well as the insular and lateral temporal regions and, to a lesser extent, the right putamen (Shaw, El-Omar, Roquet, et al., 2021). These regions map remarkably well onto a clearly delineated mesocorticolimbic circuit associated with the experience of pleasure. In SD, anhedonia has been shown to associate with grey matter intensity decrease in a predominantly right-lateralised frontotemporal brain network

(Shaw, El-Omar, Ramanan, et al., 2021). Key regions included the right orbitofrontal cortex and right temporal pole, along with the anterior cingulate cortex, and the cerebellum, bilaterally (Shaw, El-Omar, Ramanan, et al., 2021). These findings underscore the importance of recognising anhedonia as a core symptom in FTD, driven by atrophy in key regions implicated in reward processing.

1.9.2. Multidimensional nature of anhedonia in FTD

Although these recent studies indicate that anhedonia is a prominent feature in FTD, its multidimensional nature remains underexplored. Much of the existing research relies on crude, self-report measures that fail to differentiate between the anticipatory and consummatory components of anhedonia (Shaw, El-Omar, Ramanan, et al., 2021; Shaw, El-Omar, Roquet, et al., 2021). This limitation raises critical questions about whether these components are differentially affected in FTD and how they contribute to the observed loss of motivation and goal-directed behaviour. Furthermore, understanding anhedonia in FTD from a multidimensional perspective requires examining the role of cognitive processes, particularly whether impairments in the anticipatory aspect of pleasure stem from difficulties imagining future rewards—a process closely tied to episodic future thinking.

1.10. Episodic future thinking

Episodic future thinking refers to the ability to mentally simulate future events, allowing individuals to anticipate future outcomes, plan, and engage in goal-directed behaviour (Atance & O'Neill, 2001; Schacter et al., 2008). This cognitive process relies heavily on brain regions involved in memory, such as the hippocampus, and prefrontal areas that support executive functions and decision-making (reviewed by Schacter et al.,

2017). Episodic future thinking is closely linked with autobiographical memory, as it involves flexibly recombining elements of past experiences to envision novel scenarios (see Schacter et al., 2007). Although episodic future thinking shares neural substrates with memory, it is considered a more recently evolved cognitive function, thought to uniquely support goal-directed behaviour by allowing individuals to simulate potential outcomes and consequences of future actions (Addis et al., 2006; Suddendorf & Corballis, 2007).

The mental construction involved in episodic future thinking engages a network anchored by the vmPFC and anterior hippocampus, where spatial and contextual elements are assembled (Monk et al., 2020; Zeidman & Maguire, 2016). This foundational "scaffold" for imagined future events is enriched by sensory-perceptual details from neocortical regions and is integrated into a cohesive, vivid simulation through posterior parietal areas like the angular gyrus and posterior cingulate cortex (Gilboa & Marlatte, 2017; Irish & Piguet, 2013; Ramanan et al., 2018). This richly detailed construction, often visually dominant, draws upon interconnected networks between the construction and visual processing systems, enabling an immersive and emotionally engaging experience (Conti & Irish, 2021; Irish & Vatansever, 2020; Ramanan et al., 2018; Rolls, 2019). A breakdown in these systems results in an inability to generate detailed representations of the future.

1.11. Episodic future thinking in FTD

Mounting evidence indicates an impaired ability to simulate future events in bvFTD and SD (Irish et al., 2012a, 2013, 2016; Irish & Piolino, 2016). Studies have demonstrated that these patients lack the capacity to generate detailed mental

representations of future scenarios, often providing vague or superficial descriptions when asked to envision upcoming events (Irish et al., 2012a; Irish, 2016). These deficits are associated with atrophy in the anterior temporal lobes, frontopolar and medial temporal regions (Irish et al., 2013; Irish & Piolino, 2016). Importantly, regions highlighted as part of the future thinking system overlap with those of the reward system, in particular the vmPFC and hippocampus. Therefore, it raises the question how damage to these regions impacts these two processes.

1.12. The role of episodic future thinking and anticipatory anhedonia

Episodic future thinking is essential for imagining and preparing for future rewards, serving as a bridge between present actions and anticipated outcomes (Bulley & Irish, 2018). By connecting present decisions with future rewards, episodic future thinking supports goal-directed motivation and adaptive behaviour. Research shows that episodic future thinking plays a critical role in regulating emotions and influencing decisions by simulating the emotional states anticipated in future scenarios (Baumgartner et al., 2008; Neroni et al., 2014). For instance, individuals with reduced episodic future thinking specificity, such as those with schizophrenia, show a tendency toward apathy, negatively impacting motivation (Raffard et al., 2013). Episodic future thinking also supports planning and necessary coping strategies by enabling individuals to envision positive outcomes, which are often more positively valanced and detailed than past memories (D'Argembeau & Van der Linden, 2004). Deficits in episodic future thinking are common in various psychiatric disorders, such as MDD and schizophrenia, where they may contribute to the persistence of symptoms by impairing goal-motivated behaviour (reviewed by Hallford et al., 2018). This connection is particularly relevant in

FTD, where deficits in episodic future thinking are well documented and may be closely tied to the breakdown in reward processing.

1.13. Episodic future thinking and anhedonia in FTD

Individuals with FTD are known to experience both anhedonia and deficits in episodic future thinking. This raises an intriguing question: could the inability to generate detailed future events in FTD be linked to impairments in anticipating future rewards? To date, no study has specifically examined episodic future thinking in the context of reward processing in FTD. Exploring this potential connection could provide valuable insights into how disruptions in future thinking contribute to the emotional and motivational symptoms characteristic of FTD, particularly in the domain of reward anticipation. By understanding this interplay, we can better delineate the cognitive and neural mechanisms underlying these impairments and identify targets for intervention.

1.14. Status of the field

While significant progress has been made in understanding anhedonia in FTD, critical gaps remain. Anhedonia has been documented as a prominent feature in FTD, marked by disruptions in reward processing closely linked to degeneration in key regions of the brain's reward circuitry, including the orbitofrontal cortex, vmPFC, and striatum (Shaw, El-Omar, Roquet, et al., 2021). Despite these advances, our understanding of how anhedonia interacts with other motivational impairments, such as apathy, and how these deficits contribute to functional decline remains limited.

Further, while research has primarily focused on the broader concept of anhedonia in FTD, the multidimensional nature of this phenomenon remains underexplored. In particular, distinct impairments in anticipatory and consummatory pleasure have yet to

be characterised in FTD. Similarly, episodic future thinking, a cognitive process essential for anticipating rewards and planning goal-directed behaviour, is well-documented as impaired in FTD. Yet, its relationship with reward processing deficits, including anhedonia, remains unclear. Finally, how anhedonia presents in FTD compared to other neuropsychiatric disorders such as MDD is yet to be directly explored.

These gaps in our understanding present a critical opportunity to advance our knowledge of how disruptions in the ability to anticipate and experience pleasure influence motivation, behaviour, and functional outcomes in FTD. Unpacking the complex interplay between these processes could provide valuable insights to guide targeted interventions aimed at improving the quality of life for individuals living with FTD.

1.15. Overall aims of this thesis

Research aimed at addressing these gaps is described in the following four experimental chapters. Specifically, Chapter 2 characterises the profile of apathy and anhedonia across dementia syndromes, including FTD, and examines their contribution to functional decline. This will highlight the pervasive yet distinct nature of motivational disturbances in dementia, emphasising the need to examine these symptoms separately across disorders. Next, Chapter 3 delves into the multidimensional nature of anhedonia in FTD, investigating the breakdown of anticipatory and consummatory components of pleasure. By identifying which aspects of reward processing are disrupted in FTD, this chapter will deepen our understanding of anhedonia in this disorder and provide insights to guide interventions aimed at enhancing patients' quality of life and alleviating caregiver burden. Following this, Chapter 4 explores the relationship between episodic future thinking and anticipatory anhedonia in FTD. In doing so, this chapter aims to clarify

whether anticipatory anhedonia in FTD is related to difficulties in imagining the future, offering a broader understanding of how these deficits may be addressed to support motivation and goal-directed behaviour in dementia. Finally, Chapter 5 adopts a transdiagnostic approach by comparing anticipatory and consummatory anhedonia in bvFTD and MDD. This comparison will reveal whether clinically relevant rates of anhedonia are comparable between these disorders, offering valuable insights into shared and distinct mechanisms that could inform targeted interventions across disorders.

The ultimate aim of this thesis is to deepen our understanding of anhedonia in FTD by examining its multidimensional nature, impact on everyday function, and its association with episodic future thinking. By addressing these complex yet crucial aspects of behaviour, this thesis seeks to inform interventions that enhance the quality of life for both patients and their carers, who are profoundly affected by these symptoms.

This chapter is an expanded version of the following peer-reviewed article:
Shaw, S.R., Horne, K.S., Piguet, O. *et al*. Profiles of motivational impairment and their relationship to functional decline in frontotemporal dementia. *Journal of Neurology* **271**, 4963–4971 (2024). https://doi.org/10.1007/s00415-024-12430-0

"Sometimes I just feel like I don't want to do anything. And those kinds of days put me down a little bit" – *individual with bvFTD*

2.1. Introduction

Motivational disturbances are prominent in FTD, leading to social withdrawal and disengagement from previously enjoyed activities (Merrilees et al., 2013). Loss of motivation in the form of apathy represents a core clinical feature of the behavioural variant of FTD (bvFTD; Rascovsky et al., 2011) and is increasingly recognised in language variants of FTD (Quang et al., 2021; Wong et al., 2020). Apathy, defined as diminished motivation (Lanctôt et al., 2017; Starkstein & Leentjens, 2008) is inherently multidimensional and can be deconstructed in terms of its impact on goal-oriented behaviour, cognitive engagement, or emotional responsiveness (Husain & Roiser, 2018; Massimo et al., 2014). Unsurprisingly, apathy is a strong predictor of functional decline in FTD, compromising the organisation, planning and initiation of basic activities of daily living including cooking, managing medication, and maintaining personal hygiene (O'Connor et al., 2016, 2017; Salech et al., 2021; S. Starkstein et al., 2006). Beyond its impact on the individual, apathy also has downstream negative effects on the social and

emotional wellbeing of the carer (Merrilees et al., 2013; Wei et al., 2020; Wong et al., 2023).

While apathy has tended to take centre stage, recent studies suggest that many of the negative behavioural symptoms of FTD (e.g., social withdrawal, lack of engagement, loss of interest) might be better conceptualised in terms of alterations in hedonic processing (Ahmed et al., 2015; Ahmed, Irish, Piguet, et al., 2016; Perry et al., 2014). Anhedonia refers to the loss of interest in previously enjoyable pursuits, such as food, sex, hobbies, and social interactions and is pervasive in neuropsychiatric disorders such as depression and bipolar disorder (Serretti, 2023; Shaw, El-Omar, Roquet, et al., 2021). Several recent studies demonstrate the presence of marked anhedonia in bvFTD and SD, representing a significant departure from pre-morbid functioning (Chokesuwattanaskul et al., 2023; Shaw, El-Omar, Ramanan, et al., 2021; Shaw, El-Omar, Roquet, et al., 2021). Importantly, while anhedonia and apathy co-occur in FTD, their neural substrates are dissociable, suggesting that anhedonia should be considered a standalone clinical symptom in FTD (Shaw, El-Omar, Roquet, et al., 2021). These observations have prompted calls for a more targeted approach to identifying distinct motivational phenotypes in FTD (Chokesuwattanaskul et al., 2023; Horne & Irish, 2023).

Despite growing awareness that apathy and anhedonia co-occur in FTD, their differential impact on functional impairment in FTD syndromes remains unclear. Studies in psychiatric disorders such as major depressive disorder, schizophrenia and bipolar disorder suggest a close coupling between anhedonia, negative functional outcomes, and disease severity (Barch et al., 2017; Pizzagalli et al., 2022). However, no study to date has explored the impact of anhedonia on functional outcomes in FTD. The objective of the present study therefore was to: (i) characterise the nature of multidimensional

motivational impairments in bvFTD and SD compared to AD participants and (ii) explore the relative contributions of multidimensional apathy and anhedonia to functional impairment in each diagnostic group.

2.2. Methods

2.2.1. Participants[1]

A total of 211 participants were recruited through FRONTIER, the frontotemporal dementia research clinic based at the Brain and Mind Centre at the University of Sydney, Australia. Within this group, 68 participants met current diagnostic criteria for clinically probable bvFTD (Rascovsky et al., 2011), 32 met criteria for SD (Gorno-Tempini et al., 2011) and 43 participants met criteria for typical AD (McKhann et al., 2011). Participant diagnoses were established by consensus among a multidisciplinary team including a senior neurologist, neuropsychologist, and occupational therapist based on comprehensive clinical investigation, neuropsychological assessment, informant interview, and review of brain atrophy on structural MRI.

Briefly, all patients diagnosed with bvFTD presented with the following core features; marked changes in personality and behaviour, emotional blunting, overeating, impulsiveness along with a decline in attention and cognitive functioning in the context of prominent grey matter atrophy of the frontal and temporal lobes on structural MRI (Rascovsky et al., 2011). SD patients showed progressive loss of conceptual knowledge manifesting in comprehension and naming difficulties, with relative preservation of phonology and fluency, visuospatial and everyday episodic memory function (Gorno-Tempini et al., 2011). SD patients demonstrated striking atrophy of the anterior temporal

[1] A large proportion of these data were previously reported in Shaw et al. (2021), with 93% overlap between study samples. Importantly, the original Shaw et al. 2021 study adopted a transdiagnostic approach and did not explore predictors of functional outcomes within specific dementia subtypes.

lobes, with a left > right predominance in the case of left-SD and the converse profile for right-SD patients. The current sample consisted of 21 left-lateralised cases and 11 right-lateralised cases but were aggregated to create an overall SD group to increase statistical power. Importantly, independent samples t-tests confirmed no significant differences in motivational profiles between left- and right-lateralised SD cases (all *p's*>.36). In contrast, AD cases presented with classic episodic memory disturbances combined with executive and visuospatial dysfunction (McKhann et al., 2011). Structural MRI revealed widespread cortical atrophy in the AD group including medial temporal, parietal and prefrontal regions (Karas et al., 2004). Patients with atypical presentations of AD such as logogenic progressive aphasia or posterior cortical atrophy were excluded. These cognitive and neural profiles are consistent with established reports in the literature for bvFTD (Rascovsky et al., 2011), SD (Hodges & Patterson, 2007) and AD (McKhann et al., 2011).

Sixty-eight healthy older control participants (age > 55 years) were recruited from the FRONTIER volunteer database and local community groups. All Controls scored 88 or above on the Addenbrooke's Cognitive Examination III screening tool (ACE-III; Hsieh, Schubert, et al., 2013; So et al., 2018), zero on the Clinical Dementia Rating Scale (Morris, 1997), and performed within normal limits on all behavioural and cognitive measures.

Exclusion criteria for all participants included a prior history of mental illness, alcohol or other drug abuse, significant head injury or limited English language proficiency. Patients scoring <40 on the ACE-III (max score = 100) were excluded due to the severity of their cognitive impairment.

2.2.2. Ethics statement

In accordance with the Declaration of Helsinki, ethical approval for these studies was obtained from the Human Research Ethics Committee (HREC) of the South Eastern Sydney Local Health District as part of the following two projects: "Memory and imagination in ageing" (approval number 2018/479) and "Clinical Assessment for Ageing and Neurodegeneration Research" (approval number 2020/224).

2.2.3. Clinical and cognitive assessment

The ACE-III was used to determine participants' overall level of cognitive function across five domains of Attention and Orientation [/18], Memory [/26], Fluency [/14], Language [/26], and Visuospatial function [/16] (Hsieh, Schubert, et al., 2013; So et al., 2018). Subdomain scores are summed to create an overall cognition score [/100] with higher scores denoting greater cognition (Hsieh, Schubert, et al., 2013; So et al., 2018).

Behavioural changes were assessed using the carer-rated Cambridge Behavioural Inventory-Revised (CBI-R; Wedderburn et al., 2008). The CBI-R includes 45 items that assess 10 functional and behavioural domains, including memory and orientation, daily living skills, self-care, abnormal behaviours, mood, beliefs, eating habits, sleep, stereotypical and motor behaviours, and motivation. Carers rate the frequency of a behaviour over the past month on a scale of 1-4, where a higher score indicates greater frequency (Wedderburn et al., 2008). Scores were converted to percentage scores, with higher scores indicating greater behavioural change (i.e. worse outcomes).

Disease duration was calculated as the number of years elapsed from reported onset of symptoms to date of testing. The depression subscale of the Depression, Anxiety and Stress Scale (DASS; Lovibond & Lovibond, 1995) was used to assess participants' self-reported mood over the past week. The depression subscale assesses features such as loss of self-esteem and motivation, feelings of hopelessness, and low positive affect.

Responses are recorded on a 4-point Likert scale ranging from 0 ("did not apply to me at all") to 3 ("applied to me very much"), with higher scores indicating greater symptom severity. For patients, each item was read aloud by the clinician and wording was clarified where necessary.

2.2.4. Carer-rated assessment of motivational disturbances

Carers rated levels of apathy and anhedonia in the patients across two time periods ("Before symptom onset" and "Current"). Carers predominantly comprised spouses or partners (80%) and lived at home with the patient, providing a reliable index of pre-morbid and current levels of motivation. A full breakdown of carer characteristics is provided in Table 2.1.

Table 2.1. Percentage frequency of carer relationship across patient groups.

		bvFTD (n=58)	**SD (n=30)**	**AD (n=42)**
Carer	Spouse (%)	80.9	75.0	83.7
	Child (%)	8.8	15.6	4.7
	Sibling (%)	1.5	6.3	2.3
	Support worker (%)	-	-	4.7
	Other (%)	8.8	3.1	4.7

Note. The 'Other' category is a mixed category comprising brother-in-law, sister-in-law, mother, and friend. AD=Alzheimer's disease; bvFTD=behavioural variant of frontotemporal dementia; SD=semantic dementia.

2.2.5. Apathy

The Dimensional Apathy Scale (DApS) was included as a validated carer-rated assessment of apathy (i) before dementia onset and (ii) at the current time (Radakovic & Abrahams, 2014). The DApS comprises three subscales assessing disrupted planning, attention and organisation (Executive); blunted emotional responses (Emotional); and

loss of spontaneous activity (Initiation). Example items from each of the subscales include: for Executive apathy, “When doing a demanding task, they have difficulty working out what they have to do”; for Emotional apathy, “They are unconcerned about how others feel about their behaviour”; and for Initiation apathy, “They think of new things to do during the day.” Carers rate each item on a 4-point Likert scale based on the frequency of occurrence in the last month from 0, ‘Hardly ever’ to 3, ‘Almost always’. Each subscale is made up of 8 items and has a maximum score of 24, resulting in a total DApS score of 72, where higher scores reflect greater apathy.

2.2.6. Anhedonia

Anhedonia was measured using the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995), a validated and widely used questionnaire designed to evaluate an individual's ability to experience pleasure. The SHAPS includes 14 items, such as “I would enjoy being with my family or close friends” and “I would be able to enjoy my favourite meal,” rated on a 4-point Likert scale (1 = strongly disagree; 4 = strongly agree). The total score ranges from 14 to 56, with lower scores indicating diminished hedonic tone, i.e., higher levels of anhedonia.

Due to lack of insight commonly seen in FTD disorders (Mendez & Shapira, 2005), we modified the SHAPS to probe carer ratings of patient anhedonia across two time points: (i) before dementia onset and (ii) current time. This method, frequently employed in neurodegenerative research, provides an objective measure of changes from the patient’s pre-morbid state to the present (Hsieh, Irish, et al., 2013; Sollberger et al., 2009). The modified carer version of the SHAPS included the same statements as the original version with all questions rephrased in the third person from the carer’s perspective, such as “They would find pleasure in small things, e.g., a bright sunny day, a

telephone call from a friend," and "They would feel pleasure when they receive praise from other people." The SHAPS has previously been shown to be sensitive to changes in hedonic tone in the three dementia syndromes of interest (for full details see Shaw, El-Omar, Roquet, et al., 2021).

2.2.7. Functional impairment

The Frontotemporal Dementia Functional Rating Scale (FRS; Mioshi et al., 2010) was used as a validated index of carer-rated functional impairment and disease staging. The FRS is a 30-item questionnaire probing the frequency of difficulties that patients experience (e.g., 'all the time', 'sometimes', 'never') across seven domains (behaviour, outing and shopping, household chores and telephone, finances, medication, meal preparation and eating, self care and mobility) in their daily lives. Logit scores are derived using Rasch analyses and can be used to categorise patients based on disease severity (5.39 to 4.12 = very mild, 3.35 to 1.92 = mild, 1.68 to -.40 = moderate, -.59 to -2.58 = severe, -3.09 to -4.99 = very severe, -6.66 = profound). Lower scores denote greater functional impairment.

2.2.8. Statistical analyses

Statistical analyses for cognitive and clinical data were performed using IBM SPSS Statistics, version 27.0. Normality of distributions was assessed using Shapiro-Wilk tests and boxplots to inspect for outliers (see Appendix Table 2.1). Where variables were normally distributed, separate univariate Analyses of Variance (ANOVAs) were used to examine group differences on continuous demographic variables (e.g., age, education) with Sidak *post-hoc* tests. Chi-square tests were used to investigate group differences on categorical variables (e.g., sex).

To compare across scales, an index of dementia-related changes in motivation was calculated based on carer ratings of premorbid (i.e., before disease onset) compared to current (i.e., time of assessment) levels of apathy and anhedonia. Patient and control groups did not differ in terms of premorbid ratings on either the SHAPS or DApS (see Appendix section 2.2.8). Therefore, separate linear regression models were run with premorbid ratings included as the predictor and current ratings included as the dependent variable (Cronbach & Furby, 1970). Standardised residuals were then extracted for each patient for the SHAPS and DApS and these residual scores were used as an index of disease-related anhedonia and apathy severity, respectively. Positive residual scores indicate an increase in symptom severity (i.e. greater apathy or anhedonia), while negative residual scores represent a decrease in symptom severity since dementia onset.

To determine whether profiles of apathy and anhedonia differed across diagnostic groups, we ran a 3 x 4 repeated measures ANCOVA controlling for sex, disease duration and overall level of cognitive function on the ACE-III. Here, we explored main effects of Group (AD, bvFTD, SD), and Domain (anhedonia, executive apathy, emotional apathy, initiation apathy), as well as relevant interactions, on apathy and anhedonia residual scores. Significant interactions and/or main effects were followed up with Sidak post hoc tests. Partial eta-squared values (η_p^2) accompany all ANOVAs and ANCOVAs as measures of corresponding effect sizes.

Partial Pearson's correlations were run in each patient group to examine associations between motivational severity scores and functional impairment (FRS), controlling for sex, disease duration and overall level of cognitive dysfunction on the ACE-III. To correct for multiple comparisons, the Benjamini-Hochberg procedure was used

(Benjamini & Hochberg, 1995), with a critical alpha level of 0.05. Finally, Fisher's *r* to *z* transformations were used to determine which variables more strongly predicted functional impairment within each group.

2.3. Results

Demographic, cognitive, and clinical characteristics of the study sample are presented in Table 2.2. Groups were not statistically different in terms of age [$F(3,207)=2.4$, $p=.07$, $\eta_p^2=.03$] but differed for sex distribution ($\chi^2=13.93$, $p=.003$) driven by significantly more males in the bvFTD group and more females in the control group (both *p's*<.05). Groups also differed for years of education [$F(3,207)=4.5$, $p=.005$, $\eta_p^2=.06$] as the bvFTD group had, on average, 1.9 fewer years of education relative to Controls ($p=.004$; all other *p*'s>.08). Patient groups had comparable disease duration (years elapsed since onset of symptoms; $p=.09$) but differed in terms of functional impairment on the FRS [FRS Logit score: $F(2,127)=3.9$, $p=.02$, $\eta_p^2=.06$], with bvFTD patients showing greater functional impairment relative to SD ($p=.04$). Importantly, using the FRS classification for disease staging, all dementia groups were categorised as being at the same level of disease severity (i.e., "moderate"). No other significant differences were observed on the FRS (all *p's*>.09).

Group differences were evident on the DASS-D [$F(3,185)=13.7$, $p<.001$, $\eta_p^2=.19$] with patients self-reporting higher levels of depression relative to Controls (all *p's*<.008). However, patient groups did not differ for self-rated depression (all *p's*>.72) or carer-rated behavioural change on the CBI-R (all *p's*>.09), despite evidence of impairment across groups. Significant group differences were evident on the ACE-III [$F(3,206)=105.1$, $p<.001$,$\eta_p^2=.61$], driven by marked cognitive impairment in patients relative to Controls (all *p's*<.001). Post hoc tests indicated that AD and SD patients were disproportionately

impaired relative to the bvFTD group (both *p's*<.001) with no difference between AD and SD (*p*=.99). These cognitive and behavioural changes are in keeping with previous studies (Devenney et al., 2015; Johnen & Bertoux, 2019; Perez et al., 2022; Ramanan et al., 2023; Sato et al., 2021).

Table 2.2. Demographic, clinical, and cognitive characteristics of study cohort

	bvFTD (n=68)	SD (n=32)	AD (n=43)	Control (n=68)	Test Statistic	Post hoc comparisons
Age [years]	64.6 (7.6)	67.9 (7.0)	66.2 (8.0)	67.5 (6.0)	F = 2.4	-
Education [years]	12.5 (3.3)	12.7 (3.2)	13.3 (3.0)	14.3 (3.2)	F= 4.5**	Control>bvFTD
Sex, M:F	47:21	14:18	26:17	27:41	χ^2= 13.9**	M>F bvFTD, F>M Controls
Disease duration [years]	6.4 (4.0)	6.5 (3.2)	5.0 (2.3)	--	F = 2.4	-
ACE-III Total [100]	76.0 (14.4)	60.7 (12.7)	62.3 (12.9)	95.4 (3.3)	F = 105.1***	Control>bvFTD>AD, SD
FRS Logit score[a]	-.21 (1.6)	0.64 (1.6)	.47 (1.3)	--	F = 3.9*	SD>bvFTD
FRS Stage	Moderate	Moderate	Moderate			
CBI-R Total [%]	37.4 (17.2)	31.0 (14.7)	30.5 (14.2)	n/a	F = 3.1	-
DASS-Depression [21]	5.2 (4.7)	4.0 (4.5)	5.0 (4.5)	1.1 (1.5)	F= 13.7***	Patients>Controls

Note. Values are in the format Mean (standard deviation) unless otherwise specified. Maximum score and/or unit of measurement for each test shown in square brackets where appropriate. [a]Lower logit scores, as derived using Rasch analyses, denote greater levels of functional impairment on the FRS. *p<.05; **p<.005; ***p<.0001; n/s=not significant; --=not applicable; ACE-III=Addenbrooke's Cognitive Examination third edition; AD=Alzheimer's disease; bvFTD=behavioural-variant of frontotemporal dementia; CBI-R=Cambridge Behavioural Inventory-Revised; DASS=Depression, Anxiety and Stress Scale; F=Female; FRS=Frontotemporal Dementia Functional Rating Scale; M=Male; SD=semantic dementia. CBI-R missing for 2 SD, 2 bvFTD. DASS-D missing for 5 AD, 6 bvFTD, 6 SD and 9 controls. Disease duration missing for 4 AD, 4 bvFTD and 1 SD. FRS missing for 1 AD, 10 bvFTD and 2 SD.

2.3.1. Disease-specific changes in severity of motivational disturbances

A repeated measures ANCOVA, controlling for sex, disease duration and overall level of cognitive dysfunction on the ACE-III, revealed a significant main effect of Group [$F(2,113)=15.9$, $p<.001$, $\eta_p^2=.23$], where, irrespective of motivational domain, bvFTD patients showed greater motivational impairments than SD ($p<.001$) and AD ($p<.001$) patients. No difference was observed between the SD and AD groups ($p=.86$). No main effect of Domain was observed [$F(3,336)=.69$, $p=.56$, $\eta_p^2=.02$].

The Group by Domain interaction was significant [$F(6,336)=6.0$, $p<.001$, $\eta_p^2=.10$]. Post hoc tests investigating the simple effect of Domain revealed distinct motivational profiles in each group. All subscales were comparably affected in bvFTD (all *p'*s>.98) reflecting a domain-general motivational impairment. In contrast, for SD, the motivational profile was dominated by significantly higher levels of anhedonia relative to executive ($p=.01$, mean difference=.64, 95%CI 0.1–1.2) and initiation ($p=.01$, mean difference=.59, 95%CI .07–1.1) apathy, but with no difference compared to emotional apathy ($p=.67$). Finally, AD patients displayed higher executive ($p=.009$, mean difference=.61, 95%CI 0.11–1.11) and initiation ($p=.004$, mean difference=.62, 95%CI 0.14–1.1) apathy compared to anhedonia (see Figure 2.1).

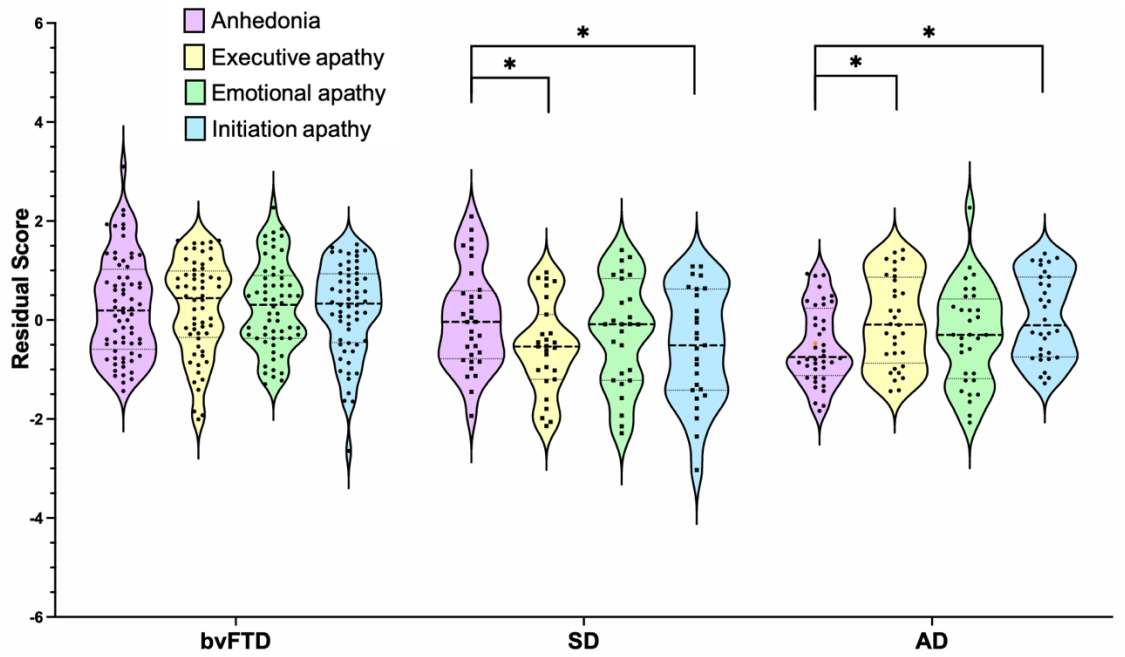


Figure 2.1. Disease-specific motivational profiles across dementia syndromes. Residual scores derived from separate linear regression models with premorbid (before dementia onset) carer ratings included as the predictor and current carer ratings included as the dependent variable for anhedonia (SHAPS) and apathy (DApS) severity. Violin plots depict the distribution of data with the width of the shaded area representing the proportion of data located there. Bolded horizontal line depicts the median, while dotted lines depict quartiles. Higher scores reflect greater severity. AD=Alzheimer's disease; bvFTD=behavioural variant frontotemporal dementia; SD=semantic dementia. Asterisks denote significant within-group differences. *p<.05.

