Prospective memory impairments in Alzheimer's disease and behavioral variant frontotemporal dementia – clinical and neural correlates

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Abstract

Background: Prospective memory (PM) refers to a future-oriented form of memory in which the individual must remember to execute an intended action either at a future point in time (Time-based) or in response to a specific event (Event-based). Lapses in PM are commonly exhibited in neurodegenerative disorders including Alzheimer's disease and frontotemporal dementia, however, the neurocognitive mechanisms driving these deficits remain unknown.

Objective: To investigate the clinical and neural correlates of Time- and Event-based PM disruption in Alzheimer's disease (AD) and the behavioral-variant of frontotemporal dementia (bvFTD).

Methods: Twelve AD, 12 bvFTD, and 12 healthy older Control participants completed a modified version of the Cambridge Prospective Memory test, which examines Time- and Event-based aspects of PM. All participants completed a standard neuropsychological assessment and underwent whole-brain structural MRI.

Results: AD and bvFTD patients displayed striking impairments across Time- and Event-based PM relative to Controls, however, Time-based PM was disproportionately affected in the AD group. Episodic memory dysfunction and hippocampal atrophy was found to correlate strongly with PM integrity in both patient groups, however, dissociable neural substrates were also evident for PM performance across dementia syndromes.

Conclusion: Our study reveals the multifaceted nature of PM dysfunction in neurodegenerative disorders, and suggests common and dissociable neurocognitive mechanisms which subtend these deficits in each patient group. Future studies of PM disturbance in dementia syndromes will be crucial for the development of successful interventions to improve functional independence in the patient's daily life.

Keywords: Alzheimer’s disease; behavioral variant frontotemporal dementia; prospective memory; episodic memory; hippocampus; parietal lobe; frontal lobe.

Introduction

Episodic memory dysfunction represents one of the most prominent and characteristic features of Alzheimer's disease (AD) [1], widely interpreted as reflecting the degeneration of the medial temporal lobes, most notably the hippocampus [2]. Episodic memory impairments in AD are cross-modal extending across standard neuropsychological tests of visual and verbal recall [3] and include the retrieval of personally relevant autobiographical memories from the past [4, 5]. While the hippocampus has been ascribed a central role in the origin of memory deficits in AD, the importance of regions beyond the medial temporal lobes in supporting successful episodic memory functioning is recognized. Notably, atrophy in parietal regions, such as the posterior cingulate cortex, and prefrontal cortices also contributes to episodic memory dysfunction in AD [6, 7].

The behavioral-variant of frontotemporal dementia (bvFTD) is a form of younger-onset dementia characterized clinically by progressive deterioration in interpersonal conduct and personality, executive dysfunction, and emotion dysregulation [8]. These features are attributable to the degeneration of orbitomesial frontal and anterior temporal lobe regions in the brain, particularly the anterior cingulate cortex (ACC) and the frontoinsular cortex [9, 10]. Mounting evidence, however, reveals marked episodic memory impairments in bvFTD, at a level comparable to that observed in disease-matched cases of AD [6, 11]. These memory deficits are attributable to the degeneration of predominantly medial and lateral prefrontal, and medial temporal lobe structures including the hippocampus [6]. Thus while episodic memory appears comparably affected in bvFTD and AD, the underlying neural substrates of these deficits diverge contingent on dementia subtype [6, 7].

Prospective memory (PM) refers to a sub-branch of episodic memory whereby an individual must remember to perform a planned action or intention at some point in the future [12] and

can be fractionated into Time- versus Event-based components depending on the type of cue which prompts recall of the planned activity. Time-based PM involves remembering to do something at a particular time or following a specific period of time whereas Event-based PM involves remembering to do something in response to an external cue. The ability to remember to do something at a later point in time allows us to think and plan beyond the present moment and is essential for successful everyday adaptive functioning. Accordingly, PM dysfunction considerably limits the capacity to function independently and is associated with a decline in independent activities of daily living, difficulties with financial management, and poor medication adherence [13, 14].

Successful PM performance draws upon multiple cognitive processes, including retrospective memory, planning, inhibition, task switching, and sustained attention or monitoring [15, 16]. This complexity is reflected at the neural level. Prefrontal regions, including the rostral prefrontal cortex (BA10), consistently activate during PM performance in healthy individuals potentially reflecting intention maintenance [17, 18]. Lesions to prefrontal regions have been shown to significantly compromise PM function [19, 20], corroborating the neuroimaging findings. Regions beyond the frontal lobes are also implicated in successful PM function. For example, parietal activation may support allocation of attention towards external stimuli and the PM intention, as well as maintenance and retrieval of the intention itself [18]. Moreover, medial temporal lobe regions, including the hippocampus, are implicated in the retrieval of an action or recognition of a cue during PM tasks [21, 22]. Finally human lesion studies [19] and functional neuroimaging studies [21, 23] point to occipital involvement, with the suggestion that representations of the PM cue may be stored in occipital sites [23]. As such, the evidence to date reveals a distributed set of brain regions which support the capacity for PM performance.

Age-related PM decline is observed across both Time- and Event-based components [24]. Notably, however, Time-based PM appears disproportionately disrupted relative to Event-based tasks in healthy older adults [24], suggesting that Time-based PM is a more cognitively difficult endeavor, potentially due to its greater dependence on self-initiated retrieval processes [24]. Compromised PM performance represents one of the most pervasive forms of memory disturbance in dementia and is viewed by caregivers as more disruptive than retrospective memory failures [25]. PM dysfunction is consistently demonstrated irrespective of dementia syndrome, with difficulties reported in Parkinson's Disease patients with cognitive impairment [26] and in amnestic and dysexecutive subtypes of Mild Cognitive Impairment [27]. In addition, while impairments of retrospective episodic memory are considered to be a characteristic feature of AD [1], a number of studies suggest that PM failures occur at least as frequently in this population and are as severe [25]. Given that PM difficulties are evident in preclinical AD and in very mild AD [28], substantial PM decline may be an early indicator of dementia [29].

To date the vast majority of studies of PM have focused on its disruption in MCI and AD [reviewed by 30], however, a recent study demonstrated marked PM dysfunction in bvFTD. Striking deficits were observed across Time- and Event-based forms of PM, with bvFTD patients scoring in line with disease-matched cases of AD [31]. These PM impairments were suggested to reflect potentially divergent underlying cognitive processes in each patient group however, the underlying neural substrates of these deficits were not explored.

The present study represents the first investigation of the neural correlates of PM disruption in AD and bvFTD syndromes. Given converging evidence pointing to dissociable neural substrates of episodic memory disruption in AD versus bvFTD [6, 7] we predicted that unique neuroanatomical correlates of PM dysfunction would emerge in each patient group. Specifically, we hypothesized that a distributed network of frontal, medial temporal, and

parietal regions would be implicated in AD, whereas predominantly anteromedial temporal and prefrontal regions would be involved in bvFTD. Importantly, given mounting evidence pointing to the involvement of the hippocampus in the genesis of EM dysfunction in bvFTD [6, 32], we predicted that the hippocampus would represent a common neural correlate across the two disease syndromes.

