Fronto-parietal contributions to episodic retrieval—evidence from neurodegenerative disorders

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Converging evidence suggests a critical role for the parietal cortices in episodic memory retrieval. Here, we examined episodic memory performance in Corticobasal Syndrome (CBS), a rare neurodegenerative disorder presenting with early parietal atrophy in the context of variable medial temporal lobe damage. Forty-four CBS patients were contrasted with 29 typical Alzheimer's disease (AD), 29 healthy Controls, and 20 progressive supranuclear palsy patients presenting with brainstem atrophy as a disease control group. Participants completed standardized assessments of verbal episodic memory (learning, delayed recall, and recognition), and underwent structural and diffusion-weighted MRI. Selective delayed recall deficits were evident in the CBS group relative to Controls, at an intermediate level to the stark amnesia displayed by AD, and Control-level performance noted in progressive supranuclear palsy. Considerable variability within the CBS group on delayed recall performance led to the identification of memory-spared ($N = 19$) and memory-impaired ($N = 25$) subgroups. Whereas CBS-Spared showed no significant memory deficits, the CBS-Impaired subgroup were indistinguishable from typical AD across all episodic memory measures. Whole-brain voxel-based morphometry analyses implicated fronto-parietal and medial temporal regions in delayed recall performance in both the CBS-Impaired and AD groups. Furthermore, diffusion tensor imaging analyses revealed correlations between delayed recall performance and altered structural connectivity between fronto-parietal and frontotemporal regions in the CBS-Impaired group. Our findings underscore the importance of a distributed brain network including frontal, medial temporal, and parietal brain regions in supporting the capacity for successful episodic memory retrieval.

[Supplemental material is available for this article.]

Episodic memory refers to the encoding, storage, and retrieval of information located within a distinct spatiotemporal framework that confers a sense of recollection or mental reliving (Tulving 2002). Successful episodic memory retrieval hinges on dynamic interactions between key nodes of a distributed "core memory network" comprising prefrontal, hippocampal, lateral temporal, medial and lateral parietal regions (for review, see Rugg and Vilberg 2013). The vast majority of studies to date have focused on the central role of the hippocampus within this memory network (see Nadel and Moscovitch 1997; Burgess et al. 2002), given its importance for binding spatiotemporal information to create holistic and stable representations of events in memory (Horner et al. 2015; Backus et al. 2016). Complementing hippocampal contributions, there has been immense interest centered on prefrontal contributions to memory, most notably in relation to conferring executive control and in assisting the search and verification of mnemonic information (Tomita et al. 1999; Dobbins et al. 2002; Simons and Spiers 2003).

Despite robust and consistent activity across functional neuroimaging (Shannon and Buckner 2004; Wagner et al. 2005; Vilberg and Rugg 2008) and electroencephalogram (Rugg et al. 1995) paradigms of episodic retrieval, the parietal cortices have received comparably less attention in the episodic memory literature. From a neuroanatomical perspective, the lateral parietal cortices are well placed to support episodic memory retrieval given their robust structural (Caspers et al. 2011) and functional (Vincent et al. 2006) connections with the hippocampus and medial temporal lobes. The consistent observation of parietal involvement in episodic memory performance has been posited to reflect the operation of a dedicated parietal memory network facilitating discrete aspects of episodic memory retrieval (Ranganath and Ritchey 2012; Gilmore et al. 2015; Sestieri et al. 2017). Episodic retrieval-related activity in parietal regions such as the angular gyrus is further predictive of specific information from recently encoded episodic memories (Kuhl and Chun 2014; Lee and Kuhl 2016). Taken together, parietal regions appear to play a critical role during episodic retrieval, warranting deeper investigation into their precise cognitive contributions.

The study of neurodegenerative disorders offers a compelling window into understanding the role of the parietal cortex in the service of episodic memory retrieval. Neurodegenerative disorders, by nature, present with diffuse and co-occurring gray and white matter damage. One such disorder presenting with early parietal lobe damage is Corticobasal Syndrome (CBS). CBS is a rare neurodegenerative disorder characterized by heterogenous motor and cognitive dysfunction, primarily due to degeneration of a cortico-subcortical network involving the primary motor, fronto-parietal cortices, and basal ganglia (Boxer et al. 2006; Upadhyay et al.

2016) and disrupted fronto-parietal white matter structural connectivity (Borroni et al. 2008; Upadhyay et al. 2016). Considerable clinical and pathological overlap is evident between CBS and other neurodegenerative brain disorders (Chahine et al. 2014). These disorders include Alzheimer's disease (AD), in which early amnesia attributable to hippocampal and medial parietal atrophy is observed (Irish et al. 2014b), as well as Progressive Supranuclear Palsy (PSP) characterized by motor symptoms (such as oculomotor apraxia and postural instability) due to early brainstem atrophy (Josephs et al. 2008).

In terms of cognitive profiles, the majority of studies have focused on executive, visuospatial, and language processing impairments in CBS (see Burrell et al. 2014), with a paucity of studies formally investigating episodic memory profiles in this syndrome. Of the studies that have been conducted, mixed findings have been reported, with observations of significant episodic memory impairments from early in the disease trajectory in some studies (Chand et al. 2006; Hu et al. 2009; Shelley et al. 2009), but not in others (Imamura et al. 2009). The focus of many of these studies (e.g., Chand et al. 2006; Hu et al. 2009), however, has been on predicting postmortem neuropathological features in CBS patients from retrospective analyses of their clinical and cognitive data. Accordingly, these studies have often included small samples (Hu et al. 2009) or single case reports (Chand et al. 2006; Imamura et al. 2009) due to the rarity of the syndrome. Moreover, in retrospective analyses of postmortem data, memory performance on clinical examination may have been interpreted as "spared" or "impaired" based on post-hoc knowledge of the underlying pathology, leading to a bias in determining the absence, extent, or severity of the memory deficit. In summary, studies of memory performance in CBS are limited and reveal conflicting findings.

The lack of research on episodic memory in CBS is somewhat surprising, given that the locus of cortical atrophy in early stages of CBS is centered on the parietal cortices, whereas medial temporal regions including the hippocampus are suggested to be relatively spared (Albrecht et al. 2017). As such, the study of CBS offers an opportunity to further understand how parietal lobe dysfunction impacts episodic memory retrieval. In this vein, the current study aimed to characterize episodic memory profiles across measures of learning, delayed recall, and recognition, in a large, well-

characterized cohort of CBS patients and to compare their profiles to a "motor" disease control (PSP), and a "memory" disease control (typical AD). Given the early burden of atrophy in the parietal and frontal lobes, in the context of variable levels of hippocampal dysfunction, we predicted that CBS patients would present with significant episodic memory difficulties relative to healthy Controls. We further sought to delineate the neural substrates of these impairments using multimodal imaging measures of gray and white matter integrity across the three neurodegenerative disorders to identify common and unique neural regions contributing to episodic memory dysfunction. While this aspect of the study was exploratory, we predicted that the parietal cortices would be commonly implicated in memory dysfunction irrespective of clinical phenotype.

Results

Demographic, clinical, and neuropsychological screening

Participant groups did not differ across sex, age, and education (all P-values >0.1; Table 1), with patient groups further matched for disease severity assessed using the Clinical Dementia Rating–Frontotemporal Lobar Degeneration Sum of Boxes score (CDR–FTLD SoB: $P > 0.1$). Patient groups showed significant cognitive dysfunction relative to Controls on a global index of cognitive function, the Addenbrooke's Cognitive Examination–Revised screening tool (ACE-R: $P < 0.001$), with no differences between neurodegenerative disorder subtypes (all P-values >0.09). Neuropsychological testing revealed characteristic profiles of cognitive impairment across each patient group, consistent with their respective clinical diagnoses (Table 1). Relative to Controls, all patient groups showed significant impairments on neuropsychological tests of attention, working memory, executive function, language and semantic processing, and visuospatial function (see Supplemental Results for full description of neuropsychological test performance in each patient group).