Sidak post hoc tests were run to assess the simple effect of Group within each motivational Domain. Anhedonia severity was not found to differ significantly between bvFTD and SD (p=.08) but was of a significantly greater magnitude in the FTD syndromes relative to AD (bvFTD mean difference=1.11, 95%CI .60–1.63; p<.001; SD mean difference=.60, 95%CI 0.01–1.18, p=.04). Executive apathy was significantly higher in bvFTD relative to SD (p<.001, mean difference=1.2, 95%CI .66–1.8) and AD (p=.03, mean difference=.57, 95%CI .66–1.8), while AD patients exhibited greater executive apathy relative to SD (p=.03, mean difference=.65, 95%CI .06–1.3). Emotional apathy was most pronounced in bvFTD relative to SD (p=.04, mean difference=.61, 95%CI .02–1.2) and AD (p=.003, mean difference=.77, 95%CI .22–1.3), with no difference between the SD and

AD groups (p=.88). Finally, initiation apathy was greatest in bvFTD relative to AD (Mean difference=.58, 95%CI .06–1.09, p=.02) and SD (Mean difference=1.2, 95%CI 0.66–1.1; p<.001), while AD patients showed higher initiation apathy relative to SD (Mean difference=.66, 95%CI 0.06–1.2, p=.03). See Appendix Figure 2.3 for further information.

Taken together, our findings indicate distinct motivational profiles in each patient group. BvFTD displayed the most profound motivational disturbances, spanning all motivational domains. The SD motivational profile was largely driven by hedonic deficits, with significantly lower levels of executive and initiation apathy. Conversely, the AD profile was characterised by initiation and executive apathy, albeit at a lower level than that observed in bvFTD, with AD patients showing the lowest level of anhedonia relative to the other groups.

2.3.2. Relationship to functional impairment

We next explored how severity of motivational changes relates to functional impairment within each patient group (Table 2.3). Importantly, neither disease duration (all *p's*>.07) nor self-reported Depression on the DASS-21 (all *p's*>.26) were found to relate to anhedonia or apathy in any of the patient groups. Figure 2.2 presents an overview of the relative associations between multidimensional motivational impairments and functional outcomes in each patient group (scatterplots presented in Appendix Figures 2.4-7).

Table 2.3. Associations between severity of motivational disturbances and functional impairment in each dementia group.

		bvFTD (n=58)	SD (n=30)	AD (n=42)
FRS	Anhedonia	-.29*	**-.68*** **	-.35
	Executive apathy	**-.62*** **	**-.55***	**-.72*** **
	Emotional apathy	**-.34***	-.32	**-.63*** **
	Initiation apathy	**-.51*** **	**-.55***	-.38

Note. AD=Alzheimer's disease; bvFTD=behavioural-variant of frontotemporal dementia; FRS=Frontotemporal Dementia Functional Rating Scale; SD=semantic dementia. Bolded values represent correlations that remain significant following Benjamini-Hochberg correction for False Discovery Rate at q=.05. *p<.05, ***p<.001.

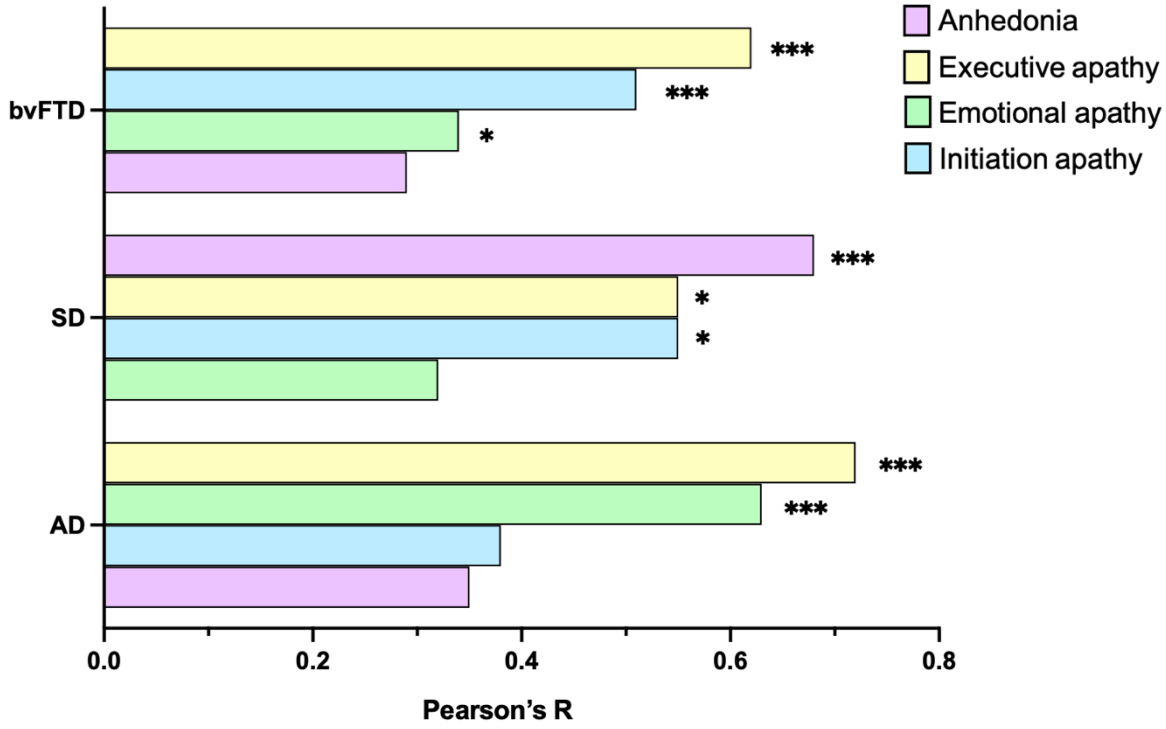


Figure 2.2. Relative associations between severity of motivational disturbances and functional impairment in dementia. Pearson r values presented as absolute values in ascending order representing the strength of association between severity of motivational impairment and functional decline in each patient group. *p<.05, ***p<.001. AD=Alzheimer's disease; bvFTD=behavioural variant of frontotemporal dementia; SD=semantic dementia.

Pearson partial correlations controlling for sex, disease duration, and overall level of cognitive dysfunction on the ACE-III revealed significant associations between functional impairment (FRS logit score) and all motivational domains in bvFTD, whereby more severe motivational disturbances were consistently related to greater functional impairment (all *p's*<.03). Fisher's r to Z transformations revealed that for bvFTD, executive apathy severity was more strongly related to functional decline than anhedonia (Z=2.24, p=.01) or emotional apathy (Z=1.95, p=.03), but did not differ from initiation apathy (Z=1.45, p=.09).

In SD, functional decline was associated with all motivational changes (all *p's*<.01), with the exception of emotional apathy (p=.16). Fisher's r to Z transformations highlighted that anhedonia was more strongly correlated with functional impairment than emotional apathy (Z=1.83, p=.03), with no other differences observed (all *p's*>.28).

Finally, in AD, greater functional impairment was associated with severity of executive (p<.001) and emotional (p<.001) apathy (all other *p values* >.06). Fisher's r to Z transformations indicated that executive apathy was more strongly correlated with functional impairment than anhedonia (Z=2.39, p=.008) and initiation apathy (Z=2.24, p=.01), but did not differ from emotional apathy (Z=.46, p=.32).

2.4. Discussion

Loss of motivation is a prominent feature of FTD, yet systematic characterisation of multidimensional changes in apathy and anhedonia has been lacking. Here, we provide a fine-grained profiling of phenotypic motivational disturbances and their respective contributions to functional impairment in FTD. Overall, we found distinct motivational profiles independent of disease severity in each dementia syndrome; a domain-general dampening of motivation in bvFTD, a predominantly anhedonic profile in

SD, and an apathetic profile driven by pronounced initiation and executive apathy in AD. Importantly, dimensions of apathy and anhedonia were differentially related to functional outcomes in each patient group suggesting the need for targeted interventions geared toward the specific motivational profile of the individual.

2.4.1. A global dampening of motivation in bvFTD

Considering first the bvFTD group, we uncovered a profile of profound motivational impairments, spanning all apathy dimensions on the DApS (executive, emotional, initiation). These changes in goal-directed behaviour were more severe relative to disease-matched cases of SD and AD, in keeping with previous studies (Merrilees et al., 2013). In addition, anhedonia was prominent in bvFTD, again of a greater magnitude than reported in AD, but comparable with the SD group, consistent with previous findings (Shaw, El-Omar, Roquet, et al., 2021). Importantly, the magnitude of apathy and anhedonia severity was comparable across all subdomains in bvFTD, indicative of a global motivational impairment in this syndrome. Despite this overall dampening of motivation in bvFTD, correlation analyses suggested that executive apathy was more strongly associated with functional decline than emotional apathy or anhedonia, while initiation apathy was as strongly related to functional decline as executive apathy. Several studies in bvFTD have documented the negative impact of apathy, as a global construct, on instrumental activities of daily living such as managing finances and shopping as well as more advanced activities such as playing games, planning, and going on holiday (reviewed by Jenkins et al., 2022; Salech et al., 2021). Crucially, our findings caution against a simple one-to-one mapping between apathy and functional outcomes and suggest that a more fine-grained approach is needed. Notably, behavioural inertia and economy of cognitive effort appear particularly important for poor

prognostic outcomes in bvFTD, while hedonic and emotional motivational changes (anhedonia, emotional apathy) do not seem to play as central a role. As such, our findings suggest that a reduction in spontaneous cognitive activities and accompanying behavioural inertia may be critical harbingers of poor functional outcomes in this syndrome (see also O'Callaghan et al., 2019).

2.4.2. Hedonic disruptions and functional impairment in SD

In contrast, SD patients were characterised largely by motivational impairments related to hedonic processing, with significantly higher levels of anhedonia relative to executive and initiation apathy. Importantly, anhedonia, executive apathy, and initiation apathy emerged as significantly associated with poor functional outcomes in SD. Our findings align with previous research linking apathy to functional decline in SD (O'Connor et al., 2016) but offer increased precision by pinpointing executive and initiation dimensions of apathy as crucial in this context. Moreover, our findings resonate with recent work highlighting changes in hedonic tone as a prominent yet overlooked feature of the SD motivational phenotype (Chokesuwattanaskul et al., 2023; Horne & Irish, 2023; Shaw, El-Omar, Roquet, et al., 2021), and one which has been largely neglected in terms of prognostic outcomes. Recent theoretical frameworks have suggested that loss of hedonic tone in SD might lead to a truncating of interest onto a restricted range of activities that are pursued compulsively, to the neglect of more adaptive behaviours (Horne et al., 2024). Our findings of a predominantly anhedonic relative to apathetic profile in SD fit well with this proposal. Rather than displaying a global apathetic profile, carers report SD patients as initiating and executing some aspects of goal-directed behaviour, often manifesting in the form of rituals or stereotypical behaviours (Horne et al., 2024). Uncovering the nature of these behaviours is an important future direction for

this work, ensuring the patient can be supported to remain independent, while also mitigating carer stress and burden. Finally, while our current SD sample included a mix of left- and right-lateralised cases, no significant differences were observed between these subgroups in terms of anhedonia or apathy. However, further investigation into the effects of laterality on motivational profiles in SD subtypes is warranted, particularly in larger cohorts, given previous findings suggesting greater anhedonia severity in right-lateralised SD cases (Shaw, El-Omar, Ramanan, et al., 2021).

2.4.3. Executive and emotional apathy as key drivers in AD

Finally, the AD motivational profile was characterised by greater executive and initiation apathy in comparison to anhedonia. This finding resonates with previous reports of less severe emotional apathy (Wei et al., 2020) and lower levels of anhedonia (Shaw, El-Omar, Roquet, et al., 2021) in AD relative to bvFTD. Importantly, correlation analyses suggested that executive and emotional apathy made the strongest contributions to functional impairment in AD. That executive apathy should be associated with functional decline in AD is not surprising, and potentially reflects widespread difficulties in the cognitive initiating, planning and implementing of goal-directed actions essential for an array of complex activities of daily living (discussed by Irish & Piolino, 2016). Our finding that emotional apathy is associated with functional decline in AD was somewhat unexpected. It may be that with disease progression, cognitive impairments in AD result in increasing social withdrawal however further empirical research will be required to substantiate this proposal. Our findings mesh well with longitudinal studies suggesting that apathy might serve as a behavioural marker of a more aggressive disease course and poorer prognosis in AD (Grossman et al., 2021; S. Starkstein et al., 2006). Given that these studies assessed apathy in a unidimensional

manner, it will be imperative to chart how the multidimensional nature of apathy changes over the AD disease course and how fluctuations across apathy components relate to different disease trajectories. This is particularly relevant in the context of younger-onset presentations of AD, for whom clinical symptoms may differ from the canonical later-onset presentation (Mendez, 2019).

2.4.4. Limitations and future directions

Several methodological considerations warrant discussion. While our emphasis was on multidimensional aspects of motivation, the SHAPS questionnaire provides a somewhat coarse snapshot of anhedonia. Future studies distinguishing between putative dimensions of anhedonia (e.g., anticipatory versus consummatory) will provide important insights in this regard. We acknowledge the need to move beyond traditional carer report questionnaires and to develop objective assays of motivated behaviours as expressed in daily life. This is particularly pertinent given that in the current study we relied on carer report for ratings of patient anhedonia and apathy, while depression symptoms were self-rated by the patient. Notably, early features of anhedonia may be subtle and therefore less amenable to carer report (e.g., loss of interest, decreased pleasure). In addition, there are currently no validated methods for measuring anhedonia in dementia, which highlights the need for multidimensional validated measures in this population. Finally, given all our patient groups were in the "moderate" stage of functional impairment, it will be crucial to systematically track how multidimensional motivational changes vary according to disease staging and dynamically evolve over the disease course. Longitudinal studies with larger sample sizes will enable us to determine whether the phenotypic motivational profiles reported here stabilise or even resolve in each

dementia syndrome, with a view to identifying critical periods of transition during which targeted interventions might have optimal efficacy.

2.4.5. Conclusions

In conclusion, this study provides a fine-grained characterisation of distinct motivational phenotypes in dementia and their respective impact on functional outcomes. Motivational disturbances in dementia are gaining increasing attention as predictors of early entry to residential care and patient mortality and are reported as some of the most difficult symptoms to manage by carers (Murley et al., 2021). Our findings underscore the importance of screening for apathy and anhedonia in younger-onset dementia populations and delineating the specific stages at which such symptoms emerge. This detailed characterisation of motivational phenotypes can inform patient stratification for targeted interventions to potentially improve functional outcomes and reduce carer stress.

"Pleasure is the engine of life; without it, why move at all?" – Unknown

3.1. Introduction

3.1.1. Anhedonia and reward processing in FTD

As demonstrated in the previous chapter, motivational profiles differ across dementia groups, with distinct patterns contributing to functional decline in each syndrome. This highlights the need to closely examine the specific nature of these impairments, particularly anhedonia, which plays a key role in goal-directed behaviour. Despite advancements in understanding reward-related symptoms, the precise definition of anhedonia continues to be debated (Cooper et al., 2018). This ambiguity partly stems from differing definitions of anhedonia in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR; American Psychiatric Association, 2022), depending on the disorder. For instance, in schizophrenia, anhedonia is narrowly defined as "the decreased ability to experience pleasure" (American Psychiatric Association, 2022, p. 88). In contrast, in major depression, anhedonia is used as a general criterion that may be satisfied through different clinical presentations, such as the loss of motivation or interest in hobbies ('wanting'), or the inability to enjoy activities ('liking', American Psychiatric Association, 2022).

While anhedonia is not currently considered among the diagnostic criteria for either bvFTD or SD (Gorno-Tempini et al., 2011; Rascovsky et al., 2011), altered reward processing is consistently documented in these patient populations (Ahmed et al., 2015,

2018; Chokesuwattanaskul et al., 2023; Ikeda et al., 2002; Miller et al., 1995; Shaw, El-Omar, Roquet, et al., 2021). Recent studies increasingly emphasise the importance and impact of these motivational and behavioural changes in FTD (E. Johnson & Kumfor, 2018; Piguet & Hodges, 2013; Shaw et al., 2024), yet how anhedonia is conceptualised within FTD remains unclear (Turner & Husain, 2022). Intuitively, one might expect that the anhedonia documented in FTD would lead to broad deficits in volitional, goal-directed behaviour. That is, if someone is unable to experience pleasure, they would be less likely to engage in behaviours that typically produce these hedonic responses. Simply stated, why do something if there is no enjoyment associated with it? However, a simplistic view of anhedonia in FTD, where one cannot experience pleasure, fails to capture the complexity of reward processing alterations in this population.

3.1.2. Behavioural manifestations of altered reward processing in FTD

Research has shown that while some aspects of reward processing are blunted in FTD, others remain intact or even *enhanced*. One of the most well-documented manifestations of altered reward processing in bvFTD is altered dietary preferences, particularly a pathological craving for sweet foods, which is captured in the diagnostic criteria (Ahmed, Irish, Henning, et al., 2016; Ikeda et al., 2002; Rascovsky et al., 2011). Beyond dietary changes, patients with FTD demonstrate increased responsiveness to a wide range of rewards, including money (Perry et al., 2015) and art (Erkkinen et al., 2018; Kearney et al., 2012) alongside music (Fletcher et al., 2013) and environmental sounds (Fletcher et al., 2015), specifically in SD. Clinical reports suggest that these behavioural changes are often hedonically charged, with many patients commonly expressing intense liking for particular colours and deriving evident pleasure from them (Chan et al., 2009; Erkkinen et al., 2018). However, these behaviours are highly heterogeneous,

ranging from exaggerated reward-seeking in some instances, to complete disengagement from other previously enjoyed activities (Chokesuwattanaskul et al., 2023; discussed by Horne & Irish, 2023; Merrilees et al., 2013; Perry & Kramer, 2015). Several studies report blunted reward processing in FTD, such as loss of intimacy (Ahmed et al., 2015), reduced interest in sex (Ahmed et al., 2015, 2018; Silverman et al., 2020), disengagement from prior activities (Birkhoff et al., 2016), alongside an insensitivity to unpleasant odours; suggesting disruptions in the brain's ability to evaluate and respond to rewarding stimuli (Perry et al., 2017). Taken together, these findings suggest that while some responses to rewards are diminished in FTD, others remain intact or are even amplified.

3.1.3. Multidimensional nature of anhedonia

Emerging evidence supports the idea that anhedonia is not a unitary construct and is better conceptualised as a multidimensional entity (Gard et al., 2006; Treadway & Zald, 2011). Two independent subcomponents of hedonic processing have been identified: anticipatory pleasure (pleasure derived from anticipating future rewards) and consummatory pleasure (pleasure experienced during the actual, in-the-moment experience of the stimulus/event) (Berridge & Dayan, 2021; Nguyen et al., 2021). The existence of two subcomponents is supported by partially distinct neural circuits, neurotransmitter systems, and behavioural outcomes (Berridge et al., 2009; for review see Der-Avakian & Markou, 2012; Nguyen et al., 2021).

3.1.4. Anticipatory pleasure

Anticipatory pleasure is posited to be driven by the brain's dopaminergic system, specifically pathways originating in the ventral tegmental area and projecting to the

nucleus accumbens and ventral striatum (Kringelbach & Berridge, 2016; Nguyen et al., 2021). Early studies in rodents revealed that dopamine release is critical for the anticipation of rewards but does not influence the pleasure derived in their consumption (Berridge et al., 2009; Robinson & Berridge, 1993). In anticipation of a reward, dopamine acts as a motivator, creating a state of incentive salience, which fuels goal-directed behaviour and increases the perceived value of future rewards (reviewed by Hazy et al., 2010; Schultz, 2024). Human neuroimaging studies have also shown the prefrontal cortex, most notably the anterior cingulate cortex and the orbitofrontal cortex, play a role, particularly in planning and evaluating expected rewards (Hadland et al., 2003; for review see Rolls, 2023; Sescousse et al., 2010).

3.1.5. Consummatory pleasure

In contrast, consummatory pleasure is believed to be less dependent on dopamine and more on opioid neurotransmission (Barbano & Cador, 2007; Berridge & Dayan, 2021). Key areas involved include the nucleus accumbens, ventral pallidum, and insula (Berridge & Dayan, 2021). The ventral pallidum and nucleus accumbens contains "hedonic hotspots" that, when activated, enhance the pleasure derived from a reward (Berridge & Dayan, 2021; Smith et al., 2009; Stark et al., 2022). Additionally, the insula is thought to contribute to the subjective emotional quality of 'liking' by processing bodily sensations associated with pleasure (Namkung et al., 2017; Sescousse et al., 2010). These areas work together to produce the rewarding sensation that characterises the peak experience of pleasure.

3.1.6. Implications of anticipatory and consummatory anhedonia across disorders

Distinguishing between these two subcomponents of anhedonia has proven valuable for understanding and guiding intervention in various neuropsychiatric disorders, such as in schizophrenia and eating disorders, where anticipatory but not consummatory pleasure is often impaired (Dolan, Reilly, et al., 2022; Z. Li et al., 2015). In these syndromes, individuals do not derive pleasure from anticipating future rewards but can still experience enjoyment during the activity itself. For example, in schizophrenia, a person may feel little excitement in anticipating, or have the motivation to attend, a social gathering. However, they may still report experiencing pleasure once they are at the social gathering and actively engaged in it, such as enjoying a conversation with a friend.

As mentioned above, conflicting patterns of reward processing have been documented in FTD, suggesting that while some aspects of pleasure may be preserved, others are compromised (Horne & Irish, 2023). However empirical studies exploring anticipatory and consummatory components of pleasure in FTD are lacking. It is important to recognise that anticipatory forms of pleasure likely draw on cognitive capacities such as the ability to envisage the future activity or event and bring to mind the associated pleasure. Studies in other populations, such as major depressive disorder, have demonstrated that deficits in episodic future thinking are closely linked to anticipatory anhedonia (Hallford et al., 2020). These findings highlight the importance of cognitive processes in generating anticipatory pleasure and underscore the need to examine similar mechanisms in dementia populations. The cognitive demands associated with an impaired capacity for episodic future thinking in dementia (Addis, Sacchetti, et al., 2009; Irish et al., 2012a, 2013) might therefore result in an anticipatory anhedonic profile. Moreover, understanding whether consummatory pleasure remains intact is equally critical, as this capacity plays a fundamental role in maintaining quality

of life for individuals with dementia. If patients are still able to experience pleasure during activities, this could provide a vital focus for interventions aimed at enhancing their well-being and supporting engagement in meaningful experiences. Understanding these subcomponents of reward processing could provide valuable insights into the behavioural changes seen in FTD, ultimately informing the development of novel interventions. Additionally, identifying how these subcomponents of pleasure relate to dementia symptoms could refine theoretical models of dementia and guide future research.

3.1.7. Aims of the current study

Therefore, the current study, had two central aims. First, we sought to examine the multidimensional nature of anhedonia in terms of anticipatory versus consummatory components, in FTD syndromes compared to AD. Given the broad reward processing deficits and widespread disruption of the brain's reward circuit in FTD (reviewed by Bocchetta et al., 2021; Perry et al., 2014; Seeley et al., 2008), we hypothesised that both anticipatory and consummatory pleasure would be diminished in both bvFTD and SD. In contrast, based on studies showing impairments in future thinking alongside relative preservation of striatal regions in AD compared to bvFTD (Addis, Sacchetti, et al., 2009; Musa et al., 2020; Ng et al., 2021), we predicted that anticipatory anhedonia would be more pronounced in AD, while consummatory pleasure would remain largely intact.

The second aim was to examine associations between anticipatory and consummatory pleasure and relevant clinical symptoms, in each diagnostic group. These subcomponents of anhedonia may differentially impact motivation and other behaviours crucial to daily functioning in FTD compared to AD. Understanding these

relationships could provide insights into syndrome-specific patterns of behavioural change and guide targeted intervention strategies. We hypothesised that anticipatory and consummatory anhedonia would uniquely relate to distinct behavioural symptoms in each dementia syndrome.

3.2. Methods

3.2.1. Participants

Participants in the current study were drawn from the broader cohort described in Chapter 2. For inclusion in the present analysis, participants were required to have completed both the SHAPS and the TEPS. As such, this chapter reports on a subset of the Chapter 2 sample for whom both anhedonia measures were available. Of the participants included in this study, 81% overlapped with those reported in Chapter 2. Diagnostic procedures, inclusion criteria, and neuropsychological testing protocols were otherwise identical to those previously outlined in Chapter 2. In this study, a total of 152 participants, including 59 patients with a clinical diagnosis of bvFTD, 25 with a clinical diagnosis of SD (21 left-lateralised and 4 right-lateralised) and 27 patients with a clinical diagnosis of typical AD, were included in the current study. 41 healthy Controls were also included.

3.2.2. Assessment of anticipatory and consummatory anhedonia

The Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006) was used to evaluate trait anticipatory and trait consummatory pleasure. The Anticipatory subscale (TEPS-A) contains 10 items that evaluate an individual's ability look forward to rewards, such as: "I get so excited the night before a major holiday I can hardly sleep" (Gard et al., 2006). In contrast the Consummatory subscale (TEPS-C) includes 8 items designed to

measure an individual's capacity to experience pleasure in the moment, for example: "I really enjoy the feeling of a good yawn" (Gard et al., 2006). Participants were required to indicate their level of agreement with each item on a 4-point Likert scale, ranging from 1 (very false for me) to 4 (very true for me), with higher scores reflecting greater hedonic tone. Similar to the approach adopted in Chapter 2, the TEPS was adapted into a carer's version, enabling carers to rate the level of pleasure experienced by patients. In this study, the TEPS demonstrated good internal consistency (TEPS-A, alpha =.88; TEPS-C, alpha =.89). Given the different number of items on each TEPS subscale, both subscale total scores were converted to percentages for comparison.

$$TEPS - A\ percentage\ score = \left(\frac{x}{40}\right) * 100$$

$$TEPS - C\ percentage\ score = \left(\frac{x}{32}\right) * 100$$

As a secondary measure the SHAPS (Snaith et al., 1995) was used to determine the global presence and severity of anhedonia (see previous study, Chapter 2 for full details). Given the SHAPS and TEPS data were not normally distributed, a log transformation was applied to normalise the distribution for group comparisons.

3.2.3. Assessment of behavioural changes

The Cambridge Behavioural Inventory Revised (CBI-R; Wear et al., 2008) was used to assess the presence of behavioural symptoms in patients (see Chapter 2 for full details). Scores were converted to percentage scores, with higher scores indicating greater behavioural change (i.e. worse outcomes).

3.2.4. Statistical analysis

Statistical analyses for cognitive and clinical data were performed using IBM SPSS Statistics, version 28.0. Prior to undertaking analysis, normality of distributions was checked using Shapiro-Wilks tests and visually inspected using box plots. Where variables were normally distributed, separate univariate ANOVAs were used to examine group differences on continuous demographic variables (e.g., age, education) with Sidak *post hoc* tests conducted to explore main effects of Group (Control, AD, bvFTD, SD). Where variables were not normally distributed (e.g., CBI-R), non-parametric Kruskal-Wallis tests, with Bonferroni correction for multiple comparisons, were run to explore group differences including contrasts for group comparisons. Chi-square tests were used to investigate group differences on categorical variables (e.g., sex).

A 2 × 2 repeated measures ANCOVA, controlling for sex and age, was run to explore profiles of anticipatory and consummatory anhedonia on the TEPS. Here, we explored main effects of Group (Control, AD, bvFTD, SD) and Domain (Consummatory anhedonia: TEPS-C, Anticipatory anhedonia: TEPS-A) as well as relevant interactions, using Sidak *post hoc* tests. Partial eta-squared values (η_p^2) accompany all ANOVAs and ANCOVAs as measures of corresponding effect sizes.

Finally, Spearman's rank correlations were used to assess the relationship between TEPS-A, TEPS-C, and key motivational and behavioural disturbances on the CBI-R in each patient group. To correct for multiple comparisons, the Benjamini–Hochberg (Benjamini & Hochberg, 1995) procedure was used, with a critical alpha level of 0.05.

3.3. Results

3.3.1. Sample characteristics

Demographic, cognitive and clinical characteristics of the study sample are presented in Table 3.1. Groups were comparable in terms of age [$F(3,148)=1.88$, $p=.14$, $\eta_p^2=.04$]. Although a significant group effect emerged for years of education [$F(3,148)=2.68$, $p=.05$, $\eta_p^2=.05$], follow up *post hoc* tests did not reveal any group differences (all *p*'s>.29). Groups differed for sex distribution ($\chi^2=18.5$, $p<.001$), driven by significantly more males in the bvFTD group and more females in the Control group (both *p*'s<.05). Significant group differences were further evident on the ACE-III [$F(3,146)=42.0$, $p<.001$, $\eta_p^2=0.46$], with all patient groups displaying profound cognitive impairment relative to Controls (all *p*'s<.001). Direct comparison of the patient groups revealed significantly greater cognitive impairment in SD and AD relative to bvFTD participants (both *p*'s<.009), with no difference between SD and AD ($p=.83$).

Patient groups differed in terms of disease duration (years elapsed since onset of symptoms) [$F(2,99)=6.0$, $p=.003$, $\eta_p^2=.12$] with bvFTD patients having a longer disease duration than both SD and AD patient groups (all *p*'s<.03). Patients also differed in terms of functional impairment on the FRS [$F(2,101)=14.8$, $p<.001$, $\eta_p^2=.23$] with SD patients showing the least, and bvFTD patients showing the greatest, functional impairment relative to all other patient groups (all *p*'s<.05).