Methods and Materials

Participants

A total of 36 subjects participated in this study: 12 with a clinical diagnosis of Alzheimer's disease (AD), 12 with a diagnosis of clinically probable behavioral-variant frontotemporal dementia (bvFTD) and 12 healthy older Control participants, all recruited through FRONTIER at Neuroscience Research Australia (NeuRA), Sydney. Dementia patients met current clinical diagnostic criteria for AD [1] or bvFTD [8]. Diagnosis was established by consensus among a senior neurologist (JRH), neuropsychologist, and occupational therapist based on extensive clinical investigations, detailed cognitive assessment, carer interviews, and evidence of atrophy on structural neuroimaging. Briefly, AD cases displayed significant episodic memory loss in the context of preserved socioemotional functioning and comportment. In contrast, bvFTD patients presented with an insidious decline in personality and socioemotional functioning accompanied by loss of insight and motivation. In addition, all bvFTD patients had normal spoken language; cases with mixed bvFTD/Primary Progressive Aphasia presentation were excluded. Only dementia patients with evidence of definitive progression over time as revealed by atrophy on MRI scans, and information from

carer reports, were included. Patients were assessed as part of their routine clinical visit, with PM testing typically taking place on the second day of a two-day visit.

Healthy Controls were recruited through the NeuRA research volunteer panel and local community groups. All Controls scored 0 on the Clinical Dementia Rating Scale [CDR; 33] and 88 or above on the Addenbrooke's Cognitive Examination Revised [ACE-R; 34]. Exclusion criteria for all participants included prior history of mental illness, movement disorders, significant head injury, cerebrovascular disease, alcohol or other drug abuse, and limited English proficiency. Ethical approval for this study was obtained from the South Eastern Sydney Local Health District and the University of New South Wales ethics committees. All participants, or their person responsible, provided informed consent in accordance with the Declaration of Helsinki.

General cognitive screening

Participants were assessed across the following neuropsychological tests: ACE-R to establish overall level of cognitive functioning [34]; verbal letter fluency [F,A,S; 35]; the Rey Auditory Verbal Learning Task to assess verbal episodic encoding and retrieval [RAVLT; 36]; the Rey Complex Figure as an index of non-verbal episodic delayed recall [37]; the Trail Making test [Parts A and B; 38] to measure set-switching and divided attention; and Digit Span Backwards, from the Wechsler Adult Intelligence Scale, to assess attention/short-term working memory [39]. Verbal semantic performance was assessed using the Naming and Comprehension subscales of the SydBat [40], and the Hayling test [41] was used as an index of response inhibition. Carers rated memory and motivation changes of patients on the Cambridge Behavioural Inventory [CBI; 42]. Finally, the functional status of patients was

determined using the Frontotemporal Dementia Functional Rating Scale [FRS; 43], which is a dementia staging tool sensitive to changes in functional abilities and presence of neuropsychiatric symptomatology.

Assessment of Prospective Memory

The procedure for this study has been described in detail elsewhere [31]. Briefly, a modified version of the Cambridge Prospective Memory Test was used to examine Time- and Event-based components of PM. This shorter version of the task instructed participants to complete three Time-based and three Event-based tasks whilst engaged in a filler task (viewing and describing humorous cartoons). The Time-based tasks required participants to execute an intended action after a specified amount of time had elapsed (e.g., request a pencil from the experimenter after 10 minutes) while the Event-based tasks required participants to execute an intended action following the occurrence of specific event (e.g., put the notebook on the floor when the alarm sounds). Instructions were read aloud verbatim from a standard script at the beginning of the session. These instructions were provided in the same order for all participants, with the Time-based PM instructions read first, as per Kamminga, et al. [31]. If necessary, an instruction was repeated, but no instruction was provided more than twice. Participants were encouraged to use a pencil and paper to assist them with remembering these instructions in order to reflect the access to memory assistance tools which exist outside of an experimental context and to reduce the working memory demands of the task. All the requisite materials for the PM task, including materials for noting the task instructions and a clock to monitor the time, were in full view of the participant for the duration of the task. Full test instructions are provided in Supplementary Information. The entire task took approximately 20 minutes to complete.

Scoring of Prospective Memory Task

PM performance was measured via two outcome scores: Time-based and Event-based PM. As outlined above, each PM subscale comprised three items, each of which contained two components: (i) the action to be executed, (ii) the cue, following which the action should be completed. For Time-based items, the cue represented a set amount of time (e.g., 5 minutes), while for Event-based items, the cue was the occurrence of a specific event (e.g., the alarm ringing). Each item was awarded a maximum of 2 points: participants were given one point for successful execution of the correct action, and one point for performing any action within 3 minutes of the specified cue. In addition, a further point was awarded to each subscale score if the participant used the provided external aids (pencil and paper) to take note of the task instructions. Thus, performance scores for each subscale ranged from 0-7. For each outcome measure, higher scores represented better PM performance.

Statistical analyses

Cognitive data were analyzed using IBM SPSS Statistics (Version 22.0). Multivariate analyses of variance (MANOVA) with Sidak post hoc tests were used to explore main effects of Group (Controls, AD, bvFTD) for all general cognitive tests. PM scores were expressed as a percentage of the maximum score for each PM subscale to increase the overall variation in scores. One overall MANOVA was used to analyze differences in Time- and Event-based PM task performance across the two groups. Paired-sample t-tests were run to investigate within-group differences between Time- and Event-based PM performance. A series of MANCOVAs were subsequently run to determine the contribution of discrete cognitive processes of interest (e.g., general cognitive function, language, motivation, episodic memory). Pearson correlations between PM performance and background neuropsychological variables were also investigated. Chi-squared tests (X^2), based on the frequency patterns of dichotomous variables (e.g., sex), were used where appropriate.

Image acquisition

Participants underwent whole-brain T1-weighted images using a 3T Philips MRI scanner with standard quadrature head coil (8 channels). The 3D T1-weighted images were acquired using the following sequences: coronal orientation, matrix 256 x 256, 200 slices, 1 x 1 mm in-plane resolution, slice thickness 1 mm, echo time/repetition time = 2.6/5.8ms, flip angle α = 19º.

Voxel-based morphometry analysis

Three-dimensional T1-weighted sequences were analyzed with FSL-VBM, a voxel-based morphometry analysis [44, 45] using the FSL-VBM toolbox from the FMRIB software package (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM/UserGuide) [46]. Briefly, brain-extracted structural images underwent tissue segmentation, and non-linear registration [47, 48] to align gray matter partial volumes to the Montreal Neurological Institute standard space (MNI152) using a using a b-spline representation of the registration warp field [49]. A study-specific template was created using the resulting images, to which the native gray matter images were re-registered nonlinearly. The registered partial volume maps were then modulated by dividing by the Jacobian of the warp field to correct for local expansion or contraction. Finally, the modulated segmented images were smoothed with an isotropic Gaussian kernel with a sigma of 3mm.

An unbiased whole-brain general linear model was employed to investigate gray matter intensity differences via permutation-based non-parametric testing [50] with 5000

permutations per contrast. Differences in cortical gray matter intensities between patients and Controls were assessed using regression models with separate directional contrasts (i.e., t-tests). Clusters were extracted using the threshold-free cluster enhancement method (tfce) and corrected for Family Wise Error (FWE) at $p < .05$.

Covariate analyses

Correlations between the two scores of interest on the PM task (Time-based PM, Event-based PM) and regions of gray matter intensity were investigated in AD and bvFTD patients combined with Controls. An unbiased voxel-wise whole-brain approach was used across all covariate VBM analyses. For additional statistical power, a covariate-only general linear statistical model was employed. A positive *t*-contrast was used in the covariate model, providing an index of association between gray matter volume and PM scores. Two separate models were created to investigate the neural substrates of Time- and Event-based PM performance, with age included as a nuisance variable. Anatomical locations of significant results were overlaid on the MNI standard brain, with maximum coordinates provided in MNI stereotaxic space. Anatomical labels were determined with reference to the Harvard-Oxford probabilistic cortical atlas.