Episodic memory performance

Episodic memory performance was assessed using the "Memory" subscale of the ACE-R test, focusing on the "name and address"

Table 1. Demographic, clinical, and cognitive characteristics of study participants

	AD	CBS	PSP	Control	Magnitude of group effect (F, η_p^2 values)	Post-hoc results (between patients)
N	29	44	20	29		
Sex (M:F)	12:17	15:29	9:11	10:19	$\chi^2 = 0.99$	
Age (years)	70 (4.0)	70.2 (6.9)	70.8 (4.6)	70.4 (1.7)	$F = 0.09$; $\eta_p^2 = 0.002$	NS
Education (years)	11.5 (3.8)	11.4 (3.5)	11.1 (3.4)	12.6 (2.1)	$F = 1.03$; $\eta_p^2 = 0.02$	NS
Disease severity (CDR-FTLD sum of boxes)	5.9 (2.9)	6.1 (4.8)	6.7 (3.2)	–	$F^\dagger = 0.26$; $\eta_p^2 = 0.002$	NS
ACE-R (100)	64 (19.7)	72.1 (17.5)	78.1 (7.6)	94.8 (3.4)	$F = 23.36$; $\eta_p^2 = 0.37$	NS
Neuropsychological tests						
Digit span forward (16)	8.6 (1.8)	8.7 (2.7)	8.0 (1.5)	11.1 (2.1)	$F = 10.01$; $\eta_p^2 = 0.20$	NS
Digit span backward (16)	4.1 (1.8)	4.6 (1.9)	4.0 (1.3)	7.5 (2.1)	$F = 20.22$; $\eta_p^2 = 0.34$	NS
TMT B-A (secs)	111.5 (85.8)	185.1 (98.2)	151.6 (78.8)	44.0 (20.3)	$F = 16.75$; $\eta_p^2 = 0.36$	NS
Hayling overall scaled (10)	3.4 (2)	3.9 (2.0)	2.6 (1.7)	6.2 (0.7)	$F = 18.38$; $\eta_p^2 = 0.39$	NS
FAS letter fluency	8.7 (3.9)	6.6 (4.4)	3.5 (2.2)	15.5 (3.9)	$F = 40.22$; $\eta_p^2 = 0.56$	AD > PSP
ACE-R language (26)	19.6 (5.4)	20.5 (4.1)	22.6 (3.0)	25.3 (0.8)	$F = 13.33$; $\eta_p^2 = 0.25$	NS
ACE-R visuospatial (16)	11.6 (4.3)	11.3 (3.6)	13.4 (2.3)	15.4 (0.8)	$F = 11.1$; $\eta_p^2 = 0.22$	NS

Note: F, F statistics from ANOVA (for all F-statistics, $df_{numerator} = 3$ and $df_{denominator} = 118$, unless indicated otherwise); η_p^2, partial eta-squared values (effect size); [†], $df_{numerator} = 2$ and $df_{denominator} = 75$; AD, Alzheimer's Disease; CBS, Corticobasal Syndrome; PSP, Progressive Supranuclear Palsy; CDR-FTLD, Clinical Dementia Rating Frontotemporal Lobar Degeneration; ACE-R, Addenbrooke's Cognitive Examination—Revised; TMT, Trail Making Test; NS, not significant ($P > 0.1$).

item. Briefly, participants are read out a name and address and required to recall it immediately. Three consecutive trials are administered, with the score on the final trial taken to reflect an "episodic learning" score (max score = 7). Following a ~12 min filled delay (where no memory tasks are administered), participants undergo a "delayed recall" trial of the name and address (max score = 7) followed by a "recognition" trial (max score = 5). Performance across learning, delayed recall, and recognition components is displayed in Figure 1 and Table 2 (see also Supplemental Table 1 for performance on other ACE-R memory measures).

Episodic learning

A significant main effect of group was found [$F_{(3,118)}$ = 11.14; P < 0.001; η_p^2 = 0.22], driven exclusively by impaired learning of the name and address in AD relative to all other groups (all P-values <0.001; Fig. 1A). In contrast, episodic new learning was relatively intact in CBS and PSP relative to Controls (both P-values >0.05), with no further differences evident between the patient groups (P > 0.1).

Delayed recall

As displayed in Figure 1B, a significant main effect of group was again present [$F_{(3,118)}$ = 42.62; P < 0.0001; η_p^2 = 0.52], reflecting compromised memory performance in AD and the CBS group relative to Controls (all P-values <0.01). PSP patients, however, continued to score in line with Controls (P > 0.1). Both CBS and PSP participants outperformed the AD group (P < 0.001), with no significant difference between CBS and PSP groups (P > 0.1).

Recognition

Finally, evidence for a significant main effect of group was found [$F_{(3,118)}$ = 9.95; P < 0.001; η_p^2 = 0.20] (Fig. 1C) driven by an exclusive impairment in AD relative to all other participant groups (all P-values <0.01), with CBS and PSP performing in line with Controls (both P-values >0.08).

In summary, evidence for distinct memory profiles across the patient groups were found. CBS patients displayed an exclusive deficit for delayed episodic recall, at an intermediate level to AD and Control groups, with relatively preserved episodic learning and delayed recognition. In contrast, AD patients displayed pervasive deficits across learning, delayed recall, and recognition measures, relative to Controls. No significant deficits in episodic memory performance were evident in the "motor control" PSP group.

Profiling CBS patients into subgroups

Considerable variability was evident for delayed recall performance within the CBS group (Fig. 1B). Accordingly, the CBS group (N = 44) was stratified into two subgroups based on delayed recall performance. CBS delayed recall scores were converted to z-scores relative to the Control group's performance. CBS patients with z-scores ≥ −1.5 on delayed recall were classified as "CBS-Spared" (N = 19), while patients with z-scores < −1.5 were classified as "CBS-Impaired" (N = 25) (Fig. 2; Supplemental Table 2), in line with cutoffs used widely in the amnestic Mild Cognitive Impairment literature (Petersen 2004). Importantly, these CBS subgroups were matched on demographic variables (age, education, sex), disease severity (CDR-FTLD SoB), and general neuropsychological performance (neuropsychological test performance on attention, working memory, executive function, language, and visuospatial processing tasks) (Supplemental Table 3). CBS-Impaired patients, however, displayed significantly poorer overall cognitive performance on a modified ACE-R score (ACE-R total minus ACE-R memory subdomain) relative to the CBS-Spared subgroup (P = 0.01) (Supplemental Table 3).

As displayed in Figure 2 and Supplemental Table 2, CBS-Spared patients outperformed the AD group across all memory measures, scoring in line with Control and PSP groups (all P-values >0.1). In contrast, the CBS-Impaired subgroup was indistinguishable from the AD group across learning, delayed recall, and recognition measures (all P-values >0.1), scoring significantly poorer than the CBS-Spared and Control groups (all P-values <0.05; Supplemental Table 2). Moreover, the CBS-Impaired group performed significantly poorer than the PSP group on episodic delayed recall and recognition (both P-values <0.05) but not episodic learning (P > 0.1).

Finally, Pearson's correlations (corrected for multiple comparisons using false discovery rate) were conducted to examine potential associations between delayed recall performance, disease severity, and general neuropsychological performance within the CBS-Impaired subgroup. Episodic delayed recall performance was found to correlate with overall language (ACE-R language score: r = 0.84; P = 0.004) and visuospatial (ACE-R visuospatial: r = 0.54; P = 0.017) performance, but not with a general measure of disease severity (i.e., CDR-FTLD SoB; (r = −0.23; P > 0.1).

Voxel-based morphometry analyses

Structural Magnetic Resonance Imaging (MRI) data were available for 108 participants (40 CBS [22 CBS-Impaired, 18 CBS-Spared], 16 PSP, 23 AD, 29 Controls). Voxel-based morphometry (VBM) analyses were used to explore associations between gray matter intensity and episodic memory performance using an unbiased whole-brain approach. Full description of gray matter atrophy profiles in patient groups are presented in Supplemental Results, Supplemental Figure 1 and Supplemental Table 4. Briefly, all patient groups presented with gray matter atrophy profiles characteristic of their respective syndromes. Direct comparison of the CBS subgroups revealed no significant differences in gray matter intensity.
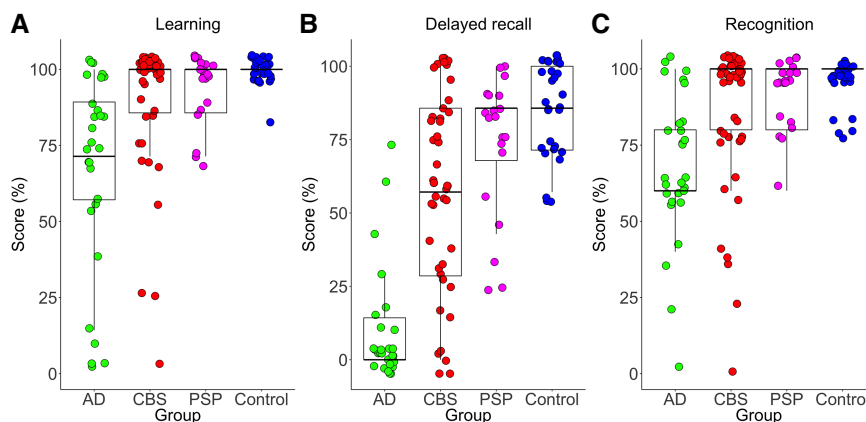

Figure 1. Episodic memory performance for all groups on the episodic memory measures from the ACE-R. Boxes depict distribution of data with *lower* and *upper* end of the box depicting the inter-quartile range, respectively. Bolded horizontal line depicts median score while whiskers depict the variability outside the *upper* and *lower* quartiles. (AD) Alzheimer's Disease, (CBS) Corticobasal Syndrome, (PSP) Progressive Supranuclear Palsy.