Table 3.1. Demographic, clinical and cognitive characteristics of study cohort

	bvFTD (n=59)	**SD (n=25)**	**AD (n=27)**	**Control (n=41)**	**Test Statistic**	**Post hoc comparisons**
Age, yrs	65.1 (8.3)	66.2 (6.1)	65.4 (7.7)	68.4 (6.1)	$F = 1.9$	n/s
Education, yrs	12.7 (3.2)	12.4 (3.4)	13.5 (2.6)	14.3 (3.2)	$F = 6.7$	n/s
Sex, M:F	46:13	12:13	15:12	15:26	$\chi = 18.5$***	M>F in bvFTD
Disease duration, yrs	7.7 (4.6)	5.3 (2.8)	5.0 (2.7)	--	$F = 6.0$**	bvFTD>SD, AD
ACE-III Total [100]	77.1 (15.6)	63.3 (13.4)	67.4 (14.9)	95.6 (3.2)	$F = 42.0$***	Control > bvFTD> SD, AD
FRS logit score[a]	-.18 (1.8)	2.1 (1.7)	.81 (1.6)	--	$F = 14.8$***	SD>AD>bvFTD

Note. Values are presented as mean (standard deviation) unless otherwise specified. Maximum score for each test shown in square brackets where appropriate. ACE-III=Addenbrooke's Cognitive Examination third edition; AD=Alzheimer's disease; bvFTD=behavioural variant frontotemporal dementia; F=Female; FRS=Frontotemporal Dementia Functional Rating Scale; M=Male; SD=Semantic dementia. FRS was not available for two bvFTD patients, one SD patient, one AD patient. Disease duration was not available for one bvFTD patient. *p<.05; **p<.005; ***p<.001; n/s = not significant; -- = not applicable. [a]Lower scores denote greater levels of functional impairment on the FRS.

3.3.2. Anhedonia across dementia syndrome

A univariate ANCOVA, controlling for age and sex, revealed a significant main effect of Group for anhedonia severity on the SHAPS [$F(3,145)=19.2$, $p<.001$, $\eta_p^2=.29$]. *Post hoc* analyses showed that relative to Controls, patients with bvFTD ($p<.001$, mean difference=.24, 95%CI 0.2-0.3) and SD ($p<.001$, mean difference=.19, 95%CI 0.1-0.3) displayed significantly higher levels of anhedonia, with no difference between bvFTD and SD groups ($p=.71$). In contrast, AD patients did not differ from Controls ($p=.20$) in terms of level of anhedonia. AD patients also showed significantly less anhedonia compared to bvFTDs ($p<.001$, mean difference=.16, 95%CI 0.1-0.3) and showed a non-statistically significant trend from SD patients ($p=.07$). See Figure 3.1.

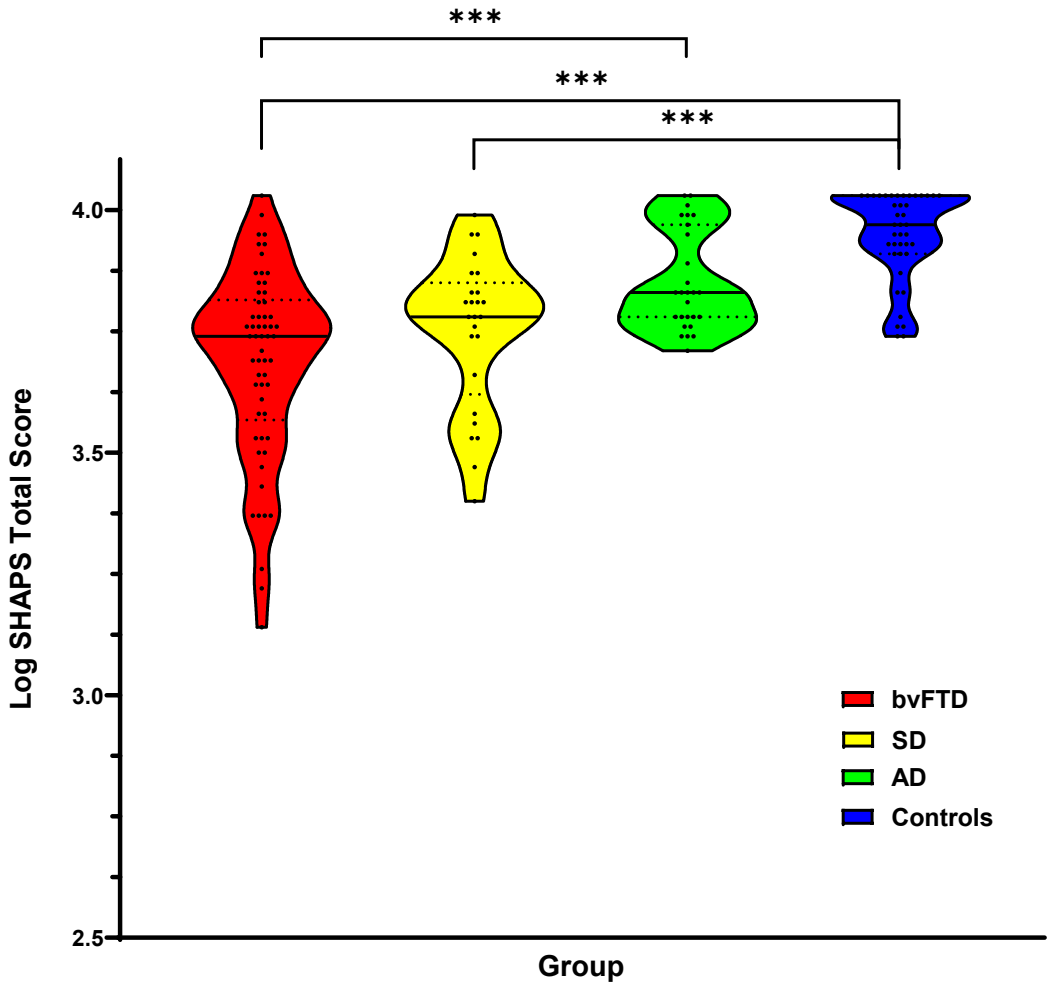


Figure 3.1. Current level of anhedonia on the SHAPS. Violin plots depict the distribution of data with the width of the shaded area representing the proportion of data located there. Bolded horizontal line depicts the median score. Scores are log transformed with lower scores reflecting greater anhedonia severity. SHAPS scores are carer-rated for patients and self-rated for Controls. AD, *n*=27; bvFTD, *n*=59; SD, *n*=24. Asterisks denote results that emerged as significant in the analyses with age and sex included as covariates. AD=Alzheimer's disease; bvFTD=behavioural variant frontotemporal dementia; SD=semantic dementia; SHAPS=Snaith Hamilton Pleasure Scale. ****p*<.001.

3.3.3. Anticipatory and consummatory anhedonia profiles across dementia syndromes

To explore whether there was an association between anticipatory and consummatory anhedonia, Pearson's correlations were conducted between TEPS-A and TEPS-C scores within each group. Significant positive correlations emerged in Controls

(*r*=.82, *p*=.001), bvFTD (*r*=.62, *p*=.001), and SD (*r*=.53, *p*=.01). However, no significant association was observed in AD (*r*=.18, *p*=.29).

Figure 3.2 displays the distinct profiles of anticipatory and consummatory anhedonia across dementia syndromes as measured by the TEPS. A repeated measures ANCOVA, controlling for age and sex, revealed a significant main effect of Group [$F(3,131)=19.7$, $p<.001$, $\eta_p^2=.31$] on the TEPS. Both bvFTD and SD patients showed significantly higher levels of anhedonia, irrespective of domain, compared to Controls (both *ps*<.001) while AD patients showed only a trend towards differing from Controls (*p*=.06). AD patients did not differ from SD patients (*p*=.35) but showed significantly less overall anhedonia than bvFTD patients (*p*<.001). No differences were found between FTD subgroups (*p*=.23). No main effect of Domain was observed [$F(1,131)=.06$, $p=.82$, $\eta_p^2=.00$] indicating no significant difference between anticipatory and consummatory anhedonia across all groups.

The Group x Domain interaction was significant [$F(1,131)=3.8$, $p=.01$, $\eta_p^2=.08$]. *Post hoc* tests examining the simple effect of Group within each Domain revealed distinct profiles of anhedonia in each patient group, relative to Controls. Anticipatory anhedonia was significantly elevated in all patient groups (bvFTD; *p*<.001, mean difference=.34, 95%CI 0.1–0.5, SD; *p*<.001, mean difference=.31, 95%CI 0.2-0.5, AD; *p*=.04, mean difference=.16, 95%CI 0.0-0.3), and was more severe in bvFTD relative to AD (*p*=.01, mean difference=.17, 95% CI 0.0-0.3) with no other group differences (all *p's*>.12).

In contrast, consummatory anhedonia was elevated exclusively in the FTD syndromes, specifically bvFTD (*p*<.001, mean difference=.36, 95%CI 0.2-0.5) and SD (*p*=.037, mean difference=.17, 95%CI 0.0–0.3) compared to Controls. No significant

difference, however, was found in terms of level of consummatory pleasure between AD and Controls (p=.30). Looking between patient groups, consummatory anhedonia was significantly higher in bvFTD relative to both SD (p=.008, mean difference=.19, 95%CI 0.0-0.3) and AD groups (p<.001, mean difference=.25, 95%CI 0.1-0.4) with no difference between SD and AD (p=.94).

Within group analysis revealed significantly higher levels of anticipatory relative to consummatory anhedonia in the majority of participant groups including SD (p<.001, mean difference=.22, 95%CI 0.1-0.3), AD (p=.003, mean difference=.12, 95%CI 0.0-0.2) and Controls (p=.03 mean difference=.03, 95%CI 0.0-0.1). In contrast no significant difference was evident between anticipatory and consummatory anhedonia in the bvFTD group (p=.10). See Figure 3.2.

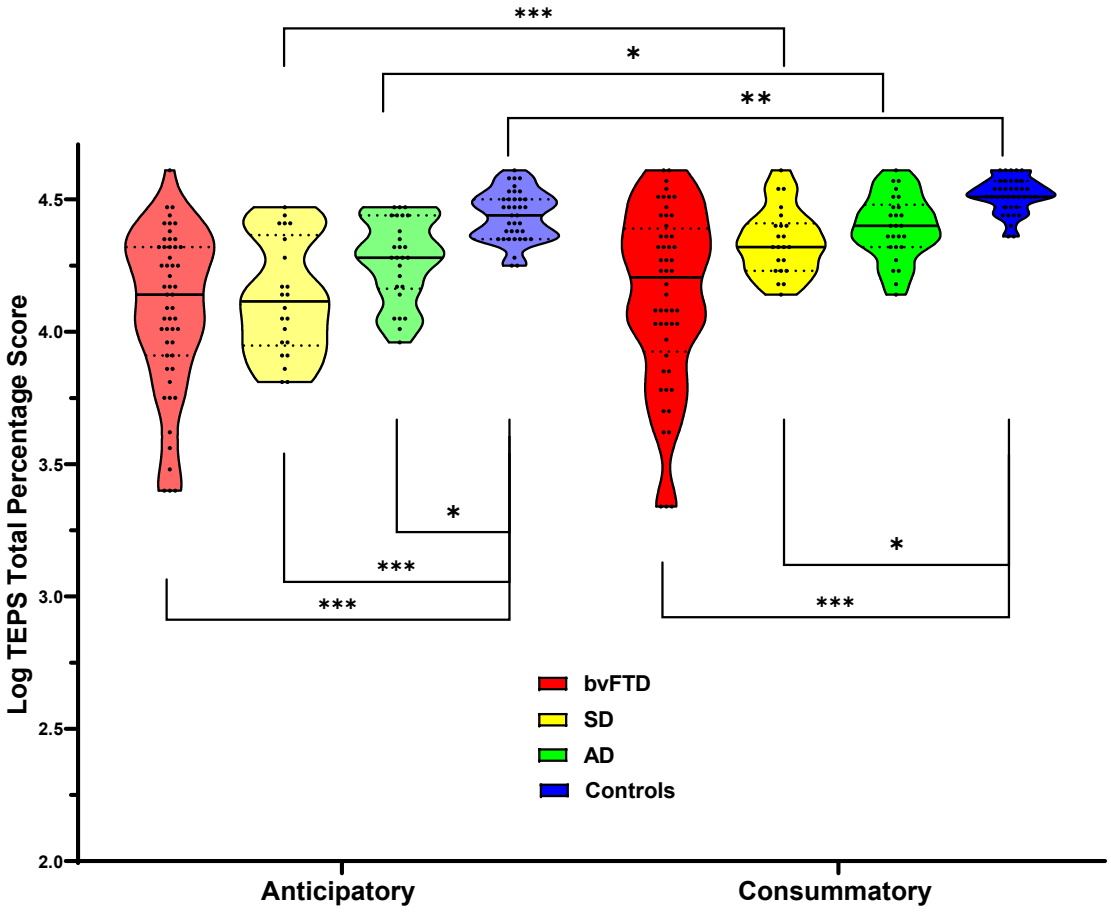


Figure 3.2. Profiles of anticipatory and consummatory anhedonia on the TEPS. Violin plots depict the distribution of data with the width of the shaded area representing the proportion of data located there. Bolded horizontal line depicts the median score. Scores are log transformed percentage scores with lower scores reflecting reduced hedonic tone (i.e., greater anhedonia severity). TEPS scores are carer-rated for patients and self-rated for Controls. AD, *n*=27; bvFTD, *n*=59; SD, *n*=24. Asterisks denote results that emerged as significant in the analyses with age and sex included as covariates. AD=Alzheimer's disease; bvFTD=behavioural variant frontotemporal dementia; SD=semantic dementia; TEPS-A=anticipatory subscale of the Temporal Experience of Pleasure Scale; TEPS-C=consummatory subscale of the Temporal Experience of Pleasure Scale. **p*<.05; ***p*<.005; ****p*<.001.

3.3.4. Cognitive drivers of anhedonia

To explore whether impairments in cognition contribute to anhedonia, we conducted Pearson's R correlations between ACE-III total scores and anticipatory and consummatory anhedonia within each patient group. A significant positive association emerged between ACE-III total scores and anticipatory anhedonia across all patient groups (bvFTD; *r*=.29, *p*=.04, SD; *r*=.50, *p*=.02, AD; *r*=.40, *p*=.04), indicating that higher cognitive functioning is associated with lower levels of anticipatory anhedonia. In contrast, no significant associations were observed between ACE-III total scores and consummatory anhedonia in any group (all *p's*>.07).

3.3.5. Behavioural changes in patient groups

Carer-rated behavioural changes on the CBI-R are summarised in Table 3.2. A significant group difference was found for overall behavioural change on the CBI-R Total [$F(2,103)=7.1$, $p=.001$, $\eta_p^2=.12$], with bvFTD patients displaying significantly greater behavioural disturbances than both SD (*p*=.002) and AD (*p*=.05) patient groups, while no difference was found between the SD and AD patients (*p*=.66).

Non-parametric tests, adjusted using the Bonferroni correction for multiple comparisons, were applied to examine group differences for each subscale of the CBI-R. Significant group differences were observed on the self-care [$H(2,104)=14.4$, $p<.001$, $\eta_p^2=.11$], everyday [$H(2,106)=13.2$, $p=.001$,$\eta_p^2=.12$], eating [$H(2,105)=23.0$, $p<.001$, $\eta_p^2=.21$], sleep [$H(2,104)=14.9$, $p<.001$, $\eta_p^2=.14$], motivation [$H(2,105)=23.2$, $p<.001$, $\eta_p^2=.23$] and stereotypical behaviour [$H(2,105)=11.3$, $p=.004$, $\eta_p^2=.10$] subscales. Specifically, bvFTD patients exhibited more pronounced changes in self-care ($p=.001$), everyday ($p=.004$), eating ($p=.008$), sleep ($p=.001$) and motivation ($p<.001$) relative to SD, and greater changes in eating ($p<.001$), stereotypical behaviour ($p=.005$) and motivation ($p=.002$) relative to AD. Whereas, AD patients only demonstrated greater changes than SD in everyday behaviours ($p=.01$). No other group differences were evident (all *p's*>0.12). No significant group differences were evident on the mood subscale of the CBI-R [$H(2,105)=1.4$, $p=.49$, $\eta_p^2=.01$].

Table 3.2. Behavioural changes on the Cambridge Behavioural Inventory-Revised

	bvFTD (n=49)	SD (n=20)	AD (n=25)	Test Statistic	Post Hoc
Total	37.0 (16.4)	23.7 (12.6)	28.3 (14.8)	F = 7.1***	bvFTD>SD
Self-Care	14.5 (20.2)	0.6 (1.8)	8.7 (12.5)	H = 14.4***	bvFTD>SD
Everyday	34.4 (28.4)	11.4 (12.5)	34.2 (25.7)	H = 13.2***	bvFTD, AD>SD
Mood	25.9 (18.1)	21.3 (19.0)	24.3 (19.0)	H = 1.4	n/s
Eating	42.9 (29.1)	20.7 (21.3)	15.5 (17.9)	H = 23.0***	bvFTD>AD, SD
Sleep	47.0 (25.7)	23.8 (22.5)	35.2 (20.2)	H = 14.9 ***	bvFTD>SD
Stereotypical	43.7 (25.8)	42.0 (31.5)	23.8 (23.3)	H = 11.3**	bvFTD>AD
Motivation	57.3 (27.8)	27.0 (23.9)	31.9 (23.9)	H = 23.2***	bvFTD>SD, AD

Note. Values are presented as mean (standard deviation) unless otherwise specified. Scores on the Cambridge Behavioural Inventory-Revised are percentage scores. AD=Alzheimer's disease; bvFTD=behavioural variant frontotemporal dementia; SD=semantic dementia. **p<.005; ***p<.001; n/s = not significant.

3.3.6. Relationship between anhedonia dimensions and behavioural changes

Next, we explored the relationship between anticipatory and consummatory anhedonia and behavioural changes on the CBI-R within each patient group (Table 3.3), corrected for multiple comparisons using the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995).

For anticipatory anhedonia, there was evidence of modest negative correlations with self-care in both bvFTD (r=-.38, p<.001) and AD (r=-.57, p=.003) as well as with motivation impairments in bvFTD (r=-.44, p<.001) and AD (r=-.59, p=.002). No such associations reached statistical significance in SD (p=.10). Similarly, for consummatory anhedonia, bvFTD and AD both demonstrated small-to-moderate associations with self-care (bvFTD; r=-.38, p<.001, AD; r=-.60, p=.002) and eating behaviours (bvFTD; r=-.34,

p=.007, AD; *r*=-.58, *p*=.004), but again, no significant associations emerged in this SD sample (*p*=.08).

Interestingly, in the SD group, higher levels of both anticipatory (*r*=-.46, *p*=.006) and consummatory (*r*=-.43, *p*=.007) anhedonia were associated with increased stereotypical behaviour severity, suggesting a potentially distinct behavioural profile in this syndrome. No other significant associations were identified (all *p's*>.10).

Exclusively within the AD group, higher levels of anticipatory anhedonia also correlated with impairments in everyday behaviours (*r*=-.59, *p*=.002) and mood (*r*=-.48, *p*=.02). Whilst higher consummatory anhedonia in AD was also found to associate with impairments in everyday behaviours (*r*=-.57, *p*=.004) and motivation (*r*=-.56, *p*=.004). No other significant associations emerged (all *p's*>.08). Fisher's *r* to *Z* transformations revealed no significant differences within groups, between the correlations of significant CBI-R subscales with TEPS-C or of those with TEPS-A.

Table 3.3. Associations between consummatory and anticipatory anhedonia and aspects of behavioural change on the CBI-R.

	TEPS-A			TEPS-C		
	bvFTD	**SD**	**AD**	**bvFTD**	**SD**	**AD**
Self-Care	**-.41****	-.16	**.57****	**-.38****	-.04	**.60****
Everyday	-.34*	-.07	**.59****	.18	-.21	**.57****
Mood	-.26	-.15	**.48***	-.12	-.02	.36*
Eating	**-.47*****	.25	.35	**-.34***	-.32	**.58****
Sleep	-.09	-.13	-.06	-.14	-.29	.24
Stereotypical	-.31	**-.46***	.31	-.15	**-.43***	.22
Motivation	**-.44*****	-.40*	**.59****	-.21	-.37	**.56****

Note. Bolded values represent correlations that remain significant following Benjamini–Hochberg correction for False Discovery Rate at q=.05. AD=Alzheimer's disease; bvFTD=behavioural variant frontotemporal dementia; CBI-R=Cambridge Behavioural Inventory Revised; SD=semantic dementia; TEPS-A=log percentage score of the anticipatory subscale of the Temporal Experience of Pleasure Scale; TEPS-C=log percentage score of the consummatory subscale of the Temporal Experience of Pleasure Scale; *p<.05, **p<.005, ***p<.001.

3.4. Discussion

To our knowledge, this study is the first to systematically investigate anhedonia in dementia using a multidimensional approach focusing on differentiating its anticipatory and consummatory subcomponents. By disentangling these two components, we reveal distinct anhedonic profiles in each syndrome – a global anhedonic profile in bvFTD, with comparable levels of anticipatory and consummatory anhedonia, an anticipatory>consummatory anhedonic profile in SD, and an exclusively anticipatory anhedonic profile in AD, with relative sparing of consummatory pleasure. Each dimension of anhedonia was associated with distinct behavioural changes across patient groups. Moreover, anticipatory anhedonia was exclusively associated with level

of cognitive decline in each dementia syndrome, suggesting distinct cognitive demands involved in anticipating pleasure. Here we consider the clinical implications of these findings.

3.4.1. Global profile of anhedonia in bvFTD

Considering first the bvFTD group, aligned with our hypothesis, we uncovered a profile of widespread anhedonia encompassing both anticipatory and consummatory dimensions on the TEPS. BvFTD patients were not only impaired relative to Controls but showed significantly more severe anhedonia relative to AD patients, consistent with previous findings (Shaw, El-Omar, Roquet, et al., 2021). Our finding of comparable anticipatory and consummatory forms of anhedonia in bvFTD suggests a global dampening of the ability to experience pleasure, consistent with the syndrome's broader clinical presentation. Key symptoms of bvFTD, such as profound motivational deficits (Radakovic et al., 2021; Rascovsky et al., 2011), align with impairments in anticipatory pleasure, as individuals may fail to derive pleasure from envisioning rewarding activities and consequently lack the motivation to pursue them. Similarly, diminished consummatory pleasure aligns with symptoms of emotional blunting and disengagement from previously enjoyed activities (Birkhoff et al., 2016; Rascovsky et al., 2011; Silverman et al., 2020), where individuals with bvFTD fail to enjoy once-pleasurable experiences.

3.4.2. How does anhedonia relate to everyday behaviours in bvFTD?

Understanding how impairments in anticipatory and consummatory pleasure affect daily life in bvFTD is critical, as these dimensions may be tied to behaviours supporting functional independence and quality of life. Chapter 2 showed anhedonia,

when measured globally, relates to functional decline in FTD. It may be that anticipatory anhedonia reduces motivation for goal-directed activities, while consummatory anhedonia likely diminishes satisfaction from these activities, compounding functional impairments.

One compelling finding was the association between both increased anticipatory and consummatory anhedonia and changes in eating behaviour in bvFTD. Changes in eating behaviour in bvFTD are one of the core diagnostic criteria (Rascovsky et al., 2011), including rigid food preferences and a preference for highly sweet (Ahmed, Irish, Henning, et al., 2016) or calorically dense foods (Ahmed et al., 2021), likely reflecting disruptions in the brain's reward system. These preferences may represent compensatory mechanisms, where individuals seek out more intense sensory rewards to offset diminished pleasure typically derived from eating (Ahmed, Irish, Piguet, et al., 2016). High-calorie, sweet foods provide an immediate and strong hedonic "hit" (Lenoir et al., 2007; Stice et al., 2008), potentially compensating for the blunted pleasure responses exhibited in bvFTD. Similar compensatory behaviours occur in other neuropsychiatric conditions, such as excessive smoking or substance use in depression, where intensified stimuli help overcome hedonic deficits (Liverant et al., 2014; Sternat & Katzman, 2016).

Beyond eating behaviours, anticipatory anhedonia in bvFTD was significantly associated with reduced motivation, as measured by the CBI-R. Anticipatory pleasure is central to initiating goal-directed behaviours, as it generates an emotional expectation of future rewards (Sherdell et al., 2012; Stefanova et al., 2020). When the capacity to anticipate rewards is diminished, individuals may fail to see the value in effortful activities, resulting in a profound lack of initiation and follow-through on goal-oriented

tasks. Impairments in spontaneous cognition may also contribute to these motivational deficits. Patients with bvFTD show significant difficulties in envisaging possible future scenarios (i.e., episodic future thinking, Irish et al., 2013; N.-A. Wilson, Ramanan, et al., 2020). Episodic future thinking allows individuals to mentally simulate the consequences of their actions, guiding decision-making and motivation (Schacter et al., 2017). When this ability is impaired, patients may lack the capacity to form a clear representation of future rewards, making it difficult to generate the motivation needed to engage in goal-directed behaviour.

This impairment may be particularly pronounced when the construction of future events must be self-generated rather than externally cued (Irish & van Kesteren, 2018). A recent study demonstrated that under conditions of low external stimulation, individuals with bvFTD exhibit a bias toward stimulus-bound thought, indicating a reduced capacity to disengage from the immediate environment and generate internally driven thoughts (O'Callaghan et al., 2019). In bvFTD, a lack of endogenous, spontaneous thought may exacerbate anticipatory anhedonia and contribute to motivational deficits, as patients lack the capacity to internally generate representations of pleasurable future states. Notably, the study by O'Callaghan and colleagues (2019) highlighted the striatum as playing a key role in these thought processes. Combined with findings implicating the frontopolar cortex, medial temporal regions, and hippocampus in future thinking impairments in bvFTD (Irish et al., 2013), this evidence demonstrates that multiple neural regions are affected in the cognitive processes supporting complex forms of mental construction in bvFTD.

3.4.3. A role for anhedonia in self-care behaviours

Interestingly, this study identified a role for both anticipatory and consummatory anhedonia in self-care behaviours in bvFTD. This is consistent with findings from Chapter 2, which demonstrated that anhedonia, globally measured using the SHAPS, predicts functional outcomes in SD. The mechanisms underlying this association remain unclear; however, multiple factors may contribute. One possibility is that impairments in goal-directed behaviour interact with an inability to mentally construct future scenarios, preventing bvFTD patients from envisioning the necessary steps for self-care routines. For example, a bvFTD patient may lack the capacity to mentally simulate the sequence of actions required to get changed out of their pyjamas. Patients may also lack the capacity to anticipate the rewarding aspects of self-care tasks, such as the refreshing feeling of putting on clean clothes and looking good, reducing their motivation to engage in such activities. The combined dampening of anticipatory and consummatory pleasure in bvFTD may therefore establish a negative feedback loop, reinforcing self-care neglect and accelerating functional decline (Merrilees et al., 2013; Shaw et al., 2024), however this proposal requires testing.

3.4.4. Profiles of anhedonia in SD

Turning our attention to SD, we observed profound anhedonia across both anticipatory and consummatory subscales in this group, in keeping with previous findings showing anhedonia in SD (Shaw, El-Omar, Ramanan, et al., 2021; Shaw, El-Omar, Roquet, et al., 2021). Notably, SD patients exhibited disproportionate impairment in anticipatory compared to consummatory anhedonia. This finding resonates with the cognitive demands associated with anticipating future rewards and suggests that these demands may be particularly challenging for individuals with SD. Anticipatory anhedonia, by its nature, requires the ability to mentally simulate future experiences and

predict their potential value (Gilbert & Wilson, 2007). These processes draw heavily on episodic future thinking and semantic knowledge (Irish et al., 2012a; Irish & Piguet, 2013; Kurtz et al., 2018; Suddendorf, 2017). In SD, anterior temporal lobe degeneration severely disrupts conceptual knowledge and semantic processing (Chan et al., 2001; Chu et al., 2024; Gorno-Tempini et al., 2011; Irish et al., 2012a; Irish & Piguet, 2013), likely impairing patients' capacity to generate coherent mental representations of future rewards. For example, envisioning the pleasure of attending a family gathering requires accessing semantic knowledge about the event and integrating this into a vivid mental simulation. In SD, deficits in these cognitive processes may disproportionately impair anticipatory pleasure.

However, it is important to note that consummatory anhedonia was also significantly impaired in SD, at a level comparable to bvFTD. Atrophy affecting regions of the brains reward system such as the orbitofrontal cortex and anterior temporal lobe in SD likely disrupts reward valuation and emotional tagging of rewards (Shaw, El-Omar, Ramanan, et al., 2021), leading to consummatory anhedonia in SD.

3.4.5. The role of anhedonia in stereotypical behaviours in SD

Importantly, the only domain of behavioural impairment to correlate with anhedonia in SD was increased stereotypical behaviours on the CBI-R. This subscale captures rigid and repetitive patterns, such as fixation on routines, preoccupation with time, or repeated use of expressions or phrases (Wear et al., 2008). Stereotypical behaviours have emerged as a prominent topic in SD research, given their pervasiveness and negative impact on both patients and caregivers (Bozeat et al., 2000; Rosen et al., 2006; Sakuta et al., 2021). Our findings reveal significant correlations between both

anticipatory and consummatory anhedonia and increased stereotypical behaviours, suggesting that hedonic deficits contribute to the rigid, repetitive behaviours characteristic of SD. These findings align with the study by Horne and colleagues (2024), which revealed lower hedonic tone predicted behavioural rigidity in SD. Profound deficits in anticipatory pleasure may disrupt the ability to simulate and predict rewarding outcomes, exacerbating the narrowing of interests and reinforcing rigid behaviours (Horne & Irish, 2023). At the neural level, their study identified degeneration of predominantly right-sided frontostriatal structures, including the nucleus accumbens, as a key correlate of rigidity in SD (Horne et al., 2024). Damage to these regions likely diminishes the hedonic response to previously enjoyable activities, reinforcing rigid engagement with a limited set of behaviours. These behaviours may also serve as compensatory mechanisms, as patients increasingly gravitate toward predictability and routine in the face of reduced capacity to derive in-the-moment pleasure from novel experiences. By linking anhedonia to stereotypical behaviours, our results provide insights into how reward-processing disruptions shape daily functioning in SD, paving the way for targeted interventions aimed at enhancing behavioural flexibility and improving patient outcomes.

3.4.6. Intact consummatory pleasure in AD

Finally, we found evidence of intact consummatory pleasure in AD, despite diminished anticipatory pleasure. This pattern distinguishes AD from bvFTD and SD and indicates that while individuals with AD may lack the capacity to anticipate or look forward to future rewards (Addis, Sacchetti, et al., 2009; Irish et al., 2012a), they can still derive enjoyment from immediate, in-the-moment experiences.

Parsing the components of anhedonia provides critical insights into the nature of reward processing in AD. The selective impairment in anticipatory pleasure mirrors deficits observed in other clinical populations, such as schizophrenia and eating disorders (Dolan, Reilly, et al., 2022; Z. Li et al., 2015), where individuals lack the capacity to anticipate rewards but still enjoy them in the moment. Anticipatory pleasure relies on cognitively demanding processes such as imagining, planning, and evaluating hypothetical scenarios - functions that are particularly vulnerable in AD (Chu et al., 2024; McKhann et al., 2011; R. S. Wilson et al., 2012). This relationship is further evidenced by the association between anticipatory anhedonia and cognitive decline in dementia.