Overlap analyses were then conducted to identify common regions of gray matter intensity decrease implicated in (i) Time-based and (ii) Event-based PM disruption irrespective of patient diagnosis [see also 51]. The statistical maps generated from the Time- and Event-based covariate analyses were scaled using a threshold of $p < .001$, following which the scaled contrasts were multiplied to create an inclusive, or overlap, mask across groups for Time- and Event-based PM performance. To determine the unique contributions to PM

performance in each patient group, an exclusive masking procedure was adopted, whereby each scaled image was subsequently multiplied by the inverse of the other scaled image to create an exclusive mask for each patient contrast (e.g. ADTimePM x inverse of BVTimePM). For the overlap and exclusive masking analyses, clusters were extracted at $p <$ .001 uncorrected, using a strict cluster threshold of 100 contiguous voxels.

Results

Demographics

The groups did not different significantly with regard to age ($F(2,33)=2.539$, $p=.094$), years of education completed ($F(2, 33) = 1.476$, $p = .243$), or sex distribution ($\chi(2) = .225$, $p = .894$). Further, the patient groups did not significantly differ with respect to disease duration (i.e. months elapsed since symptom onset) ($F(1, 22) = .095$, $p = .761$) (see Table 1).

General cognitive functioning

Neuropsychological test results are displayed in Table 1. In brief, group differences were evident for global cognitive functioning ($F(2, 33) = 18.434$, $p <.0001$), with both patient groups demonstrating significantly poorer performance on the ACE-R screening task relative to Controls (AD, $p < .0001$; bvFTD, $p = .004$). In addition, there was the suggestion that AD patients were more cognitively impaired than bvFTD patients, ($p = .050$). In contrast, bvFTD displayed significantly more behavioral disturbances relative to AD patients, as rated by caregivers on the CBI, in terms of abnormal behavior ($t = -2.66$, $p = .014$), stereotypical behavior ($t = -2.50$, $p = .020$) and apathy ($t = -3.33$, $p = .003$), however, ratings of changes in

memory were not found to differ between the patient groups (t = .815, p = .424). Disease severity reflected in changes in one's ability to complete everyday tasks and presence of behavioral symptoms (e.g., lack of interest in tasks, impulsivity), as measured by the FRS, was also significantly worse in bvFTD patients compared to AD patients (F(1, 20) = 10.501, p = .004).

Neuropsychological testing revealed cognitive profiles characteristic of AD and bvFTD (Table 1). Briefly, both patient groups displayed significant verbal episodic memory impairments relative to Controls on the RAVLT (F(2, 27) = 16.099, p < .0001; AD p < .0001; bvFTD, p < .0001) with no significant difference between the patient groups (p = .999). Similarly, visual episodic memory on the RCF was significantly compromised relative to Controls (F(2, 28) = 18.733, p < .0001; AD & bvFTD p < .0001) with comparable performance in the patient groups (p = .959). In contrast, visual episodic recognition memory on the Doors and People Test Part A was found to be relatively intact in AD (p = .071) and bvFTD (p = .135). A significant group effect was evident on the Trail Making Test Part A (F(2, 29) = 3.366 p = .048) driven by reduced speed of processing in AD (p = .057) but not in bvFTD (p = .896). Difficulties in set-shifting on the Trail Making Test Part B-A were also evident (F(2, 24) = 6.483 p = .006) again driven by the AD group (p = .004; bvFTD, p = .438). Working memory difficulties on the Digit Span Backwards task were found (F(2, 30) = 12.411, p < .0001) with deficits present in both AD (p < .0001) and bvFTD (p = .004) relative to Controls, but no significant difference between the patient groups (p = .646). Letter fluency was also compromised in the patient groups relative to Controls (F(2, 31) = 9.824, p < .0001; AD, p = .019; bvFTD p < .0001). Semantic processing impairments emerged on the Naming (F(2, 30) = 8.821, p = .001) and Comprehension (F(2, 30) = 8.145, p = 001) subscales of the SydBAT. While Naming was affected in both patient groups (AD, p = .001; bvFTD, p = .015), only AD patients displayed significant Comprehension impairments

relative to Controls (AD, $p = .001$; bvFTD, $p = .490$). Finally, both patient groups displayed significant deficits in terms of response inhibition on the Hayling task ($F(2, 27) = 14.379$, $p < .0001$); AD, $p = .005$; bvFTD $p < .0001$).

INSERT TABLE 1 AROUND HERE.

Prospective Memory Performance

Time- and Event-based PM

Figure 1 displays the percentage correct scores for Time- and Event-based PM performance in the participant groups. A multivariate analysis of variance (MANOVA) revealed a significant main effect of group for Time- ($F(2, 33) = 34.476$, $p < .0001$) and Event-based ($F(2,33) = 25.730$, $p < .0001$) PM performance. Sidak post hoc tests revealed significant Time-based impairments in AD and bvFTD patients relative to Controls (all p values < .0001), with AD patients disproportionately affected in comparison with their bvFTD counterparts ($p = .002$). For Event-based PM, both patient groups were impaired relative to Controls (all p values < .0001) with comparable performance evident between the patient groups ($p = .322$).

Within-group comparisons revealed comparable performance across Time- and Event-based PM tasks in the AD ($p = .293$) and bvFTD ($p = .420$) patient groups, however, a difference on the threshold of significance was observed in Controls with the suggestion that Event-based performance was higher relative to Time-based PM ($p = .054$).

To ensure that PM performance was not predominantly driven by overall level of cognitive functioning, we repeated the above analyses controlling for ACE-R total cognitive scores. The same pattern of results was evident with marked deficits for Time-based PM in both AD ($p < .0001$) and bvFTD ($p = .015$) relative to Controls, with AD patients continuing to score significantly lower than the bvFTD group ($p = .030$). Similarly, both patient groups showed marked Event-based PM impairments relative to Controls (AD: $p = .004$; bvFTD: $p = .003$) with no differences between the patient groups ($p = .843$). Finally, comparable PM performance was observed on the Time- and Event-based subscales across the participant groups (all p values > .2). As such, PM dysfunction in AD and bvFTD does not appear to be mediated by a general decline in cognitive functioning.

****INSERT FIGURE 1 AROUND HERE****

Correlations between PM performance and background neuropsychological tests

Table 2 displays the correlations between Time- and Event-based PM performance and neuropsychological variables in the participant groups. Pearson R correlations revealed significant associations between verbal episodic memory integrity and Time-based PM performance ($r = .741$, $p = .006$) in bvFTD. In contrast, Event-based PM performance was found to strongly correlate with episodic memory integrity in AD (RCF: $r = .868$, $p = .002$; RAVLT: $r = .849$, $p = .016$) and in Controls (RCF: $r = .653$, $p = .029$). No other significant relationships were evident across any of the other neuropsychological tests of global cognitive functioning, attention, executive function, language, or motivation (all p values > .07).

****INSERT TABLE 2 AROUND HERE****

Analyses of covariance

To determine whether distinct cognitive processes play a modulating role in PM performance in dementia, we conducted a series of analyses of covariance (ANCOVA) using the following variables: SydBAT Comprehension to assess language and semantic processing, delayed recall on the RAVLT and delayed recall on the RCF as indices of verbal and visual episodic memory processes, respectively, and CBI Motivation to measure levels of apathy.