Table 2. Episodic memory performance for all groups on the learning, delayed recall, and recognition components from the ACE-R memory subscale

	AD	CBS	PSP	Control	Magnitude of group effect (F, η_p^2 values)	Post-hoc results (between patients)
Learning (%)	68.4 (33.1)	88.9 (22.4)	93.5 (10.8)	99.5 (2.6)	$F = 11.14$; $\eta_p^2 = 0.22$	CBS = PSP > AD
Delayed recall (%)	12.3 (24.9)	58.4 (32.5)	72.8 (23.5)	85.7 (15.2)	$F = 42.62$; $\eta_p^2 = 0.52$	CBS = PSP > AD
Recognition (%)	69.6 (24.8)	85.0 (24.4)	93.0 (11.7)	96.5 (7.6)	$F = 9.95$; $\eta_p^2 = 0.20$	CBS = PSP > AD

Note. F, F statistics from ANOVA (for all F-statistics, $df_{numerator} = 3$ and $df_{denominator} = 118$); η_p^2, partial eta-squared values (effect size); AD, Alzheimer's Disease; CBS, Corticobasal Syndrome; PSP, Progressive Supranuclear Palsy; ACE-R, Addenbrooke's Cognitive Examination—Revised.

Gray matter correlates of delayed recall performance

Delayed recall performance in the CBS-Impaired subgroup was associated with gray matter intensity decrease in the bilateral hippocampi and amygdalae, posterior cingulate cortices, and angular gyri. In addition, bilateral cerebellum and striatum (pallidum, putamen), right orbitofrontal cortex, and left inferior/middle frontal gyri were implicated (Fig. 3; Supplemental Table 5).

Delayed recall performance in AD was significantly associated with gray matter intensity decrease in the bilateral medial temporal lobes (including hippocampi), temporal poles, inferior and superior temporal gyri, posterior cingulate cortices, and angular gyri. Frontal brain regions including the bilateral anterior cingulate cortices, medial prefrontal cortices, and right middle frontal gyrus were also implicated. Results for the CBS-Spared and PSP group are presented in the Supplemental Results section.

Common and unique neural substrates of delayed recall disruption

To explore common neural substrates of delayed recall disruption between CBS-Impaired and AD patients, the statistical contrasts (for CBS-Impaired and Controls combined, and AD and Controls combined) emerging from the VBM correlation analyses were scaled (using a threshold of $P_{uncorrected} < 0.001$ with $k \geq 100$ voxels) and multiplied to create an overlap mask across groups (Irish et al. 2014b). This technique revealed that the regions commonly associated with delayed memory impairments in CBS-Impaired and AD patients included the bilateral anterior cingulate and insular cortices, bilateral temporal poles, bilateral hippocampi and amygdalae, bilateral angular gyri, and bilateral posterior cingulate cortices (Supplemental Fig. 2; Supplemental Table 6).

Evidence for distinct neural substrates of episodic memory dysfunction in the CBS-Impaired and AD groups was obtained using an exclusive masking technique (Irish et al. 2014b). Regions exclusively implicated in episodic memory dysfunction in AD included the bilateral medial prefrontal and anterior cingulate cortices, temporal fusiform cortex, and inferior and superior temporal gyri. In contrast, delayed recall disruption in CBS-Impaired was uniquely associated with gray matter intensity decrease in bilateral orbitofrontal and fronto-polar cortices, inferior and middle frontal gyri, superior parietal lobule, cerebellar, and striatal (pallidum and putamen) regions (Supplemental Fig. 2; Supplemental Table 7).

Diffusion tensor imaging analysis

Diffusion-weighted MRI data were available for 107 participants (40 CBS [22 CBS-Impaired, 18 CBS-Spared], 16 PSP, 22 AD, 29 Controls). Diffusion tensor imaging analyses were conducted to examine whole-brain changes in white matter microstructure (i.e., fractional anisotropy or FA) and their associations with episodic memory performance across groups. Full description of white matter atrophy profiles in patient groups is presented in Supplemental Results and Supplemental Table 8. Briefly, all patient groups presented with white matter atrophy profiles characteristic

of their respective syndromes. Direct comparison of the CBS subgroups did not reveal any significant differences in whole-brain FA of white matter microstructure.

Correlations between FA and delayed recall performance

Masks for five white matter tracts were created from the Johns Hopkins probabilistic white matter atlas (Mori et al. 2005): the inferior longitudinal fasciculus (ILF: connecting the occipital and temporal lobes), superior longitudinal fasciculus (SLF: connecting the occipital, parietal, temporal, and frontal lobes), uncinate fasciculus (connecting the anterior temporal and orbitofrontal regions), the cingulum bundle (connecting frontal and temporal lobes), and the hippocampal part of the cingulum bundle (connecting the medial temporal lobes to parietal and occipital lobes). These tracts were chosen as connecting the main gray matter substrates of delayed recall performance across patient groups in the VBM correlation analyses (see also Supplemental Table 5; Irish et al. 2014a).

For the CBS-Impaired group, decreased FA in the bilateral cingulum bundles (hippocampal parts), bilateral superior longitudinal fasciculus bundles, and the right cingulum bundle correlated significantly with delayed recall performance (all r-values >0.4, all P-values <0.05) (Fig. 4; Supplemental Table 9). No significant correlations emerged in the CBS-Spared, AD (all P-values >0.1), and PSP groups (all P-values >0.07) (Supplemental Table 9).

Discussion

Episodic memory dysfunction is the hallmark cognitive feature of AD, given widespread damage to cortical and subcortical neural
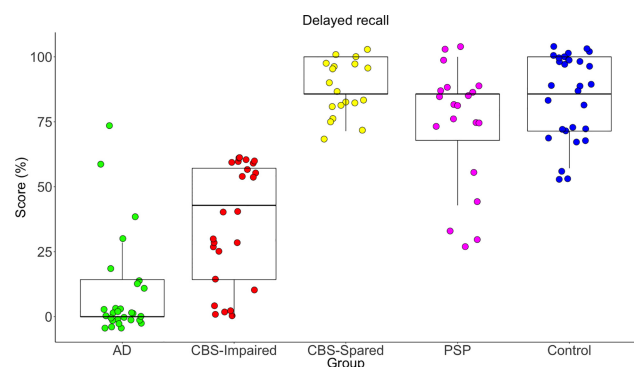