Importantly anticipatory anhedonia in AD was associated with behavioural deficits including reduced self-care, everyday functioning, and motivation. The inability to anticipate future rewards may undermine motivation to engage in goal-directed activities, leading to increased functional impairments. This is further compounded by executive dysfunction, a hallmark feature of AD (Boyle et al., 2003), which disrupts the planning and organization of activities, reducing participation in potentially rewarding experiences. Additionally, increased anticipatory anhedonia was linked to greater changes in mood. The inability to anticipate rewards may deprive individuals of a sense of purpose, reinforcing feelings of hopelessness and exacerbating depressive symptoms, a phenomenon observed in other disorders, such as MDD, with anticipatory deficits (Treadway & Zald, 2011).

Importantly, the results indicate that consummatory pleasure remains relatively intact in AD. This aligns with evidence of preserved positive emotional processing in AD, including reports of positive responses to happy faces (Guaita et al., 2009; Werheid et al.,

2011) and the capacity for music to evoke positive reactions (Maia, 2019; Matziorinis & Koelsch, 2022). Similarly, AD patients report enjoyment when engaging in art (Flatt et al., 2015), and continue to express pleasure and interest in response to various stimuli (Cohen-Mansfield et al., 2011). This relative preservation of consummatory pleasure may reflect the neurodegenerative profile of AD, which predominantly affects the hippocampus and parietal regions while sparing key reward-related structures such as the striatum (Chapleau et al., 2016; Halabi et al., 2013).

The association between consummatory anhedonia and eating behaviour in AD is unexpected and may be driven by multiple factors, including sensory decline (Murphy, 2019), cognitive impairment (McKhann et al., 2011), and metabolic changes (Yu et al., 2023). Reduced taste perception may diminish the hedonic response to food, while memory deficits, reduced autonomy, and a decreased concern for eating may further disrupt dietary habits, highlighting the need for a more comprehensive understanding of these interactions.

The preservation of consummatory pleasure in AD offers important clinical implications, as it suggests that interventions leveraging immediate sensory experiences, such as music and art therapy, may remain effective (Cowl & Gaugler, 2014; Popa et al., 2021a). These therapies bypass the cognitive demands of anticipating rewards and directly engage preserved capacities for in-the-moment pleasure, highlighting their potential to enhance quality of life in AD.

3.4.7. Limitations

Several methodological considerations warrant discussion. First, the carer-reported measures of hedonic experience rely heavily on retrospective recall, which may

be influenced by the memory ability of the carers. This is particularly the case for those carers rating patients with longer disease durations, requiring them to recall events further in the past to compare pre- and post-onset experiences (W. Liu et al., 2012; Olsen et al., 2015). In addition, these tools were adapted for proxy-reporting, with carers instructed to complete items based on their observations of the person's current behaviour and responses. However, several TEPS items reference internal states, such as imagining an experience or deriving pleasure from anticipating a sensory stimulus, which may not be readily observable in daily life. Carers may infer these states based on broader behavioural cues (e.g., reduced activation, diminished expressiveness), introducing a layer of interpretation that may not accurately reflect the patient's internal experiences. As a result, retrospective carer reports may not fully capture the dynamic and fluctuating emotional experiences in daily life. Future research could benefit from employing experience sampling methods (ESM), which allow for real-time, repeated sampling and may provide more reliable and accurate estimates than retrospective reports (Vanhollebeke et al., 2024).

Additionally, the cross-sectional design of this study captures a single time point, limiting our ability to understand how anhedonia and behavioural changes evolve over time in these syndromes. Since the progression of atrophy in SD typically moves from more frontal cortical areas to dorsal subcortical regions as the disease advances (Hodges & Patterson, 2007), it is possible that in milder SD cases, the disproportionate impact on frontal regions primarily impairs anticipatory pleasure and consummatory pleasure becomes comparably impacted with disease progression. We note that this study is correlational, and the direction of these findings remains unclear. It is therefore plausible that difficulties in everyday activities, such as dressing and feeding oneself,

contribute to diminished anticipation and enjoyment in everyday activities. Longitudinal studies would offer valuable insights into the progression of these symptoms across the disease course and would allow us to track the emergence of different anhedonic profiles in these syndromes. Finally, while this study focuses on the behavioural manifestations of anhedonia, it does not explore the neurobiological mechanisms underlying these deficits. Future research incorporating neurobiological measures, such as MRI and fMRI could provide a more comprehensive understanding of the pathways driving these changes.

3.4.8. Conclusion

In conclusion, this study is the first to examine distinct profiles of anticipatory and consummatory anhedonia across dementia syndromes, revealing syndrome-specific patterns of reward processing deficits. Our findings provide novel evidence of associations between anhedonia and distinct changes in everyday behaviour that vary across dementia syndromes. While the cross-sectional design prevents us from confirming the directionality of these relationships, the associations between anhedonia and behavioural changes underscore the pervasive impact of reward processing deficits in dementia. These findings emphasise the need for targeted interventions that differentially address anticipatory and consummatory anhedonia in bvFTD, SD and AD with the potential to mitigate specific behavioural disruptions and enhance quality of life in these populations.

"I can't think of anything sorry. I mean, when you go to the theatre, you just go, you sit down, you watch the show, and sort of that's it. And if I don't know what I'm going to see, I don't know what to imagine, do I? I don't think it's going to happen"
– Individual with semantic dementia

4.1. Introduction

The previous chapter explored the differential profiles of anticipatory and consummatory anhedonia across dementia syndromes and their association with behavioural changes. These findings highlighted unique profiles across syndromes and how the capacity to experience pleasure is deeply intertwined with multiple aspects of daily life and functional well-being. However, the mechanisms driving these impairments remain unclear, particularly whether deficits in experiencing pleasure arise from broader cognitive changes inherent to dementia. This highlights the need to examine how other cognitive processes may contribute to these impairments, providing a more comprehensive understanding of the interplay between cognitive and affective disruptions in dementia.

4.1.1. Imagining the future

Alongside the capacity to experience pleasure, the ability to imagine the future is a fundamental human activity that occupies a significant portion of our waking life, with some studies suggesting it accounts for nearly a third of our internal cognition (Atance & O'Neill, 2001; Gilbert & Wilson, 2007). Future thinking is widely recognised as a distinctive and essential human capacity that plays a crucial role in shaping well-being (Suddendorf & Corballis, 2007). For humans, the ability to project oneself into the future

serves an adaptive function, enabling the previewing of potential events and their consequences. This capacity allows individuals to simulate the emotional impact of anticipated situations, thus preparing them to respond effectively to future challenges (Ayton et al., 2020; T. D. Wilson & Gilbert, 2003). Similarly, imagining a future reward enables individuals to simulate the hedonic response that would be associated with achieving that goal, a phenomenon known as anticipatory pleasure.

4.1.2. Anticipatory pleasure

The enjoyment derived from imagining future rewarding experiences is distinct from the immediate pleasure experienced during the actual consumption of a reward. For example, the pleasure of anticipating eating a favourite meal differs from the sensory enjoyment of the act itself. Anticipatory pleasure, which precedes the actual consumption of the reward, is often reported as being stronger than the emotional experience during the event itself (Schubert et al., 2020; T. D. Wilson & Gilbert, 2003). This ability to anticipate pleasure plays a fundamental role in motivating behaviour and directing goal-oriented actions (Treadway & Zald, 2011).

Diminished anticipatory pleasure has significant negative consequences, including reduced engagement in rewarding activities (Engel et al., 2013; Sherdell et al., 2012) with broader implications for psychosocial functioning (Foussias et al., 2011). In particular, lower levels of anticipatory pleasure are predictive of diminished responsiveness to rewards (Foussias & Remington, 2010), reduced motivation to pursue rewarding experiences (Foussias & Remington, 2010; Treadway & Zald, 2011) and poorer functional outcomes (Foussias et al., 2011). These findings underscore the critical role of anticipatory pleasure in driving behaviour and maintaining adaptive functioning.

Theories surrounding the temporal aspects of pleasure suggest that the ability to experience anticipatory pleasure depends on one's capacity to generate and sustain mental representations of potential future events (Caruso et al., 2024; Cocquyt & Palombo, 2023; Hallford et al., 2020). Ineffective or inaccurate visualisation of future rewarding scenarios can hinder this capacity and hence the motivation to pursue such rewards (Renner et al., 2019, 2021). Research also demonstrates that creating more vivid and detailed simulations of future experiences enhances their perceived likelihood of occurrence (Szpunar & Schacter, 2013), thereby increasing motivation to engage in these activities (Renner et al., 2019).

Research on depression has demonstrated a strong relationship between impairments in episodic future thinking and diminished anticipatory pleasure (Holmes et al., 2016; Ji et al., 2019). Individuals with depression anticipate fewer positive future events and report lower anticipatory pleasure (Bjärehed et al., 2010; MacLeod & Salaminiou, 2001). Notably, a study by Hallford et al. (2020) found that individuals with depression simulated future events with reduced specificity, vividness, plausibility, and less use of mental imagery and first-person perspective. These deficits were associated with significantly lower state anticipatory pleasure, with diminished detail, mental imagery, and personal significance emerging as unique predictors (Hallford et al., 2020). While these findings underscore the link between episodic future thinking and anticipatory pleasure in psychiatric populations, this relationship has yet to be examined in the context of dementia.

4.1.3. Episodic future thinking in FTD

The relationship between episodic future thinking and anticipatory pleasure is particularly relevant in the context of FTD. Compared to healthy controls, individuals with FTD exhibit marked deficits in episodic future thinking (Irish et al., 2012a, 2013; Irish & Piolino, 2016). Studies have demonstrated that these individuals lack the capacity to generate detailed mental representations of future scenarios, often providing vague or superficial descriptions when asked to envision upcoming events (Irish et al., 2013). These deficits are associated with atrophy in frontopolar and anteromedial temporal regions (Irish et al., 2013; Irish & Piolino, 2016; L. Liu et al., 2021). These impairments may hinder anticipatory pleasure which relies on the ability to imagine detailed, vivid future scenarios. Specifically, difficulties in simulating positive future events may result in diminished anticipatory pleasure and reduced motivation to pursue rewarding behaviours (Engel et al., 2013; Sherdell et al., 2012).

Investigating the interplay between reward processing and episodic future thinking in FTD is critical, as it could inform therapeutic interventions aimed at mitigating anhedonia. Clarifying how deficits in future thinking undermine anticipatory pleasure may not only reveal the distinct mechanisms driving anhedonia in FTD but also help determine whether standard approaches, such as behavioural activation therapy, are appropriate or if tailored strategies are required. These insights could ultimately guide more effective interventions, improving motivation, functional outcomes, and quality of life for affected individuals.

4.1.4. Aims and hypothesis

Therefore, the aim of the current study was to examine the relationship between episodic future thinking and anticipatory pleasure in bvFTD, SD and AD patients. To

assess past and future thinking, patients completed a modified version of the Autobiographical Memory Interview (Levine et al., 2002), in which the emotional valence of past and future event construction was manipulated. We then examined the association between the number of episodic details generated in positive and neutral valence conditions and anticipatory pleasure as measured by the TEPS-A. We hypothesised two key outcomes. First, we expected significant impairments in episodic future thinking across the bvFTD, SD, and AD patient groups compared to healthy controls in line with previous research (Addis, Sacchetti, et al., 2009; Irish et al., 2012a, 2013). Second, we predicted that deficits in episodic future thinking would correlate with decreased anticipatory pleasure in all patient groups, and that this effect would be most pronounced for positively valanced events.

4.2. Methods

4.2.1. Participants

In total, 30 patients with dementia (bvFTD, *n*=10; SD, *n*=10; AD, *n*=10) and 20 older healthy control participants were recruited through FRONTIER. All patients were diagnosed as per standard diagnostic criteria (detailed in Chapter 2).

4.2.2. Neuropsychological testing

All participants underwent standard neuropsychological testing procedures as described in Chapter 2, to determine the level of impairment across core cognitive domains. The Rey Auditory Verbal Learning Test (RAVLT; Schmidt, 1996) was used as an index of verbal episodic encoding and retrieval. On the RAVLT, participants are presented with a list of 15 words (List A) read aloud by the experimenter and are asked to immediately recall as many words as they can. This procedure is repeated across five

trials. Then, a second list of 15 words (List B) is read aloud, followed by a recall test. Afterwards, recall for List A is tested again. Following a 30-minute delay, participants are asked to recall List A once more. The number of words recalled after this delay is used as a measure of delayed free recall. Higher scores indicate better verbal memory with a maximum score of 15. Due to the heavy semantic loading of the RAVLT, patients with SD did not complete this task.

Delayed non-verbal recall was assessed using the Rey Complex Figure (RCF; Rey, 1941). Participants are shown a complex geometric figure and asked to copy it. Following a 3-minute delay, participants are asked to reproduce the figure from memory. One point is given for the accuracy of the drawing, and one point for the correct placement of each element, with a maximum score of 36.

The FAS test was used as a measure of verbal fluency (Sherman et al., 2020). Participants are required to orally generate as many words as possible within one minute starting with the letter F, A and S (Total 3 minutes). The total score is calculated based on the number of words produced across the three letter trials (F, A, and S). Repeated words, or the same word but with a different ending (e.g., walk, walks, walking) as well as proper nouns are not counted towards the total score. The Trail Making Task (parts B-A) was used as an index of executive function (Reitan, 1958). Part A of the task is a paper-and-pencil task which requires participants to quickly connect numbers (1-24) in order. The numbers are spread across the page in no particular order. Performance is assessed based on the time taken to complete the task (in seconds), with the number errors also being recorded. Part B differs from Part A by requiring participants to switch between ascending numbers and letters (e.g., 1-A-2-B-3-C ... up to 12-L-13). The time taken to complete the task is

recorded in seconds, and any errors made are tracked. Trail A measures processing speed, while Trail B evaluates executive function. The difference in completion times between Trail B and Trail A (B-A) serves as an indicator of switching ability, with longer response times reflecting poorer performance.

4.2.3. Assessment of anhedonia and apathy

The Snaith Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995) was used to determine the presence and severity of anhedonia. The Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006) was used to assess anticipatory and consummatory dimensions of pleasure. The Dimensional Apathy Scale (DApS; Radakovic & Abrahams, 2014) was used to assess executive, emotional and initiation dimensions of apathy. See Chapter 2, for full details of the above tests.

4.2.4. Assessment of episodic past and future thinking

The ability to recall autobiographical past and future events was assessed using a modified version of the adapted Autobiographical Interview (Addis, Pan, et al., 2009). Participants were asked to describe both positive and neutral events that they could either recall from the previous year or imagine occurring in the following year. To ensure the task was suitable for dementia populations, the number of trials per condition was reduced to two. Valence was manipulated to include both neutral and positively cued events, while temporal condition was also varied, requiring participants to recall past experiences and generate novel future events. This resulted in a 2 × 2 design. Each trial was randomised for both valence (positive or neutral) and temporal condition (past or future), leading to four counterbalanced task versions. The task was structured in blocks, meaning that all events related to one temporal condition were completed before

proceeding to the next. This block design was used to minimise cognitive load and to ensure that participants fully understood the task instructions.

Before starting the task, participants were given detailed verbal instructions, explaining that they would be asked to recall specific events from the past year or imagine potential events in the upcoming year. To ensure the events were autobiographical, participants were told they must be personally involved in the event rather than describing something that happened to someone else. For the past condition, participants were prompted to "Recall an event from the past year... A specific event that happened on one particular day," and for the future condition, they were asked to "Imagine a future event in the next year. A specific event that happens on one particular day" (See Table 4.1). In terms of valence, participants were instructed to describe either a “really positive, enjoyable event” [Positive] or a “neutral event that was neither extremely enjoyable nor extremely unpleasant” [Neutral]. Participants were encouraged to provide as much detail as possible, with the requirement that events be specific to a particular day and last no longer than 24 hours (Levine et al., 2002). Future events were also required to be realistic and grounded in the participant's current plans, ensuring they were not simply reimagined past events. The instructions were displayed on the screen throughout the task until participants came to a natural end.

Table 4.1. Example task cues across each valence and time condition for the past-future thinking test

Past Events (last year)	Future events (next year)
1 x positively cued event *"What I would like you to do is to think about a really enjoyable experience that happened to you last year. It should be something that stands out for you, a really happy memory that you can remember well."*	1 x positively cued event *"I would like you to try to imagine a really enjoyable, positive, event happening to you next year. You can talk about anything that you have planned to do or something that you would like to do next year"*
1 x neutrally cued event *"What I would like you to do is to try and remember an event that was not particularly positive or negative, it was just ordinary or neutral that happened to you last year. It should be something that was neither particularly enjoyable nor particularly unpleasant"*	1 x neutrally cued event *"I would like you to try to imagine an event that is not particularly positive or negative, it's just ordinary or neutral happening to you next year. It should not be something that you are particularly looking forward to or something that you are dreading."*

4.2.5. Structured probing

After their initial descriptions, follow-up questions adapted from the Autobiographical Interview (Levine et al., 2002) were used to prompt additional details, including queries like: *"Are there any other details you can add?", "When will this happen?", "Can you give me a rough date for this event?", "Where will this take place?"*, and *"How will you be feeling at this time in terms of any emotion?"*. No time limit was imposed, and descriptions typically lasted between 2–5 minutes.

4.2.6. Scoring of past and future events

The past-future thinking test lasted approximately 20 minutes, with responses digitally recorded for later transcription using Otter.ai and analysis. Event descriptions were scored using the standardised procedure from the original Autobiographical Interview (Levine et al., 2002). Each event transcript was divided into individual pieces of information or details, which were categorised as either 'internal' or 'external'. Internal details were those directly related to the main event, situated within a specific time and place, while external details encompassed tangential information, unrelated facts, repetitions, or semantic knowledge. The internal and external details were then summed to create composite scores for each category.

All transcripts were scored by myself using the standardised scoring method. To ensure reliability, a secondary rater, who was blind to the study's hypotheses and participant diagnoses, independently scored a random sample of 20 events (constituting 20% of the total data, as recommended by Syed & Nelson, 2015). High inter-rater reliability was achieved, with intraclass correlation coefficients of .79 for internal details and .75 for external details.

4.2.7. Statistical analysis

Statistical analyses for cognitive and clinical data were performed using IBM SPSS Statistics, version 28.0. Prior to undertaking analyses, normality of distributions was checked using Shapiro Wilks tests and box plots. Where variables were normally distributed, separate univariate ANOVAs were used to examine group differences on continuous demographic variables (e.g., age, education) with Sidak *post hoc* tests conducted to explore main effects of Group (Control, AD, bvFTD, SD). Chi-square tests were used to investigate group differences on categorical variables (e.g., sex). Partial eta-

squared values (η_p^2) accompany all ANOVAs and ANCOVAs as measures of corresponding effect sizes.

For episodic future thinking, a mixed model ANCOVA controlling for ACE-III was conducted exploring main effects of Group (bvFTD, SD, AD, controls), Condition (past, future) and Valence (positive, neutral) as well as relevant interactions, using Sidak *post hoc* tests. Spearman's R correlations were run to explore associations between episodic past and future thinking and anticipatory anhedonia and apathy. To correct for multiple comparisons, the Benjamini–Hochberg (Benjamini & Hochberg, 1995) procedure was used, with a critical alpha level of 0.05.

4.3. Results

4.3.1. Demographics and neuropsychological performance

Demographic, cognitive and clinical characteristics of the study sample are presented in Table 4.2. Groups were comparable in terms of age [$F(3,46)=1.81$, $p=.16$, $\eta_p^2=.12$], years of education [$F(3,46)=.95$, $p=.42$, $\eta_p^2=.06$] and sex distribution ($\chi^2=3.5$, $p=.10$). Significant group differences were evident on the ACE-III [$F(3,46)=18.0$, $p<.001$, $\eta_p^2=.54$], with all patient groups displaying profound cognitive impairment relative to Controls (all *p*'s<.001). A direct comparison of the patient groups showed significantly greater cognitive impairment in the SD and AD groups compared to bvFTD participants (both *p*'s<.05), with no significant difference observed between the SD and AD groups ($p=.32$). In terms of letter fluency on the FAS, Controls performed better than patients (all *p*'s<.001), however the patient groups did not significantly differ from one another (all *p'*s>.23).

Patient groups did not differ significantly in terms of disease duration (years elapsed since onset of symptoms) [$F(2,24)=1.1$, $p=.35$, $\eta_p^2=.10$]. Patients differed in terms of functional impairment on the FRS [$F(2,27)=7.2$, $p=.03$, $\eta_p^2=.35$] with bvFTD patients showing greater functional impairment relative to SD ($p=.01$). Notably, based on the FRS classification for disease staging, all dementia groups were classified as being in the "moderate" stage of disease. No other significant differences were found on the FRS (all *p's*>.07).

Short-term verbal memory differed between the groups [RAVLT: $F(2,37)=13.2$, $p=.001$, $\eta_p^2=.41$], with compromised performance in both bvFTD and AD groups relative to Controls (RAVLT; both *p's*<.001). No difference was observed between AD and bvFTD patients ($p=.14$; SD did not complete this task). Groups also differed on delayed non-verbal recall [RCF-3 min: $F(3,46)=17.3$, $p=.03$, $\eta_p^2=.24$], with bvFTD and AD patients showing significantly poorer performance relative to Controls and SD patients. SD patients did not differ from Controls ($p=.09$). No other group differences were evident (all *p's*>.08). Finally, bvFTD and AD patients showed significantly impaired set switching relative to Controls (Trail Making Test B-A; [$F(3,46)=8.2$, $p=.03$, $\eta_p^2=.12$]), with no significant differences between Controls and SD evident ($p=.09$).

Table 4.2. Demographic, clinical and cognitive characteristics of study cohort

	bvFTD (n=10)	SD (n=10)	AD (n=10)	Control (n=20)	Test Statistic	Post hoc comparisons
Age, yrs	63.9 (8.3)	65.3 (5.6)	62.0 (5.4)	67.2 (5.2)	$F = 1.8$	n/s
Education, yrs	13.1 (4.7)	11.7 (3.8)	12.4 (3.1)	13.9 (2.8)	$F = 1.0$	n/s
Sex, M:F	7:3	4:6	5:5	7:13	$\chi = 3.5$	n/s
Disease duration, yrs	8.6 (5.6)	5.5 (4.0)	5.8 (3.4)	--	$F = 1.1$**	n/s
ACE-III Total [100]	75.2 (16.8)	70.1 (13.4)	68.6 (14.8)	96.2 (2.6)	$F = 18.0$***	Control > bvFTD > SD, AD
Letter fluency	23.4 (11.0)	24.1 (11.4)	26 (17.3)	41 (12.6)	$F = 14.2$**	Control > AD, SD, bvFTD
Trails B-A, sec[a]	92.5 (63.4)	74.6 (70.2)	135. 7 (102.1)	46.2 (25.2)	$F = 8.3$*	Control < bvFTD, AD
RAVLT (15)	2.4 (2.3)	n/a	2.8 (2.1)	10.0 (2.4)	$F = 10.3$**	AD, bvFTD < Controls
RCF 3-minute recall (36)	4.5 (4.9)	14.3 (4.2)	4.8 (5.0)	13.2 (5.8)	$F = 17.3$***	AD, bvFTD < Controls, SD
FRS logit score[b]	-.32 (1.0)	1.2 (1.3)	0.7 (1.7)	--	$F = 7.2$**	SD> bvFTD
FRS Stage	Moderate	Moderate	Moderate	--	--	--

Note. Values are presented as mean (standard deviation) unless otherwise specified. Maximum score for each test shown in square brackets where appropriate. ACE-III=Addenbrooke's Cognitive Examination third edition; AD=Alzheimer's disease; bvFTD=behavioural variant frontotemporal dementia; F=Female; FRS=Frontotemporal Dementia Functional Rating Scale; M=Male; RCF=Rey Complex Figure. RAVLT=Rey Auditory Verbal Learning Task. SD=Semantic dementia. FRS was not available for two bvFTD patients, one semantic dementia, one Alzheimer's disease patient. Disease duration was not available for one bvFTD patient. RAVLT not assessed in semantic dementia *p<.05; **p<.005; ***p<.001; n/s=not significant; -- = not applicable. [a]Lower scores denote better executive functioning. [b]Lower scores denote greater levels of functional impairment on FRS.

4.3.2. Anhedonia and apathy

Detailed analysis of the SHAPS, TEPS and DApS measures is provided in Appendix Table 4.1. Briefly, in comparison to controls, all patient groups displayed significantly higher levels of anhedonia on the SHAPS as well as significantly higher levels of anticipatory and consummatory anhedonia on the TEPS. All patient groups also showed elevated executive, emotional and initiation apathy on the DApS compared to controls.

4.3.3. Episodic future thinking

A repeated-measures multivariate ANCOVA controlling for ACE-III total, was run to explore main effects of Group (bvFTD, SD, AD, Control), Condition (past, future) and Valence (positive, neutral) on the production of internal details. Figure 4.1 displays past and future internal details generated in each participant group.

An overall main effect of Group was found [$F(3,47)=11.2$, $p<.001$,$\eta_p^2=.29$], driven by significantly lower levels of internal details, irrespective of Valence and Condition, provided by the patient groups relative to Controls (all *p's*<.001). A main effect of Condition [$F(1,37)=24.2$, $p<.001$,$\eta_p^2=.20$] reflected the fact that, irrespective of Group and Valence, more details were provided in the Past compared to the Future condition ($p=.005$). These effects were qualified by a significant Condition × Group interaction [$F(3,47) = 8.8$, $p=.001$,$\eta_p^2=.32$] reflecting a significant Past > Future effect in the Control ($p=.006$) and SD ($p<.001$) group but not in bvFTD ($p=.23$) or AD ($p=.17$).

A main effect of Valence also emerged [$F(1,47)=24.2$, $p<.001$,$\eta_p^2=.20$] driven by the fact that irrespective of Group or Condition, participants generated more internal details for Positive than Neutral events ($p=.03$). Further to this, a Group × Valence interaction [$F(3,47) = 3.6$, $p=.05$,$\eta_p^2=.02$] revealed that irrespective of whether the event was in the

Past or the Future, Controls provided more internal details for Positive compared to Neutral events (p=.009), with no other significant differences (all p's>.07). A significant Condition × Valence interaction [$F(3,47) = 5.8$, p=.04,η_p^2=.03] reflected the fact that, irrespective of Group, more internal details were provided for Past Positive events compared to Past Neutral events (p<.03). No other significant differences were evident (all p's>.07).

Finally a significant Condition × Valence × Group interaction was found [$F(6,92)$=27.2, p<.001,η_p^2=.31]. This 3-way interaction reflected that Controls significantly outperformed both AD and bvFTD patients for Past Positive (both p's<.001) and Past Neutral (both p's<.001). In contrast, SD patients scored in line with Controls (both p's>.08) and provided significantly higher levels of internal details for Past Neutral relative to AD (p=.04) and bvFTD patients (p=.03), with no differences between the patient groups for Past Positive (all p's>.17). For Future thinking, Controls provided significantly higher levels of internal details relative to all patient groups across Positive (all p's<.02) and Neutral (all p's<.01) conditions with no differences between the patient groups (all p's>.09).

Within-group comparisons revealed a Positive > Neutral effect in Controls, with higher levels of internal details across Past (p=.002) and Future conditions (p=.005). In SD, the Positive > Neutral effect was only evident in the Past condition (p=.03) with no difference between number of details for Positive and Neutral events in the Future condition (p=.13). No such Positive > Neutral effect was evident in the bvFTD or AD groups (all p's>.09).

Finally, within group comparisons revealed a Past > Future effect for Controls for Positive (p=.03) but not Neutral events (p=.26). SD patients showed a Past > Future effect, generating significantly higher levels of internal details for Past compared to Future events across both Positive (p=.03) and Neutral conditions (p=.01). Contrastingly bvFTD and AD patients showed similar impairments across both Past and Future events regardless of whether they were Positive or Neutral (all *p's*>.09).

In summary, retrieval and construction of personal events was differentially impacted depending on dementia group. Patients with bvFTD and AD showed parallel impairments across both past and future conditions with no effect of valence. In contrast, despite a relative sparing of recent episodic memory in SD, significant deficits in the construction of future events were evident, alongside a positivity bias observed only in the past condition.

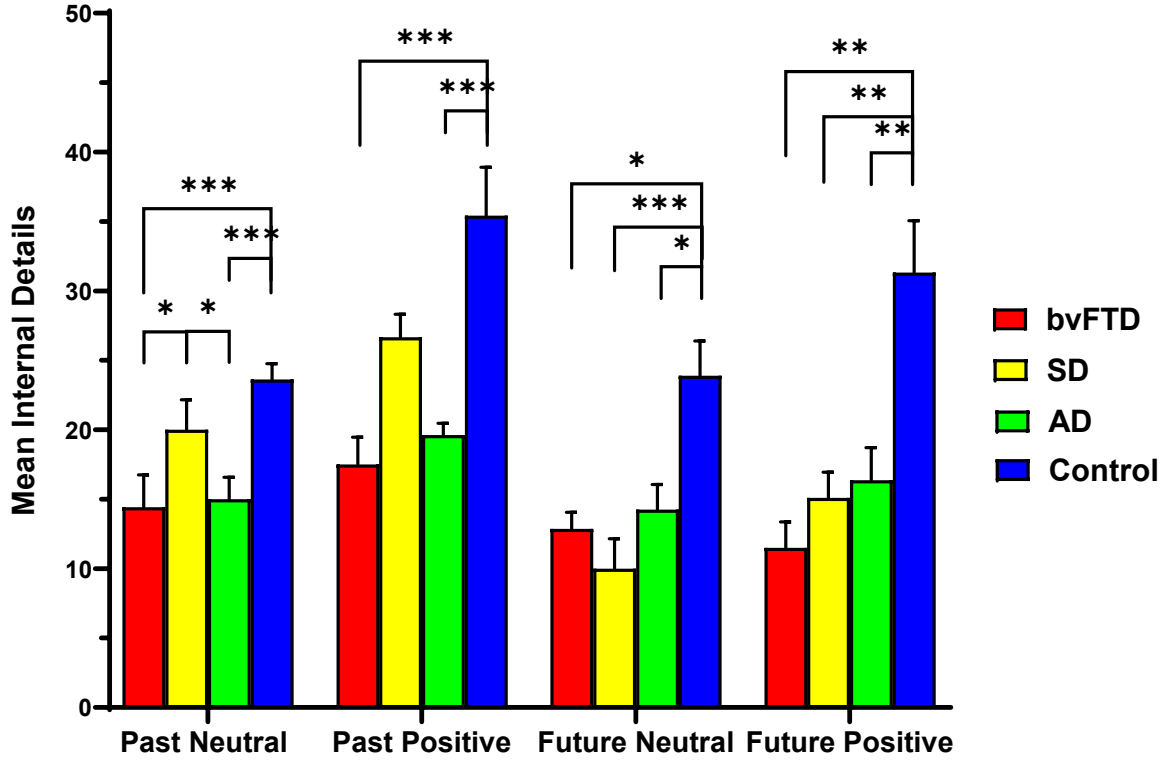


Figure 4.1. Bar chart showing the average number of internal details generated following probing across participant groups and valence on the episodic past–future thinking task. Error bars depict standard error of the mean. AD=Alzheimer's disease; bvFTD=behavioural variant frontotemporal dementia; SD=semantic dementia; *p<.05; **p<.005; ***p<.001.