Despite controlling for general language and comprehension performance on the SydBAT, group impairments continued to persist across both Time- ($F(2, 29) = 21.014$ $p < .0001$; AD: $p < .0001$; bvFTD: $p = .003$) and Event-based ($F(2, 29) = 13.917$, $p < .0001$; AD: $p < .0001$; bvFTD: $p = .001$) PM subscales. Notably, however, when we controlled for verbal episodic delayed recall on the RAVLT, overall group differences persisted for Time- based PM ($F(2, 26) = 7.230$, $p = .003$), however, these differences were driven exclusively by the AD group ($p = .005$; bvFTD: $p = .423$). In contrast, for Event-based PM, controlling for verbal episodic memory processes served to ameliorate the overall group effect ($F(2, 26) = 2.882$, $p = .074$) bringing both patient groups in line with Control performance (AD: $p = .072$; bvFTD: $p = .207$). Controlling for visual delayed episodic recall on the RCF failed to negate the overall group effect for either Time-based ($F(2, 27) = 8.827$, $p = .001$) or Event-based ($F(2, 27) = 4.071$, $p = .028$) PM, as AD patients continued to show impairments irrespective of subscale relative to Controls (Time: $p = .002$; Event, $p = .034$). In contrast, bvFTD patients were now found to score in line with Controls (Time, $p = .151$; Event, $p = .321$).

Finally, we investigated the role of apathy in mediating PM performance and found that controlling for motivation levels on the CBI failed to negate the group effect for either Time- ($F(2, 31) = 27.865$, $p < .0001$) or Event-based PM ($F(2, 31) = 15.871$, $p < .0001$), however Sidak post hoc tests revealed a differential effect contingent on patient group. For Time-based PM, group differences continued to persist in both AD ($p < .0001$) and bvFTD ($p = .022$), however, controlling for apathy negated the Event-based PM deficit in bvFTD ($p = .213$), but not in AD ($p < .0001$).

As such, these analyses suggest that decline in episodic memory processes may, in part, mediate Time- and Event-based PM dysfunction in bvFTD, with an additional role evident for levels of motivation in modulating Event-based PM. In AD, episodic memory disruption represents a candidate mechanism for Event-based PM impairments however the neurocognitive processes mediating Time-based PM deficits in AD remain unclear.

Voxel-based morphometry analyses

Gray matter atrophy in AD and bvFTD

Figure 2 displays the patterns of brain atrophy displayed by (A) AD and (B) bvFTD patients relative to Controls using the threshold free cluster enhancement method (TFCE) and corrected for Family-Wise Error (FWE) at $p < .05$. Briefly, AD patients displayed widespread neural atrophy involving the prefrontal, lateral and medial temporal regions including the bilateral hippocampi, as well as extending posteriorly to include significant parietal atrophy involving the bilateral supramarginal and angular gyri, bilateral occipital cortices, and the left precuneus. BvFTD patients showed pronounced changes in bilateral medial and lateral prefrontal regions including the orbitofrontal cortex and anterior cingulate cortex, extending

into the insular cortices bilaterally, as well as lateral and medial temporal regions including the bilateral hippocampi. Posterior regions were significantly affected including the bilateral occipital cortices, and the right angular and supramarginal gyrus (Table 3). Direct comparisons of the patient groups failed to reveal significant clusters at the $p < .05$ FWE corrected threshold. These patterns of atrophy are consistent with previous reports in AD [52] and bvFTD [53].

****INSERT FIGURE 2 AROUND HERE****.

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Neural substrates of Time-based PM

Figure 3A displays the common and unique neural correlates of Time-based PM performance in AD and bvFTD. Regions commonly implicated in Time-based PM disruption, irrespective of group, included the bilateral hippocampi, bilateral amygdalae, as well as lateral temporal regions including the left temporal pole and left temporal fusiform cortex (see Table 4). Exclusive masking analyses revealed a distributed network of regions implicated in Time-based PM disruption in AD, including the bilateral orbitofrontal cortex and frontal pole, bilateral temporal poles, bilateral hippocampus, bilateral occipital cortices, and the left angular gyrus. In contrast, regions exclusively implicated for Time-based PM disruption in bvFTD were centered on the left frontal and left anteromedial temporal lobes including the temporal fusiform cortex, temporal pole, hippocampus, and orbitofrontal cortex (see Table 4).

Neural substrates of Control Time-based PM performance are presented in Supplementary Information.

****INSERT FIGURE 3 AROUND HERE****.

****INSERT TABLE 4 AROUND HERE****.

Neural substrates of Event-based PM

Figure 3B displays the common and unique neural correlates of Event-based PM performance in AD and bvFTD patients. Our overlap analyses failed to reveal any significant overlap in the neural substrates of Event-based PM disruption across the patient groups. Regions exclusively implicated in AD included the right orbitofrontal cortex, left hippocampus, bilateral middle temporal gyrus and right temporal pole, extending posteriorly to include the left superior parietal lobule and bilateral angular gyrus, as well as the right precuneus, and left occipital pole. In contrast, for bvFTD patients, regions exclusively in the temporal lobes including notably the bilateral hippocampus and left lateral temporal cortices were implicated for Event-based PM disruption (see Table 5). Neural substrates of Control Event-based PM performance are presented in Supplementary Information.

****INSERT TABLE 5 AROUND HERE****.

Discussion

This study represents the first investigation of the neural correlates of PM dysfunction in the neurodegenerative disorders of AD and bvFTD. On a behavioral level, our findings reveal marked PM disruption across the patient groups, with Time-based PM disproportionately affected in AD relative to bvFTD participants. Notably, the integrity of episodic memory emerged as a key modulator of performance irrespective of PM subtype in bvFTD, and for Event-based PM disruption in AD. This observation was corroborated on the neural level with the hippocampus emerging as a common region implicated irrespective of group or PM task. Interestingly, levels of motivation were also found to modulate Event-based PM performance in bvFTD, while the mechanisms underpinning Time-based disruption in AD remain unclear. Our findings demonstrate that while commonalities exist in the neural substrates of PM dysfunction in AD and bvFTD, discrete neural systems underlie PM dysfunction in each group. Here, we discuss the implications of our findings for understanding PM dysfunction in dementia syndromes.

The present findings converge with a growing body of evidence pointing to significant episodic memory dysfunction in bvFTD extending across laboratory [6, 11], autobiographical memory [5] and source memory [54, 55] tasks. Notably our findings corroborate a previous study in which marked PM impairments were observed in bvFTD across both Time- and Event-based PM subscales [31]. Importantly, here we demonstrate that episodic memory processes significantly modulate the capacity for PM performance, irrespective of PM domain, as controlling for delayed episodic recall significantly ameliorated PM deficits in the bvFTD group. General levels of motivation, as measured on the CBI, were also found to significantly influence Event-based PM performance in bvFTD suggesting that the origin of Event-based disruption is multifactorial. As such, difficulties in retrieving the to-be-

remembered information, coupled with increased levels of apathy characteristically seen in this syndrome represent the chief candidate cognitive mechanisms driving PM impairments in bvFTD. The interplay between apathy and episodic memory processes in bvFTD remains underexplored and it will be important to determine how loss of motivation impacts the capacity to encode, store and retrieve new information in this syndrome.

Our proposal of a central role for episodic memory processes in PM disruption in bvFTD was confirmed on the neuroanatomical level with the hippocampus consistently implicated irrespective of PM subtask in this syndrome. Hippocampal atrophy is well documented in bvFTD [32] and has been shown to correlate robustly with episodic memory dysfunction in this group [6]. Accordingly, compromised PM performance in bvFTD may reflect disruption of the retrospective memory search processes required to retrieve the intended action, a process which is mediated by the hippocampus [56]. Notably, for Time-based PM performance, predominantly left-lateralized regions including the temporal fusiform cortex, parahippocampal gyrus, inferior temporal gyrus, and temporal pole were implicated, reflecting a predominantly anteromedial system, largely implicated in episodic memory performance, that is compromised in bvFTD [6].