Figure 2. Delayed episodic memory performance for CBS subgroups. Boxes depict distribution of data with *lower* and *upper* end of the box depicting the inter-quartile range, respectively. Bolded horizontal line depicts median score while whiskers depict the variability outside the *upper* and *lower* quartiles. (AD) Alzheimer's Disease; (CBS-Impaired) Corticobasal Syndrome-Impaired memory (<−1.5 *z*-score on delayed recall), (CBS-Spared) Corticobasal Syndrome-Spared memory (≥−1.5 *z*-score on delayed recall), (PSP) Progressive Supranuclear Palsy.
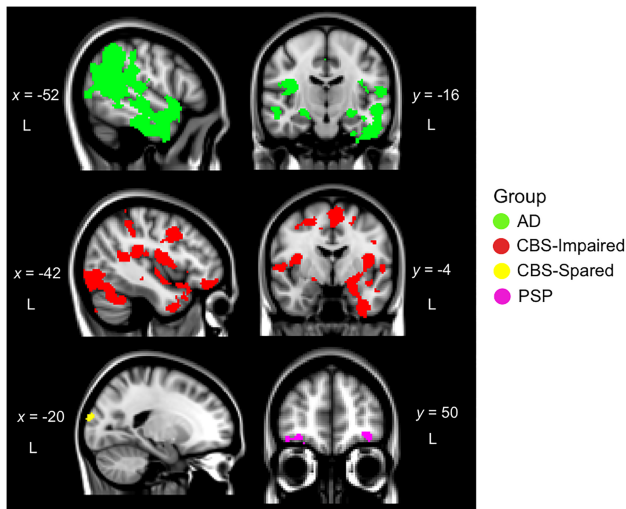
Figure 3. Regions of significant gray matter intensity decrease that correlate with delayed episodic recall performance. All *x* and *y* coordinates reported are Montreal Neurological Institute (MNI) coordinates. Colored voxels show regions that emerged as significant in the VBM analyses at a strict uncorrected threshold of $P < 0.001$ with a cluster threshold of 100 contiguous voxels. All clusters reported at $t > 3.56$. Age was included as a covariate in the analyses. Clusters are overlaid on the MNI standard brain; (L) Left, (AD) Alzheimer's Disease, (CBS-Impaired) Corticobasal Syndrome-Impaired memory (< -1.5 *z*-score on delayed recall), (CBS-Spared) Corticobasal Syndrome-Spared memory (≥ -1.5 *z*-score on the delayed recall), (PSP) Progressive Supranuclear Palsy.

circuits essential for the encoding, storage, and retrieval of information (Dickerson and Eichenbaum 2010). Mounting evidence, however, reveals episodic memory dysfunction across a range of dementia syndromes, including behavioral-variant frontotemporal dementia, semantic dementia, and logopenic progressive aphasia (McKinnon et al. 2006; Irish et al. 2011, 2014b, 2016; Ramanan et al. 2016), which becomes increasingly pronounced with disease evolution (Ramanan et al. 2017; Irish et al. 2018). Our findings indicate the presence of marked impairments exclusively for delayed recall in a distinct subgroup of patients with Corticobasal Syndrome, reflecting the breakdown of core nodes of the episodic memory network.

The most striking finding to emerge from this study was the presence of a selective delayed recall impairment in the CBS group. These deficits were driven by a subset of CBS patients (referred to as CBS-Impaired) and were of a similar magnitude as those observed in typical amnesic AD patients. Episodic amnesia in both CBS-Impaired and AD groups, moreover, reflected the degeneration of a core medial temporal and parietal memory network comprising the bilateral hippocampi, angular gyri, and posterior cingulate cortices (Rugg and Vilberg 2013; Gilmore et al. 2015). The hippocampus and surrounding medial temporal lobe structures have been long considered the most critical contributors to episodic encoding and retrieval, with global anterograde amnesia forming a prototypical clinical feature of medial temporal lobe damage (Scoville and Milner 1957; Squire and Zola-Morgan 1991; Corkin 2002). Our findings corroborate the importance of the hippocampus for episodic memory function, yet also speak to the participation of regions beyond the medial temporal lobes, most notably posterior parietal regions, in supporting this endeavor. Here we reveal that co-occurring degeneration of posterior parietal and medial temporal regions contributes to an amnesic profile in neurodegenerative disorders, including those not traditionally classified as amnesic. Mounting evidence reveals disrupted episodic retrieval as a result

of posterior cortical damage (see for example Ahmed et al. 2018a, b). Similarly, patients with angular gyrus lesions demonstrate difficulties in retrieving multimodal (i.e., audio-visual stimuli) episodic information (Berryhill et al. 2007; Davidson et al. 2008; Ben-Zvi et al. 2015) with concomitant reductions in their subjective confidence of recollected memories (Hower et al. 2014). Unlike hippocampal amnesics, however, these patients show relatively preserved encoding abilities (Ben-Zvi et al. 2015), suggesting a selective role for parietal regions during episodic retrieval.

We have previously suggested that the angular gyrus may be critical for the integration and processing of multimodal sensory-perceptual and contextual information that enables the detail-rich retrieval of episodic memories (Ramanan et al. 2018b; see also Shimamura 2011; Bonnici et al. 2016). This role appears to be time-invariant, extending to the construction of perceptually detailed atemporal and future-oriented mental scenarios (Berryhill et al. 2010; Thakral et al. 2017; Ramanan et al. 2018a). Notably, however, our VBM correlation analyses also implicated neighboring parietal regions in episodic memory function. One such region to emerge was the superior parietal lobule, whose attentional role is well-established in supporting "top–down," goal-directed search for perceptual information in the environment (Corbetta and Shulman 2002; Sestieri et al. 2010). During episodic memory retrieval, the superior parietal lobule is posited to play a similar role in governing top–down attention, allowing the retrieval of specific episodic information (Cabeza et al. 2008; Sestieri et al. 2017). Our analysis also implicated a role for medial parietal regions, including the posterior cingulate cortex, in episodic memory function. This region forms a structural hub of the posterior neocortex, anchoring multiple brain networks (Hagmann et al. 2008). The posterior cingulate cortex further plays an important role in self-referential aspects of cognition (see Brewer et al. 2013; Wong et al. 2017), including the reinstatement and consolidation of episodic memories (Bird et al. 2015). Early dysfunction of the posterior cingulate cortex reliably predicts the onset of neurodegenerative syndromes like AD (Minoshima et al. 1997) as well as impairments across an array of putative episodic memory functions such as episodic retrieval (Irish et al. 2014b), autobiographical memory (Irish et al. 2018), scene construction and future thinking (Irish et al. 2012, 2015) in this syndrome. As such, our findings confirm the importance of key regions within a posterior memory network (Gilmore et al. 2015), centered on the hippocampus but including lateral and medial parietal regions, and suggest that degeneration of these regions manifests in stark episodic memory impairments irrespective of clinical phenotype.

Beyond the core medial temporal-posterior parietal regions implicated, we also found evidence for disease-specific neural substrates of episodic memory impairment. In the CBS-Impaired group, cerebellar and striatal regions emerged as critical to episodic delayed recall performance, whereas the inferior/middle temporal gyri, temporal poles, and temporal fusiform cortices were implicated exclusively in AD corroborating previous findings from our group (Irish et al. 2014b). Cerebellar and striatal contributions to cognitive endeavors, including episodic retrieval, have traditionally been conceptualized as reflecting motor planning and execution rather than primary cognitive or recollection-related activity. Emergent perspectives, however, challenge this view to suggest that these regions may directly facilitate successful episodic retrieval potentially via an "internal representation" of the external world, allowing us to coordinate, adapt, and shape behavior in response to external demands and changes in the environment (Koziol et al. 2014). Striatal involvement in cognitive endeavors has been conceptualized as involvement in "cognitive control," allowing the tagging of salient and behaviorally relevant episodic information during memory consolidation (Scimeca and Badre 2012), yet recent studies suggest that coordinated striatal-medial
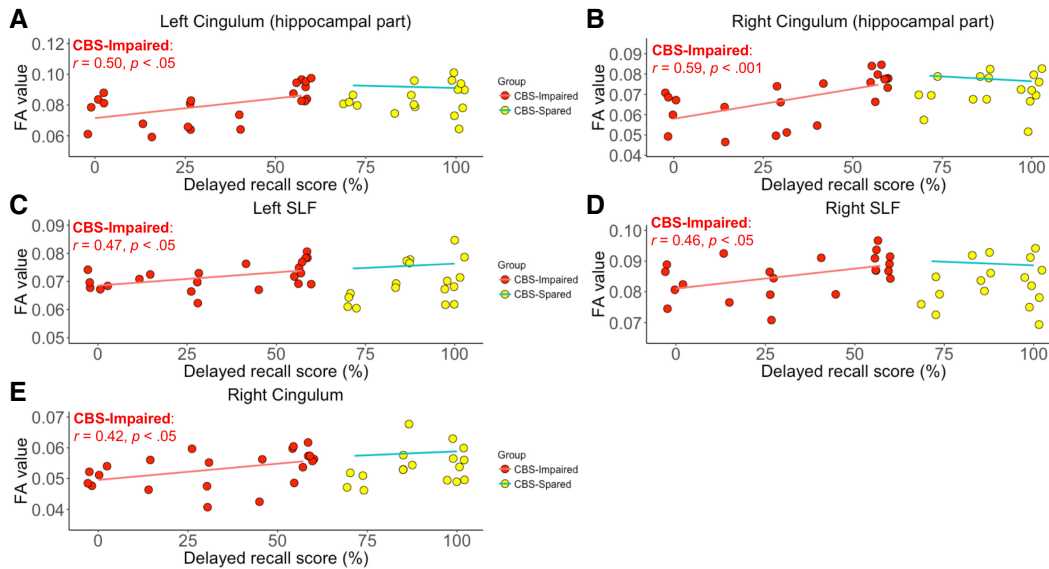
Figure 4. Relationship between Fractional Anisotropy values and episodic delayed recall performance for CBS-Impaired and CBS-Spared groups. Plotted data indicate a positive relationship between FA values and delayed recall performance for the CBS-Impaired group, with the magnitude of this relationship depicted using Pearson's correlation coefficient (r). Correlations between FA value for all selected tracts and delayed recall performance for the CBS-Spared group were nonsignificant (all P-values >0.1). (FA) fractional anisotropy, (CBS-Impaired) Corticobasal Syndrome-Impaired memory (<-1.5 z-score on delayed recall), (CBS-Spared) Corticobasal Syndrome-Spared memory (≥-1.5 z-score on the delayed recall), (SLF) Superior Longitudinal Fasciculus.

