Hippocampal atrophy and intrinsic brain network alterations relate to impaired capacity for mind wandering in neurodegeneration

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Abstract

Mind wandering represents the human capacity for internally focussed thought, and relies upon dynamic interactions between default and frontoparietal networks. The majority of studies in the field have characterised mind wandering in healthy people, yet there is limited understanding of how this capacity is affected in clinical populations. The present study used a validated thought sampling task, to probe the capacity for mind wandering in two neurodegenerative disorders; the behavioural variant of frontotemporal dementia (n=28) and Alzheimer's disease (n=22), compared to healthy older controls (n=28). These disorders were selected due to their canonical profiles of neural dysfunction across key sites of the default and frontoparietal networks. Behaviourally, mind wandering frequency was found to be reduced in the patient groups, leading to an increase in stimulus-bound thoughts. These behavioural profiles were associated with distinct regions of grey matter loss, as revealed by voxel-based morphometry, predominantly in the hippocampal complex and striatum. Resting state functional connectivity further revealed associations between impaired mind wandering performance and altered connectivity within and between regions of the frontoparietal and default networks. Together, these findings are the first to describe altered mind wandering in neurodegenerative disorders, which was associated with hippocampal atrophy and aberrations in the functional integrity of the default and frontoparietal networks. These results corroborate current theoretical frameworks emphasising that cooperation between default and frontoparietal regions is critical for producing and sustaining internally focussed thought. Notably this study reveals a new dimension of cognitive dysfunction not previously documented in neurodegenerative disorders.

Significance statement

Humans spend much of their waking life engaged in introspection or "mind wandering". Convergent neuroimaging studies have established the underlying brain systems that support this complex ability in healthy individuals, yet it remains unclear how mind wandering is altered in neuropsychiatric conditions. We reveal stark reductions in mind wandering, coupled with an increased propensity for stimulus-bound thought, in dementia syndromes. Alterations in mind wandering were associated with structural and functional brain changes in the hippocampus, default and frontoparietal networks; key regions implicated in internal mentation in healthy individuals. Our findings provide a unique clinical validation of current theoretical models of mind wandering, and reveal a new dimension of cognitive dysfunction not previously charted in dementia.

Mind wandering – the ability to disengage from the external environment and direct attention inwardly to a stream of thought – is fundamental to the human experience. Dynamic interactions within and between large-scale brain networks govern the initiation and maintenance of mind wandering (1, 2). Of particular interest in this context are interactions between the default network and the frontoparietal control network (3-7).

In a recently proposed framework, spontaneous and unconstrained internally oriented thought is generated by fluctuations in the medial temporal lobe system of the default network, with weak influence from frontoparietal regions (2). More deliberative thought, for example planning or thinking through a problem, corresponds to reduced variability in the medial temporal system, and increased coupling between the frontoparietal network and default network core (2). The medial temporal lobe system therefore emerges as influential in the origin of spontaneous thoughts, with frontoparietal control regions becoming increasingly important for subsequent elaboration and metacognitive processing (8).

Exploring mind wandering in clinical populations can provide unique information about its cognitive and neural substrates. Altered mind wandering is documented in many clinical populations, and may constitute an important neurocognitive endophenotype across disorders. Perseverative mind wandering that is more frequent or salient, with negative content, has been reported in depressive rumination, neuroticism and dysphoria (9-11). These perseverative and ruminative styles of mind wandering are suggested to reflect an overly constrained mode of function in the default network, leading to excessive stability of thoughts (2). In contrast, higher rates of unintentional, spontaneous mind wandering are associated with increased obsessive-compulsive and attention-deficit/hyperactivity symptomatology in non-clinical samples (12, 13). Similarly, higher frequencies of mind wandering have been noted in schizophrenia, which correlate with the severity of positive symptoms (14). An unconstrained default network, due to local hyperactivity or relaxed influence from frontoparietal regions, may underpin such excessive variation and incoherence of thoughts, as seen in psychosis (2). Crucially, however, no study to date has directly investigated the relationship between mind wandering capacity and network alterations in neuropsychiatric populations. Instead, putative neural correlates of mind wandering in clinical disorders have been inferred based on the known network alterations in those diseases. As such, it remains unclear how pathological brain states impact the frequency and phenomenology of mind wandering.

The present study directly tests whether regional changes in the default and frontoparietal networks are associated with alterations in mind wandering capacity, by focusing on neurodegenerative disorders. These syndromes afford a unique opportunity to study the impact of network level dysfunction on mind wandering, given well established pathology primarily targeting, but not restricted to, key nodes of the default and frontoparietal networks (15-17). This approach is an important extension to recent work confirming that focal lesions to nodes of the default network, in the hippocampus and medial prefrontal cortex, impact mind wandering (18, 19). Moreover, on the cognitive level, mind wandering is supported by distinct component processes, many of which are disrupted in neurodegenerative populations with dementia. These underlying processes include flexible allocation of internally vs. externally focussed attention. Also, episodic memory, prospection, mental imagery, and socio-emotional processing, which form the content of mind wandering; and, working memory processes, which sustain a stream of thought, buffering it from distraction (20-22). Dementia syndromes are associated with marked disruption across many of these component processes, for example autobiographical memory retrieval (23, 24), mental simulation (25-27), working memory and attentional allocation (28, 29). Given this well-established dysfunction in key brain regions, and the disruption of core cognitive processes fundamental to constructing and maintaining spontaneous thought, it follows that distinct changes in the frequency and phenomenology of mind wandering should be present in dementia (30). No study to date, however, has empirically investigated the capacity for mind wandering in dementia, yet this line of enquiry is crucial to establish how damage to functional brain networks impacts internally generated thought processes, whilst yielding important new insights into the cognitive symptomatology of these syndromes.

To that end, we explored mind wandering capacity in two dementia subtypes: Alzheimer's disease (AD) and behavioural variant frontotemporal dementia (bvFTD). AD, characterised by prominent memory deficits, is associated with pathological changes in the default and frontoparietal networks, particularly the hippocampus, medial temporal lobe subsystem and posterior cingulate cortex, extending into prefrontal and parietal regions with disease progression (17, 31-33). In contrast, bvFTD is distinguished by behavioural dysfunction, including disinhibition, apathy, loss of empathy, emotional blunting, stereotypical behaviours, and loss of insight (34). Early pathological changes in bvFTD

are most prominent in regions comprising the salience and default networks, including the dorsomedial and ventromedial prefrontal cortices, as well as widespread changes across the insula, amygdalae, thalamus and striatum with disease progression (17, 31, 35, 36).

Quantifying the nature and content of mind wandering in clinical disorders is inherently challenging, presumably reflecting the dearth of studies in this field. Dominant experimental approaches typically require subjects to monitor or self-identify extraneous thoughts during performance of an ongoing cognitive task (3, 37-39). Such approaches, however, rely on dual-tasking and metacognitive capacities that are diminished in dementia, limiting the extent to which reliable conclusions can be drawn from existing measures. To circumvent these methodological constraints, we employed the "Shape Expectations" task – a paradigm developed to measure mind wandering under conditions of low cognitive demand, which was validated in non-pathological ageing and performance was shown to correlate with resting state variations in default network connectivity (40). In keeping with existing frameworks, the task quantifies mind wandering as thoughts unrelated to the current environment or to the task at hand (21, 41), and it can be used to quantify mind wandering propensity along a conceptual continuum.

The objectives of this study were twofold. First, we aimed to quantify the capacity for mind wandering in dementia syndromes during conditions of low cognitive demand using a validated experimental task. Second, we sought to characterise how disease-related alterations in (i) regional grey matter, and (ii) seed-based functional connectivity in the default and frontoparietal networks, relate to changes in mind wandering performance. In doing so, we aimed to validate current frameworks of mind wandering in a clinical model, by showing that the integrity of the default and frontoparietal networks is essential to support mind wandering capacity.

Results

Overall mind wandering performance

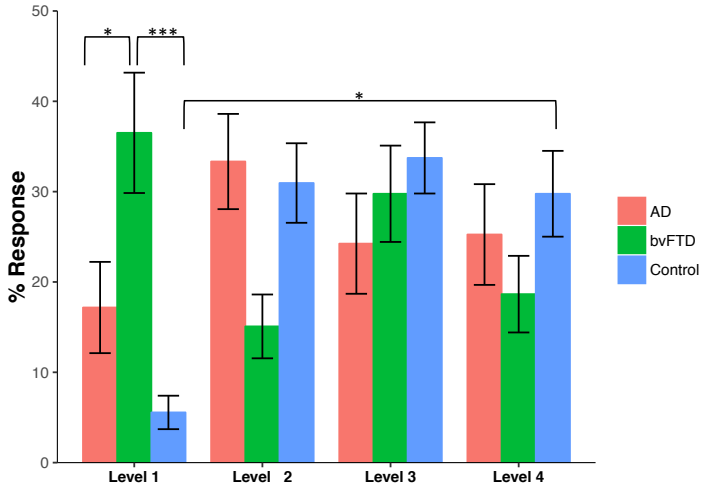
The Shape Expectations task probes mind wandering capacity under conditions of low cognitive demand using an experience-sampling procedure across 9 experimental trials (see (40)). The scoring system conceptualises mind wandering along a continuum, ranging from 1 to 4; level 1 represents stimulus-bound thought and level 4 represents mind wandering. To

calculate overall mind wandering performances, total percentages of each level across the task were calculated (i.e., total counts of 1s, 2s, 3s or 4s divided by 9 trials).