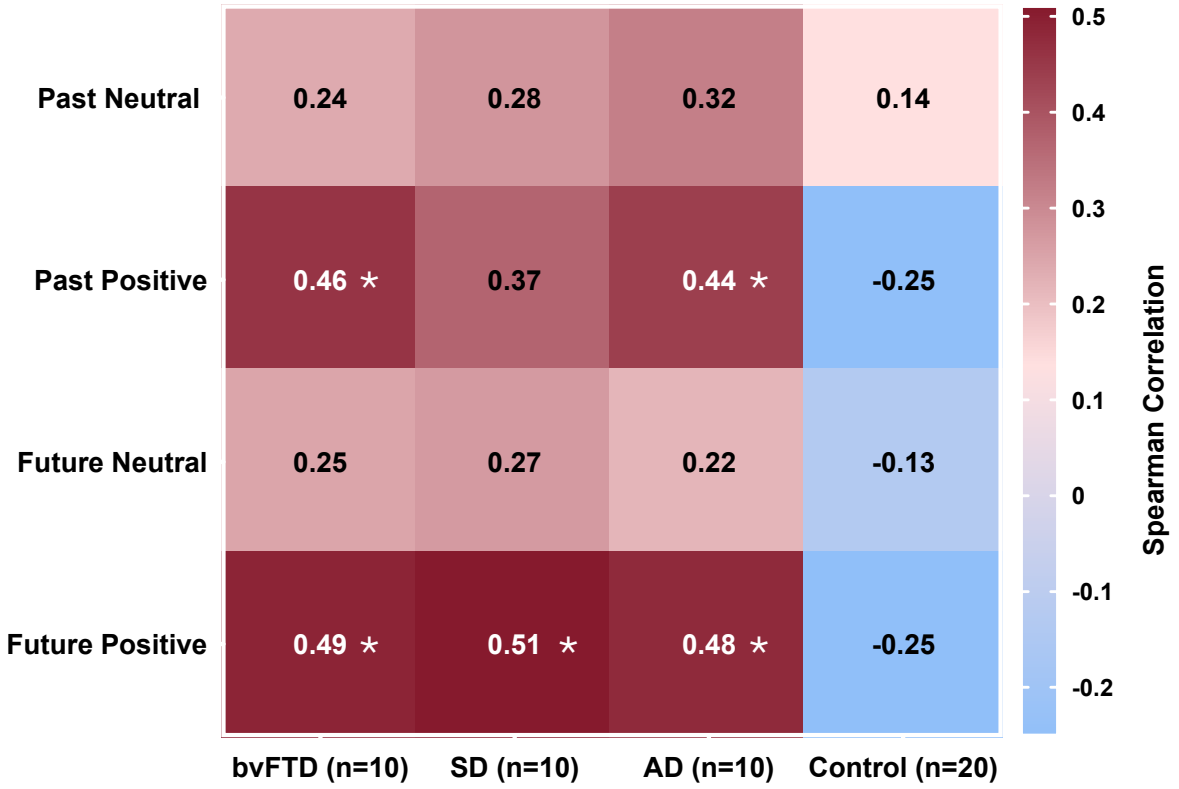
4.3.4. Correlations between past and future thinking and anticipatory anhedonia

Spearman's correlations were conducted to explore potential associations between future thinking performance and anticipatory anhedonia in each patient group separately (Figure 4.2). All correlations were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control for false discovery rates.

In the both the bvFTD and AD group, lower TEPS-A scores (greater anticipatory anhedonia) were significantly associated with fewer internal details for both past (both p's<.04) and future (both p's<.03) positive events. This association was not observed for

neutral events, whether past or future (all *p's*>.06). In the SD group, greater anticipatory anhedonia was associated with reduced internal detail generation exclusively for future positive events (*p*=.009). No other correlations in this group were significant (all *p's*>.07). No significant associations were observed between performance on the experimental task and TEPS-A in the Control group (all *p's*>.31). Fisher's r-to-z transformations revealed no significant differences between any of the significant correlations.

Figure 4.2. Correlations between anticipatory anhedonia and episodic past-future thinking task conditions.



Note. Correlation heatmap for behavioural variant frontotemporal dementia (bvFTD), semantic dementia (SD), Alzheimer's disease (AD) and Controls showing associations between different conditions on the past-future thinking task and anticipatory anhedonia. Values in boxes represent two-tailed Spearman correlation values where lower scores on TEPS-A reflect reduced hedonic tone (i.e., greater anticipatory anhedonia severity). Colour gradient key on the right indicates the magnitude of the correlation, ranging from -.2 (light blue) to 0.5 (dark red). *Indicates values that remain significant following Benjamini-Hochberg correction for false discovery rate at q=.05.

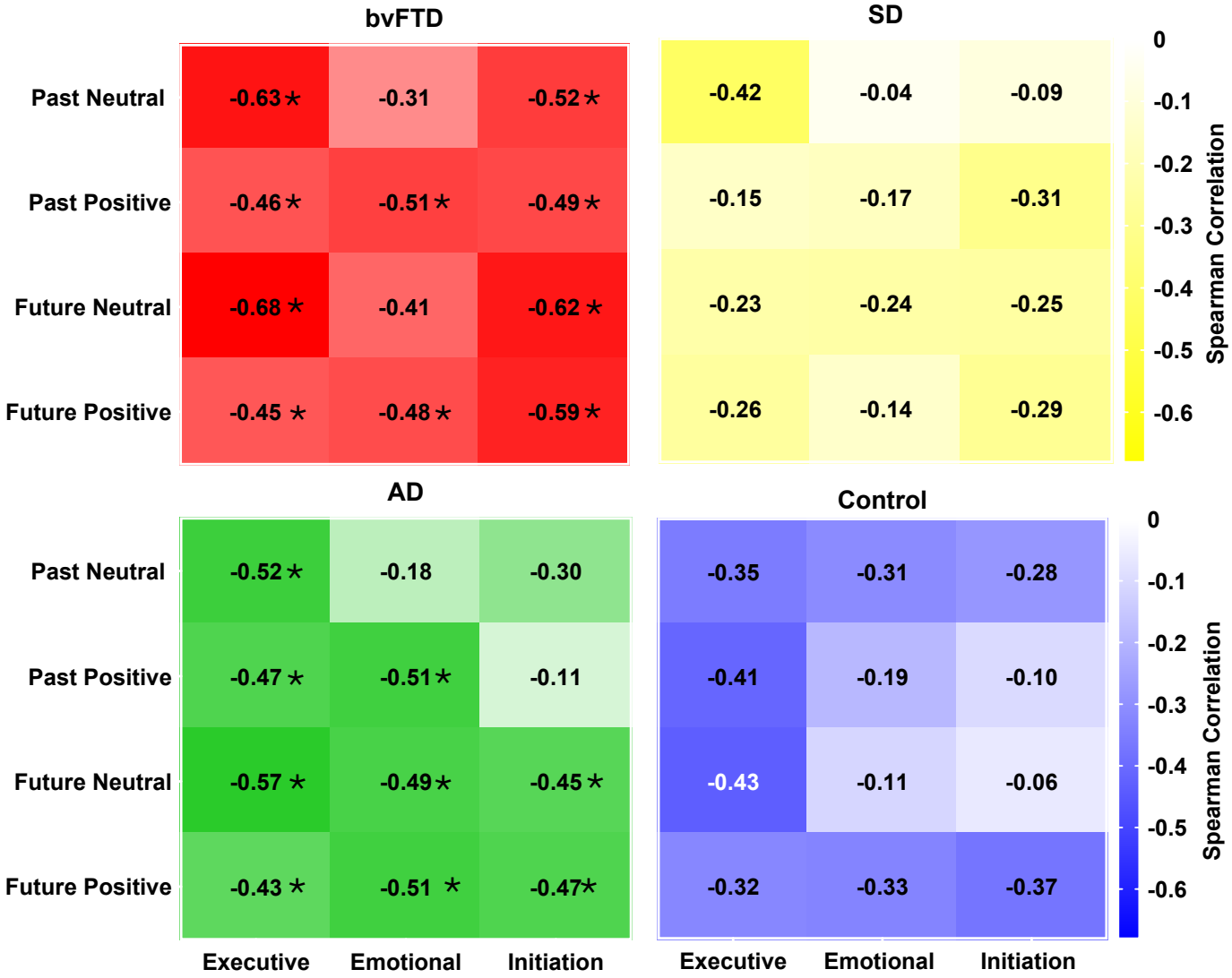
4.3.5. Correlations between past and future thinking and apathy

In the bvFTD group, greater executive and initiation apathy on the DApS were significantly associated with fewer internal details provided across all event types (all *p's*<.04, see Figure 4.3). Interestingly, higher emotional apathy was associated with fewer details generated for positive past (*p*=.008) and future events (*p*=.02), but not neutral events (all *p's*>.15).

For AD, executive apathy was associated with fewer internal details irrespective of temporal condition or valence (all *p's*<.08). Higher emotional apathy correlated with fewer internal details for all future events (positive; *p*=.01, neutral; *p*=.007), as well as past positive events (*p*=.009) but not past neutral events (*p*=.44). Additionally, greater initiation apathy was linked to fewer internal details for future (both *p's*<.02) but not past (both *p's*>.26) events.

No associations were found between level of internal detail or measures of apathy in SD or Controls (all *p's*>.09). Fisher's r-to-z transformations within groups revealed no significant differences between significant correlations.

Figure 4.3. Correlations between apathy subtypes and episodic past-future thinking conditions.



Note. Correlation heatmap for behavioural variant frontotemporal dementia (bvFTD), semantic dementia (SD), Alzheimer's disease (AD) and Controls showing associations between different conditions on the episodic past-future thinking task and each apathy subscale of the Dimensional Apathy Scale. Values in boxes represent two-tailed Spearman correlation values where higher apathy scores reflect more severe apathy. Colour gradient key on the right indicates the magnitude of the correlation, ranging from -.1 (white) to -.6 (dark blue). *Indicates values that remain significant following Benjamini-Hochberg correction for false discovery rate at q=.05.

4.4. Discussion

This study is the first to explore the relationship between anticipatory anhedonia and episodic past-future thinking in dementia syndromes. Consistent with prior research, significant deficits in episodic future thinking were observed in AD, SD and bvFTD patients (Addis, Sacchetti, et al., 2009; Irish et al., 2012a, 2013; Irish & Piolino, 2016). Importantly, we observed a relationship between a compromised capacity to generate detailed, future scenarios and severity of anticipatory anhedonia, with distinct patterns observed across dementia syndromes. These findings provide novel insights into the cognitive and affective mechanisms likely underpinning motivational impairments in dementia, particularly highlighting how episodic future thinking deficits may contribute to anticipatory anhedonia.

4.4.1. Valence effects in episodic thinking

One of the most important findings from this study is the differential effects of valence on episodic past and future thinking in dementia. Notably, Controls exhibited a strong positivity bias, generating richer and more detailed descriptions for positive events in both past and future conditions. This positivity bias, a feature of autobiographical memory, likely reflects the inherently rewarding nature of recalling or imagining positive events, which facilitates greater engagement and more vivid mental simulations (Marsh et al., 2019; Ünal & Besken, 2020). In SD, consistent with previous research, patients demonstrated profound deficits in future event simulation despite preserved episodic recall (Irish et al., 2012a, 2016). However, the positivity bias was evident only for past events, with participants providing more detailed descriptions of positive memories compared to neutral ones. The relatively intact retrieval of recent episodic memories in SD has been described in detail previously (Irish et al., 2011, 2012a, 2012b) however, here

we demonstrate that positive recent memories may in fact be more accessible to retrieval in this syndrome. Positive valence mechanisms are proposed to enhance the richness and vividness of recollected experiences (Kensinger, 2009). As such, it is possible that positively valanced stimuli retain their reward value in SD, bolstering retrieval from the recent past, (i.e., a form of reward learning, see also Horne et al., under revision). In contrast, we did not observe the positive valence bias in the future thinking condition, as SD patients displayed comparable deficits in simulating positive and neutral future events. One possible explanation is that the cognitive demands of future simulation in SD are too great for valence to exert a meaningful effect. Constructing novel future scenarios requires the flexible recombination of episodic details within a broader semantic framework. While SD patients may retain some access to positive past experiences, the degradation of semantic knowledge likely prevents them from integrating these details into a coherent future event. Without the necessary conceptual scaffolding to structure an event, they may be unable to generate a meaningful narrative to which positive details and vividness can be added, resulting in similarly impoverished future simulations across valence conditions.

In contrast, AD and bvFTD patients showed impairments in both past and future thinking, with no evidence of a positivity bias. Deficits in both past and future thinking have been well-documented in AD and bvFTD (Addis, Sacchetti, et al., 2009; Irish et al., 2012a, 2013), however, our findings suggest that positive valence did not appear to ameliorate these impairments. A global impairment in past and future thinking was predicted in bvFTD, reflecting the intersection of mental construction difficulties and emotion processing disturbances (N.-A. Wilson, Ahmed, et al., 2020). In AD, however, the absence of a positivity bias was somewhat surprising, particularly given that emotion

processing is typically less affected, at least in the early stages of the disease (Goodkind et al., 2015; Kumfor et al., 2013; Lazar et al., 2017). One possible explanation is that the severity of the amnesic deficit in AD precludes the retrieval of positive memories from the past, thereby limiting their availability as a source for constructing future events. Without access to a sufficiently detailed repository of autobiographical memories, AD patients may be unable to generate richly detailed future scenarios, regardless of valence.

4.4.2. The role of positive mental simulation in anticipatory anhedonia

A key finding from this study was the association between impaired episodic future thinking for positive events and anticipatory anhedonia across all dementia syndromes. Considering first the SD group, we found a significant association between poorer internal detail generation for future positive events and greater anhedonia severity. Importantly, this relationship between anticipatory anhedonia and internal detail generation was not present for neutral events. Our finding suggests a potential link between the ability to imagine novel, positive, future events and the capacity to anticipate pleasure in SD. Given that generating novel content is impaired in SD (Irish et al., 2012b, 2012a), this deficit may be a key driver of anticipatory anhedonia in this population. As semantic knowledge deteriorates, individuals lose the ability to construct rich, emotionally salient future scenarios, diminishing the anticipation of pleasure. In turn, they become increasingly reliant on recent experiences to guide behaviour, leading to rigid and repetitive patterns of thought and behaviour, further exacerbating anticipatory anhedonia (Horne & Irish, 2023). Importantly, the direction of these associations remains unclear as it is also possible that a diminished capacity to anticipate pleasure from future events may lead to a reduction in the detail and emotional significance of these imagined experiences, making them less vivid and appealing.

Notably, both bvFTD and AD patients exhibited significant impairments in past-future thinking across both positive and neutral conditions, generating fewer internal details overall compared to Controls. However, within these groups, the reduction in internal details for positive, but not neutral, events was significantly associated with higher levels of anticipatory anhedonia. This finding points to a possible interplay between one's ability to construct or recall emotionally valanced events and the capacity to anticipate future pleasurable outcomes. This association likely stems from disruptions in positive valence processing, which allows individuals to attach emotional significance to rewarding experiences, making them more salient and engaging (Sander & Nummenmaa, 2021). In bvFTD and AD, the association extended across both temporal conditions suggesting a broader breakdown in the ability to engage with positive emotional content, impacting both memory recall and future event construction. Notably, this association was absent for neutral events, highlighting the distinct cognitive and affective demands required for emotionally valanced scenarios compared to neutral ones. One possibility is that neutral events, by definition, lack intrinsic emotional or motivational significance. While positive memories serve as important cognitive tools for anticipating pleasure and guiding goal-directed behaviour, neutral events are typically routine, everyday occurrences that do not elicit strong affective responses. As such, difficulties in recalling or constructing neutral events are unlikely to impact the ability to anticipate pleasure, as these scenarios do not contribute to reward-based decision-making or behavioural motivation.

4.4.3. Correlations between apathy and past/future thinking

Distinct associations also emerged between different dimensions of apathy and episodic recall/reconstruction across dementia subtypes. In both bvFTD and AD,

reduced detail generation for both past and future events across all conditions was associated with executive apathy. This association may reflect a general lack of motivation and drive, leading to reduced effort in engaging with the task and describing events in detail (Wei et al., 2020). Similarly, in bvFTD, diminished internal detail across all event types was linked to initiation apathy. This suggests that an impaired ability to mentally construct specific and richly detailed autobiographical events may, in turn, contribute to a diminished sense of initiation. In contrast, AD patients showed a unique relationship between future event generation and initiation apathy, indicating that difficulties in initiating tasks, such as selecting an event to describe, may lead to reduced episodic detail when constructing future scenarios. However, the direction of these changes remains unclear. Whether reduced future simulation leads to initiation and executive apathy or vice versa is an important question for future research.

Notably, reduced generation of detail for positive events was found to correlate with emotional apathy in bvFTD and AD. This suggests that diminished emotional engagement and affective responsiveness may specifically impair the ability to reconstruct and imagine emotionally valanced experiences (Wei et al., 2020).

Strikingly, we did not find a significant association between past or future thinking performance and dimensions of apathy in SD. However, given the relatively small sample size, these null findings should be interpreted with caution given the potential for Type II errors. Several correlations were moderate in magnitude, raising the possibility that meaningful associations may exist but were not detected due to limited statistical power. This stands in contrast to our earlier finding of a link between future thinking impairments and anticipatory anhedonia in this group. As their broader semantic knowledge base

deteriorates, SD patients increasingly rely on familiar recent experiences as templates for future behaviour, reinforcing repetitive and inflexible patterns (Horne & Irish, 2023). In this context, the absence of a relationship between past-future thinking and apathy may reflect the fact that SD patients remain engaged with a narrow set of meaningful experiences, which continue to guide behaviour despite their inability to construct richly detailed future scenarios. While these behaviours may lack flexibility, they do not necessarily indicate a diminished drive to act.

4.4.4. Limitations and future directions

This study has several limitations. As an exploratory study with a relatively small sample, these findings require replication in larger cohorts to confirm their validity and generalizability. The difficulty participants faced in generating neutral events raises questions about the task's sensitivity in distinguishing episodic memory deficits from broader cognitive impairments. Neutral events are often highly schematic, drawing on semantic and general world knowledge rather than richly detailed personal experiences. As a result, performance on this task may reflect semantic memory integrity as much as episodic retrieval ability. Furthermore, neutral events tend to be routine or repetitive experiences, which may be recalled more easily due to their overlearned and script-like nature, rather than true episodic recollection. Future studies could incorporate event plausibility ratings or alternative methods to distinguish between truly episodic memories and schematic reconstructions. Another limitation concerns the accuracy of reported neutral events. It is challenging to determine whether an event described by a participant genuinely occurred in the past year or represents a recurring, non-emotional, or highly schematic experience that is easier to retrieve and describe.

Furthermore, performance on the episodic simulation task may have been influenced by several unmeasured factors, such as the temporal distance of imagined events, the use of mental imagery or sensorial vividness, and participants' affective state during task engagement. Given the small sample size, even subtle group differences on these dimensions may have impacted the richness of detail generated and the strength of observed associations. Future studies should consider incorporating subjective ratings of emotional valence, vividness, or affect during task performance to better disentangle these influences.

Importantly, the direction of the observed correlations remains unclear. Future research will be critical in determining whether impairments in future thinking lead to a reduction in anticipatory pleasure, or whether an inability to experience pleasure diminishes the capacity to imagine future positive events. Understanding the causal nature of these relationships will provide valuable insights into the mechanisms underlying motivational impairments in dementia and inform the development of targeted interventions.

4.4.5. Conclusion

In summary, this study provides preliminary evidence linking anticipatory anhedonia and episodic future thinking in dementia syndromes. By uncovering the interplay between cognitive and affective processes, our findings contribute preliminary insights to a growing understanding of the mechanisms underlying motivational impairments in neurodegenerative conditions. Future research should build on these findings by utilising larger sample sizes and clarifying the directionality of these

relationships, ultimately paving the way for the development of specifically targeted interventions to improve the quality of life for patients and their caregivers.

5.1. Introduction

The previous chapters provided a detailed investigation of anhedonia in FTD, uncovering distinct motivational profiles and their associations with future thinking and functional impairments. Notably, bvFTD patients exhibited a global impairment spanning both anticipatory and consummatory dimensions of anhedonia, with reduced anticipatory pleasure linked to impairments in episodic future thinking for positive events. These findings represent a significant step forward in the study of anhedonia in FTD, by providing empirical evidence for how different dimensions of anhedonia manifest across dementia subtypes and highlighting cognitive mechanisms that may contribute to these deficits. Here, we consider the importance of contextualising these results within broader transdiagnostic frameworks to deepen our understanding of the mechanisms underlying anhedonia across clinical populations.

While anhedonia is a relatively new focus in FTD research, it is well recognised as a transdiagnostic feature across neuropsychiatric disorders (Guineau et al., 2023; Lalousis et al., 2024; Trøstheim et al., 2020; Turner & Husain, 2022). As a transdiagnostic construct, anhedonia contributes to significant impairments in motivation and functional outcomes in patients with major depressive disorder (MDD), schizophrenia, substance use disorders, anxiety, bipolar disorders and Parkinson's disease (Guineau et al., 2023; Trøstheim et al., 2020). Further, more severe anhedonia in mood disorders is linked to heightened psychosocial impairment (Vinckier et al., 2017), elevated suicidal ideation (Ducasse et al., 2018), increased psychiatric and medical comorbidities

(Leventhal et al., 2010; Willame et al., 2022) as well as poorer quality of life (Pizzagalli et al., 2022). These findings highlight the profound impact of anhedonia across clinical populations and emphasise the need to elucidate the mechanisms that drive this symptom.

While substantial research has focused on anhedonia in mood disorders and its potential treatments (Serretti, 2023; Whitton & Pizzagalli, 2022), emerging evidence suggests that anhedonia may also serve as an early indicator of FTD (Shaw, El-Omar, Roquet, et al., 2021). Although both bvFTD and mood disorders feature pronounced anhedonia (Shaw, El-Omar, Roquet, et al., 2021; Trøstheim et al., 2020), it remains unclear whether the clinical manifestations of anhedonia are comparable.

5.1.1. Why compare bvFTD and mood disorders?

Comparing the nature and severity of anhedonia in bvFTD to that observed in mood disorders (e.g., MDD and bipolar disorder) provides a unique opportunity to elucidate overlapping and distinct clinical presentations. Both disorders share symptoms such as lack of interest, decreased motivation, low energy, and impaired concentration (Urban-Kowalczyk et al., 2022). The most common initial manifestations of bvFTD are apathy, loss of interest, lack of initiative and inactivity (Rascovsky et al., 2011). These findings often result in a clinical picture that is misinterpreted as a primary mood disorder such as MDD or bipolar disorder (Cardarelli et al., 2010; Zapata-Restrepo et al., 2021). Consequently, bvFTD patients are frequently misdiagnosed with mood disorders—approximately 50% are initially diagnosed with primary psychiatric disorders rather than a neurodegenerative disease (Tanaka et al., 2020). However, a persistently low mood, a defining feature of mood disorders, is not typically observed in bvFTD

(Gregory, 1999; Urban-Kowalczyk et al., 2022). Conversely, mood disorders can occasionally be misdiagnosed as bvFTD (Shinagawa et al., 2016). This diagnostic challenge underscores the importance of distinguishing depressive symptoms, such as anhedonia, that may signal early neurodegenerative processes from those unrelated to dementia.

Accurate differentiation is critical due to the markedly different outcomes, patient management strategies, family counselling needs, and caregiver education associated with bvFTD and mood disorders (Woolley et al., 2011). Relatives of bvFTD patients often cite inaccurate diagnosis as a major challenge, compounding the distress of managing the disease (Chow et al., 2011). Misdiagnosis has significant repercussions, including delays in accessing appropriate care, increased financial burden due to unnecessary and ineffective treatments, and prolonged emotional distress due to diagnostic uncertainty (reviewed by Giebel et al., 2024). Additionally, misdiagnoses impose substantial costs on healthcare systems, stemming from repeated assessments, inappropriate referrals, and misdirected treatments, further straining limited resources (reviewed by Giebel et al., 2024). Understanding how anhedonia compares across bvFTD and mood disorders may clarify these diagnostic ambiguities and enhance clinical accuracy.

Initial, detailed investigations of anhedonia in bvFTD suggest that it may manifest differently from mood disorders, with neurodegeneration likely compounding deficits across both anticipatory and consummatory pleasure. Chapter 3 revealed a global impairment in both anticipatory and consummatory anhedonia in bvFTD, whereas studies in mood disorders suggest that the primary deficit lies in anticipatory pleasure (Keren et al., 2018; Long et al., 2022; Schulz et al., 2024). Furthermore, different cognitive

mechanisms may underpin anhedonia in each syndrome. In bvFTD, widespread neurodegeneration disrupts multiple cognitive processes including executive function, emotional regulation, and reward processing which severely impairs the ability to generate, maintain or act upon rewarding experiences (Wong et al., 2023). These deficits, compounded by an inability to internally generate thoughts (O'Callaghan et al., 2019) and difficulties with episodic future thinking (Irish et al., 2013), likely prevent individuals from anticipating and engaging in pleasurable activities. In contrast, anhedonia in mood disorders appears to be driven by blunted reward responses (Whitton & Pizzagalli, 2022), pessimistic expectations (Beck et al., 2024; Korn et al., 2014) and negative rumination (S. L. Johnson et al., 2008) rather than an inability to mentally simulate future events (Gamble et al., 2019). Indeed, Gamble et al. (2019) conducted a comprehensive meta-analysis examining the relationship between depression and future specificity, finding that while individuals with depression exhibited reduced specificity for positive future events, their ability to simulate future scenarios remained largely intact, particularly for negative and neutral events. These differences suggest that distinct cognitive processes contribute to anhedonia in mood disorders and bvFTD. Differentiating between neurodegenerative and mood-related anhedonia could not only enhance diagnostic precision and reduce the risk of misdiagnosis but help guide the use of specific treatment approaches for these conditions.

Despite the importance of understanding anhedonia across bvFTD and mood disorders, no study to our knowledge has directly compared the clinical manifestation of anhedonia in these disorders. To address this gap, this study aimed to (i) compare overall levels of anhedonia in bvFTD compared to a mood disorder group (MDD and bipolar disorder) and (ii) to examine differences in anticipatory and consummatory anhedonia

across these conditions. Additionally, we used an item-level approach to analyse the TEPS, allowing for a more detailed examination of symptom profiles in each group. We hypothesised that individuals with bvFTD would exhibit greater consummatory and anticipatory anhedonia than individuals with a mood disorder due to the compounding effect of underlying neurodegenerative changes. Additionally, we sought to evaluate the prevalence of clinically significant anhedonia in bvFTD relative to a subset of individuals with MDD. We further predicted that clinically significant anhedonia would be more prevalent in the bvFTD group, despite higher rates of clinically significant depression in MDD.

5.2. Methods

5.2.1. Participants

The current study included a secondary analysis of data from a total of 212 participants, comprising 59 bvFTD patients and 41 demographically-matched healthy control participants, as well as 80 individuals with a mood disorder and separate sample of 32 healthy demographically-matched healthy control participants. Of the mood disorder participants, 72.5% (n=58) had a unipolar mood disorder (current MDD (n=49)/ current dysthymia (n=1) or MDD in partial remission (n=8)) and 27.5% (n=22) had bipolar mood disorder (BD type I or II, depressed (n=16), mixed (n=1), or hypomanic (n=3)).

5.2.2. Dementia sample

Recruitment of the dementia sample and their control group followed the same procedure outlined in Chapter 2. All bvFTD patients were diagnosed as per standard diagnostic criteria (Rascovsky et al., 2011), whilst controls performed within normal limits on all behavioural and cognitive measures (detailed in Chapter 2).

5.2.2.1. Assessment of anhedonia in the dementia sample

Anhedonia was assessed using the Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995) and the Temporal Experience of Pleasure Scale (Gard et al., 2006) (TEPS), see Chapter 2 for full details. To reduce cognitive load in the dementia sample, the Likert scale for the TEPS was modified from a 6-point to a 4-point scale to match the SHAPS, such that participants rated their responses from 1 (very false for me) to 4 (very true for me). Item 11 on the anticipatory subscale of the TEPS had previously been modified to better reflect typical experiences of older adults[2]. As such this item was excluded from the analysis due to differences in its wording across the study samples. The anticipatory subscale of the TEPS remained reliable after the exclusion of Item 11 (Cronbach's alpha=0.7). On both questionnaires (SHAPS and TEPS) lower scores indicated a lower level of hedonic tone, i.e. a higher level of anhedonia. Both the SHAPS and TEPS were modified to create a carer's version for the dementia sample, allowing carers to assess patients' experiences both before the onset of dementia and at the present time.

To determine whether the use of SHAPS and TEPS carer ratings in bvFTD introduced a potential confounding effect of carer depression or stress, Pearson's correlation analyses were conducted to assess the relationship between carer self-ratings of depression and stress, and the SHAPS, TEPS-A, and TEPS-C scores. No significant correlations were found across any of the variables (SHAPS; p>.70, TEPS-A;

[2] The original item was: *"When I'm on my way to an amusement park, I can hardly wait to ride the roller coasters."* In the dementia sample, this was modified to: *"When they are on the way to a party or family gathering, they can hardly wait to see everyone."*

p>.33, and TEPS-C; *p*>.36), indicating that carer ratings of anhedonia in the patient group were not associated with their own levels of depression or stress.

5.2.2.2. Assessment of cognition and depression in dementia sample

The Addenbrooke's Cognitive Examination III (ACE-III; Hsieh, Schubert, et al., 2013; So et al., 2018) was used to assess overall cognitive function in the dementia sample, and the depression subscale of the Depression, Anxiety, and Stress Scale 21 (DASS-21; Lovibond & Lovibond, 1995) was used to examine depression, with higher scores indicating greater symptom severity. See Chapter 2 for full details.

5.2.3. Mood disorder sample

This study involved a secondary analysis of data collected as part of a longitudinal, naturalistic study investigating reward learning in individuals with mood disorders and controls (see Whitton et al., 2021 for full details). In this parent study, a novel recruitment approach was adopted, whereby participants were initially recruited based on their performance on a behavioural measure of reward learning (The Probabilistic Reward Task) rather than solely by clinical diagnosis. This allowed for the inclusion of participants representing a broad spectrum of reward responsiveness. Adults seeking treatment for mood disorders (n=80) were recruited from Massachusetts General Hospital and McLean Hospital, while healthy controls (n=32) were recruited from the community in Massachusetts. All participants needed to be fluent in English, have normal or corrected-to-normal vision, and be right-handed. The exclusion criteria included illicit drug use (verified by a positive urine drug screen), history of seizure disorder, or history of head injury or loss of consciousness. For the mood disorder group, the inclusion criteria were presence of mood-related psychopathology (depression,

mixed episode, or hypomania) severe enough to cause distress or impairment, as assessed through the Structured Clinical Interview for DSM-IV (First, 2002). Exclusion criteria for this group included electroconvulsive therapy in the past two years, psychosis, or other exclusionary comorbidities (see Whitton et al., 2021).