temporal activity may be essential for episodic memory processing (Murty et al. 2015). Future studies exploring how damage to these divergent regions differentially impacts aspects of episodic retrieval will be imperative to further understand the broader role of core versus ancillary memory regions.

Finally, our diffusion tensor imaging analyses revealed large scale white matter changes in the structural connectivity within the episodic memory subsystem unique to memory-impaired CBS and AD patients. Interestingly, however, the only significant associations to emerge between delayed recall performance and white matter integrity were in the CBS-Impaired subgroup. Specifically, disrupted structural connectivity between parietal and frontal lobes (through the superior longitudinal fasciculus) and medial temporal and frontal lobes, via parietal cortices (through hippocampal and cingulate arms of the cingulum bundle) was associated with delayed recall performance in these patients. Microstructural damage to fronto-parietal and frontotemporal white matter structural connections have previously been implicated in episodic memory dysfunction in syndromes such as amnestic Mild Cognitive Impairment (Rose et al. 2006) and AD (Irish et al. 2014a), as these long-range fibres form subcortical routes essential to communicating information relevant to the retrieval of episodic information. In the context of episodic amnesia, the degeneration of the cingulum bundle deserves particular attention. This tract forms key structural connections between medial temporal, posterior cingulate/parietal, and medial frontal cortices (Jones et al. 2013; Bubb et al. 2018), all of which form key nodes of the episodic retrieval network. The cingulum bundle is further vulnerable to early microstructural damage in neurodegenerative syndromes like AD (Choo et al. 2010; Bubb et al. 2018) and CBS (Upadhyay et al. 2016). We tentatively speculate that early parietal degeneration in CBS may propagate subcortically toward the medial temporal lobes via the cingulum bundle. In AD patients, in contrast, the converse temporal profile may manifest with parietal damage witnessed as secondary to early medial temporal dysfunction. Our cross-sectional design precludes the examination of the white matter origins of episodic memory dysfunction, however, future studies incorporating longitudinal

multimodal gray and white matter neuroimaging metrics in CBS will prove particularly informative in this regard.

Our findings hold a number of theoretical implications. The recent shift toward network approaches to cognition underscores the importance of moving beyond traditional hippocampal-centric models of memory retrieval. In showcasing large-scale gray and white matter damage to fronto-parietal and medial temporal episodic memory networks, our findings reinforce the critical contributions of the posterior neocortex to episodic memory function. A number of clinical implications also warrant mentioning. A recurrent theme in the clinical neurology literature is the stark heterogeneity of CBS, across clinical, cognitive, and pathological levels (Chahine et al. 2014). Our finding of a severely amnesic subgroup of CBS patients underscores this marked heterogeneity at clinical presentation and the ongoing challenge in establishing a reliable diagnosis in this syndrome. It will be important for future studies to longitudinally track clinical, cognitive, and neural degeneration in CBS to elucidate distinct cognitive trajectories, providing crucial information to carers and clinicians regarding prognosis and management of this syndrome.

A number of methodological issues deserve attention in the current context. First, a majority of our patients have not yet come to autopsy, and in the absence of amyloid PET imaging data, we can only speculate as to the underlying pathological mechanisms that drive memory impairments in these patients. Given the fact that a significant proportion of CBS patients harbor AD pathology (Shelley et al. 2009), it is intuitive to propose that the CBS-Impaired subgroup make up a large proportion of such cases. Second, although the ACE-R is a well-validated and widely used screen of global cognitive function, the address recall subtest used in the current study is not a validated measure of episodic memory per se. Nevertheless, our findings converge well with previous investigations of episodic memory in healthy (Chen et al. 2017) and neurodegenerative populations (Frisch et al. 2013) suggesting this clinical tool could be adopted for use as a proxy measure of episodic memory. Longitudinal studies incorporating detailed, ecologically valid memory assessments and histopathological data,

however, will be crucial to replicate and extend the results presented here. Moreover, the findings from our VBM overlap and exclusion masking analyses were not borne out of interaction models, rather, reflect the common clusters which surpassed a specified threshold. It is therefore possible that, in addition to disease-general and disease-specific mechanisms, regions emerging in these analyses may be mediated by factors beyond group membership. Finally, our gray matter correlational analyses between groups are reported uncorrected at $P < 0.001$, using a strict cluster extent threshold of 100 contiguous voxels to mitigate against Type I and Type II errors (Lieberman and Cunningham 2009). Importantly, this approach is far more conservative than the traditional correction for multiple comparisons using false discovery rate, and is consistent with recently published methods in the dementia literature (Whitwell et al. 2010; Irish et al. 2018). Replication of our findings in a larger cohort is nevertheless warranted.

In conclusion, this study is the first to demonstrate a pervasive memory impairment in a subgroup of CBS patients, mirroring the typical profile displayed by amnesic AD patients. These delayed recall deficits were attributable to the degeneration of multiple nodes of the core memory network, and disrupted white matter connectivity between parietal, medial temporal, and frontal regions. In uncovering memory impairments in a subgroup of CBS patients, our findings hold implications for structurally and functionally fractionating the episodic memory subsystem, helping to further understand the genesis and evolution of episodic memory dysfunction in neurodegenerative disorders.

Materials and Methods

Participants

A total of 122 participants were recruited through FRONTIER, the frontotemporal dementia research group in Sydney, Australia. Forty-four patients meeting current diagnostic criteria for CBS were included (Mathew et al. 2012; Armstrong et al. 2013). Briefly, CBS patients presented with the following core features—insidious disease onset and gradual progression without sustained response to levodopa treatment, along with at least two major (akinetic-rigid syndrome, limb apraxia, speech, and language impairment) and at least two minor (myoclonus, asymmetrical dystonia, alien limb syndrome, dyscalculia or cortical sensory loss, executive or visuospatial deficits) symptoms.

As a "motor" disease control group, 20 patients with a clinical diagnosis of PSP were enrolled, who presented with a progressive disorder featuring either vertical supranuclear palsy, or slowing of vertical saccades and notable postural instability resulting in falls, having accounted for other mandatory exclusion criteria in line with current diagnostic criteria (Höglinger et al. 2017). As an "amnesic" disease control group, 29 patients with a clinical diagnosis of probable AD with predominantly amnestic presentation (McKhann et al. 2011) were included. Diagnoses were established by consensus among a multidisciplinary team comprising a senior neurologist (J.R.H), a clinical neuropsychologist, and an occupational therapist. All participants underwent a comprehensive clinical and neuropsychological assessment, and structural neuroimaging. In addition, 29 healthy controls were recruited through research volunteer panels and local community clubs. All healthy controls scored 88 or above on the ACE-R (Mioshi et al. 2006)—a global index of cognitive functioning (comprising attention and orientation, memory, fluency, language, and visuospatial subdomains), and scored 0 on the CDR-FTLD scale (Knopman et al. 2008). Exclusion criteria for all participants included a history of stroke, epilepsy, significant traumatic brain injury, alcohol and other drug abuse, other primary neurological, psychiatric or mood disorders, and limited English proficiency.