Figure 1 displays the percentage of responses at each scoring level of the mind wandering continuum. A repeated measures ANOVA revealed no main effect of response level ($F(3, 225) = 1.59$, $p = .193$), however, a significant main effect of group ($F(2, 75) = 4.67$, $p < .05$) was present. Between group Sidak post-hoc comparisons revealed significantly higher levels of stimulus-bound responses (Level 1) in bvFTD compared to control ($p < .0001$) and AD ($p < .05$) participants. Numerically, controls had less stimulus bound instances than AD patients although this difference was not statistically significant ($p = .30$). Further, bvFTD patients showed attenuated Level 2 responses relative to the AD and control groups (p values $< .05$).

A significant group by response level interaction was observed ($F(6, 225) = 4.60$, $p < .0001$). Within-group post-hoc tests revealed significantly fewer stimulus-bound responses (Level 1) in controls relative to all other response categories (all p values $< .05$). In contrast, stimulus-bound responses were significantly elevated in the bvFTD group relative to Level 2 responses ($p < .05$). Finally, AD responses did not differ significantly across the four levels (p values $> .20$).

Figure 1 – Overall proportion of mind wandering scores across groups



Legend **–** % responses across the mind wandering continuum. Asterisks show main results of group differences at Level 1, with controls producing significantly less Level 1 responses relative to all other levels. Level 1 responses represent stimulus-bound thoughts; Level 4 responses are fully-fledged instances of mind wandering. Error bars represent standard error of the mean. *$p < .05$; **$p < .01$; ***$p < .001$

Effect of trial duration on mind wandering frequency

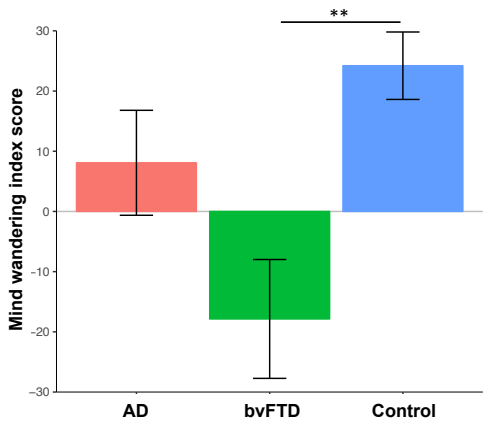
As the experimental trials were of varying durations (Short: ≤20 s, Medium: 30-60 s, Long: ≥90 s), we explored whether trial length was related to the average score obtained across each of the three trial durations. There was a significant main effect of trial duration ($F(2, 150) = 15.33$, $p < .0001$) with higher average scores achieved on long trials, relative to all short and medium durations (p values < .0001), irrespective of group. There was a significant main effect of group ($F(2, 75) = 4.24$, $p = .018$), indicative of bvFTD patients achieving lower average scores relative to controls across all durations (p=.014). No other significant differences were evident at the group level (p values > .3), and the group x duration interaction was not significant ($F(4, 150) = 1.66$, p =.163) (See Supplementary Figure 1).

Mind wandering index score

To compare the frequency of level 1 (stimulus bound) with level 4 (mind wandering) responses, an index score was created by subtracting the % level 1 responses from % level 4. A larger, positive index score reflects a tendency to engage in mind wandering as opposed to stimulus bound thought, with negative scores reflecting the reverse profile.

Figure 2 shows the average mind wandering index score across participant groups, providing a measure of the propensity to engage in mind wandering versus stimulus bound thought (i.e., % Level 4 – % Level 1 responses). Significant group differences were observed ($F(2, 75) = 7.12$, $p < .01$), driven exclusively by the bvFTD group. Relative to controls, bvFTD patients displayed an increased propensity for stimulus-bound thought at the expense of mind wandering ($p < .01$). In contrast, no such differences were evident in the AD group (p = .453), although their mind wandering index was numerically lower than that of controls.

Figure 2 – Average mind wandering index score across participant groups

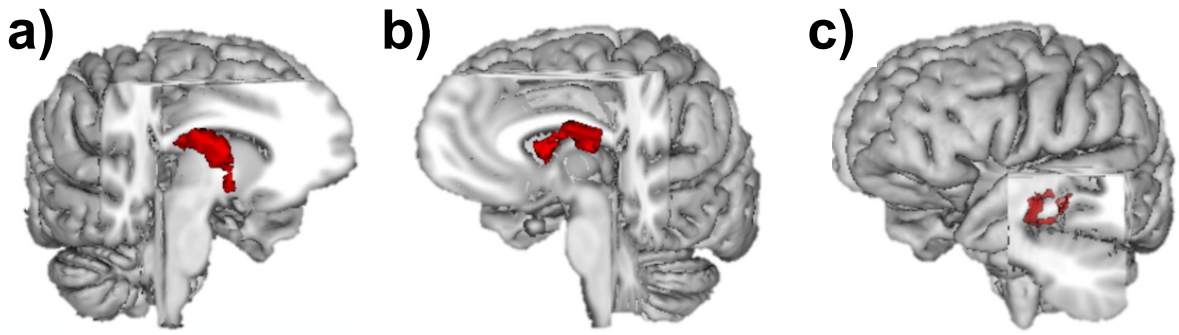


Legend **–** Mind wandering index score (i.e., % difference in Level 4 minus Level 1 responses), reflecting the propensity to engage in mind wandering relative to stimulus bound thought, averaged across groups. Higher scores reflect an increased propensity to engage in mind wandering as opposed to stimulus bound thought; with lower scores reflecting a tendency toward stimulus bound thought. Error bars show the standard error of the mean. $^{**}p < .01$.

Grey matter correlates of mind wandering performance

Voxel-based morphometry was used to determine the relationship between scores on the mind wandering index and regional grey matter loss. Figure 3 displays the common grey matter regions that covaried with the mind wandering index score in AD and bvFTD patient groups. Three distinct grey matter clusters were identified including: (i) a right striatal cluster encompassing the caudate head, extending to the nucleus accumbens; (ii) a left striatal cluster including the dorsal caudate and extending posteriorly to the thalamus; and (iii) a medial temporal lobe cluster involving the left hippocampus and parahippocampal gyrus. (See Supplementary Table 2 for maxima co-ordinates and voxel size).

Figure 3 – Common grey matter regions associated with the mind wandering index score across the patient groups



Overlap analysis showing grey matter regions significantly associated with the mind wandering index score in both bvFTD and AD patients. a) Right striatum cluster: right caudate head extending to nucleus accumbens; b) Left striatum cluster: left dorsal caudate extending to thalamus; c) Left hippocampal/parahippocampal gyrus cluster. Results reported at $p < .005$ uncorrected with a cluster extent threshold of 100 contiguous voxels.

For all participants, mean grey matter volumes were then extracted from the regions identified in the overlap analysis. These regional volumes were plotted to show the directionality of the relationship between mind wandering index and grey matter. As illustrated in Supplementary Figure 2, grey matter volume in each of the three key regions was positively correlated with the mind wandering index score: right striatum: $r = .56$, $p < .0001$; left striatum: $r = .67$, $p < .0001$; hippocampus/parahippocampus: $r = .50$, $p < .0001$.

This is consistent with decreased grey matter in these regions being associated with a reduced mind wandering frequency and concomitant increase in stimulus-bound thought.