For the initial analysis, anhedonia in bvFTD was compared to this broader mood disorder cohort. However, in subsequent analyses, comparisons were narrowed to individuals experiencing a current depressive episode (MDD) to more directly assess differences in clinically significant anhedonia and depression between groups.

5.2.3.1. Control sample for the mood disorder group

Controls were required to have no past or current use of psychotropic medication, no current or lifetime DSM-IV psychiatric disorder (American Psychiatric Association, 2000), no first-degree relative with a known mood or psychotic disorder, and a Beck Depression Inventory-II (Beck et al., 1996) score below 10. Controls were excluded if they had recently taken an exclusionary medication (see Whitton et al., 2021). The McLean Hospital Institutional Review Board approved all procedures, and all participants provided written informed consent after receiving a full description of the study prior to participating.

5.2.3.2. Assessment of anhedonia in the mood disorders sample

In the mood disorders sample, anhedonia was measured using the SHAPS where responses were scored on a 4-point Likert scale (1= strongly agree, 4= strongly disagree) with higher scores indicating more severe anhedonia. SHAPS scores for the mood disorder sample were reversed to match the dementia sample such that in both samples, higher scores indicated a greater capacity for pleasure. The TEPS was used to assess trait

anticipatory (TEPS-A, 10 items[3]) and consummatory (TEPS-C, 8 items) pleasure (Gard et al., 2006). Participants rated their agreement with each item using a 6-point Likert scale, ranging from 1 (very false for me) to 6 (very true for me), with higher scores indicating a greater capacity for pleasure.

5.2.3.3. Assessment of cognition and depression in the mood disorder sample

All participants in the mood disorder group were required to score above 25 on the Mini Mental State Examination meaning they were all cognitively healthy at the time of testing. The Beck Depression Inventory-II (BDI-II; Beck et al., 1996) was used to assess the severity of depressive symptoms in the mood disorder sample. The BDI-II is a 21-item self-report inventory that measures symptoms of depression, including mood, cognitive, and physical symptoms. Each item is rated on a 4-point Likert scale ranging from 0 to 3, with higher scores indicating greater severity of depression. Total scores range from 0 to 63, with cutoffs as follows: minimal depression (0–13), mild depression (14–19), moderate depression (20–28), and severe depression (29–63).

5.2.4. Data harmonisation

Given the cognitive impairments in the dementia sample and the differences in the scoring of the TEPS, each patient group (bvFTD and mood disorder) was initially compared to their respective control group. To harmonise the data we calculated scaled SHAPS, TEPS and depression scores for each patient group as a percentage of their respective control group.

[3] Item 11 from the TEPS anticipatory subscale was excluded from analyses to maintain consistency across samples.

For this study, both DASS-D and BDI-II scores were reversed so that lower scores indicated greater levels of depression and then converted to percentage scores (referred to as depression scores). This adjustment was made to maintain consistency across anhedonia measures when calculating scaled scores.

To scale the bvFTD group to their respective control group, four separate univariate ANCOVAs were conducted, examining the SHAPS, TEPS-A, TEPS-C and depression (percentage DASS-D) scores with sex, age, education, and ACE-III total included as covariates. The Estimated Marginal Mean (EMM) for each variable - SHAPS (85.4), TEPS-C (80.5), TEPS-A (73.7), Depression (94.8) - was extracted from the control group. These EMMs were then used to calculate each bvFTD patient's scaled score as a percentage of their respective control group, adjusting for differences in sex, age, education, and cognitive impairment.

The same process was applied to the mood disorders group, controlling for sex, age and education scaling their scores relative to their respective control group. The following EMMs were extracted for the mood disorders control group: SHAPS (91.5), TEPS-A (80.1), TEPS-C (83.9), depression (percentage BDI-II score; 99.0). These EMMs were then used to calculate each mood disorder patient's scaled score as a percentage of their respective control group, adjusting for differences in sex, age and education. This approach enabled direct comparisons between scaled anhedonia and depression scores in the bvFTD and mood disorder groups.

5.2.5. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics, version 28.0. Prior to undertaking analyses, normality of distributions was checked using Shapiro Wilks

tests and box plots. Where variables were normally distributed, independent samples *t* tests were used to examine group differences on continuous demographic variables (e.g. age, education). Chi-square tests were used to investigate group differences on categorical variables (e.g. sex).

To explore differences in anhedonia, three separate univariate ANCOVAs, controlling for sex and age, were run on the scaled SHAPS, TEPS-A and TEPS-C scores, using Sidak *post hoc* tests. To examine differences in depression, a univariate ANCOVA, controlling for sex and age, was run on the scaled depression scores, using Sidak *post hoc* tests. Partial eta-squared values (η_p^2) accompany all ANCOVAs as measures of corresponding effect sizes.

To examine item-level differences between the mood disorder and bvFTD groups, multiple Mann–Whitney U tests were conducted to compare the ordinal response distributions of all TEPS items. This approach was chosen because the study sample size was insufficient to reliably estimate the parameters of latent variable models within each subgroup (Jiang et al., 2016). Mann–Whitney U tests were employed using 17 items of the TEPS between bvFTD and mood disorder groups. For each group comparison, *p*-values were adjusted using the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995) to maintain a 5% false discovery rate (FDR). To illustrate the effect size of each comparison, we reported the non-parametric Probability of Superiority (PS) effect size (Ruscio, 2008; Vargha & Delaney, 2000). The PS value, which ranges from 0 to 1, represents the likelihood that a randomly chosen individual from one group will have a higher score than a randomly chosen individual from the other group. A PS value of 0.5

indicates that the group distributions are equal, while values of 0 or 1 indicate complete separation between the groups (Kraemer & Kupfer, 2006).

5.3. Results

5.3.1. Demographic and clinical comparisons

Demographic and clinical characteristics of the groups are summarised in Appendix section 5.3.1. Briefly, the bvFTD group was significantly older than the FRONTIER control group and had lower levels of education and cognitive performance. The mood disorder group did not differ from their respective mood disorder control group in terms of age, sex, or education. Importantly, both patient groups demonstrated significantly higher levels of anhedonia on the SHAPS as well as significantly worse consummatory and anticipatory anhedonia on the TEPS when compared to their respective control group. As anticipated, the bvFTD group was significantly older than the mood disorder group and had fewer years of education, with sex distribution differing across the groups (Males > Females). Detailed comparisons are outlined in Appendix section 5.3.2.

5.3.2. Anhedonia profiles in bvFTD compared to the mood disorder sample

Figure 5.1 displays levels of anhedonia on the SHAPS, anticipatory anhedonia on the TEPS-A and consummatory anhedonia on the TEPS-C for bvFTD patients scaled relative to their control group versus a mood disorder cohort scaled relative to their control group across each measure. Three separate univariate ANCOVAs controlling for sex and age[4] revealed no difference between the bvFTD and mood disorder group in

[4] Education was not included as a covariate in the ANCOVA as previous analyses indicated that its inclusion did not alter the results. Additionally, education was not expected to influence anhedonia severity in the same manner as age and sex.

terms of levels of anhedonia on the scaled SHAPS [$F(1,126)=1.0$, $p=.32$, $\eta_p^2=.009$] or anticipatory anhedonia on the scaled TEPS-A [$F(1,135)=.02$, $p=.80$, $\eta_p^2=.00$]. In contrast, bvFTD patients displayed significantly greater consummatory anhedonia on the scaled TEPS-C relative to the mood disorders group [$F(1,135)=4.5$, $p=.04$, $\eta_p^2=.03$].

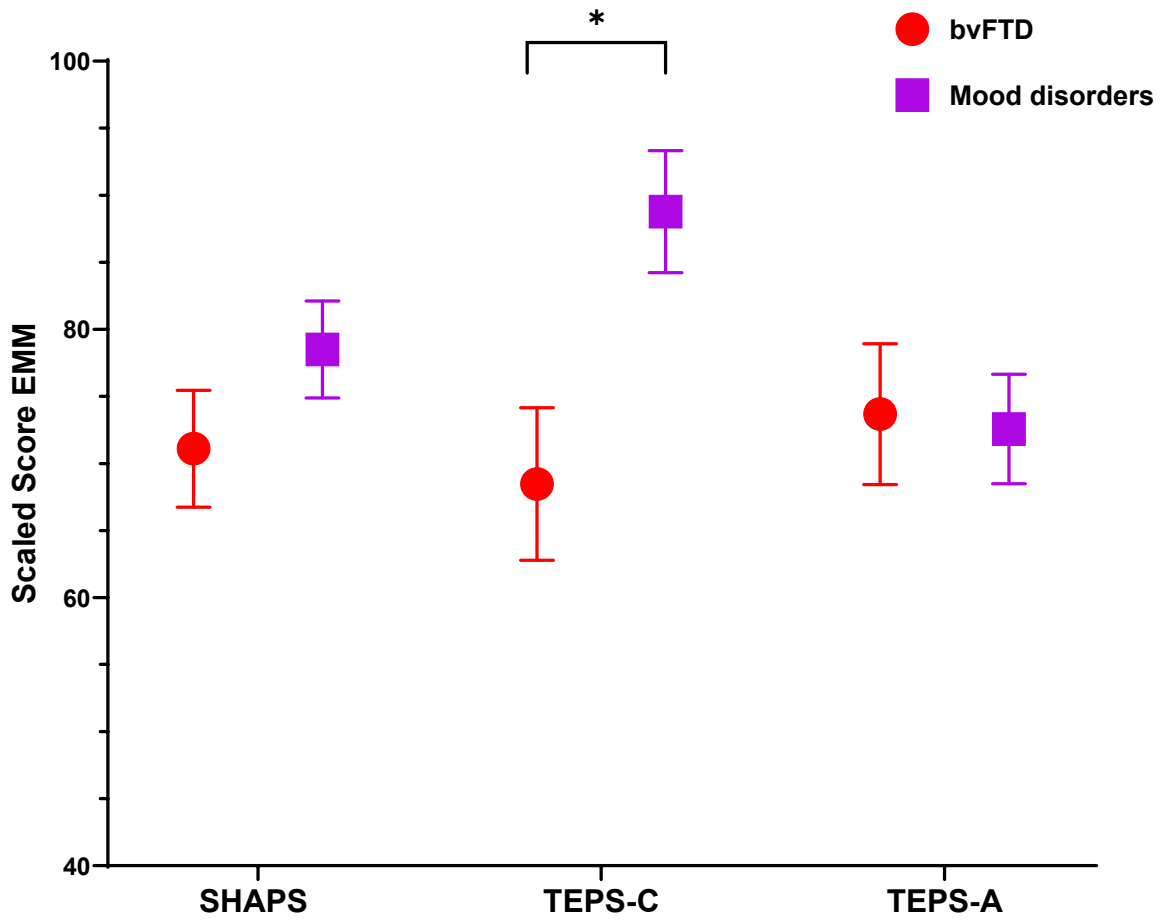


Figure 5.1. Severity of anhedonia in bvFTD and mood disorder group. Circles depict the estimated marginal means (EMM) of three separate ANCOVAs controlling for sex and age. Error bars indicate the SEM. SHAPS, TEPS-A and TEPS-C scores are percentage scores scaled relative to their respective control group with lower scores reflecting reduced hedonic tone/greater levels of anhedonia. bvFTD=behavioural variant frontotemporal, *n*=59; Mood disorders, *n*=80; SHAPS=Snaith Hamilton Pleasure Scale, TEPS-A=Anticipatory subscale of the Temporal Experience of Pleasure Scale; TEPS-C=Consummatory subscale of the Temporal Experience of Pleasure Scale. Asterisks denote results that emerged as significant in the analyses. *$p<.05$.

5.3.3. Item level analysis of the TEPS

We next conducted an item-level analysis to determine whether specific TEPS items contributed to the above group differences. All analyses were corrected for multiple comparisons using the Benjamini-Hochberg procedure. Item-level analyses (Table 5.1) revealed significant differences between the bvFTD and mood disorder groups on 4 of the 17 TEPS questionnaire items. Participants in the bvFTD group displayed significantly more severe anhedonia on 3 consummatory items: Item 2 (‘*The sound of crackling wood is very relaxing for me’*, $p<.001$, $PS=.73$), Item 4 (‘*I love the sound of rain on the windows when I am lying in a warm bed’,* $p<.001$, $PS=.70$), Item 5 (‘*The smell of freshly cut grass is enjoyable to me*, $p=.001$, $PS=.66$), as well as on one anticipatory item, Item 17 (‘*When ordering something off the menu, I can imagine how good it will taste’,* $p=.003$, $PS=.6$).

Table 5.1. Item-level analyses of the TEPS between bvFTD and mood disorder patients

TEPS item	Anhedonia construct	bvFTD[a] (n=58)	Mood disorders[a] (n=80)	U	*p* value	PS (0-1)
The sound of crackling wood in the fireplace is very relaxing	Consummatory	13/12/17/9	1/9/37/33	2973	**<.001**	0.73
I love the sound of rain on the windows when I'm lying in my warm bed	Consummatory	8/16/15/16	2/6/31/41	3060	**<.001**	0.70
The smell of freshly cut grass is enjoyable to me	Consummatory	13/16/14/11	5/11/38/26	2872	**.001**	0.66
I enjoy taking a deep breath when I walk outside	Consummatory	10/11/21/11	4/12/43/21	2536	.05	0.50
A hot cup of coffee or tea on a cold morning is very satisfying to me	Consummatory	3/7/21/26	9/12/33/26	1929.5	.114	0.42
I love it when people play with my hair or massage my head	Consummatory	19/12/14/11	13/13/30/24	2756.5	.02	0.62
I really enjoy the feeling of a good yawn	Consummatory	9/9/25/8	12/22/36/10	1778	.211	0.44
I appreciate the beauty of a warm sunset	Consummatory	8/11/22/16	12/7/37/24	2577	.186	0.57
When something exciting is coming up in my life, I really look forward to it	Anticipatory	7/12/19/20	3/7/56/14	2287.5	.886	0.49
When I think about eating my favourite food, I can almost taste how good it is	Anticipatory	7/16/16/14	4/14/40/22	2540	.05	0.60

I don't look forward to things like eating out at restaurants	Anticipatory	16/14/15/12	24/38/14/4	1768	.023	0.39
I get so excited the night before a major holiday I can hardly sleep	Anticipatory	17/18/14/9	25/30/21/4	1961.5	.115	0.42
When I think of something tasty like a piece of chocolate, I have to have some	Anticipatory	7/10/16/23	8/31/24/17	1761.5	.031	0.39
Looking forward to a pleasurable experience is in itself pleasurable for me	Anticipatory	12/13/22/10	5/10/51/14	2548	.234	0.56
I look forward to a lot of things in my life	Anticipatory	14/23/15/4	9/28/38/5	2596	.111	0.58
When ordering something off the menu, I imagine how good it will taste	Anticipatory	9/19/20/5	2/15/47/16	2762	**.003**	0.65
When I hear about a new movie starring my favourite actor, I can't wait to see it	Anticipatory	24/16/11/4	16/23/35/6	2732	.015	0.62

Note. [a]Number of participants in the group with responses of 0/1/2/3 on each item. Bolded values remain significant after FDR correction using the Benjamini and Hochberg method. bvFTD=behavioural variant frontotemporal dementia, PS=Probability of Superiority effect size, TEPS=Temporal Experience of Pleasure Scale.

5.3.4. Clinically significant anhedonia

We then wanted to determine whether the number of individuals with clinically significant levels of anhedonia (determined using the SHAPS) differed between bvFTD and a subset of the mood disorders sample who met current criteria for MDD (n=49; i.e., excluding those who were currently in partial remission). Currently, there is no established clinical cut-off for the continuous scoring of the SHAPS. For this study, a proxy threshold was determined, defining caseness as scores exceeding 1.96 standard deviations above the general population mean, based on data from the Trøstheim et al (2020) meta-analysis. Using this approach, a SHAPS score of 25 or higher was identified as indicative of clinical anhedonia symptoms (Alsayednasser et al., 2022).

Using this approach, 81% of the bvFTD sample and 71% of the MDD group met the criteria for clinically significant anhedonia (Table 5.2.). A Chi squared test did not reveal any significant differences between the proportion of clinically anhedonic individuals in the bvFTD and MDD groups (χ^2=1.6, *p*=.24).

Table 5.2. Number of individuals in each group with clinically significant anhedonia

	Anhedonic	**Not Anhedonic**	**Total**
BvFTD	47	11	58
MDD	31	13	43
Total	81	20	101

Note. Numbers represent the number of people exceeding the cut off for clinically relevant anhedonia(i.e., scores exceeding 1.96 standard deviations above the general population mean) based on data from the Trøstheim et al (2020) meta-analysis. bvFTD = behavioural variant frontotemporal dementia. MDD = Major depressive disorder.

5.3.5. Depression in bvFTD compared to the mood disorder sample

Firstly, differences in depression, as measured by the DASS-21 in the bvFTD group and on the BDI-II for the mood disorder groups were examined. A univariate ANCOVA

controlling for sex and age revealed no difference between the bvFTD and mood disorder group on their scaled depression scores [$F(1,129)=2.4$, $p=.13$, $\eta_p^2=.02$].

5.3.6. Clinically significant depression

We then wanted to determine whether the number of clinically depressed individuals differed between the bvFTD group and a subset of the mood disorders sample who met the current criteria for MDD and were not in remission (n=49). To do this we divided individuals into mild-minimal and moderate-severe depression based on categorical classification cut-offs of the BDI-II and DASS-D (see Table 5.3). A Chi squared test revealed significant differences between the number of clinically depressed individuals in the bvFTD and MDD group ($\chi^2=26.9$, $p<.001$). Specifically, significantly fewer bvFTD patients were classed as depressed (moderate – severe cut off) than not depressed (mild – minimal cut off; $p<.05$). Conversely, significantly more individuals with MDD were classed as depressed than not depressed ($p<.05$). This indicates that although the bvFTD and MDD groups showed comparable levels and prevalence of clinically significant anhedonia, they differed in the proportion of individuals meeting the criteria for clinically significant depression.

Table 5.3. Number of individuals in each group with clinically relevant depression.

	Mild-Minimal depression	**Moderate-severe depression**	**Total**
BvFTD	38	15	53
MDD	10	39	49
Total	48	54	102

Note. Numbers represent the number of people in each clinical category for depression. These categories were determined using the self-rated depression subscale of the Depression, Anxiety and Stress Scale for the bvFTD group and the Beck Depression Inventory for the MDD group. bvFTD=behavioural variant frontotemporal dementia. MDD=major depressive disorder.

5.4. Discussion

This exploratory study is the first to directly compare the prevalence and severity of anhedonia in individuals with bvFTD and individuals with mood disorders. Overall, our findings suggest that anhedonia is comparable in bvFTD and mood disorders in terms of overall prevalence and severity on the SHAPS yet differs in terms of anticipatory and consummatory dimensions. Specifically, bvFTDs demonstrated similar impairments in anticipating pleasure to a mood disorders sample, while individuals with mood disorders showed relatively preserved consummatory pleasure. Here, we consider how these findings contribute to understanding the clinical and diagnostic significance of anhedonia in bvFTD and mood disorders by examining its anticipatory and consummatory subcomponents.

5.4.1. Comparable prevalence and severity of overall anhedonia in bvFTD and mood disorders

Using the SHAPS as a global measure of hedonic capacity, we found comparable levels of anhedonia in bvFTD as that displayed by the mood disorders group. This is the first study, to our knowledge, to directly compare these clinical disorders and suggests that anhedonia is not solely a hallmark of mood disorders but also a prominent feature of bvFTD. While anhedonia has traditionally been linked to mood disorders, our findings highlight the urgent need to recognise its significance in bvFTD, where it appears equally severe. Notably, the proportion of individuals exhibiting clinically significant anhedonia on the SHAPS did not differ between the bvFTD (81%) and a MDD (71%) subgroup. This finding underscores the fact that anhedonia in bvFTD is not only comparable in severity to that in mood disorders but is also just as prevalent as in individuals diagnosed with MDD.

5.4.2. Differentiating bvFTD from MDD in terms of anhedonia subdimensions

We next deconstructed anhedonia into anticipatory and consummatory subcomponents on the TEPS. Interestingly we found comparable levels of anticipatory anhedonia in bvFTD and mood disorders suggesting that disruptions in the ability to anticipate pleasure may be a transdiagnostic feature of these conditions. This finding has important clinical implications, particularly in the early stages of bvFTD. Given that patients with bvFTD may stop looking forward to events and fail to express excitement at future pleasurable experiences, their symptoms could be misinterpreted as depression, leading to misdiagnosis. This diagnostic overlap is particularly concerning, as early-stage bvFTD patients may initially present with blunted affect and reduced motivation, traits commonly associated with mood disorders (American Psychiatric Association, 2022). Misdiagnosis could result in treatment with antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), which may not only be ineffective but could also exacerbate symptoms in bvFTD. SSRIs can increase apathy (Masdrakis et al., 2023) and blunt emotional responsiveness (Marazziti et al., 2019), potentially worsening the very symptoms they are intended to treat. Furthermore, inappropriate treatment could delay access to tailored interventions, such as behavioural or environmental strategies aimed at enhancing engagement and quality of life in bvFTD (Kortte & Rogalski, 2013; Vlotinou et al., 2023). The presence of anticipatory anhedonia in both bvFTD and mood disorders underscores the need for greater clinical awareness to prevent misclassification, treatment using inappropriate medication and ensure appropriate intervention.

Importantly, we found significant group differences in the severity of consummatory anhedonia, with bvFTD patients exhibiting greater impairments than individuals with mood disorders. Previous research has indicated that the primary deficit

in MDD lies in anticipatory pleasure rather than consummatory pleasure (Keren et al., 2018; Schulz et al., 2024), while our findings in Chapter 3 suggest that anhedonia dimensions may be universally impaired in bvFTD. Here, we extend on this work by suggesting that the ability to experience pleasure in the moment may be crucial in distinguishing bvFTD from mood disorders.

While our findings suggest a possible way to differentiate bvFTD from MDD, the underlying mechanisms driving such changes remain unclear. Previous research has linked anhedonia in FTD to atrophy in the orbitofrontal and medial prefrontal cortex (Shaw, El-Omar, Roquet, et al., 2021), regions crucial for reward consumption and hedonic processing (Horst & Laubach, 2013; Rolls, 2023). Degeneration in these areas may profoundly impact bvFTD patients' ability to experience pleasure in-the-moment.

It is also possible that heightened consummatory anhedonia in bvFTD reflects additional sensory processing alterations. Successful processing of salient sensory stimuli requires a number of subprocesses, accurately identifying relevant stimuli within the environment, representing sensory objects, evaluating their emotional and reward value, and integrating this information with physiological and motor responses to guide appropriate behaviour (Beissner et al., 2013; Critchley et al., 2000; Ng et al., 2021). In neurodegenerative conditions such as bvFTD, these processes become disrupted, leading to altered physiological, emotional and behavioural responses to salient sensory signals (Fletcher et al., 2015; Fletcher et al., 2015; Fletcher et al., 2015a, 2015b). Which are exemplified by the phenotypes of aberrant hedonic valuation and reward processing (Ahmed et al., 2018; Fletcher et al., 2015; Perry et al., 2014). Given that consummatory pleasure is closely linked to sensory experiences such as taste and smell, cognitive

impairments in bvFTD may interfere with the disambiguation of rewarding stimuli, thereby exacerbating consummatory anhedonia.

5.4.3. Sensory processing and pleasure deficits in bvFTD

In support of this hypothesis, our item analysis of the TEPS in bvFTD pointed to greater deficits on consummatory items that involve a sensory component, particularly those related to auditory and olfactory experiences. Specifically, bvFTD patients showed reduced pleasure in response to sound-related stimuli (e.g., *"The sound of crackling wood is very relaxing for me"*) and olfactory stimuli (e.g., *"The smell of freshly cut grass is enjoyable to me"*). Notably, this pattern was also evident in the anticipatory subscale of the TEPS, where bvFTD patients demonstrated impairments on an item related to gustatory imagery (*"When ordering something off the menu, I can imagine how good it will taste"*). These findings suggest a specific deficit in the capacity to derive pleasure from sensory experiences, extending beyond consummatory pleasure to the anticipation of sensory rewards. This profile of impairment in bvFTD, relative to mood disorders, supports the proposal that disruptions in sensory-affective processing (Jimenez et al., 2020; Marshall et al., 2019) may contribute to the more pronounced consummatory anhedonia observed in this group.

5.4.4. Is anhedonia in bvFTD independent of depression?

The high prevalence of clinically significant anhedonia in bvFTD raises an important question: to what extent might this symptom be driven by depression? While the present study examined depression using self-report tools (DASS-21 in bvFTD; BDI-II in mood disorders), it is important to distinguish between the presence of depressive symptoms and a formal diagnosis of MDD. A judgment of clinical depression cannot be

made solely based on rating scale scores, as these tools often capture overlapping features such as apathy and anhedonia that are core to bvFTD but not necessarily indicative of a depressive episode. This is especially pertinent in bvFTD, where behavioural symptoms may mimic those observed in MDD without fulfilling formal diagnostic criteria.

In the present study, although some individuals in the bvFTD group met the cut-off for moderate to severe depressive symptoms on the DASS, this should not necessarily be interpreted as a direct proxy for clinical depression. Rather, it reflects elevated endorsement of symptoms that may stem from neurodegenerative changes, not mood disturbance per se. Importantly, however, consistent with prior findings, anhedonia in bvFTD appears to occur in the absence of key MDD features, such as pervasive low mood or psychological distress, and has been shown to involve neural substrates distinct from those associated with depression (Shaw, El-Omar, Roquet, et al., 2021). The present findings support the view that anhedonia in bvFTD is not reducible to depressive symptomatology alone. While it remains possible that some patients may experience comorbid depression, the data suggest that in many cases, anhedonia reflects a syndrome-specific disruption in reward processing, independent of mood disorder pathology. Future research may benefit from identifying and excluding individuals with MDD-consistent features to create a “pure” non-depressed bvFTD subgroup, which would allow for further examination of whether similar anhedonic profiles persist in the absence of mood disturbance.

While differences in rating methods (self-report vs. carer-report) may have influenced the observed proportions of anhedonia and depression, it is also crucial to

consider that self-report measures in bvFTD may underestimate anhedonia. Given that bvFTD patients often exhibit limited insight into their own behavioural and emotional changes (Mendez & Shapira, 2011), their subjective reports may not fully capture the extent of their hedonic deficits.

5.4.5. Limitations

As a largely exploratory study, several limitations warrant consideration. A key challenge in comparing these groups stems from the inherent differences in syndrome profiles, age distributions, and underlying pathologies. While we scaled and matched variables as best as possible, future research would benefit from examining anhedonia within more precisely matched cohorts. First, differences in depression assessment across groups may have influenced the results. The use of non-identical measures for depression in the bvFTD and mood disorder samples may have captured slightly different aspects of depressive symptoms, potentially affecting direct comparisons. Future research should implement a standardised depression measure across both groups to confirm and refine these findings. Second, the age discrepancy between groups presents a further consideration. The mood disorder group primarily comprised younger adults (mean age=29), whereas the bvFTD group included middle-to-older aged (mean age=65) individuals. This raises the question of whether anhedonia presents differently across stages of the lifespan. Future studies incorporating age-matched comparisons, particularly with later-onset depression, would provide clearer insights into potential distinctions in anhedonia between neurodegenerative and primary mood disorders. Third, differences in the demographic composition of control groups may have introduced potential bias to the scaled scores and, consequently, influenced the group comparisons. Specifically, the bvFTD group was scaled to a control group that differed in

terms of several demographic variables, whereas the mood disorder group was scaled to a more demographically similar control group. Therefore, findings should be interpreted with caution, and future research using more closely matched control groups is warranted. Lastly, the reliance on carer-rated versus self-reported measures of anhedonia presents a methodological challenge, particularly given the observed differences in consummatory pleasure. Although we accounted for potential confounds such as carer depression and stress, assessing an individual's subjective experience of pleasure through a caregiver's perspective has its limitations. Outward expressions of enjoyment may not fully reflect internal hedonic experience, making it difficult to disentangle true anhedonic symptoms from affective blunting. Future research would benefit from incorporating objective or behavioural measures of hedonic responses, such as experience sampling methods or real-time physiological responses to rewarding stimuli, to complement carer ratings and enhance the validity of hedonic assessments.

It is important to acknowledge that 81% of the bvFTD sample and 71% of the MDD group met the criteria for clinically relevant anhedonia in this study. In contrast, a large-scale study of 440 individuals with MDD reported that 91% exceeded this cut-off (Alsayednasser et al., 2022), suggesting that anhedonia rates in our MDD sample may be slightly lower than those observed in larger cohorts. One potential explanation for this discrepancy lies in the recruitment strategy used for the mood disorder sample. Unlike typical clinical cohorts, this study specifically sampled individuals across the full reward learning spectrum, as determined by performance on a behavioural measure of reward learning, the Probabilistic Reward Task (see Whitton et al., 2021). This recruitment approach, which aimed to ensure a balanced distribution of reward learning abilities, may have resulted in the inclusion of individuals with MDD who exhibited relatively lower

levels of anhedonia compared to those in purely clinical samples. This discrepancy highlights the need for future research with larger and more representative samples to determine the generalisability of our findings and further clarify the prevalence and nature of anhedonia across these clinical populations.

5.4.6. Conclusion

This study suggests that anhedonia is highly prevalent and comparable in severity between bvFTD and mood disorders, yet differences in consummatory pleasure may help distinguish these conditions. While both groups exhibited similar impairments in anticipatory pleasure, individuals with bvFTD showed greater deficits in consummatory pleasure, particularly in sensory-driven experiences. Clarifying these underlying mechanisms is essential for refining differential diagnosis, especially in the early stages of bvFTD, where anhedonia-related symptoms may be misattributed to depression.

Chapter 6
General Discussion

Anhedonia is a critical predictor of poorer functional outcomes, increased disease burden, and diminished treatment response across neuropsychiatric conditions, often manifesting alongside motivational deficits such as apathy (Khazanov et al., 2020; Pizzagalli et al., 2022; Wong et al., 2024). While extensively studied in mood disorders, its presence, mechanisms, and impact in dementia remain underexplored (Turner & Husain, 2022). This thesis aimed to address this gap through four empirical studies. Firstly, Chapter 2 investigated the motivational profiles present across different dementia syndromes and their relationship to functional decline. This study revealed distinct motivational profiles within each dementia syndrome, with apathy and anhedonia differentially related to functional outcomes across patient groups. To further delineate the nature of anhedonia in dementia, Chapter 3 adopted a multidimensional approach to examine how anticipatory and consummatory anhedonia differ across dementia syndromes and how these differences related to changes in behaviour. Our findings uncovered syndrome-specific anhedonic profiles and demonstrated a role for anhedonia in specific behavioural changes. Chapter 4 explored the cognitive underpinnings of reward processing by investigating the relationship between anticipatory anhedonia and episodic future thinking in dementia. These results highlight the interplay between disrupted future-oriented cognition and reward processing deficits in dementia. Finally, adopting a transdiagnostic perspective, Chapter 5 compared the severity and prevalence of anhedonia in bvFTD and mood disorders. Despite similar levels of overall anhedonia, the groups diverged in several clinically meaningful ways. These findings contribute to a better understanding of reward dysfunction in dementia

and highlight the importance of considering anhedonia as a multidimensional and transdiagnostic symptom.