PM performance is typically conceptualized as a frontally-mediated function [16], and impairments in this domain in bvFTD would ostensibly be viewed as relating to frontal lobe degeneration. Interestingly, we found significant involvement of the left orbitofrontal cortex albeit exclusively on the Time-based task in bvFTD. Lesions to the orbitofrontal cortex are associated with impulsivity and alterations in time perception [57] leading to a profound myopia for the future [58]. As such, Time-based PM deficits in bvFTD may, in part, stem from an impaired capacity to accurately perceive time, and indeed temporal processing difficulties are present in this disorder [59]. Time perception therefore represents a

particularly interesting line of enquiry in light of recent findings revealing marked impairments in the ability to successfully project forwards to envisage the future in bvFTD [reviewed by 60]. Notably, future thinking deficits in bvFTD are attributable to atrophy in the right hippocampus and right frontopolar regions [61], underscoring the role of prefrontal and medial temporal lobe interactions in supporting future-oriented memory processes.

While the neural substrates of PM dysfunction in bvFTD resided predominantly in anteromedial brain regions, a more widespread network was implicated in the AD group. Unsurprisingly, AD patients displayed marked deficits irrespective of PM subscale, however, Time-based PM appeared disproportionately disrupted relative to the bvFTD group. Notably, this profile of PM deficits in AD did not merely reflect a general decline in cognitive functioning, as the same overall pattern of results persisted despite controlling for level of cognitive function using the ACE-R. Interestingly, Event-based PM deficits were ameliorated when we controlled for delayed verbal episodic retrieval processes, replicating our finding in the bvFTD group and pointing towards a common underlying cognitive mechanism driving Event-based PM disruption in both dementia subtypes.

The genesis of Time-based disruption in AD, however, remains unclear, as our covariate analyses failed to reveal a distinct modulator of this form of PM disruption. Disorientation to time is a hallmark clinical feature of AD [1] and it has been suggested that such temporal confusion relates to the degeneration of pathways connecting the hippocampus with posterior parietal structures [62]. Our voxel-based morphometry analyses supports the involvement of the hippocampus and parietal regions such as the angular gyrus, within a distributed network of other frontal, lateral temporal, and occipital regions. A number of studies point to the potential role of the frontal poles in supporting the capacity for time estimation [22, 63] and it is interesting in this regard that the bilateral frontal poles were also implicated in the AD

group. Given that Time-based PM tasks require the individual to predict the future time point at which a response should be enacted, it has been proposed that frontopolar involvement might reflect the capacity to envisage one's future behavior [22]. Notably, simulation of future events and information is grossly compromised in AD [64] with frontopolar regions strongly implicated in these deficits [65]. Accordingly, atrophy in frontopolar regions in AD may disrupt a time perception mechanism that is central to all forms of future-oriented thinking, including PM and future simulation. While we did not explore the contribution of time perception and PM performance in this study, systematic investigation of the interplay between these processes in the dementias is warranted. Further, we did not determine the capacity for patients to accurately read, or indeed remember, the specified times during the Time-based PM trials. Given that deficits in clock reading are prominent in AD [66], use of a clock as an external aid on PM tasks may not prove as effective as Event-based cues such as an alarm, culminating in the differential PM profiles observed here.

In keeping with previous studies of episodic memory dysfunction in AD [6, 7], we also found significant parietal involvement underpinning PM deficits in AD. Activation of parietal regions such as the angular gyrus and supramarginal gyrus, in concert with the prefrontal cortices, is consistently reported in functional neuroimaging studies of PM performance in healthy individuals [18]. These sites form part of a broader cognitive control network, which supports sustained attention and goal-directed cognition, as well as a range of cognitively demanding tasks such as planning and problem-solving [67]. Recent studies indicate that disruption of this frontoparietal cognitive control network in AD adversely impacts episodic memory performance [68]. Our finding of bilateral angular gyri involvement irrespective of PM subtype in AD is therefore notable. While the precise functions of the angular gyrus remain unclear, degeneration of this region in AD may disrupt the integration of information and imparting of meaning towards an intended action [69]. Our findings resonate with the

conceptualization of PM as lying at the interface between the domains of memory and attention, with successful PM performance requiring a shift between external stimuli (e.g., cues) and representations of intentions stored in memory [18]. While the precise neurocognitive mechanisms driving Time-based PM deficits in AD remain unclear, our behavioral and neuroimaging analyses underscore the multifactorial nature of PM dysfunction in AD, likely reflecting the deterioration of episodic memory, compromised time perception mechanisms, and disruption of core cognitive control processes.

Finally, our neuroimaging analyses revealed the involvement of the lateral occipital cortices and occipital poles across Time- and Event-based forms of PM in AD. The exact role of occipital regions in PM, and indeed in general episodic memory, remains to be elucidated, however, it is notable that lesions involving occipital regions are associated with gross impairments in retrospective and prospective memory [70]. It has further been suggested that occipital cortical regions may support cue encoding during PM tasks [18, 23]. It will be important for future studies to delineate the contribution of these regions in order to understand how occipital atrophy in AD impacts PM performance.

The clinical implications of our findings are important when we consider the pervasive nature of PM disruption across dementia syndromes. PM is crucial for the successful execution of many everyday tasks essential for functional independence, for example, remembering to take medication, or to turn off the stove after cooking. In the context of dementia patients who are characterized by marked functional impairments, deficits in PM are particularly disquieting and may further contribute to decline in independent activities of daily living, difficulties with financial management, and poor medication adherence [13, reviewed by 14]. Our covariate analyses point to a central role for episodic memory processes in Time- and Event-based PM dysfunction in bvFTD, and Event-based PM in AD. Interestingly, during

testing it was observed that the patients did typically respond to the occurrence of the Event-based cues, suggesting that our findings do not reflect a detection problem *per se*. For example, patients would note and respond to an alarm (one of the Event-based cues signaling that the planned action was to be executed) by pointing out that the alarm had gone off. Nevertheless, they did not give an indication that the alarm signified anything of importance. Thus, it appears that the significance of the cue is lost in dementia suggesting that Event-based impairments reflect, in part, a breakdown in the association between cue and action. Alternatively, increased levels of apathy in bvFTD may render the patient indifferent to such external cues.

A number of methodological limitations warrant consideration. Firstly, our sample size is relatively small, and it will be important to replicate our findings in a larger sample. The PM task we used in this context, although sensitive to PM deficits in AD and bvFTD, arguably lacks ecological validity in terms of the type of difficulties that dementia patients might experience in their everyday lives. Future studies of PM in dementia using more ecologically valid measures will be essential to clarify how the deficits we report here manifest in the everyday environment of the individual. In addition, while the PM task is highly sensitive to memory dysfunction in AD and bvFTD, it is important to note that the task affords low specificity in terms of diagnostic utility. The disproportionate disruption of Time-based PM in AD relative to bvFTD warrants further investigation, as the mechanisms driving this impairment in AD remain unclear. While the AD patients were more cognitively impaired relative to the bvFTD group on a number of cognitive screening tasks, covarying for overall levels of cognitive functioning did not alter our main findings. It may be, however, that the Time-based PM task is more cognitively demanding than the Event-based subscale, as healthy Controls tended to perform significantly higher on the Event-based task. In addition, we did not counterbalance the order of Time- and Event-based conditions in this study and it

remains unclear how the use of our distraction task (identifying humor from cartoon scenes) could potentially influence PM performance. These methodological issues speak to the complexity of PM assessment using traditional pencil and paper tasks, and we suggest that future studies exploring PM in dementia should ensure that Time- and Event-based PM subscales are matched in terms of task difficulty and scoring. Finally, we did not ask patients to describe the approach they took to complete the task, particularly whether they relied on any compensatory techniques, and they were not asked to rate their experience of PM disruption on this task or in their daily lives. It would be interesting to ascertain whether the striking PM deficits observed on the experimental task used here correlate with subjective reports of PM dysfunction, or whether loss of insight which emerges in dementia syndromes alters awareness of PM deficits.