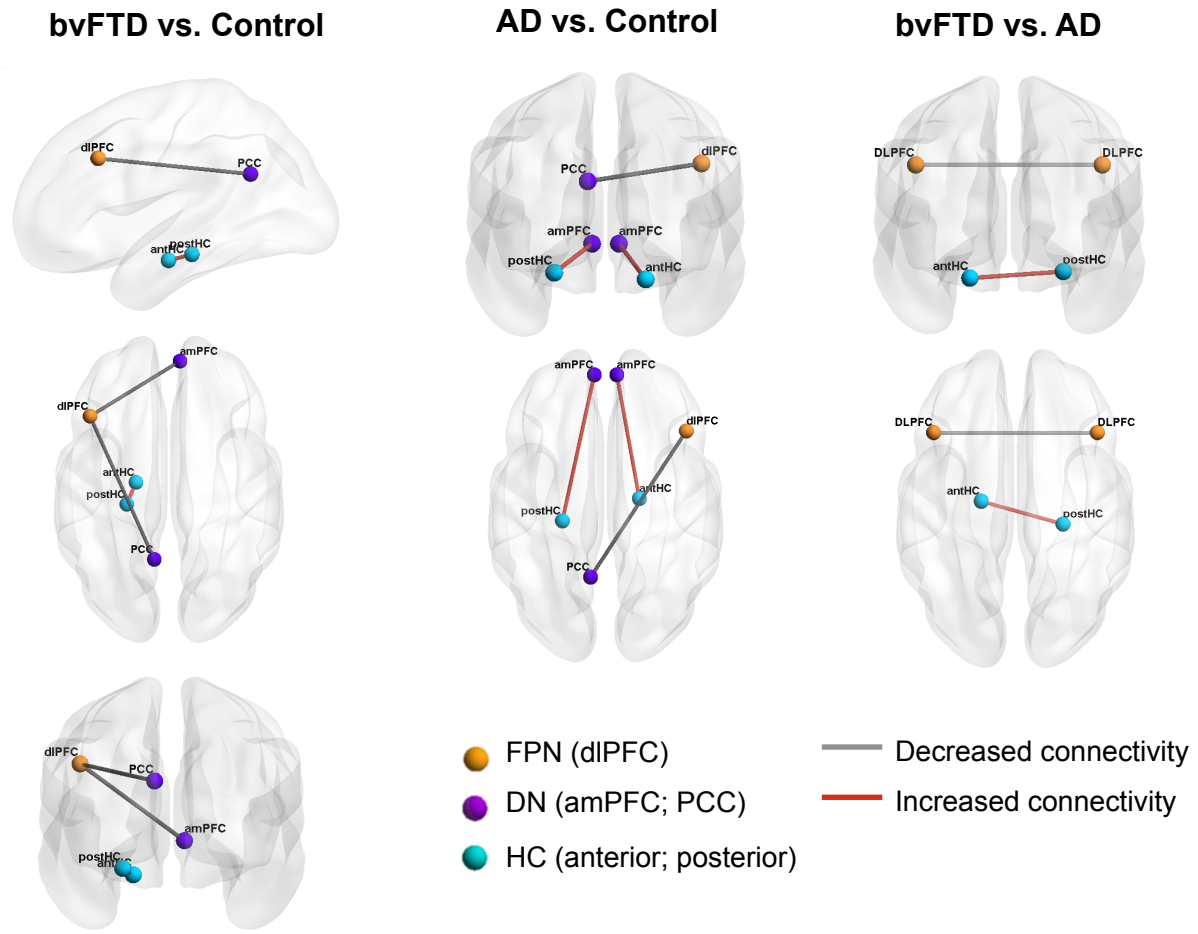
Seed region connectivity and mind wandering performance

The relationship between seed region connectivity and the mind wandering index score was then examined. Regions where the relationship between mind wandering index and connectivity differed significantly between the groups are shown in Figure 4. Attenuated mind wandering performance in bvFTD relative to controls, as captured by the mind wandering index, was associated with a pattern of reduced core and frontal connectivity, but increased intra-hippocampal connectivity. Specifically, bvFTD patients' mind wandering index score was associated with reduced connectivity between the left DLPFC and left PCC ($Z = -2.63$, $p < .05$), and between the left DLPFC and right amPFC ($Z = -2.36$, $p < .05$), in the context of stronger connectivity between the left anterior and posterior hippocampus ($Z = 2.19$, $p < .05$).

Relative to controls, AD patients' mind wandering index was associated with reduced core and dorsal PFC connectivity between the left PCC and right DLPFC ($Z = -2.19$, $p < .05$), in the context of increased connectivity between the hippocampus and medial PFC (right anterior hippocampus to right amPFC: $Z = 2.58$, $p < .05$; left posterior hippocampus to left amPFC: $Z = 2.04$, $p < .05$).

Comparing the two patient groups, the mind wandering index in bvFTD patients was associated with weaker inter-hemispheric dorsolateral connectivity relative to AD (left DLPFC to right DLPFC: $Z = -2.10$, $p < .05$) and stronger inter-hemispheric hippocampal connectivity (left anterior to right posterior hippocampi: $Z = 2.09$, $p < .05$). No other between group comparisons emerged as significant.

Figure 4 – Seed region connectivity and mind wandering performance



Seed regions where the relationship between mind wandering index and connectivity differed significantly between the groups. FPN = frontoparietal network; DN = default network; HC = hippocampus. Results shown in neurological convention (i.e., left and right side of brain shown on left and right side of image).

Discussion

Our results provide an empirical demonstration of distinct changes in mind wandering capacity in two dementia syndromes, associated with discrete grey matter correlates and functional connectivity changes in the default and frontoparietal networks. To our knowledge, this is the first investigation of mind wandering in dementia, and its associated neural correlates. These findings corroborate current theoretical frameworks that emphasise the essential role of the medial temporal lobe, and interactions between the default and frontoparietal networks, in the generation and evolution of mind wandering (2).

Our most striking behavioural finding was a clear bias toward stimulus-bound thought, at the expense of fully-fledged instances of mind wandering, in individuals with bvFTD. This

manifested as a negative mind wandering index, suggesting an inability to shift or progress thoughts beyond stimuli in the immediate environment. By contrast, healthy older controls displayed a positive mind wandering index, reflecting preferential engagement in mind wandering under periods of low cognitive demand, in line with previous findings using this task (40). This tendency to mind wander in healthy individuals is to be expected given the monotonous nature of the stimuli, and minimal task requirements, designed to provoke off-task thought. While a decreased propensity to engage in mind wandering versus stimulus bound thought (as evidenced by the mind wandering index) was observed in AD relative to controls, these differences did not emerge as statistically significant. Whether the mind wandering index would continue to decrease in AD with disease progression remains an important question that longitudinal studies would be well placed to address. Nevertheless, taken together, the behavioural data suggests distinct changes in the distribution of Level 1 to Level 4 responses on the Shape Expectations task in dementia syndromes, with a shift towards stimulus-bound forms of thought at the expense of mind wandering.

Existing evidence suggests that component processes supporting mind wandering are compromised in dementia, most notably those processes involving memory-based constructive simulation (30, 42). AD and bvFTD patients display comparable episodic memory dysfunction (43-45). Both groups also display marked impairments in future-oriented forms of thinking, including prospective memory (46, 47) and constructive simulation of future episodes (26, 48, 49). Accordingly, reductions in mind wandering performance commensurate with the magnitude of these memory-based constructive impairments might be predicted. Our results, however, suggest that mind wandering capacity is more vulnerable in bvFTD, as it was significantly impaired relative to controls. In contrast to AD, bvFTD is associated with marked behavioural rigidity, manifesting as preservative behaviour and adherence to stereotypical routines (50, 51). This has been quantified via cognitive tasks where bvFTD patients show limited verbal generativity (29), and reduced capacity for divergent and flexible thinking (52) and problem solving (53). An intriguing possibility exists whereby this narrowed behavioural and cognitive repertoire in bvFTD may reflect, in part, the reduced ability to generate spontaneous thoughts and to transition flexibly between them.

Our neuroimaging findings underscore the role of key regions of the default and frontoparietal networks in supporting internally generated thought, corroborating previous

reports in healthy individuals (3, 6, 7). Irrespective of dementia subtype, mind wandering index scores were associated with decreased connectivity between the default network core (PCC) and the frontoparietal network (dlPFC). Cooperation between the frontoparietal and default network is thought to support processes relevant to mind wandering, including autobiographical planning, recollection, mental simulation, and creativity (54-57). Indeed, higher trait levels of deliberative mind wandering in healthy individuals are associated with increased cortical thickness, and increased functional connectivity, in regions that bridge the default and frontoparietal networks and promote their integration (58). Limited evidence from task-based fMRI of AD patients also supports this cooperative network interaction, whereby performance on memory tasks is not only mediated by default network regions, but also depends on recruitment of prefrontal executive regions, including the dlPFC (59, 60). The posterior cingulate cortex may play a key role in default-frontoparietal network cooperation, by maintaining connectivity with the default network and simultaneously facilitating integration between other default network and frontoparietal regions in a dynamic and context-dependent manner (57). PCC dysfunction in dementia might therefore impair the maintenance of deliberative thought processes. Given that changes in the PCC are evident from the mild cognitive impairment stages that precede Alzheimer's disease (61), the impact of relatively focal PCC dysfunction on mind wandering style in prodromal AD warrants further attention.