6.1. Key findings

This thesis advances our understanding of anhedonia in dementia by demonstrating that reward and motivational impairments manifest in distinct yet overlapping ways across dementia syndromes. By adopting a multidimensional framework, this work highlights how anticipatory and consummatory anhedonia can be dissociated in dementia and gives clues to possible underlying syndrome-specific cognitive mechanisms. Importantly, our findings reveal that anhedonia is not only a symptom of mood disorders but also a key driver of behavioural and functional changes in dementia, suggesting the need for more precise diagnosis and management of these syndromes. Additionally, this thesis provides novel evidence that cognitive processes, such as episodic future thinking, are associated with anticipatory anhedonia in dementia. This indicates that deficits in future-oriented cognition may contribute to the inability to anticipate pleasure, as individuals with bvFTD lack the capacity to mentally simulate positive future experiences. Collectively, these insights reinforce the need for a transdiagnostic approach to anhedonia, recognising its relevance across both psychiatric and neurodegenerative conditions and paving the way for improved diagnosis and symptom management.

6.2. Syndrome-specific profiles of anhedonia

A key finding of this thesis is that anhedonia and motivation manifest in distinct ways across dementia syndromes, indicating the potential presence of syndrome-specific differences in reward system dysfunction. While a multidimensional lens has

previously been applied to apathy in dementia (Wei et al., 2020), systematic exploration of anhedonia from a multidimensional framework had not yet been conducted. Here we demonstrate the importance of deconstructing anhedonia into its anticipatory and consummatory subcomponents.

Using this approach, we uncovered distinct anhedonic profiles in each dementia syndrome. First, bvFTD patients showed a global hedonic impairment, where pleasure was blunted both in-the-moment and in the anticipation of pleasure, reflecting a broad disruption of reward processing. SD patients displayed a global impairment but with a clear anticipatory > consummatory pattern, suggesting greater difficulty in projecting and anticipating future rewards than in experiencing in-the-moment pleasure. Finally, in AD, anticipatory anhedonia was evident, yet AD patients retained the capacity to experience pleasure in the moment. This finding supports a dissociation between 'wanting' (motivation) and 'liking' (hedonic experience; Berridge & Dayan, 2021), suggesting that while AD patients can experience pleasure in response to rewards, they are impaired in their ability to anticipate and motivate their behaviour towards future rewards. These findings provide critical insights into the clinical manifestations of reward dysfunction in dementia, which in turn raises important questions about the potential cognitive and neural mechanisms that drive such profiles. We next consider possible mechanisms of anhedonia in each of the dementia syndromes of interest.

6.2.1. Cognitive drivers of anticipatory anhedonia

Theories of affective forecasting suggest that the ability to anticipate pleasure in the future is considerably more cognitively demanding than experiencing pleasure in response to an immediate reward. Anticipatory pleasure requires a combination of

cognitive processes, including episodic future thinking, reward processing, and internally generated thought (D'Argembeau et al., 2010; Gard et al., 2006; Schacter et al., 2017; Strauss et al., 2011), all of which are impaired in dementia (Irish & Piolino, 2016; Kvavilashvili et al., 2020; O'Callaghan et al., 2019; Perez et al., 2022). Therefore, cognitive impairments specifically in generating, mentally simulating and maintaining a future event and its associated pleasure, may contribute to create a predominantly anticipatory anhedonic profile, irrespective of dementia subtype.

In partial support of this hypothesis, we provided the first preliminary evidence to implicate episodic future thinking dysfunction as a potential cognitive mechanism contributing to anticipatory anhedonia. Specifically, we found that individuals with dementia generated significantly less detailed future events compared to controls, and the severity of these deficits was closely associated with anticipatory anhedonia. Deficits in episodic future thinking prevent individuals with dementia from constructing vivid and emotionally salient future scenarios, likely making it difficult to generate motivation for rewarding activities. This impairment was particularly evident in SD, where anticipatory anhedonia was disproportionate relative to consummatory anhedonia. Damage to anterior temporal regions in SD results in profound semantic knowledge deficits, which in turn severely disrupts the capacity for episodic and semantic future simulation (Irish et al., 2012a). This severe semantic loss means that patients lose access to structured representations of typical events, making it difficult to anticipate their associated pleasure. For example, if a patient with SD no longer has a script for a "birthday party" or a "trip to the zoo," they lack the fundamental scaffold necessary to anticipate the pleasure and emotional significance of these experiences. Without access to these

structured representations, future events become decontextualised and devoid of meaning, further exacerbating anticipatory anhedonia.

In bvFTD, cognitive impairments extend beyond future simulation deficits to executive dysfunction, emotional blunting, and a loss of insight, all of which may compromise reward anticipation. Patients with bvFTD show severe impairments in endogenously driven cognition (O'Callaghan et al., 2019), meaning they are unable to internally generate thoughts about potential future rewards, making it difficult to engage in self-directed reward-seeking behaviour. Deficits in spontaneous thought generation, prevent individuals with bvFTD from initiating mind-wandering or internally guided future thinking. Instead, they remain anchored to the external environment, unable to construct or sustain representations of internally generated rewards (O'Callaghan et al., 2019). Given that introspection is severely disrupted in bvFTD (Hazelton et al., 2023), patients may find it particularly difficult to anticipate future pleasure, as this process relies on an ability to reflect on one's own mental state and project forward in time. Collectively, these difficulties would compromise the capacity to generate and sustain internally guided thoughts that support goal-directed action (Szczepanski & Knight, 2014). Without these self-generated representations of future rewards, individuals with bvFTD may exhibit a passive and disengaged behavioural profile, further exacerbating their motivational impairments. Together, these findings suggest that cognitive disruptions compromise the ability to anticipate, plan, and seek out rewarding experiences in FTD.

In AD, anticipatory anhedonia may arise from a combination of executive dysfunction and episodic memory impairment. Similar to bvFTD, cognitive processes which drive the imagining, planning and evaluating of future rewards, are particularly

vulnerable in AD and likely contribute to anticipatory anhedonia (Chu et al., 2024; McKhann et al., 2011; R. S. Wilson et al., 2012). A core feature of AD is progressive episodic memory loss (McKhann et al., 2011), which has profound implications for future-oriented cognition. Constructing vivid, emotionally salient future scenarios depends on the ability to draw upon past rewarding experiences as a template for what to expect. However, if individuals with AD cannot recall previous pleasurable experiences, they lack the necessary foundation to simulate and anticipate similar rewards in the future. For example, if an AD patient does not remember the joy of a past birthday party, they may be unable to imagine, plan for or feel motivated to attend another one in the future. Another possibility is that executive dysfunction, rather than episodic memory impairment, contributes to anticipatory anhedonia in AD. However, the strong relationship between reduced episodic detail in both past and future events and anticipatory anhedonia suggests that memory deficits play a more prominent role. Without access to rich autobiographical memories, individuals with AD lack the experiential framework needed to simulate and anticipate future rewards.

Together, these findings highlight distinct but overlapping cognitive mechanisms underlying anticipatory anhedonia in dementia and provide a cognitive framework for understanding the motivational deficits observed across dementia syndromes.

6.2.2. Neural substrates underlying a disrupted experience of pleasure

Understanding how neural atrophy differentially impacts anticipatory and consummatory pleasure is beyond the scope of the current thesis. However, this remains an important direction for future research, as it is essential for refining neurobiological

models of reward dysfunction and identifying potential therapeutic targets tailored to syndrome-specific impairments.

The global hedonic impairment in bvFTD may be driven by widespread atrophy in fronto-subcortical circuits, including the orbitofrontal cortex, ventromedial prefrontal cortex, and striatum, all of which are critical for reward processing (Bertoux et al., 2015; Eldaief et al., 2023; Murley & Rowe, 2018; Nguyen et al., 2021). Damage to these regions may disrupt the integration of reward-based information, contributing to both anticipatory and consummatory anhedonia in bvFTD. In SD, the heightened impairment in anticipatory pleasure relative to consummatory pleasure may stem from pronounced neurodegeneration in the anterior temporal lobes, including the amygdala and associated limbic structures which are crucial for generating mental representations of future events and anticipating emotional outcomes (Šimić et al., 2021; Tyng et al., 2017). Critically, damage to these regions also disrupts semantic knowledge (Hodges & Patterson, 2007; Mion et al., 2010), further impairing the ability to construct meaningful future scenarios and predict rewarding experiences, contributing to greater deficits in anticipatory anhedonia. Finally, the preservation of consummatory pleasure in AD may be due to the characteristic pattern of atrophy in AD. Neurodegeneration in AD primarily affects the hippocampus and parietal regions, while sparing key areas of the reward system, such as the striatum (Chapleau et al., 2016; Halabi et al., 2013). However, longitudinal neuroimaging studies have demonstrated that as AD pathology advances, the striatum becomes increasingly vulnerable to atrophy (Planche et al., 2022). The preservation of consummatory pleasure observed in the current study likely reflects the early disease stage of the AD sample, when striatal integrity remains relatively intact. As the disease progresses and striatal atrophy becomes more pronounced, corresponding

declines in consummatory pleasure might be expected. Thus, while early-stage AD patients may not present with consummatory anhedonia, longitudinal studies will be required to track the evolution of this component of anhedonia over time.

6.3. The functional implications of anhedonia in dementia

Anhedonia is increasingly recognised as a key contributor to functional decline in psychiatric disorders, yet its role in dementia remains underexplored. This thesis is the first to identify anhedonia, alongside executive and initiation apathy, as a predictor of functional decline in SD. These findings align with previous research demonstrating that anhedonia is a significant predictor of poorer functional outcomes in MDD (Wong et al., 2024). The inability to experience pleasure, coupled with difficulty in initiating and generating rewarding mental imagery, may contribute to the rigidity and functional decline commonly observed in SD. The interplay between diminished reward anticipation and executive dysfunction may restrict engagement in novel or adaptive behaviours, further exacerbating impairment in daily functioning (Horne & Irish, 2023).

Although apathy was a strong predictor of functional decline in AD and bvFTD, this thesis highlights a critical role for anhedonia as an early clinical feature, particularly in bvFTD where it was related to changes in eating, self-care and motivation. In AD, anhedonia was associated with declines in motivation, self-care and mood, further implicating it as a key factor in behavioural changes. Although the precise mechanisms underlying these associations remain unclear, multiple factors (e.g. disrupted future thinking, planning and goal-directed behaviour) likely contribute and warrant further investigation. These findings reinforce the need to recognise anhedonia as a core

symptom of dementia, particularly bvFTD, and to incorporate it into early diagnostic frameworks and targeted interventions.

6.4. Differentiating bvFTD from other neuropsychiatric disorders

Comparing anhedonia in bvFTD to mood disorders, like MDD, provides a unique opportunity to elucidate overlapping and distinct clinical features. Both conditions share symptoms such as lack of interest, decreased motivation, low energy, and impaired concentration (Urban-Kowalczyk et al., 2022). In bvFTD, the most common initial manifestations are apathy, loss of interest, lack of initiative and inactivity, with a clinical picture often misinterpreted as MDD (Cardarelli et al., 2010). Consequently, approximately 50% of bvFTD patients are initially diagnosed with primary psychiatric disorders such as MDD rather than a neurodegenerative disease (Tanaka et al., 2020).

Accurate differentiation of bvFTD from neuropsychiatric syndromes is critical due to distinct differences in their underlying pathology, prognoses, treatment approaches, and caregiver needs (Woolley et al., 2011). Misdiagnosis of FTD delays appropriate care, increases financial burden and exacerbates emotional distress for families (Chow et al., 2011; reviewed by Giebel et al., 2024). Notably, despite similar proportions of clinically significant anhedonia between the bvFTD and MDD groups, clinically significant depression was far more prevalent in the MDD sample. This finding challenges the hypothesis that anhedonia in bvFTD merely reflects co-occurring depressive symptomatology. Instead, it suggests that anhedonia may be dissociable from depression in bvFTD, supporting the need for a transdiagnostic approach to understanding anhedonia.

Critically, our findings suggest that assessing multidimensional anhedonia profiles could facilitate more accurate diagnosis of bvFTD, particularly given the pronounced consummatory anhedonia observed in this group compared to mood disorders. These impairments seemed most pronounced for sensory-related experiences such as enjoying the taste or smell of food. This is particularly noteworthy, as altered eating behaviours are a hallmark feature of bvFTD (Rascovsky et al., 2011) and findings from this thesis suggest that both anticipatory and consummatory anhedonia may contribute to these disruptions. This highlights anhedonia as a potential critical early marker of bvFTD, one that occurs well in advance of other behavioural changes. It is possible that anhedonia emerges early, operating in the background from the onset of neurodegeneration and subtly driving behavioural disruptions from the start. In line with this theory, studies have shown bvFTD patients presented with psychiatric symptoms on average 4.6 years prior to diagnosis (Solje et al., 2015). Greater attention to these early hedonic changes could facilitate earlier detection and improve diagnostic accuracy.

6.4.1. The need for improved assessment tools in dementia

While these findings offer valuable insights, they also point to the need for improved assessment tools to ensure we capture the specific clinical presentations of anhedonia in dementia populations. Many existing measures of anhedonia were developed for use in mood disorders, targeting populations that are typically younger, have intact insight, show no cognitive decline and function independently in the community. These tools often rely on self-report measures that assume a level of introspection and cognitive capacity that may not be present in dementia. In contrast, bvFTD is a neurodegenerative syndrome that typically emerges in mid-to-late adulthood and leads to progressive deterioration in motivation, insight, and behavioural regulation.

Carers often modify the patient's environment, limiting activities due to safety concerns and behavioural changes. Standard anhedonia measures fail to account for these real-world constraints, as well as the distinct motivational and sensory alterations observed in bvFTD, leading to potential underestimation or mischaracterization of motivational deficits in this population.

6.5. Theoretical implications

6.5.1. Theoretical models of pleasure and the dual-process perspective

A key contribution of this thesis is the empirical support for dual-process models of pleasure (Berridge & Dayan, 2021; Berridge & Kringelbach, 2015). These models propose two distinct but interacting systems: the 'liking' system, which is responsible for consummatory pleasure and the 'wanting' system, which drives anticipatory pleasure and motivational salience. The findings presented in this thesis align with this framework by demonstrating distinct patterns of anticipatory and consummatory anhedonia across dementia syndromes. In particular, the preservation of consummatory pleasure despite severe anticipatory anhedonia in AD suggests a selective impairment in the 'wanting' system rather than a global hedonic deficit. Importantly, by studying these processes in neurodegenerative disorders, our findings challenge the unitary conceptualisation of anhedonia.

6.5.2. Toward a transdiagnostic framework of anhedonia

Traditionally, anhedonia has been conceptualised as a hallmark symptom of mood disorders. However, its presence in dementia suggests a shared neurobiological foundation across disorders. This perspective aligns with the Research Domain Criteria (RDoC) framework, which advocates for dimensional approaches that examine symptom

domains across conditions rather than relying on categorical disorder classifications (Cuthbert & Insel, 2013). This thesis contributes to this transdiagnostic shift by demonstrating both commonalities and distinctions in anhedonia across neuropsychiatric and neurodegenerative conditions. Both bvFTD and MDD groups demonstrated anticipatory anhedonia yet bvFTD was associated with greater sensory-related consummatory anhedonia. Furthermore, the presence of anhedonia in bvFTD without sustained low mood suggests that anhedonia can exist independently of depressive affect, reinforcing the need for a more precise symptom-based classification system. Moving beyond categorical disorder labels and towards symptom dimensions informed by neurobiology may improve both diagnostic precision and treatment approaches. Additionally, the integration of cognitive factors, such as episodic future thinking deficits, into transdiagnostic models of anhedonia may offer new insights into how reward processing is disrupted across psychiatric and neurodegenerative conditions.

6.5.3. Integrating models of motivation into mainstream neuropsychiatry

Neurodegenerative disease research has traditionally remained separate from mainstream psychiatric models of motivation and reward. This thesis underscores the need for cross-disciplinary integration to refine our understanding of anhedonia. Insights from dementia research can enhance neuropsychiatric models in several ways. Unlike mood disorders, where anhedonia is often confounded by depressive symptoms, some FTD cases could provide a prominent anhedonic phenotype, devoid of sustained low mood and depression. Moreover, disease progression in dementia offers unique insights into how reward-processing networks deteriorate over time, allowing for the development of dynamic models of anhedonia. Additionally, mapping atrophy patterns

to specific reward deficits in dementia may help refine psychiatric models, particularly in disorders where clear neuroanatomical correlates of anhedonia are less evident. The findings from this thesis suggest that reward system dysfunction in dementia is not merely a late-stage consequence of neurodegeneration but instead follows distinct trajectories shaped by syndrome-specific pathological changes.

6.5.4. Reconciling the literature on future thinking and anhedonia

Traditional models of anhedonia have primarily focused on reward system dysfunction without fully considering the cognitive mechanisms that support motivation and reward anticipation. This thesis highlights episodic future thinking as a potential cognitive driver of anticipatory anhedonia, particularly in FTD. The inability to construct vivid, detailed, emotionally salient simulations of positive future events may contribute to a reduced expectation of pleasure, ultimately dampening motivation and goal-directed behaviour. These findings align with emerging research suggesting that deficits in future thinking contribute to reward dysfunction in psychiatric disorders (Guo et al., 2022; Hallford et al., 2020). By demonstrating that episodic future thinking impairments are associated with anhedonia in FTD, this work extends theoretical models of reward dysfunction beyond psychiatric disorders to neurodegenerative disease.

Whether anhedonia represents a transdiagnostic symptom across bvFTD and mood disorders remains an open question. While both conditions share disruptions in reward anticipation, the underlying mechanisms appear to differ. In bvFTD, anhedonia may primarily stem from cognitive impairments, such as deficits in future thinking and spontaneous thought generation, whereas in mood disorders, it is more closely tied to dysregulated reward circuitry. This suggests that anhedonia in these conditions may be

better conceptualised as a case of equifinality, where the same clinical endpoint, anhedonia, is reached through distinct pathological pathways.

Taken together, these findings raise several interesting theoretical questions. Is anticipatory anhedonia in dementia primarily driven by cognitive dysfunction, such as impairments in future thinking, or do disruptions in reward circuitry also play a role? Which brain regions are crucial in the development of anhedonia, and can we develop new assessment protocols that are sensitive and suitable for use in dementia populations?

In addition to the prospective components of future thinking, the process of remembering and emotionally re-engaging with past rewarding experiences, known as savouring, may also play an important role in how individuals anticipate future pleasure. The capacity to draw on richly encoded past events is thought to support the construction of future scenarios (Schacter et al., 2007), providing affective detail and motivational salience (Bowen & Madan, 2025). In this context, anhedonia may reflect not only a failure to imagine pleasurable futures but also a diminished capacity to re-experience and derive value from previously rewarding events. This has implications for how individuals complete measures of anticipatory pleasure, such as the TEPS, as responses may be shaped as much by remembered affect as by imagined reward. Disruption to autobiographical memory in dementia likely undermines both these components, weakening the foundation from which future pleasure can be simulated.

6.6. Clinical Implications

Understanding how anhedonia manifests differently across dementia syndromes has important implications for treatment strategies, particularly the need for individualised

interventions rather than a one-size-fits-all approach. This thesis demonstrated that apathy and anhedonia differentially predict functional outcomes across dementia syndromes. Recognising these differences is important for designing interventions tailored to the specific motivational deficits of each patient. Apathy-driven impairments may require external motivational support (e.g., structured prompting, help generating ideas), while anhedonia-related impairments may benefit from sensory-driven hedonic engagement strategies or scaffolding to support episodic future thinking for positive events.

In terms of functional implications, this thesis highlighted a relationship between anhedonia and compromised performance of several everyday activities, though the directionality of this relationship remains unclear. Future research should explore whether improving dementia patients' ability to perform tasks such as self-care behaviours can, in turn, enhance their capacity for pleasure and engagement in everyday life. Interventions such as environmental modifications to simplify routines and reduce cognitive load may help mitigate barriers to engaging in pleasurable activities (Woodbridge et al., 2018).

6.6.1. Leveraging sensory-based therapies in dementia

Given the relative preservation of consummatory pleasure in AD, interventions that capitalise on immediate sensory experiences may be more effective. In particular music and art therapy have shown promise in stimulating in-the-moment pleasure responses, even in advanced dementia (Cowl & Gaugler, 2014; Popa et al., 2021b). These interventions bypass the need for cognitive planning or anticipation, engaging intact hedonic circuits directly and may be effective in promoting motivation in AD patients.

6.6.2. Addressing stereotypical behaviours and rigidity in SD

Patients with SD exhibit high levels of anticipatory anhedonia and a reduced ability to generate detailed novel future scenarios which may contribute to rigid, stereotypical behaviours (Horne & Irish, 2023). Targeted interventions could focus on gradually introducing small variations into patients' routines to promote behavioural flexibility and expand their behavioural repertoire. For example, behavioural activation techniques that encourage engagement in rewarding activities may help disrupt the cycle of stereotypical behaviours. One study demonstrated the effectiveness of using a lollipop as a novel intervention to reduce stereotypical vocally disruptive behaviours in an FTD patient (Kennedy et al., 2023). This highlights the potential of creative, individualised strategies for managing challenging symptoms. Caregivers might similarly introduce novel, non-threatening experiences in controlled environments, such as trying new foods or engaging in activities with low cognitive demand. By slowly expanding the range of activities, patients may re-engage with pleasure in everyday life, thereby improving both anhedonia and behavioural flexibility. Clinically, this thesis also shows that intact episodic memory supports valence-driven engagement in SD which could be leveraged in therapeutic interventions. For example, encouraging SD patients to recall and engage with previous pleasurable memories through reminiscence therapy might help motivate current behaviour and ultimately enhance well-being (Woods et al., 2018).

6.6.3. Applicability of behavioural activation therapy in dementia

Individuals with dementia exhibit significant impairments in episodic future thinking, making it difficult for them to generate detailed, spontaneous representations of future events (Irish et al., 2013). In contrast, while individuals with MDD often retain the ability to construct future events, their future thinking is negatively biased and less

specific, affecting their anticipation of pleasure (Hallford, 2019; MacLeod & Byrne, 1996; Tang et al., 2023). Recognising these differences is crucial for tailoring interventions. Behavioural Activation Therapy, widely used in depression, encourages individuals to engage in activities they anticipate enjoying (Veale, 2008). The therapy follows a structured process: patients schedule an activity, predict their level of enjoyment, engage in the activity, and then reflect on their actual experience (Veale, 2008). This reinforcement cycle relies heavily on prospective thinking and reinforcement learning. However, given the severe impairments in generating positive future scenarios in dementia demonstrated in this thesis, the traditional behavioural activation model may be less effective. Instead, alternative approaches such as externally guided prospection may be more beneficial (Hallford et al., 2022). Given that self-initiated future thinking is impaired, interventions that provide structured prompts or external guidance could help patients engage with rewarding activities. Additionally, introducing structured variations in daily routines with external support may help stimulate engagement without relying on the patient's ability to generate and anticipate future rewards.

6.7. Methodological considerations

Assessing subjective experiences such as anticipatory and consummatory pleasure presents significant methodological challenges, particularly in dementia populations. Traditional self-report measures rely on introspection, memory recall, and linguistic comprehension, all of which may be compromised in neurodegenerative conditions. Measures such as the TEPS-A subscale is cognitively demanding as it requires participants to imagine and evaluate hypothetical scenarios, such as anticipating the enjoyment of a beach holiday. For individuals with SD, semantic impairments, such as difficulties interpreting the word "beach" and an inability to

construct mental representations of such scenarios, likely inflate their scores of anticipatory anhedonia. In contrast, the TEPS-C subscale, which captures in-the-moment pleasure, relies more on immediate sensory or emotional experiences and imposes fewer cognitive demands.

Beyond these cognitive challenges, the TEPS may not exclusively measure anticipatory pleasure as intended. Some items involve abstract concepts that most likely elicit an appraisal of one's current functioning rather than just the capacity to anticipate pleasure from future events. This issue is particularly pronounced in dementia, where environmental limitations, such as restricted activities, loss of independence, and caregiver-imposed constraints, drastically shape daily experiences of pleasure. Unlike individuals with MDD, who may have access to a wider range of activities but lack motivation to engage, dementia patients may be physically or socially restricted from engaging in pleasurable experiences altogether. These real-world constraints further complicate the interpretation of anhedonia scores, as lower pleasure ratings may stem from limited opportunities in addition to reward processing disturbances.

Additionally, the TEPS refers to concrete activities which may not be contextually relevant for all respondents (e.g., "*When I'm on my way to an amusement park, I can hardly wait to ride the roller coasters*"). Such examples assume certain life experiences and cultural contexts, which may not be applicable across different age groups, cognitive profiles, or care settings. These speak to the broader issue of are we truly measuring "in-the-moment" experiences of pleasure through self-report questionnaires? By design, questionnaires require participants to recall a past event (e.g., eating their favourite meal), internally reflect on how they felt at the time, and then provide an emotional

appraisal rating. This indirect nature of measurement raises questions about whether consummatory pleasure can ever be fully captured using retrospective self-report methods. Importantly, this limitation is further exacerbated in dementia, where self-report is replaced by carer ratings. Carers must observe and recall outward behaviours of the person with dementia, interpreting whether pleasure was experienced. This additional layer of subjective interpretation introduces further potential bias and measurement error, highlighting the challenge of how best to assess these constructs objectively.

Future research should prioritise the development of more ecologically valid assessment methods, such as real-time behavioural observations, experience sampling techniques, and physiological markers of pleasure responses. By moving beyond traditional questionnaire-based assessments, we may develop a more accurate and comprehensive understanding of anhedonia and reward dysfunction in dementia.

Given our findings of differential anticipatory and consummatory anhedonia profiles in dementia, future research could utilise personally relevant emotional stimuli to enhance ecological validity of anhedonia assessments. Instead of relying solely on abstract scenarios, a novel experimental paradigm could investigate real-time hedonic experience using personally relevant stimuli. For example, family photographs, favourite meals or scents, music or personally significant objects could be used to examine dynamic hedonic responses. Combining these stimuli with real-time neural imaging (fMRI) and physiological markers (e.g., heart rate variability, pupil dilation) would allow for a more objective measure of consummatory pleasure than retrospective questionnaire data, reducing potential recall biases. Future research could compare

spontaneous vs. cued episodic simulation in bvFTD and mood disorders to further disentangle anhedonia and future thinking deficits in the two groups. This would help deepen our understanding of the commonalities and differences underlying both anhedonia and future thinking in mood disorders and dementia.

In addition to improving ecological validity, future research could consider alternative methods of assessing episodic future thinking that move beyond narrative-based paradigms. For example, future thinking fluency tasks, which ask individuals to generate multiple future events within specific timeframes, can provide a measure of generativity and temporal organisation without requiring detailed episodic elaboration. Likewise, dimensions such as sensorial vividness and emotional richness of imagined events may offer important insights into the qualitative aspects of future simulation and how these relate to anticipatory anhedonia.

Furthermore, a consistent challenge in this thesis lies in differentiating depressive symptoms from clinically diagnosed depression in individuals with bvFTD. While measures such as the DASS were used to assess depressive symptom severity, these tools do not provide a clinical diagnosis of MDD. This distinction is critical, as symptoms such as apathy and anhedonia may be misinterpreted as indicators of mood disturbance in bvFTD. As such, elevated depression scores on rating scales may reflect neurodegenerative changes rather than a comorbid depressive episode. The extent to which depressive symptoms may confound interpretations of anhedonia in FTD remains an important consideration. Future research should aim to incorporate standardised diagnostic interviews or exclude participants with key MDD features to better isolate the syndrome-specific nature of anhedonia in bvFTD. This would help clarify whether the

observed anhedonic deficits reflect intrinsic disease processes or are influenced by co-occurring mood disorders.

Finally, an important limitation across the studies presented in this thesis is the relatively small sample size, particularly within the dementia subgroups. While consistent with typical sample sizes in neurodegenerative research, the modest numbers limit the generalisability of the findings and reduce the power to detect more subtle effects. This is especially relevant for subgroup comparisons and correlation analyses, where meaningful effect sizes may not have reached statistical significance due to low power. As such, findings, particularly those reporting null effects, should be interpreted with caution, as some may reflect Type II errors rather than the true absence of an association. Replication in larger, well-powered cohorts will be essential to confirm and extend these results.

6.8. Concluding remarks

This thesis has provided an in-depth exploration of anhedonia in dementia, offering new insights into how its multidimensional nature manifests across dementia syndromes. Crucially, these findings highlight the role of anhedonia in functional decline and behavioural disturbances, underscoring the need to consider anhedonia as an important clinical symptom in dementia. Evidence presented in this thesis also reveals a link between episodic future thinking and anticipatory anhedonia, shedding light on the cognitive mechanisms that may underpin reward dysfunction in dementia. These novel findings have important implications for targeted interventions, providing clinicians with new evidence to help enhance goal-directed behaviour and motivation. By informing and guiding interventions, this research ultimately aims to improve the quality of life of both

individuals with FTD and their caregivers, helping to promote more meaningful engagement and hopefully greater enjoyment of the little things in life.

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Appendix

Chapter 2

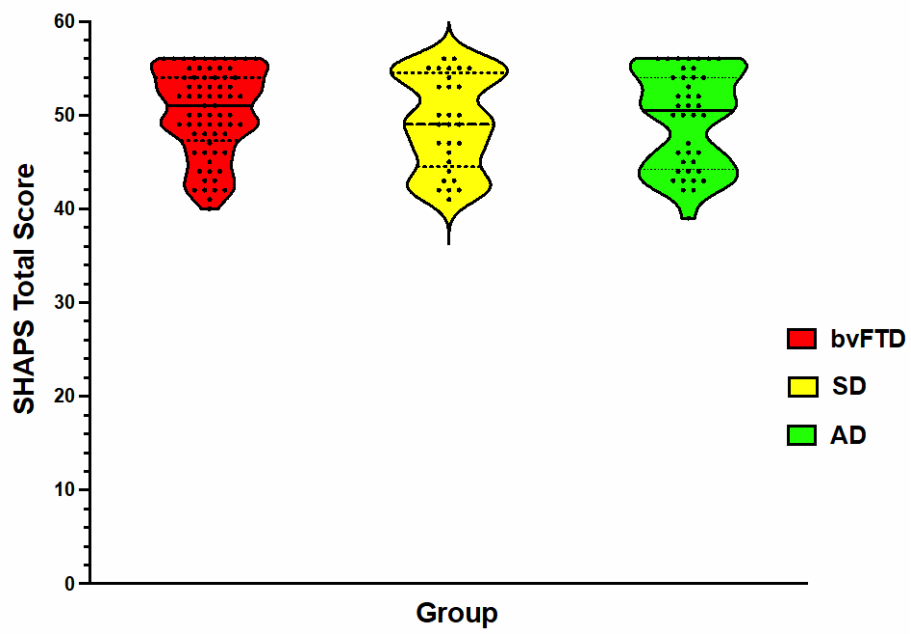
Appendix Table 2.1 Tests of normality for main study variables of interest

	bvFTD (n=58)	**SD (n=30)**	**AD (n=42)**
Anhedonia	.06	.57	.10
Executive apathy	.09	.19	.08
Emotional apathy	.26	.28	.65
Initiation apathy	.07	.34	.07
FRS	.08	.50	.39

Note. Shapiro-Wilks tests of normality were conducted to determine whether data for the main study variables of interest were normally distributed. Anhedonia severity was measured using the Snaith-Hamilton Pleasure Scale (SHAPS) whilst apathy was measured using the Dimensional Apathy Scale (DApS). AD=Alzheimer's disease; bvFTD=behavioural variant of frontotemporal dementia; FRS=Frontotemporal Dementia Functional Rating Scale; SD=semantic dementia.