Ethics approval for this study was granted by the University of New South Wales and the South Eastern Sydney Local Health District human ethics committee. All participants, or their person responsible, provided written informed consent in accordance with the Declaration of Helsinki.

General neuropsychological assessment

All participants underwent comprehensive neuropsychological testing to assess attention, working memory, executive function, language and semantic processing, and visuospatial function. Cognitive profiles for each patient group are described in detail in Table 1. Finally, the CDR-FTLD SoB score was used as an index of disease severity (Knopman et al. 2008).

Episodic memory assessment

In keeping with previous studies, the memory subscale of the ACE-R was used to assess verbal episodic learning, delayed recall, and recognition in dementia syndromes (Irish et al. 2016). The primary scores of interest in this context pertained to the Name and Address component, comprising Learning (three acquisition trials with final trial scored: max score = 7), delayed recall following a 15-min delay (max score = 7), and recognition (max score = 5). To allow direct comparison across the memory subtests, all scores were converted to percentages (i.e., raw scores/maximum subtest score × 100).

Statistical analyses

Behavioral analyses were conducted using RStudio v3.3.2. Prior to analysis, scores on all variables were plotted and checked for normality of distribution via Shapiro–Wilk tests. Analyses of Variance (ANOVAs) were used to compute mean differences across groups for demographic data, neuropsychological test scores, and episodic memory performance. Post-hoc differences were calculated using Sidak corrections. Pearson's coefficients (r-values) were used to examine two-tailed correlations between delayed recall performance, disease severity, and general neuropsychological performance. All correlations were corrected for multiple comparisons using "false discovery rate" method. Effect sizes are denoted using partial eta-squared values (η_p^2).

Image acquisition

One hundred and eight participants (40 CBS, 16 PSP, 23 AD, 29 Controls) underwent whole-brain T_1-weighted imaging using a 3T Philips MRI scanner with standard quadrature head coil (eight channels) using the following sequences: coronal orientation, matrix 256 × 256, 200 slices, 1 × 1 mm in-plane resolution, slice thickness = 1 mm, echo time/repetition = 2.6/5.8 msec, flip angle α = 8°. One hundred and seven participants (40 CBS, 16 PSP, 22 AD, 29 Controls) additionally underwent diffusion-weighted MRI using the following sequences: two sets of whole-brain echo planar images with 32 noncollinear gradient directions, matrix 96 × 96 mm, 55 slices, voxel size = 2.5 mm³, repetition time/echo time/inversion time: 8400/68/90 msec, b-value = 1000 sec/mm², field of view = 240 × 240 mm.

VBM analyses

VBM analyses were used to identify voxel-by-voxel changes in gray matter intensity across groups using the FSL-VBM toolbox (Ashburner and Friston 2000) from the FMRIB software package (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/fslvbm/index.html) (Smith et al. 2004). Structural MR images were brain-extracted (BET: Smith 2002) followed by tissue segmentation using FMRIB's Automatic Segmentation Tool (FAST: Zhang et al. 2001) The FMRIB nonlinear registration approach (FNIRT: Andersson et al. 2007a,b) was then used to align the brain-extracted images to the MNI standard space (MNI52), using a b-spline representation of the registration warp field (Rueckert et al. 1999). A study-specific template was created from the resulting images, to which a nonlinear reregistration of native gray matter images was performed. The registered partial volume maps were then modulated by dividing by the Jacobian of the warp field, to correct for local

expansion or contraction. Finally, the modulated segmented images were smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

An unbiased whole-brain general linear model was used to investigate gray matter intensity differences between the groups via permutation-based nonparametric testing (Nichols and Holmes 2002) with 5000 permutations per contrast. Differences in cortical gray matter intensities in AD, CBS, PSP patients, and Controls were assessed using regression models with separate directional contrasts (i.e., t-tests). Age was included as a nuisance variable in the atrophy analysis. Clusters were extracted using the threshold-free cluster enhancement method (TFCE) and corrected for Family-Wise Error at $P < 0.05$.

Correlations were performed exploring the relationship between delayed episodic memory performance and gray matter intensity across the entire brain. For additional statistical power, a correlation-only statistical model was used using a positive t-contrast to index the association between gray matter intensity and memory performance. Specifically, correlation cluster analyses were performed across participant groups and for each patient group combined with Controls to identify disease-specific associations, with age entered as a nuisance covariate. Anatomical locations of statistical significance were overlaid on the MNI standard brain with maximum coordinates provided in MNI stereotaxic space. The Harvard-Oxford probabilistic atlas and the Juelich histological atlas (with histology-based regional parcellation of the parietal cortices) were used to determine anatomical labels. Clusters in all VBM correlation analyses were reported uncorrected at a strict threshold of $P < 0.001$. To further reduce the potential for false positive results, a conservative cluster extent threshold of 100 contiguous voxels was used.

Finally, overlap and exclusive masking techniques were used to determine common and unique neural correlates of episodic memory performance in patient groups (Irish et al. 2014b).

Diffusion tensor imaging analysis

Tract-based Spatial Statistics (TBSS) in FSL were used to perform a skeleton-based analysis of white matter fractional anisotropy (FA). For each participant, raw diffusion-weighted images were corrected for eddy-currents and coregistered using nonlinear registration (FNIRT: Andersson et al. 2007a,b) to MNI standard space using their respective 3D T_1-weighted structural MR image. This template was subsampled at 2 mm^3, due to the coarse resolution of diffusion tensor imaging data (i.e., 2.5 mm^3). Following image registration, a tensor model was fitted to the diffusion-weighted image and FA maps were generated for each participant. Finally, FA maps were averaged to produce a group mean FA image. A skeletonized algorithm (Smith et al. 2006) was then applied to define a group template of the lines of maximum FA, corresponding to the centres of white matter tracts. For each participant, FA values were projected onto this group template skeleton, and extracted for use in subsequent correlation analysis with delayed recall performance. The output clusters were tested using permutation-based nonparametric testing as outlined for the VBM analysis. Age was included as a nuisance variable in this analysis. Clusters were reported using the threshold-free cluster enhancement method and corrected for Family-Wise Error at $P < 0.05$. To determine anatomical labels, the Johns Hopkins University White Matter atlas and the ICBM-DTI-WM atlas labels were used, integrated into FSLview (Mori et al. 2008; Oishi et al. 2008).

Correlations between delayed recall performance and FA values from selected tracts were examined using Pearson's correlations (r-values) corrected for multiple comparisons using the "false discovery rate" method to control for Type-I error (Benjamini and Hochberg 1995).

Competing interest statement

The authors declare that they have no conflict of interest.

References

Ahmed S, Irish M, Loane C, Baker I, Husain M, Thompson S, Blanco-Duque C, Mackay C, Zamboni G, Foxe D, et al. 2018a. Association between precuneus volume and autobiographical memory impairment in posterior cortical atrophy: beyond the visual syndrome. *Neuroimage Clin* **18:** 822–834. doi:10.1016/j.nicl.2018.03.008

Ahmed S, Loane C, Bartels S, Zamboni G, Mackay C, Baker I, Husain M, Thompson S, Hornberger M, Butler C. 2018b. Lateral parietal contributions to memory impairment in posterior cortical atrophy. *Neuroimage Clin* **20:** 252–259. doi:10.1016/j.nicl.2018.07.005

Albrecht F, Bisenius S, Morales Schaack R, Neumann J, Schroeter ML. 2017. Disentangling the neural correlates of corticobasal syndrome and corticobasal degeneration with systematic and quantitative ALE meta-analyses. *NPJ Parkinsons Dis* **3:** 12. doi:10.1038/s41531-017-0012-6

Andersson JLR, Jenkinson M, Smith S. 2007a. Non-linear optimisation. In *FMRIB Technical Report TR07JA1*. University of Oxford FMRIB Centre, Oxford.

Andersson JLR, Jenkinson M, Smith S. 2007b. Non-linear registration, aka spatial normalisation. In *FMRIB Technical Report TR07JA2*. University of Oxford FMRIB Centre, Oxford.

Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, Boxer AL, Dickson DW, Grossman M, Hallett M, et al. 2013. Criteria for the diagnosis of corticobasal degeneration. *Neurology* **80:** 496–503. doi:10.1212/WNL.0b013e31827f0fd1

Ashburner J, Friston KJ. 2000. Voxel-based morphometry–the methods. *Neuroimage* **11:** 805–821. doi:10.1006/nimg.2000.0582

Backus AR, Bosch SE, Ekman M, Grabovetsky AV, Doeller CF. 2016. Mnemonic convergence in the human hippocampus. *Nat Commun* **7:** 11991. doi:10.1038/ncomms11991

Benjamini Y, Hochberg Y. 1995. Controlling the false discovery rate - a practical and powerful approach to multiple testing. *J R Stat Soc B Met* **57:** 289–300. doi:10.1111/j.2517-6161.1995.tb02031.x

Ben-Zvi S, Soroker N, Levy DA. 2015. Parietal lesion effects on cued recall following pair associate learning. *Neuropsychologia* **73:** 176–194. doi:10.1016/j.neuropsychologia.2015.05.009

Berryhill ME, Phuong L, Picasso L, Cabeza R, Olson IR. 2007. Parietal lobe and episodic memory: bilateral damage causes impaired free recall of autobiographical memory. *J Neurosci* **27:** 14415–14423. doi:10.1523/JNEUROSCI.4163-07.2007

Berryhill ME, Picasso L, Arnold R, Drowos D, Olson IR. 2010. Similarities and differences between parietal and frontal patients in autobiographical and constructed experience tasks. *Neuropsychologia* **48:** 1385–1393. doi:10.1016/j.neuropsychologia.2010.01.004

Bird CM, Keidel JL, Ing LP, Horner AJ, Burgess N. 2015. Consolidation of complex events via reinstatement in posterior cingulate cortex. *J Neurosci* **35:** 14426–14434. doi:10.1523/JNEUROSCI.1774-15.2015

Bonnici HM, Richter FR, Yazar Y, Simons JS. 2016. Multimodal feature integration in the angular gyrus during episodic and semantic retrieval. *J Neurosci* **36:** 5462–5471. doi:10.1523/JNEUROSCI.4310-15.2016

Borroni B, Garibotto V, Agosti C, Brambati SM, Bellelli G, Gasparotti R, Padovani A, Perani D. 2008. White matter changes in corticobasal degeneration syndrome and correlation with limb apraxia. *Arch Neurol* **65:** 796–801. doi:10.1001/archneur.65.6.796

Boxer AL, Geschwind MD, Belfor N, Gorno-Tempini ML, Schauer GF, Miller BL, Weiner MW, Rosen HJ. 2006. Patterns of brain atrophy that differentiate corticobasal degeneration syndrome from progressive supranuclear palsy. *Arch Neurol* **63:** 81–86. doi:10.1001/archneur.63.1.81

Brewer JA, Garrison KA, Whitfield-Gabrieli S. 2013. What about the "Self" is Processed in the Posterior Cingulate Cortex? *Front Hum Neurosci* **7:** 647. doi:10.3389/fnhum.2013.00647

Bubb EJ, Metzler-Baddeley C, Aggleton JP. 2018. The cingulum bundle: anatomy, function, and dysfunction. *Neurosci Biobehav Rev* **92:** 104–127. doi:10.1016/j.neubiorev.2018.05.008

Burgess N, Maguire EA, O'Keefe J. 2002. The human hippocampus and spatial and episodic memory. *Neuron* **35:** 625–641. doi:10.1016/S0896-6273(02)00830-9

Burrell JR, Hodges JR, Rowe JB. 2014. Cognition in corticobasal syndrome and progressive supranuclear palsy: a review. *Mov Disord* **29:** 684–693. doi:10.1002/mds.25872

Cabeza R, Ciaramelli E, Olson IR, Moscovitch M. 2008. The parietal cortex and episodic memory: an attentional account. *Nat Rev Neurosci* **9:** 613–625. doi:10.1038/nrn2459

Caspers S, Eickhoff SB, Rick T, von Kapri A, Kuhlen T, Huang R, Shah NJ, Zilles K. 2011. Probabilistic fibre tract analysis of cytoarchitectonically defined human inferior parietal lobule areas reveals similarities to macaques. *Neuroimage* **58:** 362–380. doi:10.1016/j.neuroimage.2011.06.027

Chahine LM, Rebeiz T, Rebeiz JJ, Grossman M, Gross RG. 2014. Corticobasal syndrome: five new things. *Neurol Clin Pract* **4:** 304–312. doi:10.1212/CPJ.0000000000000026

Chand P, Grafman J, Dickson D, Ishizawa K, Litvan I. 2006. Alzheimer's disease presenting as corticobasal syndrome. *Mov Disord* **21:** 2018–2022. doi:10.1002/mds.21055

Chen HY, Gilmore AW, Nelson SM, McDermott KB. 2017. Are there multiple kinds of episodic memory? An fMRI investigation comparing autobiographical and recognition memory tasks. *J Neurosci* **37:** 2764–2775. doi:10.1523/JNEUROSCI.1534-16.2017

Choo IH, Lee DY, Oh JS, Lee JS, Lee DS, Song IC, Youn JC, Kim SG, Kim KW, Jhoo JH, et al. 2010. Posterior cingulate cortex atrophy and regional cingulum disruption in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* **31:** 772–779. doi:10.1016/j.neurobiolaging.2008.06.015

Corbetta M, Shulman GL. 2002. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* **3:** 201–215. doi:10.1038/nrn755

Corkin S. 2002. What's new with the amnesic patient H.M.? *Nat Rev Neurosci* **3:** 153–160. doi:10.1038/nrn726

Davidson PS, Anaki D, Ciaramelli E, Cohn M, Kim AS, Murphy KJ, Troyer AK, Moscovitch M, Levine B. 2008. Does lateral parietal cortex support episodic memory? Evidence from focal lesion patients. *Neuropsychologia* **46:** 1743–1755. doi:10.1016/j.neuropsychologia.2008.01.011

Dickerson BC, Eichenbaum H. 2010. The episodic memory system: neurocircuitry and disorders. *Neuropsychopharmacology* **35:** 86–104. doi:10.1038/npp.2009.126

Dobbins IG, Foley H, Schacter DL, Wagner AD. 2002. Executive control during episodic retrieval: multiple prefrontal processes subserve source memory. *Neuron* **35:** 989–996. doi:10.1016/S0896-6273(02)00858-9

Frisch S, Dukart J, Vogt B, Horstmann A, Becker G, Villringer A, Barthel H, Sabri O, Muller K, Schroeter ML. 2013. Dissociating memory networks in early Alzheimer's disease and frontotemporal lobar degeneration - a combined study of hypometabolism and atrophy. *PLoS One* **8:** e55251. doi:10.1371/journal.pone.0055251

Gilmore AW, Nelson SM, McDermott KB. 2015. A parietal memory network revealed by multiple MRI methods. *Trends Cogn Sci* **19:** 534–543. doi:10.1016/j.tics.2015.07.004

Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O. 2008. Mapping the structural core of human cerebral cortex. *PLoS Biol* **6:** e159. doi:10.1371/journal.pbio.0060159

Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, Mollenhauer B, Müller U, Nilsson C, Whitwell JL, et al. 2017. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. *Mov Disord* **32:** 853–864. doi:10.1002/mds.26987

Horner AJ, Bisby JA, Bush D, Lin WJ, Burgess N. 2015. Evidence for holistic episodic recollection via hippocampal pattern completion. *Nat Commun* **6:** 7462. doi:10.1038/ncomms8462

Hower KH, Wixted J, Berryhill ME, Olson IR. 2014. Impaired perception of mnemonic oldness, but not mnemonic newness, after parietal lobe damage. *Neuropsychologia* **56:** 409–417. doi:10.1016/j.neuropsychologia.2014.02.014

Hu WT, Rippon GW, Boeve BF, Knopman DS, Petersen RC, Parisi JE, Josephs KA. 2009. Alzheimer's disease and corticobasal degeneration presenting as corticobasal syndrome. *Mov Disord* **24:** 1375–1379. doi:10.1002/mds.22574

Imamura A, Wszolek ZK, Lucas JA, Dickson DW. 2009. Corticobasal syndrome with Alzheimer's disease pathology. *Mov Disord* **24:** 152–153. doi:10.1002/mds.21877

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

Irish M, Addis DR, Hodges JR, Piguet O. 2012. Considering the role of semantic memory in episodic future thinking: evidence from semantic dementia. *Brain* **135:** 2178–2191. doi:10.1093/brain/aws119