The mind wandering index was also associated with hyper-connectivity within the hippocampus in bvFTD, and from the hippocampus to the amPFC in AD. Furthermore, in both patient groups, decreased grey matter in the left hippocampus and parahippocampus correlated with reduced mind wandering. Convergent measures have shown that neural activity in the hippocampus and parahippocampus (8), entorhinal cortex (62) and temporal cortex (63) precedes spontaneous free recall of episodic memories. This accords with a large body of rodent work implicating hippocampal sharp wave ripple events (SWRs) in the replay (and preplay) of previously learnt or future behavioural sequences (64-67). In combined intracranial recordings with resting state fMRI in anesthetised monkeys, hippocampal SWRs precede increased activation of the default network (68). Together, these findings link spontaneous activation in the hippocampus and surrounding regions with both recall and prospection, which may then engage the default network more broadly to support the elaboration of memories and simulations. Consistent with this proposal, higher trait levels of

spontaneous mind wandering are correlated with increased functional connectivity in medial temporal regions of the default network, and with increased cortical thickness in the retrosplenial cortex (58) – a region adjacent to the posterior hippocampal and parahippocampal regions identified in our VBM analysis. A critical role for the hippocampus in mind wandering was also recently confirmed, as individuals with selective bilateral hippocampal damage exhibited reduced diversity in their mind wandering content (18). Our findings complement and extend these results by confirming that functional and structural alterations in the hippocampus and parahippocampus mediate alterations in mind wandering in dementia.

Taken together, our results suggest that disrupted capacity for mind wandering in both AD and bvFTD reflects a combination of decreased frontoparietal-default network connectivity and increased hippocampal connectivity. Direct comparison of the patient groups revealed this pattern to be amplified in bvFTD, as their mind wandering index was associated with reduced bilateral dlPFC connectivity and increased bilateral hippocampal connectivity, relative to AD. This resonates with our behavioural finding of disproportionately impaired mind wandering in the bvFTD group. Abnormalities in the default and frontoparietal networks are well established in AD and bvFTD; however, comparatively greater salience network dysfunction is observed in bvFTD, encompassing the anterior cingulate cortex and anterior insula (17, 69). Reduced causal influence from the salience network over the default network has also been shown during a reasoning task in bvFTD (70). The salience network is proposed to mediate dynamic shifts between default and executive control networks (71), facilitating transitions between external and internal focus. Greater salience network dysfunction and its reduced causal influence over the default network may impair bvFTD patients' ability to direct attention away from the external environment. This may disrupt the capacity for internally oriented thought as attention remains focussed on external information, consistent with the high levels of stimulus-bound thought bvFTD patients exhibited on our task.

Finally, we found an association between striatal grey matter loss and reduced mind wandering, irrespective of dementia subtype. The basal ganglia represents a network hub vulnerable to degeneration across neurodegenerative disorders (72), and abnormalities across the striatum are suggested to contribute to an array of cognitive and neuropsychiatric features in these conditions (73). We speculate that the involvement of the basal ganglia in supporting

large scale network communication (74) may explain its association with attenuated mind wandering in dementia. This is consistent with known functional connectivity between the striatum and large-scale cortical networks, including default and frontoparietal (75), and the convergence of these functional networks in distinct zones of the striatum (76). Striatal degeneration may impair the integration of information from disparate brain networks, which is necessary to support more abstract forms of cognition, for example mind wandering. As the dynamic integration and segregation of network communication is increasingly recognised as important for mind wandering (1, 77), further investigation of the striatal influence over large scale network topology in this context is warranted.

In summary, to our knowledge, this is the first study to empirically measure mind wandering capacity in dementia syndromes, and reveals a definitive shift towards stimulus-bound thought at the expense of mind wandering. This narrowed range of internal mentation relates to hippocampal and striatal grey matter loss, and functional changes in the default and frontoparietal networks. Our findings corroborate current theoretical frameworks which emphasise the cooperation between default and frontoparietal regions in producing and sustaining internally focussed thought (2). Future work is needed to identify the trait level and phenomenological characteristics of altered mind wandering in dementia, and to determine how reductions in this adaptive and enriching cognitive capacity relates to broader cognitive and behavioural symptoms in these syndromes. Given the ubiquity of mind wandering in everyday life, we stress the importance of understanding how loss of this fundamental human capacity impacts wellbeing and sense of self in individuals living with dementia.

Methods and Materials

Case selection

Twenty-eight individuals meeting diagnostic criteria for bvFTD, 22 with a clinically probable diagnosis of AD, and 28 healthy controls were involved in the study. See Supplementary Information and Supplementary Table 1 for recruitment details, demographics and clinical characteristics.

Mind wandering experimental task

Participants viewed static, two-dimensional coloured geometric shapes presented individually on a computer screen, following which they were prompted to report on their thoughts that

arose during stimulus presentation. The task consisted of 9 trials, each presenting a commonplace shape (e.g., blue square, yellow circle) for varying durations (Short: ≤20 s, Medium: 30-60 s, Long: ≥90 s).

In the scoring continuum, Level 1 represents stimulus-bound thoughts and Level 4 represents mind wandering, i.e., thoughts completely unrelated to the stimulus or the task at hand. Levels 2 and 3 represent intermediary responses. The final score awarded for each trial is the highest level achieved on that trial, ranging from 1-4. Total percentages of each level across the task were calculated, as well as the mind wandering index comparing the extent of Level 1 vs. Level 4 responses. The mind wandering index was used as the covariate in the neuroimaging analysis, rather than the percentage of mind wandering (level 4) as many patients scored 0 for this, leading to reduced variance in the sample. The scoring protocol and representative responses are included in Supplementary Information; stimulus materials for the task are available from the authors upon request.

VBM analysis of mind wandering performance

To examine the relationship between grey matter intensity and mind wandering performance, separate voxelwise GLMs were conducted within the bvFTD and the AD patient groups (not combined with controls) using the mind wandering index score as a covariate in the design matrix. An overlap analysis was conducted using the results from each covariate analysis to identify grey matter regions that were commonly implicated across the patient groups. The contrasts of the statistical maps generated from the bvFTD and AD covariate analyses were scaled to a common threshold ($p < .005$, uncorrected) and multiplied to create an inclusive, or overlap, mask across patient groups. A conservative cluster extent threshold of 100 contiguous voxels was employed to guard against false positive findings. (Pre-processing and group-level comparisons are reported in Supplementary material).

Seed region connectivity and mind wandering performance

Seed location was based on previously published co-ordinates of key hubs within the default network, frontoparietal network, and hippocampus (see Supplementary Information for co-ordinates). Group differences in the relationship between seed region connectivity and the mind wandering index score were examined. To establish the relationship between connectivity and mind wandering performance, within each of the three groups, participants' mind wandering index scores were correlated with each pairwise edge for 13 seed-regions of

interest. Dunn and Clark statistics were calculated to compare these correlations between the groups at a significance level of $p < .05$ (i.e. $Z \geq |2|$). (Pre-processing and group-level comparisons are reported in Supplementary material).

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Supplementary material

Materials and methods

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1. Case selection, demographics and clinical characteristics

Case selection

Twenty-eight individuals meeting current diagnostic criteria for bvFTD (1) and 22 individuals with a clinically probable diagnosis of AD (2) were recruited from the FRONTIER research group in Sydney, Australia. Briefly, bvFTD patients presented with marked changes in behaviour and personality, social and emotional dysregulation and executive dysfunction. AD patients were characterised by significant episodic memory dysfunction, temporal disorientation, and visuospatial deficits, with relatively preserved socio-emotional function. Patient groups showed characteristic patterns of brain atrophy on structural magnetic resonance imaging (MRI). Global cognitive function was assessed using the Addenbrooke's Cognitive Examination-Revised (ACE-R; 3), covering domains of attention and orientation, memory, fluency, language, and visuospatial function. The Cambridge Behavioural Inventory-Revised (CBI-R; 4) was included as an informant-rated scale to assess functional status and behavioural disturbance. Twenty-eight age-matched control participants were recruited from a volunteer research panel and screened for cognitive impairment using an established cut-off of 88 or above on the ACE-R. Exclusion criteria for all participants included prior history of mental illness, significant head injury, movement disorders, cerebrovascular disease, alcohol and other drug abuse, and limited English proficiency. The study was approved by the South Eastern Sydney Local Area Health and University of New South Wales ethics committees and all participants provided informed consent in accordance with the Declaration of Helsinki.

Demographics and clinical characteristics

Demographic details and clinical characteristics of study participants are presented in Supplementary Table 1. The groups were matched for gender distribution ($\chi^2 = 1.7$, $p = .419$), however age differences were present ($F(2,75) = 4.8$, $p = .011$) reflecting that bvFTD patients were significantly younger than controls ($p = .016$). Global cognitive function differed across the groups (ACE-R: $F(2,75) = 47.1$, $p < .0001$), with both patient groups performing significantly worse than controls (p values $< .0001$). While AD patients displayed greater cognitive impairment relative to bvFTD (ACE-R: $p = .036$), greater functional and behavioural decline was evident in the bvFTD relative to AD group (CBI-R: ($t(48) = -2.7$, $p = .009$). Patient groups were matched for disease duration (years elapsed since onset of symptoms: $t(48) = .698$, $p = .488$)

Supplementary Table 1. Demographics and clinical characteristics of study participants.

	bvFTD	AD	Controls	bvFTD vs Control	AD vs Control	bvFTD vs AD
N	28	22	28	-	-	-
Sex (M:F)	17:11	15:7	14:14	n.s.	n.s.	n.s.
Age	61.5 (8.9)	67.0 (9.6)	67.9 (6.4)	*	n.s.	n.s.
Disease duration[§]	4.4 (3.3)	5.1 (3.9)	-	-	-	n.s.
CBI-R (% endorsed)	35.5 (11.1)	25.4 (13.8)	-	-	-	**
ACE-R total (max 100)	75.9 (14.1)	67.7 (12.9)	96.2 (2.6)	***	***	*

Standard deviations presented in parentheses. n.s. = non significant; * = $p < .05$; ** = $p < .01$; *** = $p < .001$

[§]Years since symptom onset; bvFTD = behavioural variant frontotemporal dementia; AD = Alzheimer's disease; CBI-R = Cambridge Behavioural Inventory-Revised (higher scores indicating greater levels of functional decline and behavioural disturbance); ACE-R = Addenbroke's Cognitive Examination-Revised.