In conclusion, this study represents the first investigation of the neural substrates of PM dysfunction in AD and bvFTD. Our findings, while preliminary, suggest that episodic memory dysfunction and loss of motivation contribute to PM deficits in bvFTD, with the hippocampus emerging as a key region in this process. In AD, episodic memory dysfunction underpins Event-based PM deficits however the processes driving Time-based PM disruption remain elusive and reflect the degeneration of a distributed network of regions in the brain. Our findings highlight the multifaceted nature of PM disturbance in dementia syndromes and point to the need for further work in this area to develop targeted remediation strategies to improve functional independence in the patient's daily life.

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Table 1. Demographic and clinical characteristics of study samples[a]

Demographics and cognitive tests	**AD (n=12)**		**bvFTD (n=12)**		**Controls (n=12)**		**F test[c]**	**Post hoc tests**
	Mean(SD)	Range	Mean(SD)	Range	Mean(SD)	Range		
Sex (M:F)	7:5		7:5		6:6		n.s.	-
Age (years)	63.3 (8.7)	50-78	63.2 (5.9)	54-74	69(7.0)	60-79	n.s.	-
Education (years)	12.6 (3.5)	9-19.5	11.6 (2.9)	8-17	13.6(2.2)	11-17	n.s.	-
Disease Duration (months)	56.8 (30.2)	17-135	60.7 (32.1)	23-116	-	0-0	n.s.	-
ACE-R (100)	67.5 (13.9)	44-89	78.8 (12.7)	43.7-90	94.7 (2.8)	90.8-100	***	Patients < Control (AD < BV; p = .050)
RAVLT delayed recall (15)	3.1 (3.4)	2-9	3.3 (3.4)	2-12	10.5 (3.2)	8-16	***	Patients < Control (AD = BV)
RCFT 3 min recall (36)	4.5 (6.3)	0-18.5	5.6 (4.3)	0-13	18.0 (6.1)	7-27	***	Patients < Control (AD = BV)
Doors A (12)	8.0 (2.2)	5-11	8.4 (2.8)	3-12	10.9 (1.5)	8-12	n.s.	-
Trail Making Test A (s)	87.7 (79.9)	22-288	48.4 (22.6)	24-96	35.6 (11.0)	21-57	*	AD > Control (p =

								.057)
Trail Making Test B-A (s)	212.0 (161.5)	47-459	108.1 (76.6)	47-271	45.1 (10.7)	32-58	**	AD > Control
Digit Span Backwards (15)	4.1 (1.4)	2-7	5.0 (2.1)	2-8	8.1 (2.4)	4-12	**	Patients < Control (AD = BV)
Letter Fluency	29.5 (18.9)	3-66	21.0 (12.5)	1-47	47.9 (12.2)	22-63	**	Patients < Control (AD = BV)
Naming (30)	20.0 (5.0)	12-28	21.5 (2.9)	17-26	26.4 (2.3)	24-30	**	Patients < Control (AD = BV)
Comprehension (30)	24.5 (3.4)	15-28	27.3 (1.7)	24-29	28.7 (1.9)	24-30	**	AD < BV, Control
Hayling Total (Scaled Score)	3.2 (1.7)	1-6	2.1 (1.9)	1-7	5.9 (1.1)	4-7	***	Patients < Control (AD = BV)
CBI Motivation (%)	31.7 (31.6)	0-80	74.2 (30.9)	10-100	-	-	**	BV > AD
CBI Abnormal (%)	12.5 (13.8)	0-45.8	35.1 (26.0)	4.2-83.3	-	-	*	BV > AD
CBI Stereotypical (%)	18.9 (19.5)	0-62.5	49.0 (36.8)	0-100	-	-	*	BV > AD
CBI Memory (%)	25.2 (13.9)	9.4-75	46.8 (27.9)	0-100	-	-	n.s	AD = BV

FRS (Rasch Score)	0.9 (1.3)	-1.3-2.49	-0.6 (1.0)	-2.2-1.1	-	-	**	BV < AD

[a] Maximum score for each test in brackets next to test name where applicable. All participants were included in the above analyses except as follows: RAVLT available for 6 AD, 11 bvFTD and 11 Controls; RCFT available for 9 AD, 11 bvFTD and 11 Controls; Doors Part A available for 8 AD, 8 bvFTD and 7 Controls; Trail Making Test A data available for 10 AD and 10 Controls; Trail Making Test B-A data available for 8 AD, 9 bvFTD and 10 Controls; Digit Span Backwards available for 10 bvFTD and 11 Controls; Letter fluency available for 11 AD and 11 Controls; SydBAT Naming and Comprehension available for 11 bvFTD and 10 Controls; Hayling Test available for 9 AD and 9 Controls; FRS data available for 11 AD and 11 bvFTD patients. * $p < .05$; ** $p < .005$; *** $p < .0001$; n.s. = non-significant; '-' not applicable.

Table 2. Correlations between Time- and Event-based prospective memory and neuropsychological test performance [a]

Group	ACE-R Total	RAVLT Delayed Recall	RCFT 3 min recall	Trail Making Test B-A	Digit Span Backwards	Naming	Comprehension	CBI motivation
TIME								
AD	.28	.41	.34	-.36	-.21	.37	.17	.04
bvFTD	.44	.74**	.38	.16	.02	-.46	-.24	-.01
Controls	-.06	-.12	.01	.12	-.21	.31	-.24	-
EVENT								
AD	.49	.85*	.87**	-.32	.10	.38	.33	-.55
bvFTD	.19	.45	-.25	-.01	.27	-.34	-.41	-.20
Controls	.08	.05	.65*	-.16	.29	.22	.32	-

[a] Trail Making Test B-A available for 8 AD, 9 bvFTD and 10 Controls. RAVLT available for 6 AD patients and 11 Controls, RCFT available for 9 AD patients, 11 bvFTD patients and 11 Controls, Digit Span Backwards available for 10 bvFTD patients and 11 Controls, Naming and Comprehension data available for 11 bvFTD patients and 10 Controls. * $p < .05$; ** $p < .01$; '-' not applicable.

Table 3. Voxel-based morphometry results showing regions of significant grey matter intensity decrease in Alzheimer's disease and behavioral-variant FTD relative to Control participants

Contrast	Regions	Side	Number of voxels	MNI coordinates		
				x	*y*	*z*
AD vs Control	Occipital pole, lateral occipital cortex, angular gyrus, supramarginal gyrus, superior parietal lobule, inferior/middle/superior temporal gyrus, temporal pole, hippocampus, amygdala, insular cortex, left precuneus	B	23,089	-22	-94	6
	Paracingulate gyrus, medial prefrontal cortex, frontal pole, orbitofrontal cortex, inferior frontal gyrus, anterior cingulate gyrus	B	12,013	-2	54	-4
	Insular cortex, central opercular cortex, parietal operculum cortex, hippocampus, amygdala, putamen	R	1215	36	-8	8
	Caudate, thalamus, hippocampus	R	702	8	6	6
	Temporal pole	L	493	-46	10	-46
bvFTD vs	Temporal fusiform cortex, insular cortex, inferior/middle/superior temporal gyrus,	B	40,961	-30	-14	-48

Control	parahippocampal gyrus, temporal pole, hippocampus, amygdala, caudate, orbitofrontal cortex, frontal pole, paracingulate cortex, anterior cingulate gyrus					
	Lateral occipital cortex, occipital fusiform cortex, occipital pole	L	838	-50	-76	-14
	Lateral occipital cortex, angular gyrus, supramarginal gyrus, parietal operculum cortex	R	599	34	-76	-2
	Occipital pole, occipital fusiform gyrus, lateral occipital cortex	R	334	22	-92	-2

All clusters reported using threshold free cluster enhancement technique (tfce) and corrected for Family-Wise Error (FWE) at $p < .05$. All clusters reported at $t > 1.9$ with a cluster threshold of 100 contiguous voxels. AD = Alzheimer's disease; bvFTD = behavioral-variant frontotemporal dementia; L = Left; R = Right; B=Bilateral; MNI = Montreal Neurological Institute.