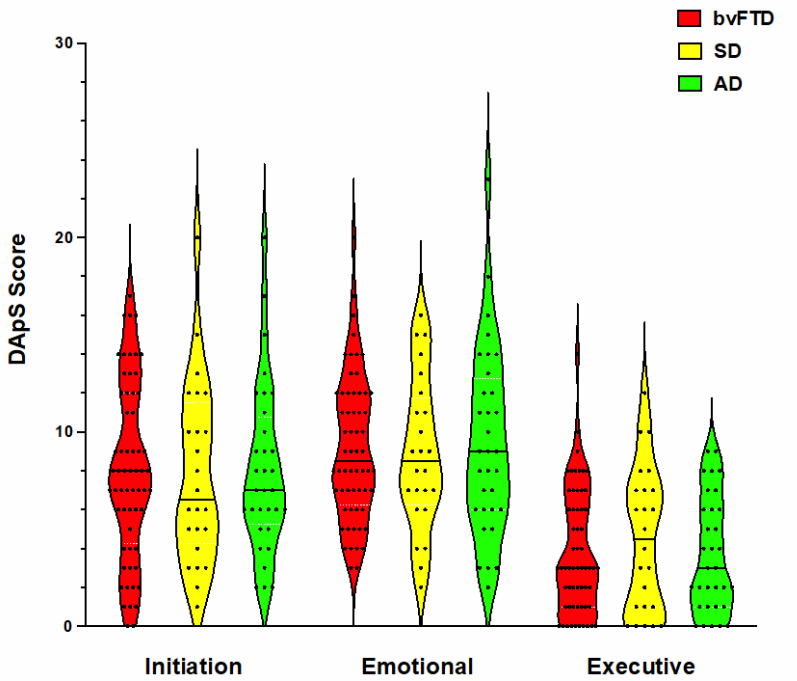
Appendix Section 2.2.8 Pre-morbid ratings of anhedonia and apathy severity in dementia.

Importantly, a univariate ANCOVA controlling for sex, disease duration, and overall level of cognitive dysfunction on the ACE-III revealed no significant group differences in terms of carer-rated premorbid levels of anhedonia [$F(2,137)=.34$, $p=.71$, $\eta_p^2=.005$].

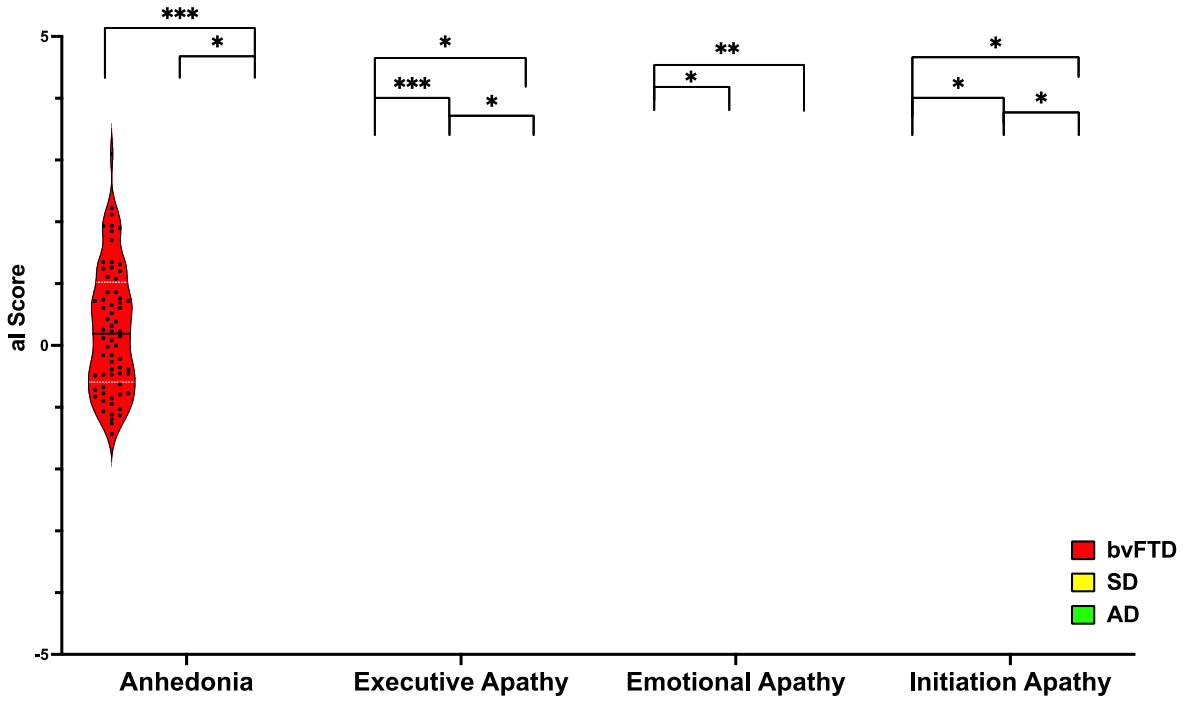


Appendix Figure 2.1 Premorbid ratings of anhedonia in dementia syndromes as rated by carers on the Snaith-Hamilton Pleasure Scale (SHAPS). Violin plots depict the distribution of data with the width of the shaded area representing the proportion of data located there. Bolded horizontal line depicts the median, while dotted lines depict quartiles. AD=Alzheimer's disease (n=43); bvFTD=behavioural variant of frontotemporal dementia (n=68); SD=semantic dementia (n=32)

Importantly, the dementia groups did not differ in terms of carer-reported levels of premorbid executive [$F(2,120)=.88$, $p=.45$, $\eta_p^2=.022$], emotional [$F(2,120)=.57$, $p=.63$, $\eta_p^2=.014$] or initiation [$F(2,120)=.11$, $p=.96$, $\eta_p^2=.003$] apathy as determined by separate ANCOVAs controlling for sex, disease duration, and overall level of cognitive dysfunction on the ACE-III.

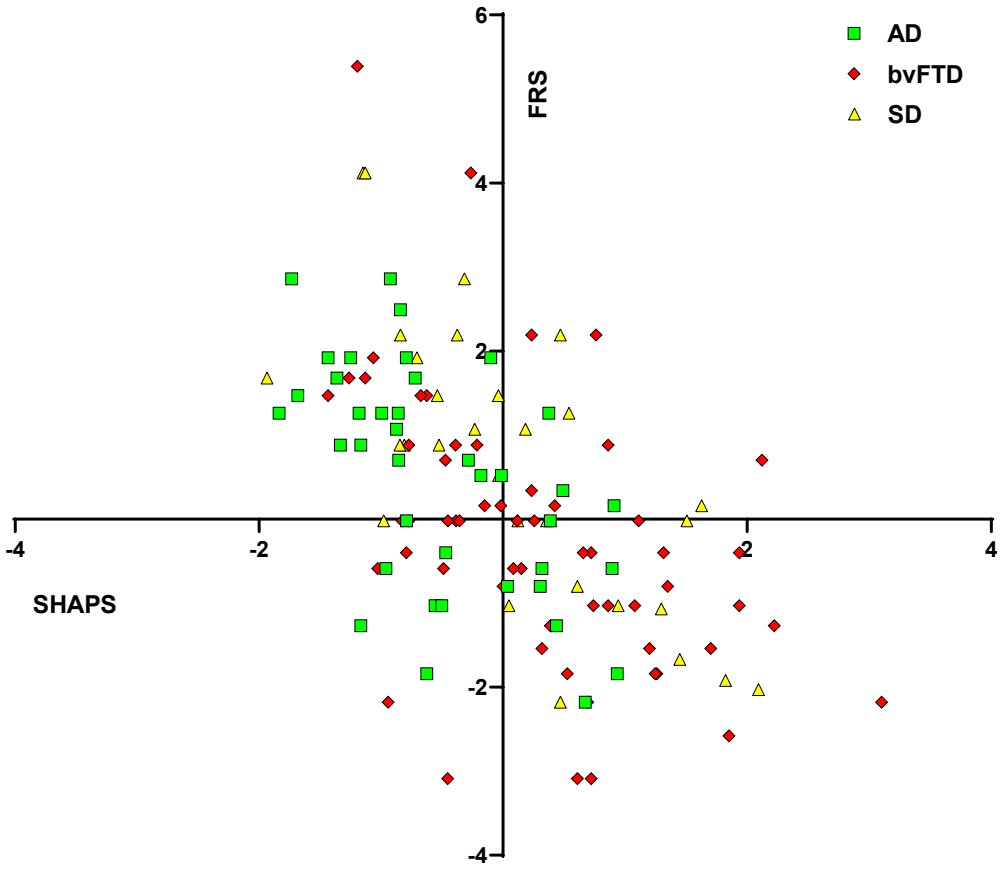


Appendix Figure 2.2 Premorbid carer-rated apathy on the Dimensional Apathy Scale (DApS). Violin plots depict the distribution of raw data with the width of the shaded area representing the proportion of data located there. Bolded horizontal line depicts the median. AD=Alzheimer's disease (n=32); bvFTD=behavioural variant of frontotemporal dementia (n=60); SD=semantic dementia (n=27).

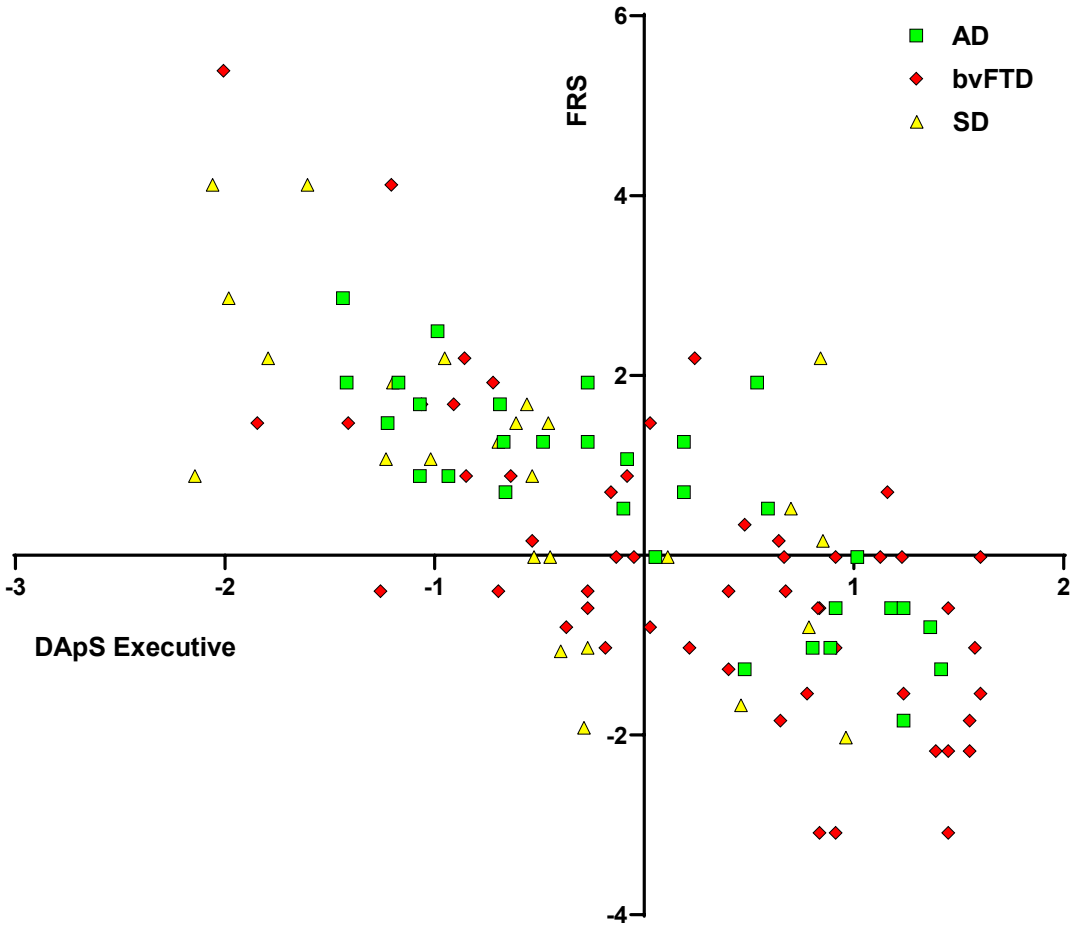


Appendix Figure 2.3 Severity of motivational disturbances in each dementia group. Anhedonia scores were taken from the Snaith Hamilton Pleasure Scale (SHAPS), while apathy subscale scores were derived from the Dimensional Apathy Scale (DApS). All scores are the residual scores (calculated based on patient population before disease onset and current SHAPS and DApS scores). AD=Alzheimer's disease; bvFTD=behavioural variant of frontotemporal dementia; SD=semantic dementia. Bolded horizontal line depicts the median. Asterisks denote results that emerged as significant in the analyses controlling for sex, disease duration, and overall level of cognitive dysfunction on the ACE-III. *p<.05, **p<.005, ***p<.001

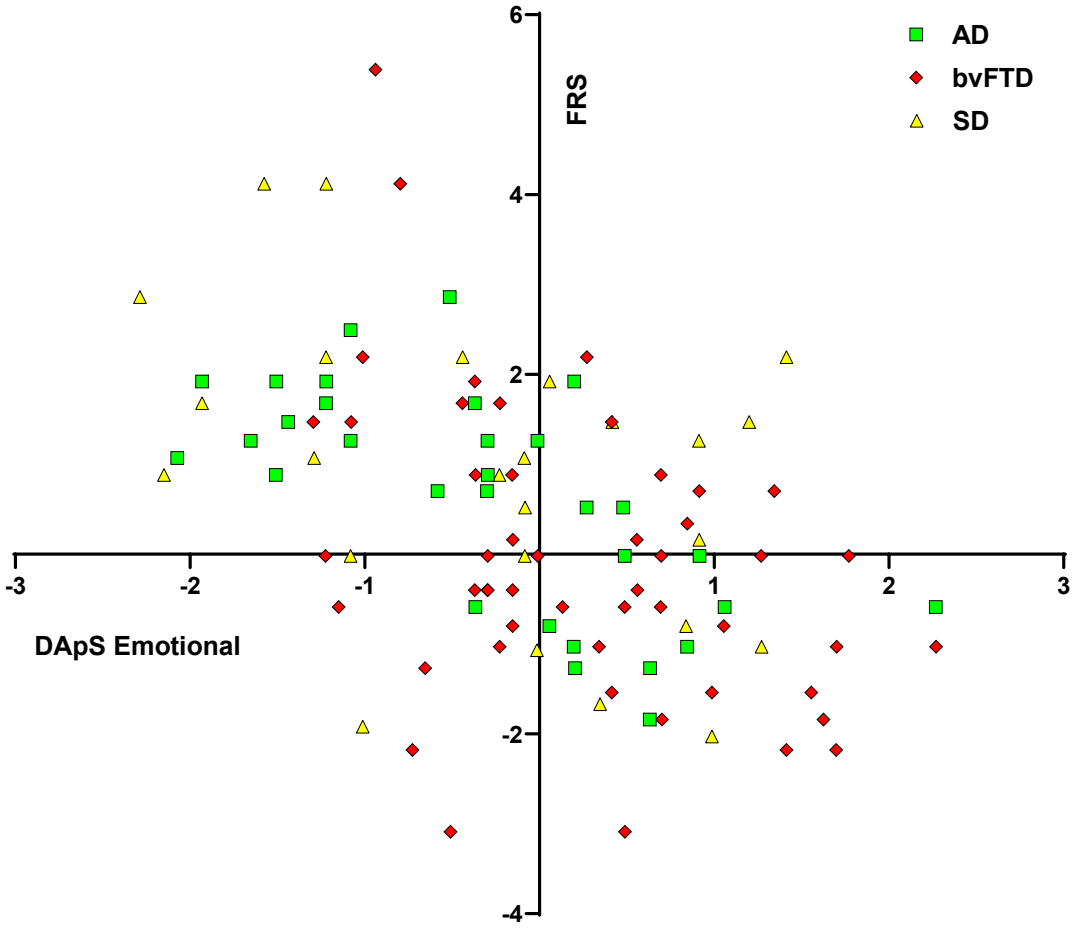
Appendix section 2.3.2 Scatterplots showing associations between anhedonia and apathy severity and functional impairment in each dementia group.



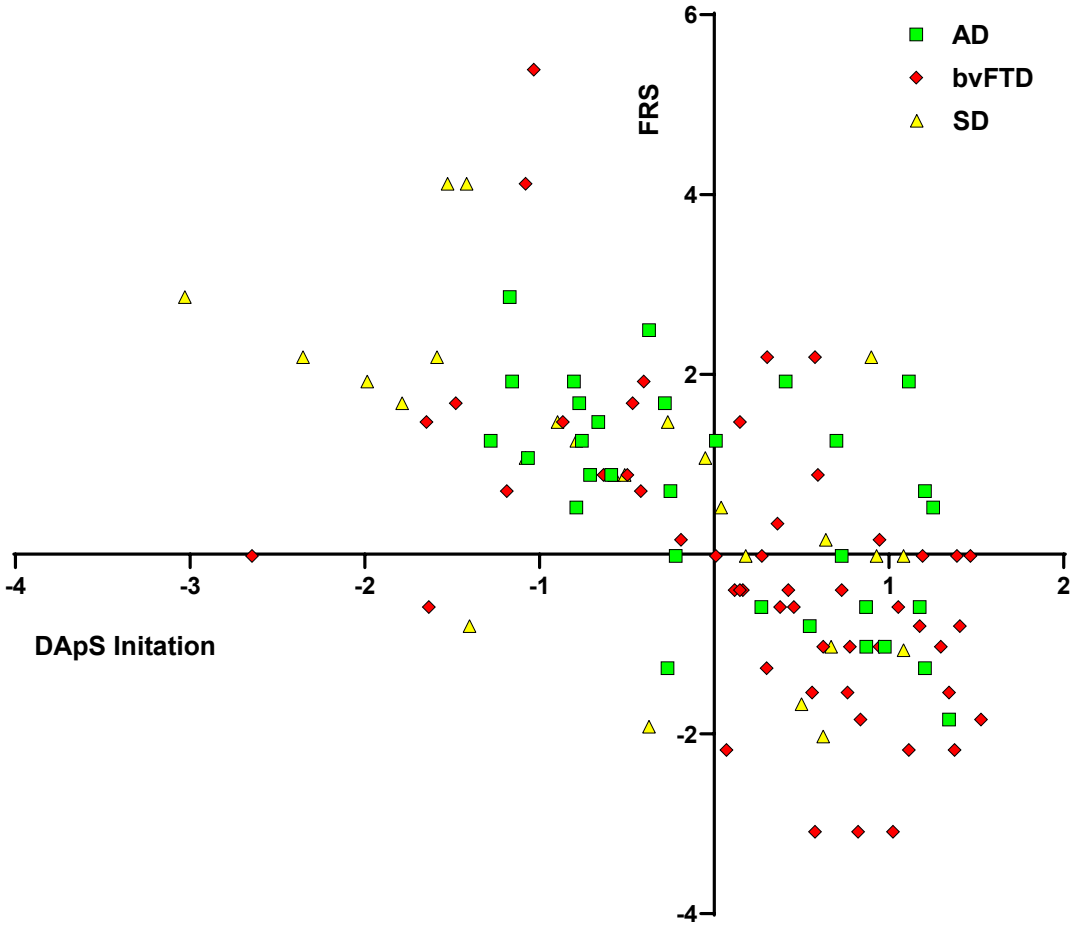
Appendix Figure 2.4 Scatterplots displaying associations between anhedonia severity on the Snaith Hamilton Pleasure Scale (SHAPS) and functional impairment on the Frontotemporal Dementia Functional Rating Scale (FRS) in each patient group. Lower scores denote greater levels of functional impairment on the FRS. All scores are the residual scores (calculated based on patient population before disease onset and current SHAPS). AD=Alzheimer's disease; bvFTD=behavioural variant of frontotemporal dementia; SD=semantic dementia.



Appendix Figure 2.5. Scatterplots showing associations between executive apathy severity and functional impairment on the Frontotemporal Dementia Functional Rating Scale (FRS) in all patient groups. Lower scores denote greater levels of functional impairment on the FRS. Executive apathy subscale scores were derived from the Dimensional Apathy Scale (DApS). All scores are the residual scores (calculated based on patient population before disease onset and current DApS scores). AD=Alzheimer's disease; bvFTD=behavioural variant of frontotemporal dementia; SD=semantic dementia.



Appendix Figure 2.6. Associations between emotional apathy severity and functional impairment on the Frontotemporal Dementia Functional Rating Scale (FRS) in all patient groups. Lower scores denote greater levels of functional impairment on the FRS. Emotional apathy subscale scores were derived from the Dimensional Apathy Scale (DApS). All scores are the residual scores (calculated based on patient population before disease onset and current DApS scores). AD=Alzheimer's disease; bvFTD=behavioural variant of frontotemporal dementia; SD=semantic dementia.



Appendix Figure 2.7 Associations between initiation apathy severity and functional impairment on the Frontotemporal Dementia Functional Rating Scale (FRS) in all patient groups. Lower scores denote greater levels of functional impairment on the FRS. Initiation apathy subscale scores were derived from the Dimensional Apathy Scale (DApS). All scores are the residual scores (calculated based on patient population before disease onset and current DApS scores). AD=Alzheimer's disease; bvFTD=behavioural variant of frontotemporal dementia; SD=semantic dementia.

Appendix Table 4.1. Group comparisons across anhedonia and apathy measures

Tests	bvFTD (n=10)	SD (n=10)	AD (n=10)	Control (n=20)	*F*	*P*	Post hoc comparisons
SHAPS (%)	63.2 (17.9)	68.6 (15.6)	73.7 (16.3)	92.8 (7.9)	29.5	<.001	Controls> AD, SD, bvFTD
TEPS-A (%)	48.6 (22.1)	52.4 (19.1)	59.4 (16.3)	78.8 (10.7)	23.8	<.001	Controls> AD, SD, bvFTD
TEPS-C (%)	57.0 (26.3)	64.6 (22.0)	67.3 (20.1)	88.6 (7.9)	17.2	<.001	Controls> AD, SD, bvFTD
Executive Apathy	16.53 (5.2)	11.26 (5.5)	14.9 (5.1)	2.7 (2.9)	53.3	<.001	bvFTD> AD, SD> Controls
Emotional Apathy	16.1 (4.7)	12.9 (4.6)	11.5 (4.8)	5.4 (2.9)	39.5	<.001	bvFTD> AD, SD > Controls
Initiation Apathy	17.9 (4.4)	14.3 (5.6)	16.6 (3.7)	6.2 (3.1)	48.3	<.001	Patients> Controls bvFTD>SD

Note. Values are presented as mean (standard deviation) unless otherwise specified. Apathy scores are total scores on each subscale of the Dimensional Apathy Scale. Anhedonia scores are percentage total scores on the SHAPS and TEPS. AD=Alzheimer's disease; bvFTD=behavioural variant frontotemporal dementia; SHAPS=Snaith Hamilton Pleasure Scale; SD=Semantic dementia; TEPS-A=Anticipatory Subscale of the Temporal Experience of Pleasure Scale; TEPS-C=Consummatory Subscale of the Temporal Experience of Pleasure Scale.

Appendix section 5.3.1 *Comparison of each patient group to their respective control group*

Dementia

BvFTD patients were initially compared to the FRONTIER controls across demographic, cognitive and clinical variables (Appendix Table 5.1). Controls were significantly older [$t(98)=2.22$, $p=.03$, $d=.49$], had more years of education [$t(98)=2.42$, $p=.02$, $d=.45$], and performed better on the ACE-III [$t(97)=7.44$, $p<.001$, $d=1.52$], in comparison to bvFTD patients. The two groups also differed for sex distribution ($\chi^2=17.4$, $p<.001$), driven by significantly more males in the bvFTD group and females in the FRONTIER control group (both p's$<.05$).

Appendix Table 5.1 Demographic, clinical and cognitive characteristics of bvFTD and FRONTIER controls

	BvFTD (n=59)	**FRONTIER Controls (n=41)**	**Test statistic**	***P* value**	**Post hoc**
Age	65.1 (8.3)	68.5 (6.1)	t=-2.2	.03	Controls > bvFTD
Sex (M: F)	46:13	15:26	X=17.4	<.001	Total: 61:39
Education	12.7 (3.2)	14.3 (3.1)	t=-2.4	.02	Controls > bvFTD
ACE-III Total	77.1	95.6	t=-7.4	<.001	Controls > bvFTD

Note. Values are presented as mean (standard deviation) unless otherwise specified. Depression data was missing for 4 controls and 6 bvFTDs. ACE-III data was missing for one bvFTD. ACE-III = Addenbrookes Cognitive Examination Third Edition, bvFTD= Behavioural Variant Frontotemporal Dementia, D= Depression, DASS= Depression, Anxiety and Stress Scale, F= Female, M= Male.

Three separate univariate ANCOVAs controlling for age, sex, education and ACE-III revealed significantly higher anhedonia in bvFTD on the SHAPS [*F(*88)=18.2, *p*<.001, η_p^2=.17], TEPS-C [*F(*89)=10.0, *p*=.002, η_p^2=.10] and TEPS-A [*F(*93)=17.6, *p*<.001, η_p^2=.16] in comparison to the FRONTIER controls (see Appendix Table 5.2). A fourth ANCOVA controlling for age, education and ACE-III also revealed significantly higher depressive symptoms in the bvFTD group compared to FRONTIER controls [*F(*83)=7.5 *p*=.007, η_p^2=.08]. The FRONTIER control EMM from these analyses were used to calculate the scaled SHAPS, TEPS-A TEPS-C and depression patient scores to scale the bvFTDs relative to the FRONTIER controls.

Appendix Table 5.2 Comparison of anhedonia on the SHAPS, TEPS-C and TEPS-A between bvFTDs and FRONTIER Controls

	BvFTD (n=59)	**FRONTIER Controls (n=41)**	**F**	**P value**	**Post hoc**	**Control EMM based on the model**
SHAPS	63.2 (17.9)	92.8 (7.9)	18.2	<.001	Control >bvFTD	85.423
TEPS -A	49.0 (22.1)	78.9 (10.7)	17.6	<.001	Control> bvFTD	73.680
TEPS- C	56.4 (26.1)	88.6 (7.9)	10.0	.002	Control >bvFTD	80.485
Depression	79.0 (22.6)	95.5 (5.0)	7.5	.007	Control>bv FTD	94.777

Note. Values are presented as mean (standard deviation) unless otherwise specified. SHAPS and TEPS scores are percentage scores. A = Anticipatory, C= Consummatory, SHAPS = Snaith Hamilton Pleasure Scale, TEPS= Temporal Experience of Pleasure Scale

Mood disorders

Demographic and clinical comparisons of the mood disorder sample are presented in Appendix Table 5.3 The mood disorder group did not differ significantly from

their control group on age, sex or education (all *p's*>.07). Four separate univariate ANCOVAs controlling for age, sex and education revealed significantly higher anhedonia on the SHAPS [$F(99)=66.7$, $p<.001$, $\eta_p^2=.40$], TEPS-A [$F(107)=50.0$, $p<.001$, $\eta_p^2=.32$] and TEPS-C [$F(107)=13.3$, $p<.001$, $\eta_p^2=.11$] and as well as higher depression scores [$F(107)=179.2$, $p<.001$, $\eta_p^2=.63$] in the mood disorders group, compared to their controls. The mood disorder control EMM from these analyses were used to calculate the scaled SHAPS, TEPS-A, TEPS-C and depression patient scores to scale the mood disorder sample relative to their controls.

Appendix Table 5.3. Demographic and clinical characteristics of mood disorder and their control group

	Mood disorders (n=80)	**Controls (n=32)**	**Test statistic**	***P* value**	**Post hoc**	**Control EMM based on the model**
Age	28.7 (9.6)	28.4 (7.7)	*t*=-.16	.87	--	
Sex (M: F)	26:54	15:17	*X*=2.04	.15	--	
Education	15.8 (2.8)	17.0 (3.2)	*t*=1.81	.07	--	
SHAPS	68.9 (14.4)	91.0 (10.1)	*F*=66.7	<.001	Controls>mood disorders	91.477
TEPS -A	62.7 (12.9)	79.5 (7.7)	*F*=50.0	<.001	Controls>mood disorders	80.153
TEPS- C	73.0 (15.3)	83.8 (10.1)	*F*=13.3	<.001	Controls>mood disorders	83.881
Depression	60.0 (16.0)	99.7 (1.0)	*F*=179.2	<.001	Controls>mood disorders	99.033

Note. Values are presented as mean (standard deviation) unless otherwise specified. SHAPS and TEPS scores are percentage scores. A = Anticipatory, C= Consummatory, SHAPS = Snaith Hamilton Pleasure Scale, TEPS= Temporal Experience of Pleasure Scale

Appendix section 5.3.2 *Comparison of bvFTD group to mood disorder group*

Demographic, clinical and cognitive variables of the bvFTD group compared to the mood disorder group are presented in Table 5.4. As expected, given the largely different

samples, the two groups differed in terms of age [$t(137)=23.2$, $p<.001$, $d=4.0$], with bvFTDs on average 36 years older than the mood disorder group. The mood disorder group also reported more years in education than the bvFTDs [$t(137)=6.1$, $p<.001$, $d=1.1$]. The two groups also differed for sex distribution ($\chi^2=28.1$, $p<.001$), driven by significantly more males in the bvFTD group and females in the mood disorder group (both p's<.05).

Appendix Table 5.4. Demographic and clinical characteristics of bvFTD compared to mood disorder sample

	BvFTD (n=59)	**Mood disorder (n=80)**	**Test statistic**	**Post hoc**
Age, yrs	65.1 (8.3)	28.7 (9.6)	*t*=23.2	bvFTD>Mood disorder
Sex (M: F)	46:13	26:54	*X*=28.1	Total: 72:67
Education, yrs	12.7 (3.2)	15.8 (2.8)	*t*=-6.1	Mood disorder> bvFTD

Note. Values are presented as mean (standard deviation) unless otherwise specified. bvFTD= behavioural variant frontotemporal dementia, F= Female, M= Male.