2. Behavioural statistical analysis

Behavioural analyses were conducted using the open-source statistical environment R (R Core Team, 2013). Demographic variables were compared via one-way ANOVA or independent samples t-tests. *A priori*, variables were plotted and checked for normality of distribution using Kolmogorov–Smirnov tests. Performance on the Shape Expectations task was compared via one-way ANOVA and repeated measures ANOVA, with Sidak post hoc comparisons.

3. Scoring details for mind wandering performance on the "Shape Expectations" task

Reported thoughts were classified as follows:

Level 1 = Nothing/labelling what is on the screen. For example, a response of "nothing" or merely labelling the shape on the screen (e.g. "yellow circle"), which indicates no specific thoughts were generated or the individual's thoughts were entirely stimulus-bound during the trial.

Level 2 = Stimulus-/task-/environmental-dependent responses. Such responses are heavily dependent on stimulus attributes, task demands, or other environmental factors. For example, "That's a nice round shape"; "Yellow is my favourite colour"; "This one is taking a long time", or, "It's cold in here".

Level 3 = Stimulus-related extrapolation. Responses signifying an intermediate zone between stimulus-bound thinking and instances of definite mind wandering. Level 3 responses do not satisfy criteria for mind wandering as they still reflect a degree of reliance on the stimulus at hand, for example, "It's like the sun [or draws a comparison to any other entity of a similar shape/colour]"; "It reminds me of an opened umbrella".

Level 4 = Mind wandering. Responses indicating thought content that is stimulus-/ task-/environment-independent, and clearly demonstrates a move beyond stimulus attributes and comparisons tied to the stimulus, i.e., these thoughts do not directly relate to any properties of the stimulus, the task, or the environmental surroundings. Examples of mind wandering include, "I thought about the people I saw today and how we chatted with them outside the unit"; "I thought of a sailing boat in the Greek Islands"; "I was wondering what time I'll be finished here and if I'll make it to the supermarket".

4. Imaging acquisition and pre-processing; and group-level analysis procedures

Imaging acquisition

Participants underwent whole-brain T1 weighted imaging using a 3T Philips MRI scanner with standard quadrature head coil (eight channels) using the following sequences: coronal orientation, matrix 256 x 256, 200 slices, 1 mm^2 in-plane resolution, slice thickness 1 mm, echo time/repetition time = 2.6/5.8 ms, flip angle $\alpha = 8°$. Structural scans were not available for three bvFTD patients, one AD patient, and three controls due to imaging contraindications (e.g., pacemaker; metallic stent).

A subset of 18 bvFTD, 15 AD, and 15 controls underwent task-free resting state imaging. T2*-weighted echo planar functional images were acquired in sequential order with repetition time (TR) = 2 s, echo time (TE) = 30 ms, flip angle = 90°, 32 axial slices covering the whole brain, field of view (FOV) = 240 mm, inter-slice gap = 0 mm, and raw voxel size = 2.1 mm by 2.6 mm by 4.5 mm thick. T1-weighted images were used for co-registration with

functional images. A single 7-min run was performed in the scanner, which consisted of the participant lying still with their eyes open. Participants were questioned immediately afterwards to ensure they had not fallen asleep during the sequence.

Voxel-based morphometry (VBM) pre-processing

Voxel-based morphometry (VBM) was performed on the three dimensional T1-weighted scans, using the FSL-VBM toolbox in the FMRIB software library package FSL (http://www.fmrib.ox.ac.uk/fsl/). Scans were skull-stripped using the BET algorithm in FSL (5) and tissue segmentation was completed using FMRIB's Automatic Segmentation Tool (FAST v4.0) (6). A study-specific grey matter template was created by canvassing the maximum equal amounts of scans across the three groups and registered to the Montreal Neurological Institute Standard space (MNI 152) using a non-linear b-spline representation of the registration warp field. Grey matter partial volume maps were non-linearly registered to the study template and modulated by dividing by the Jacobian of the warp field, to correct for any contraction/enlargement caused by the non-linear component of the transformation (7). After normalisation and modulation, the grey matter maps were smoothed using an isotropic Gaussian kernel (standard deviation = 3 mm; full width half maximum = 8 mm).

VBM group comparisons

Group differences in grey matter intensity across patients and controls were compared using a voxelwise general linear model (GLM). Significant clusters were formed using the threshold-free cluster enhancement (TFCE) method (8) via permutation-based nonparametric testing with 5000 permutations per contrast (9). Group differences in grey matter intensity were assessed using t-tests, tested for significance at $p < .01$, corrected for multiple comparisons via family-wise error (FWE) correction across space. Age was added as a covariate in the analysis given the significant age differences between the control and bvFTD groups. Relative to controls, both patient groups showed characteristic patterns of widespread grey matter atrophy, as shown in Supplementary Table 3 and Supplementary Figure 3.

Resting state fMRI (rsfMRI) pre-processing

rsfMRI scans were pre-processed using FEAT (FMRI Expert Analysis Tool), from the FSL FMRIB software library. Scans were motion corrected using MCFLIRT (10); six motion parameters (estimated by MCFLIRT) and cerebrospinal fluid and white matter signals were regressed out using the CompCor strategy (11). Mean framewise displacement (FD) values

were calculated from MCFLIRT. Mean FD values were: controls = 0.149 ± 0.06; AD = 0.117 ± 0.33; bvFTD = 0.247 ± 0.19. There were no differences in FD values between the groups: AD vs. control t = 1.449; p = 0.159; bvFTD vs control t = 1.861; p = 0.148; AD vs. bvFTD t = 1.598; p = 0.117. Mean FD was also shown not to correlate significantly with the mind wandering index scored used as a covariate in the imaging analysis (r = -0.147; p = 0.324). Following these pre-statistics, linear registrations were performed using FLIRT: participants' rsfMRI scans were registered to their T1 scans that had been skull-stripped using BET; and the T1 scans were registered to standard space (MNI 152). These transformations were concatenated and applied to the raw EPI scans, registering the rsfMRI scans to standard space.

rsfMRI seed region definition

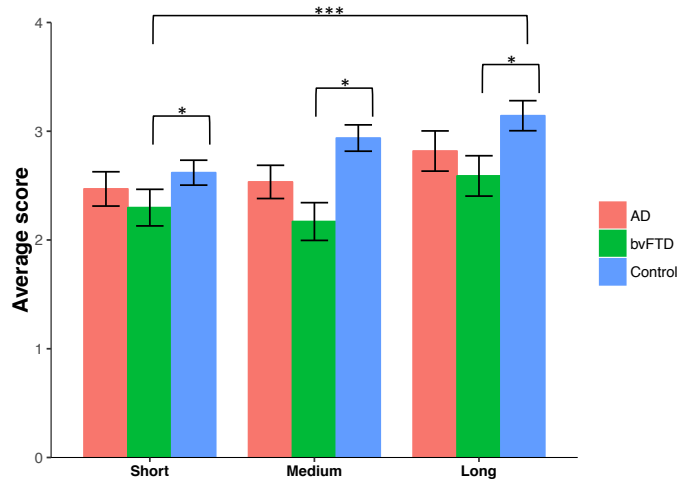
Seed regions of interest of a 4mm diameter were created in standard space, using the fslmaths function in FSL. The location of the seeds was selected based on previously published co-ordinates of key hubs within the default network (12), frontoparietal network (13), and hippocampus (14). The default network seeds included the hippocampal formation (HF; ±22 -20 -26), a midline core, which included the posterior cingulate cortex (PCC; ±8 -56 26) and the anteromedial prefrontal cortex (amPFC; ±6 52 -2); and the ventromedial prefrontal cortex (vmPFC; 0 26 -18) (12). Frontoparietal network seeds included the dorsolateral prefrontal cortex (right DLPFC; 43 22 34, left DLPFC; -43 22 34) (13). The hippocampus was seeded posteriorly (left -23 -26 -15, right 25 -26 -15) and anteriorly (left -18 -14 -18, right 18 -14 -18) (14). Using FLIRT, the ROIs were registered to individuals' rsfMRI scans using the transformations derived during pre-processing. Seed region results were visualised with BrainNet viewer (15).