Table 4. Voxel-based morphometry results showing regions of significant grey matter intensity decrease associated with Time-based prospective memory performance in AD and bvFTD.

Contrast	Regions	Side	Number of voxels	MNI coordinates		
				x	*y*	*z*
Overlap	Hippocampus, amygdala	L	216	-26	-8	-24
	Hippocampus (posterior)	L	196	-36	-32	-10
	Temporal pole, temporal fusiform cortex	L	163	-30	2	-44
	Hippocampus, amygdala	R	115	26	-12	-24
Exclusive to AD	Lateral occipital cortex, occipital pole	R	1,824	50	-78	-8
	Middle temporal gyrus, angular gyrus, lateral occipital cortex	L	949	-48	-56	0
	Occipital pole	L	625	-16	-98	-18
	Orbitofrontal cortex, frontal pole	L	589	-30	34	-22
	Inferior frontal gyrus, middle frontal gyrus	L	323	-40	16	20
	Temporal pole	L	305	-28	14	-48
	Temporal pole	R	173	40	4	-46
	Hippocampus, amygdala	R	164	26	-12	-26
	Postcentral gyrus	L	158	-40	-24	36
	Temporal pole, orbitofrontal cortex	L	158	-22	4	-20
	Parahippocampal gyrus, hippocampus	R	133	36	-36	-10

	Inferior temporal gyrus	L	126	-60	-24	-30
	Anterior cingulate cortex	L	116	0	32	12
	Hippocampus (posterior)	L	114	-36	-34	-10
	Hippocampus, amygdala	L	108	-28	-8	-24
	Temporal pole	R	105	40	12	-20
	Orbitofrontal cortex, frontal pole	R	102	10	30	-28
Exclusive to bvFTD	Temporal fusiform cortex, parahippocampal gyrus, hippocampus (anterior), temporal pole, insular cortex, orbitofrontal cortex	L	1,114	-26	-6	-52
	Inferior temporal gyrus, middle temporal gyrus	L	412	-50	-4	-36
	Temporal fusiform cortex, hippocampus (posterior)	L	100	-38	-28	-12

All clusters extracted using overlap and exclusive masking technique and reported using voxel-wise contrasts and uncorrected at $p < .001$ and with a cluster extent threshold of 100 contiguous voxels. Age is included as a nuisance variable in all contrasts. All clusters reported at $t > 3.5$. L = Left; B = Bilateral; MNI = Montreal Neurological Institute.

Table 5. Voxel-based morphometry results showing regions of significant grey matter intensity decrease associated with Event-based prospective memory performance in AD and bvFTD.

Contrast	Regions	Side	Number of voxels	MNI coordinates		
				x	*y*	*z*
Overlap	No significant clusters					
Exclusive to AD	Middle temporal gyrus (temporooccipital part), angular gyrus, lateral occipital cortex	L	607	-44	-56	2
	Postcentral gyrus, precentral gyrus	L	307	-44	-26	36
	Hippocampus, amygdala	L	297	-28	-10	-22
	Middle temporal gyrus (temporooccipital part), angular gyrus	R	192	52	-56	6
	Occipital pole	L	190	-24	-102	0
	Precuneus	R	167	10	-70	28
	Occipital pole	L	154	-16	-98	-18
	Superior parietal lobule, angular gyrus	L	136	-32	-54	40
	Inferior temporal gyrus, temporal pole	R	131	40	4	-48
	Orbitofrontal cortex	R	117	10	30	-28
Exclusive to bvFTD	Inferior temporal gyrus, middle temporal gyrus, hippocampus, amygdala	L	469	-44	-16	-40
	Hippocampus	R	147	30	-10	-28

All clusters extracted using overlap and exclusive masking technique and reported using voxel-wise contrasts and uncorrected at $p < .001$ and with a cluster extent threshold of 100 contiguous voxels. Age is included as a nuisance variable in all contrasts. All clusters reported at $t > 3.5$. L = Left; B = Bilateral; MNI = Montreal Neurological Institute.

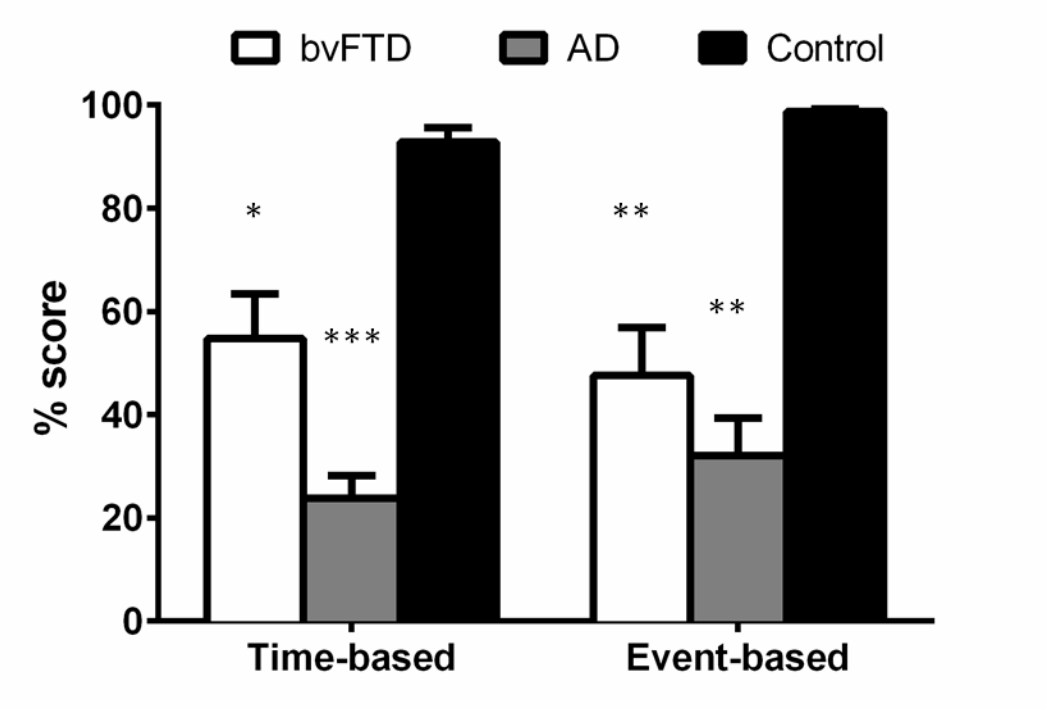

Figure 1. Prospective memory performance across Time-based and Event-based subscales in Alzheimer's disease (AD), behavioral-variant frontotemporal dementia (bvFTD), and Control participants. Error bars represent standard error of the mean. *$p < .05$; **$p < .005$; ***$p < .0001$.