Group comparisons of seed region connectivity

Patterns of seed region connectivity were initially examined. Within the groups, one sample t-tests were conducted between each pairwise edge for the 13 regions of interest, corrected for multiple comparisons using a false discovery rate of $q \leq .05$. Group differences in seed region connectivity are shown in Supplementary Figures 4 and 5.

5. Average mind wandering index scores as a function of trial duration

Supplementary Figure 1 Average scores achieved as a function of trial duration



Legend – Average scores achieved per trial across short, medium and long stimulus presentation durations (Short: ≤20 seconds, Medium: 30-60 seconds, Long: ≥90 seconds). Asterisks denote main effect for trial duration, with higher scores achieved for longer relative to medium and short trial lengths; and lower scores for bvFTD relative to controls across all durations. Error bars represent standard error of the mean. *$p < .05$; ***$p < .001$

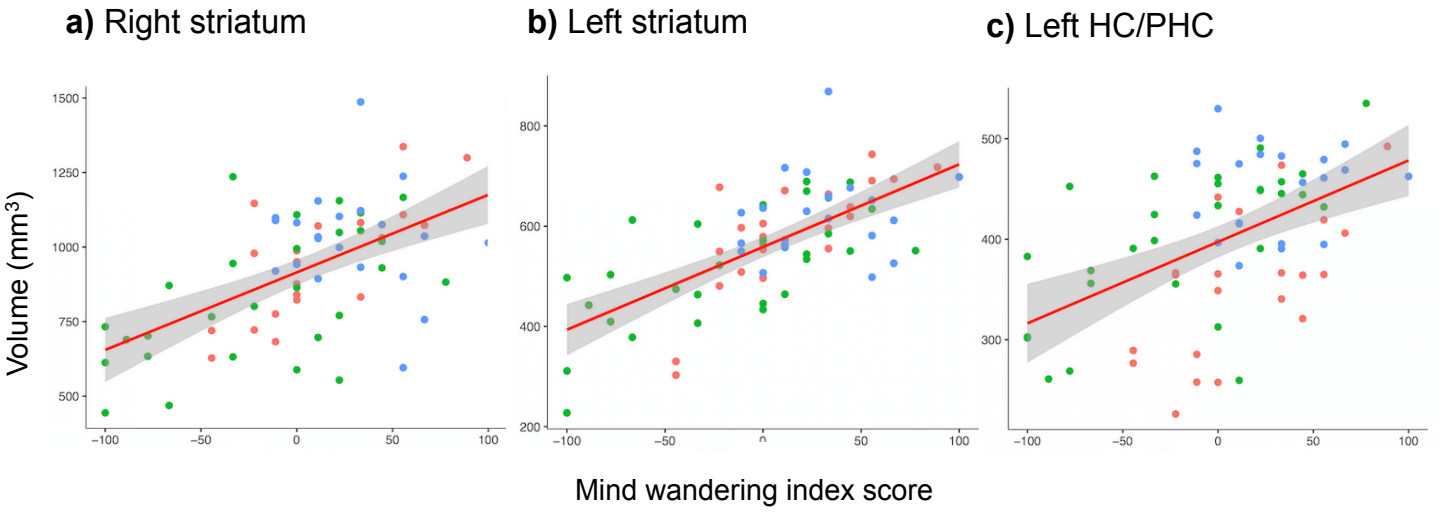
6. Mind wandering index voxel-based morphometry (VBM) overlap analysis: co-ordinates and directionality plot

Supplementary Table 2. Voxel-based morphometry (VBM) overlap analysis showing common grey matter correlates of mind wandering performance in bvFTD and AD patients.

Regions	***Hemisphere (L/R/B)***	***MNI coordinates for voxel of maximal intensity***			***Number of voxels***	***p***
		X	***Y***	***Z***		
Caudate head; nucleus accumbens	R	12	0	16	316	.001
Dorsal caudate, thalamus	L	-14	-4	14	263	.001
Posterior hippocampus; parahippocampal gyrus	L	-24	-38	-6	114	.001

Results derived from an overlap masking procedure, using voxelwise approach and reported at $p < .005$ uncorrected with a cluster extent threshold of 100 contiguous voxels. L = Left, R = Right; MNI = Montreal Neurological Institute

Supplementary Figure 2 – Association between grey matter volume of the three clusters of interest and mind wandering index scores for all participants



Relationship between grey matter volumes in the three significant clusters and mind wandering index score, plotted for all participant groups: controls (blue), bvFTD (green), AD (red). a) Right striatal cluster; b) Left striatal cluster; c) Left hippocampal/parahippocampal cluster. Grey matter volumes in mm^3

7. Voxel-based morphometry (VBM) group comparisons

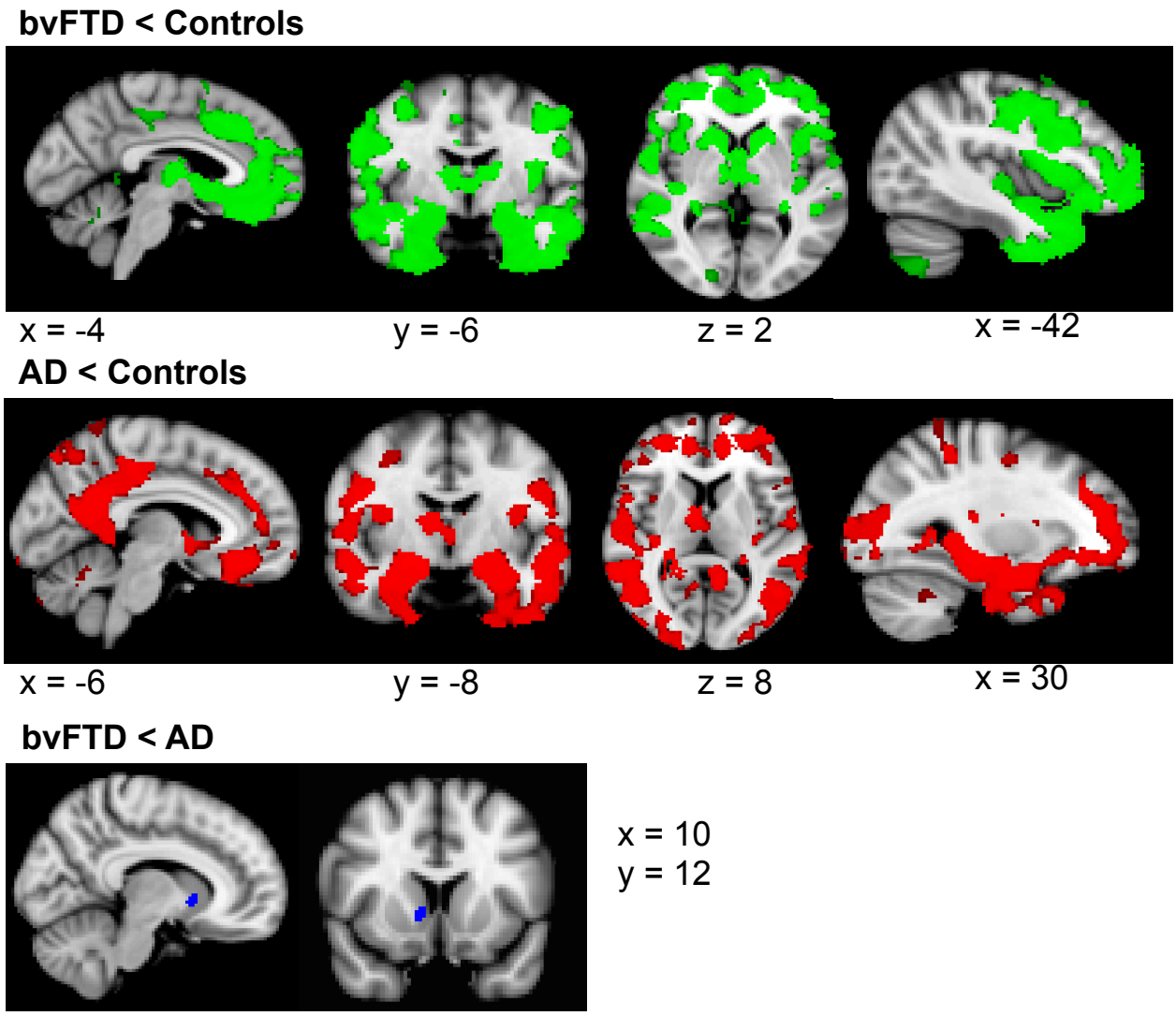
Results of the VBM group comparisons are shown in Supplementary Table 3 and Supplementary Figure 3. Relative to controls, bvFTD patients displayed reduced grey matter intensity in the bilateral prefrontal and insular cortices, anteromedial temporal lobes, hippocampus, amygdala, striatum and thalamus. Relative to controls, AD patients showed significant bilateral hippocampal grey matter intensity reduction, in the context of wider medial temporal, as well as lateral and medial parietal and prefrontal grey matter loss. These atrophy profiles are consistent with previous reports in bvFTD (e.g., (16) and AD (e.g., (17). Comparisons between bvFTD and AD did not survive at the level of $p < .01$ FWE corrected, however, at a less conservative threshold of $p < .05$ FWE, bvFTD patients displayed reduced grey matter intensity in the right ventral caudate and nucleus accumbens compared to AD.

Supplementary Table 3. Voxel-based morphometry (VBM) analysis showing regions of significant grey matter difference between groups.

Regions	*Hemisphere (L/R/B)*	*MNI coordinates for voxel of maximal intensity*			*Number of voxels*	*p*
		X	*Y*	*Z*		
bvFTD < Controls						
Frontal pole, frontal orbital/medial cortex, subcallosal cortex, inferior frontal gyrus, paracingulate/anterior cingulate cortices, middle/superior frontal gyri, pre/post centraol gyri, insular cortex, caudate, putamen, nucleus accumbens, thalamus, amygdala, hippocampus, temporal pole, medial temporal cortex	B	30	-8	-52	51,560	.000
Occipital pole; intracalcarine cortex	R	22	-90	-4	350	.004
Cerebellum (Crus II; VIIb)	L	-42	-66	-54	318	.004
Parietal operculum cortex	L	-44	-36	26	53	.008
AD < Controls						
Frontal pole, orbital frontal cortex, inferior frontal gyrus, paracingulate/anterior cingulate cortices, caudate, nucleus accumbens, thalamus, amygdala, hippocampus, temporal pole, medial temporal cortex, temporal parietal junction, posterior cingulate cortex/retrosplenial cortex, superior parietal lobe, occipital lobe	B	58	-24	-24	50,741	.000
Cerebellum (Crus I; VI)	R	26	-56	-32	305	.007
Cerebellum (Crus I; Crus II)	L	-52	-60	-44	272	.006
Cerebellum (Crus I; Crus II; VI)	R	46	-44	-42	162	.004
bvFTD < AD						
Ventral caudate, nucleus accumbens	R	12	10	-2	23	.044

Control vs. patient results FWE corrected at $p < .01$ and at a cluster threshold of greater than 50 contiguous voxels; patient comparisons at FWE corrected at $p < .05$ and at a cluster threshold of greater than 20 voxels; t values > 2.5

Supplementary Figure 3 Profiles of grey matter intensity decrease across patient groups



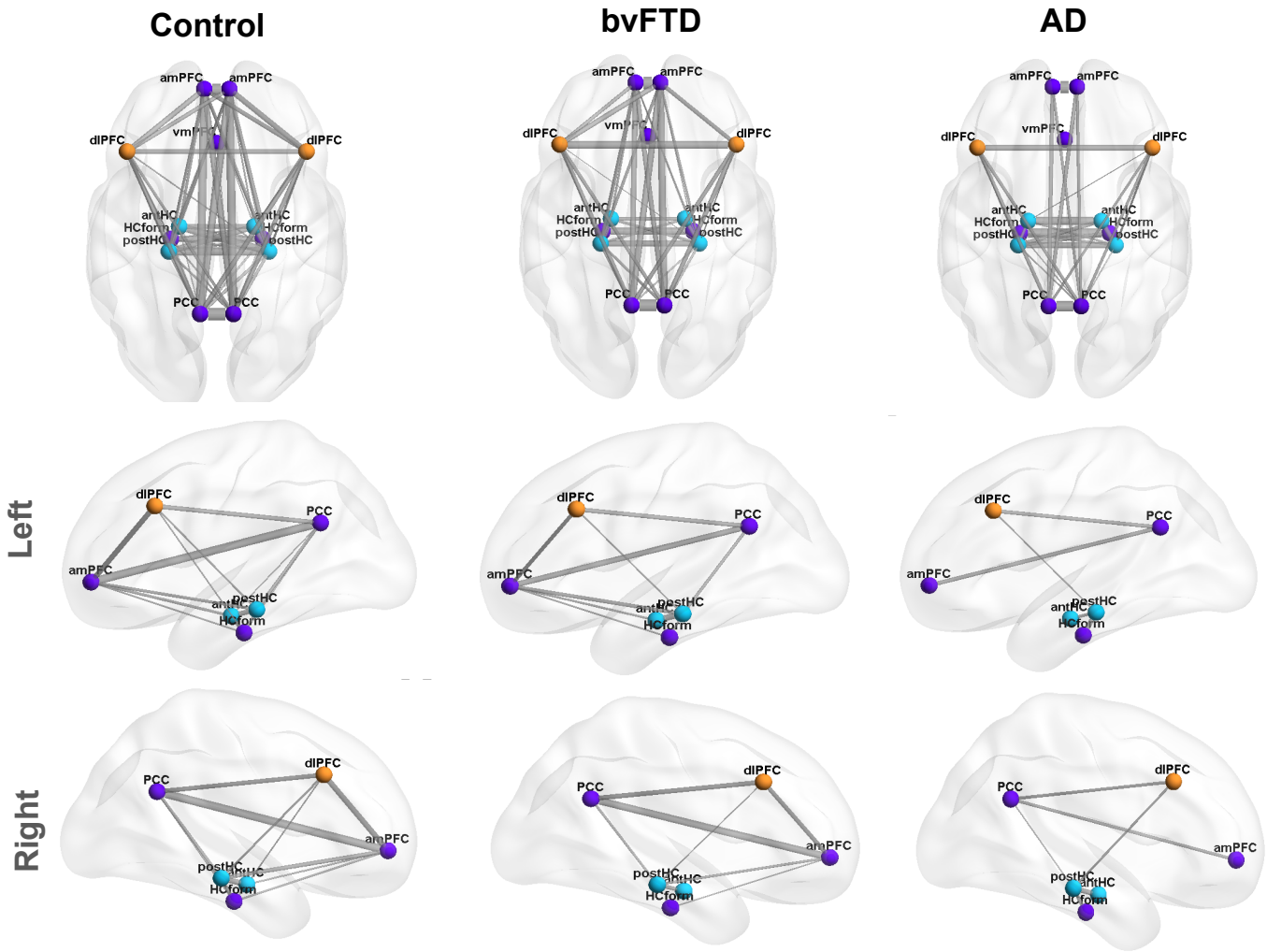
Legend – Voxel-based morphometry (VBM) analysis showing regions of significant grey matter intensity decrease in bvFTD relative to Controls (green)*, in AD relative to Controls (red)*, and in bvFTD relative to AD (blue)§. *Results FWE corrected at $p < .01$ and at a cluster threshold of greater than 50 contiguous voxels. § Results FWE corrected at $p < .05$ and at a cluster threshold of greater than 20 contiguous voxels. Left=left, Right = right.

8. Group comparisons of seed region connectivity

Results are shown in Supplementary Figures 4 and 5 a,b,c. The patient and control groups had a substantial amount of overlapping connectivity patterns between the ROIs that survived at FDR $q = .05$. However, compared to controls, the bvFTD group exhibited an absence of significant connectivity between the PCC and vmPFC, and PCC and several hippocampal regions, as well as between hippocampal regions (see Supplementary Figure 4a). Compared

to controls, the AD group showed an absence of significant connectivity between prefrontal regions, and also between prefrontal and hippocampal regions; the AD group also showed significant connectivity between the left anterior hippocampus and right dlPFC that was not evident in controls (see Supplementary Figure 4b). Comparing between the patient groups, apart from their overlapping connectivity patterns, bvFTD patients also showed significant connectivity between prefrontal and hippocampal regions that was not evident in AD. In contrast, the AD group showed significant hippocampal connectivity that was not evident in bvFTD (see Supplementary Figure 4c).