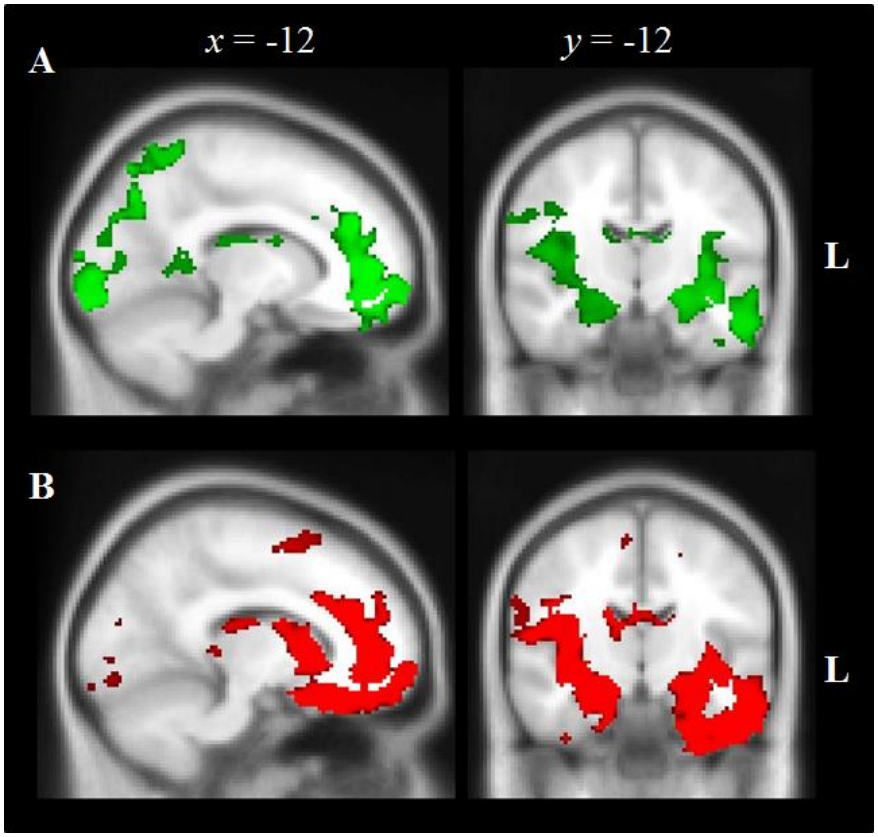

Figure 2. Regions of significant gray matter intensity decrease in (A) AD versus Controls and (B) bvFTD versus Controls (MNI coordinates: x = -12, y = -12, z = 18). Colored voxels show regions that were significant in the voxel-based morphometry analyses at $p < .05$ corrected for Family-Wise Error using the threshold free cluster enhancement method (tfce). Clusters are overlaid on the Montreal Neurological Institute standard brain. L = Left.

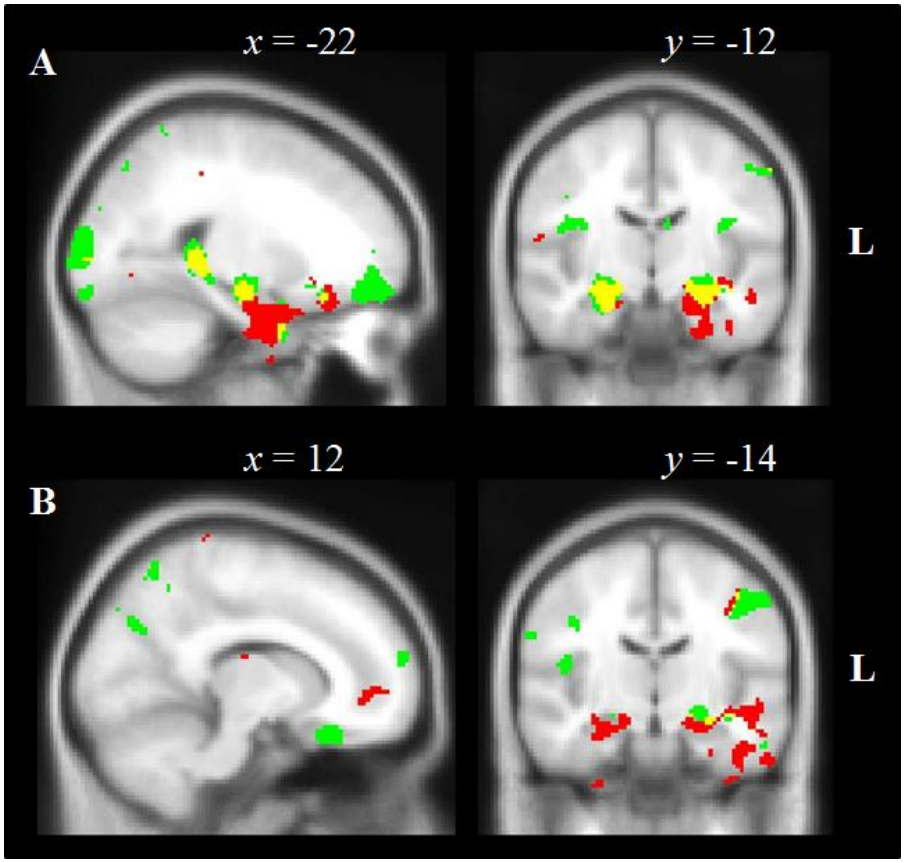

Figure 3. VBM analyses showing brain regions in which gray matter intensity correlates significantly with (A) Time-based and (B) Event-based PM performance in dementia. Age is included as a nuisance variable in all covariate analyses. Colored voxels show regions that were significant in the voxel-based morphometry covariate analyses at $p < .001$ uncorrected with a cluster extent threshold of 100 contiguous voxels. All clusters reported $t > 3.5$ and depict a positive association between gray matter integrity and PM performance. Green clusters represent regions exclusively implicated in AD; red clusters represent regions exclusively implicated in bvFTD; yellow clusters denote regions of overlap between the two patient groups. Clusters are overlaid on the Montreal Neurological Institute standard brain. L = Left.

Supplementary Information 1

Voxel-based morphometry results showing neural substrates of Prospective Memory performance across Time- and Event-based subscales in healthy Control participants.

Contrast	Regions	Side	Number of voxels	MNI coordinates		
				x	*y*	*z*
Time-based	Temporal pole, insular cortex, orbitofrontal cortex	L	337	-48	10	-18
	Postcentral gyrus	L	244	-54	-24	50
	Supramarginal gyrus	L	177	-54	-42	48
	Insular cortex	R	150	32	16	6
	Temporal pole	R	147	54	12	-20
	Lateral occipital cortex	R	136	38	-64	-4
	Intracalcarine cortex, lingual gyrus	L	105	-26	-76	4
	Planum Polare, central opercular cortex	R	104	56	-2	-2
Event-based	No significant clusters					

All clusters reported using voxel-wise contrasts and corrected for False Discovery Rate (FDR) at $p < .05$. All clusters reported at $t > 4.9$. L = Left; R = Right; MNI = Montreal Neurological Institute.

Supplementary Information 2

Prospective Memory Task instructions adapted from Kamminga et al. (2014).

"In this task, I am going to ask you to do a number of different things. Some of these actions should be completed at certain times and some of them must be done after a specific event. I will read aloud some instructions to you and I want you to remember to do the action. There are 6 different actions in total. You should use the pencil and paper here to make notes to help you to remember the instruction. Also, you can use your watch or this clock to help you keep track of the time."

The following task instructions are then read verbatim to participants. An instruction may be repeated one additional time if necessary. As the experimenter reads the instructions, they must gesture to the corresponding item on the table in front of the participant (e.g., stopwatch, notebook). The experimenter must ensure that the participant can clearly see the clock and that he/she understands all of the test instructions prior to commencing the task.

Time-based PM task instructions	
1.	In 15 minutes' time, I want you to remind me <u>not to forget my keys</u>
2.	In 10 minutes' time, please <u>ask me for a pencil</u>
3.	In 5 minutes' time, please <u>close the notebook</u> on the table
Event-based PM task instructions	
1.	When the alarm rings, please <u>put this notebook on the floor</u>
2.	When I tell you there are 10 minutes left, <u>please give me this stopwatch</u>
3.	When I tell you we have finished the session, <u>please give me this message</u>