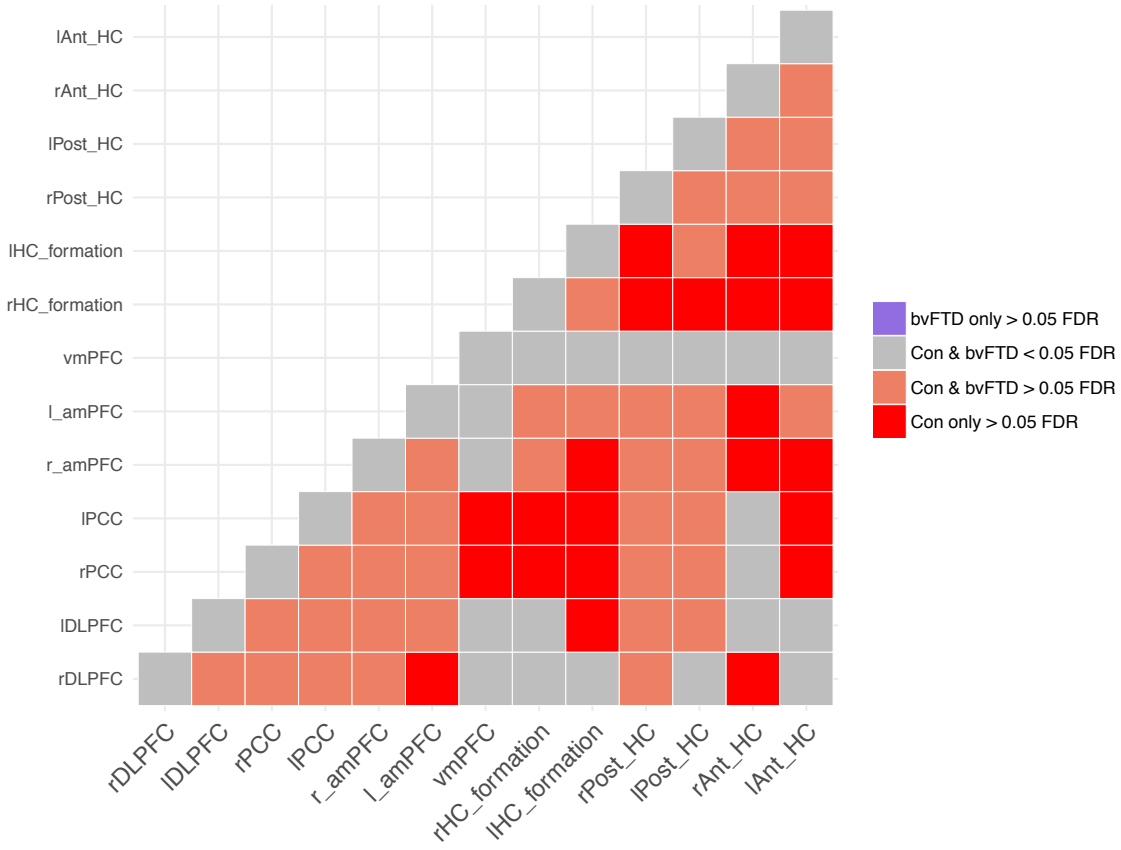
Supplementary Figure 4 Seed region connectivity patterns for each group



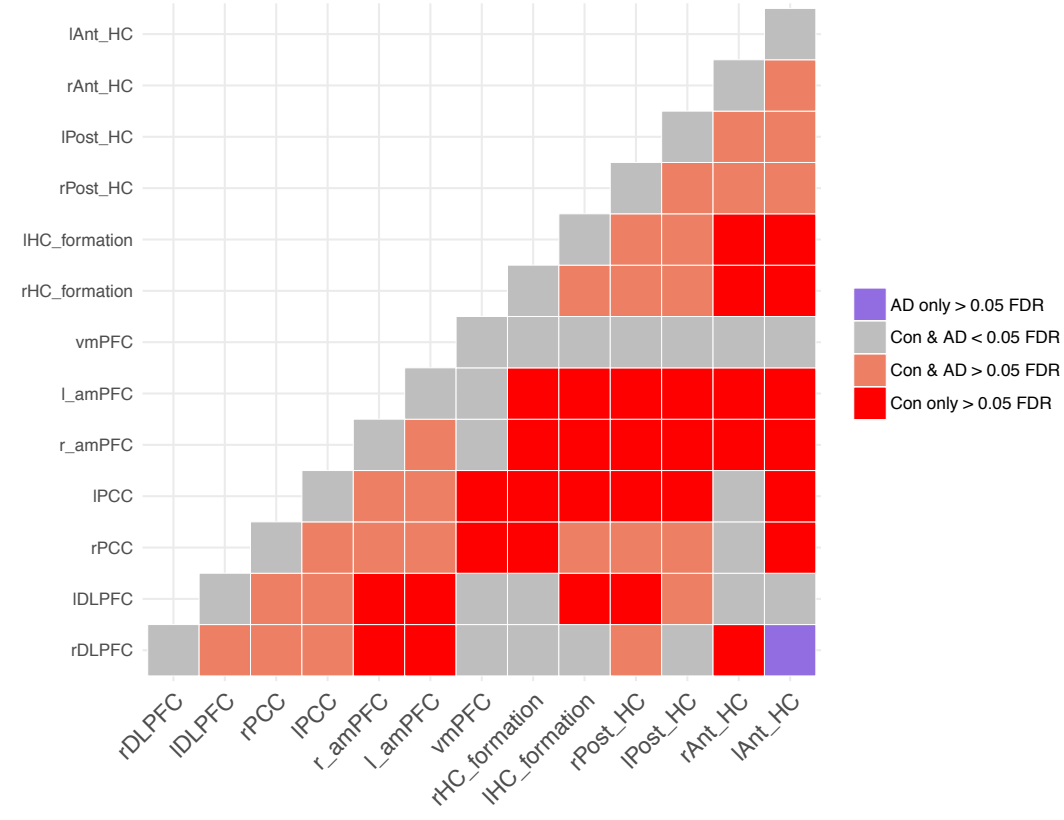
Legend – Grey lines show significant connectivity between the seed regions (ROIs) at FDR q = .05. Lines are weighted by connectivity strength. ROIs are sampled from default, frontoparietal and hippocampal regions: Purple = default network; Yellow = frontoparietal network; Blue = hippocampus. dlPFC = dorsolateral prefrontal cortex; PCC = posterior cingulate cortex; amPFC = anteromedial prefrontal cortex; vmPFC = ventromedial prefrontal cortex; HCform = hippocampal formation; postHC = posterior hippocampus; antHC = anterior hippocampus.

Supplementary Figure 5 Group differences in significant seed region connectivity

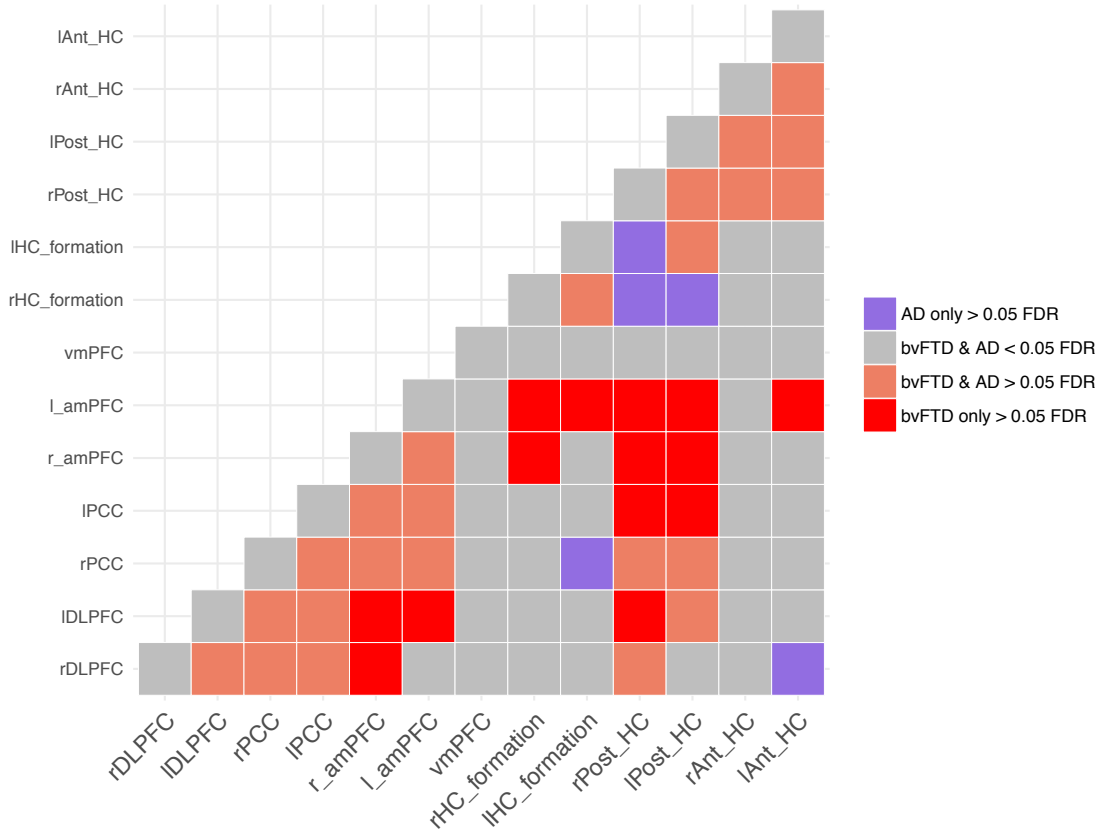
a) bvFTD vs Control



a) AD vs Control



c) bvFTD vs AD



Legend **–** l = left; r = right; ant_HC = anterior hippocampus; post_HC = posterior hippocampus; HC_formation = hippocampal formation; vmPFC = ventromedial prefrontal cortex; amPFC = anteromedial prefrontal cortex; PCC = posterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex.

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