Irish M, Hornberger M, El Wahsh S, Lam BY, Lah S, Miller L, Hsieh S, Hodges JR, Piguet O. 2014a. Grey and white matter correlates of recent and remote autobiographical memory retrieval–insights from the dementias. *PLoS One* **9:** e113081. doi:10.1371/journal.pone.0113081

Irish M, Piguet O, Hodges JR, Hornberger M. 2014b. Common and unique gray matter correlates of episodic memory dysfunction in frontotemporal dementia and Alzheimer's disease. *Hum Brain Mapp* **35:** 1422–1435. doi:10.1002/hbm.22263

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

Irish M, Bunk S, Tu S, Kamminga J, Hodges JR, Hornberger M, Piguet O. 2016. Preservation of episodic memory in semantic dementia: the importance of regions beyond the medial temporal lobes. *Neuropsychologia* **81:** 50–60. doi:10.1016/j.neuropsychologia.2015.12.005

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

Jones DK, Christiansen KF, Chapman RJ, Aggleton JP. 2013. Distinct subdivisions of the cingulum bundle revealed by diffusion MRI fibre tracking: implications for neuropsychological investigations. *Neuropsychologia* **51:** 67–78. doi:10.1016/j.neuropsychologia.2012.11.018

Josephs KA, Whitwell JL, Dickson DW, Boeve BF, Knopman DS, Petersen RC, Parisi JE, Jack CR Jr. 2008. Voxel-based morphometry in autopsy proven PSP and CBD. *Neurobiol Aging* **29:** 280–289. doi:10.1016/j.neurobiolaging.2006.09.019

Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, Miller BL, Mercaldo N. 2008. Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain* **131:** 2957–2968. doi:10.1093/brain/awn234

Koziol LF, Budding D, Andreasen N, D'Arrigo S, Bulgheroni S, Imamizu H, Ito M, Manto M, Marvel C, Parker K, et al. 2014. Consensus paper: the cerebellum's role in movement and cognition. *Cerebellum* **13:** 151–177. doi:10.1007/s12311-013-0511-x

Kuhl BA, Chun MM. 2014. Successful remembering elicits event-specific activity patterns in lateral parietal cortex. *J Neurosci* **34:** 8051–8060. doi:10.1523/JNEUROSCI.4328-13.2014

Lee H, Kuhl BA. 2016. Reconstructing perceived and retrieved faces from activity patterns in lateral parietal cortex. *J Neurosci* **36:** 6069–6082. doi:10.1523/JNEUROSCI.4286-15.2016

Lieberman MD, Cunningham WA. 2009. Type I and Type II error concerns in fMRI research: re-balancing the scale. *Soc Cogn Affect Neurosci* **4:** 423–428. doi:10.1093/scan/nsp052

Mathew R, Bak TH, Hodges JR. 2012. Diagnostic criteria for corticobasal syndrome: a comparative study. *J Neurol Neurosurg Psychiatry* **83:** 405–410. doi:10.1136/jnnp-2011-300875

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, et al. 2011. The diagnosis

of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7:** 263–269. doi:10.1016/j.jalz.2011.03.005

McKinnon MC, Black SE, Miller B, Moscovitch M, Levine B. 2006. Autobiographical memory in semantic dementia: implication for theories of limbic-neocortical interaction in remote memory. *Neuropsychologia* **44:** 2421–2429. doi:10.1016/j.neuropsychologia.2006.04.010

Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. 1997. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol* **42:** 85–94. doi:10.1002/ana.410420114

Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. 2006. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry* **21:** 1078–1085. doi:10.1002/gps.1610

Mori S, Wakana S, Nagae-Poetscher LM, van Zijl P. 2005. *MRI atlas of human white matter*. Elsevier, Amsterdam.

Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, Hua K, Faria AV, Mahmood A, Woods R, et al. 2008. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage* **40:** 570–582. doi:10.1016/j.neuroimage.2007.12.035

Murty VP, DuBrow S, Davachi L. 2015. The simple act of choosing influences declarative memory. *J Neurosci* **35:** 6255–6264. doi:10.1523/JNEUROSCI.4181-14.2015

Nadel L, Moscovitch M. 1997. Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr Opin Neurobiol* **7:** 217–227. doi:10.1016/S0959-4388(97)80010-4

Nichols TE, Holmes AP. 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp* **15:** 1–25. doi:10.1002/hbm.1058

Oishi K, Zilles K, Amunts K, Faria A, Jiang H, Li X, Akhter K, Hua K, Woods R, Toga AW, et al. 2008. Human brain white matter atlas: identification and assignment of common anatomical structures in superficial white matter. *Neuroimage* **43:** 447–457. doi:10.1016/j.neuroimage.2008.07.009

Petersen RC. 2004. Mild cognitive impairment as a diagnostic entity. *J Intern Med* **256:** 183–194. doi:10.1111/j.1365-2796.2004.01388.x

Ramanan S, Flanagan E, Leyton CE, Villemagne VL, Rowe CC, Hodges JR, Hornberger M. 2016. Non-verbal episodic memory deficits in primary progressive aphasias are highly predictive of underlying amyloid pathology. *J Alzheimers Dis* **51:** 367–376. doi:10.3233/JAD-150752

Ramanan S, Bertoux M, Flanagan E, Irish M, Piguet O, Hodges JR, Hornberger M. 2017. Longitudinal executive function and episodic memory profiles in behavioral-variant frontotemporal dementia and Alzheimer's disease. *J Int Neuropsychol Soc* **23:** 34–43. doi:10.1017/S1355617716000837

Ramanan S, Alaeddin S, Goldberg ZL, Strikwerda-Brown C, Hodges JR, Irish M. 2018a. Exploring the contribution of visual imagery to scene construction - evidence from posterior cortical atrophy. *Cortex* **106:** 261–274. doi:10.1016/j.cortex.2018.06.016

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

Ranganath C, Ritchey M. 2012. Two cortical systems for memory-guided behaviour. *Nat Rev Neurosci* **13:** 713–726. doi:10.1038/nrn3338

Rose SE, McMahon KL, Janke AL, O'Dowd B, de Zubicaray G, Strudwick MW, Chalk JB. 2006. Diffusion indices on magnetic resonance imaging and neuropsychological performance in amnestic mild cognitive impairment. *J Neurol Neurosurg Psychiatry* **77:** 1122–1128. doi:10.1136/jnnp.2005.074336

Rueckert D, Sonoda LI, Hayes C, Hill DLG, Leach MO, Hawkes DJ. 1999. Nonrigid registration using free-form deformations: application to breast MR images. *Ieee T Med Imaging* **18:** 712–721. doi:10.1109/42.796284

Rugg MD, Vilberg KL. 2013. Brain networks underlying episodic memory retrieval. *Curr Opin Neurobiol* **23:** 255–260. doi:10.1016/j.conb.2012.11.005

Rugg MD, Cox CJ, Doyle MC, Wells T. 1995. Event-related potentials and the recollection of low and high frequency words. *Neuropsychologia* **33:** 471–484. doi:10.1016/0028-3932(94)00132-9

Scimeca JM, Badre D. 2012. Striatal contributions to declarative memory retrieval. *Neuron* **75:** 380–392. doi:10.1016/j.neuron.2012.07.014

Scoville WB, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psychiatry* **20:** 11–21. doi:10.1136/jnnp.20.1.11

Sestieri C, Shulman GL, Corbetta M. 2010. Attention to memory and the environment: functional specialization and dynamic competition in human posterior parietal cortex. *J Neurosci* **30:** 8445–8456. doi:10.1523/JNEUROSCI.4719-09.2010

Sestieri C, Shulman GL, Corbetta M. 2017. The contribution of the human posterior parietal cortex to episodic memory. *Nat Rev Neurosci* **18:** 183–192. doi:10.1038/nrn.2017.6

Shannon BJ, Buckner RL. 2004. Functional-anatomic correlates of memory retrieval that suggest nontraditional processing roles for multiple distinct regions within posterior parietal cortex. *J Neurosci* **24:** 10084–10092. doi:10.1523/JNEUROSCI.2625-04.2004

Shelley BP, Hodges JR, Kipps CM, Xuereb JH, Bak TH. 2009. Is the pathology of corticobasal syndrome predictable in life? *Mov Disord* **24:** 1593–1599. doi:10.1002/mds.22558

Shimamura AP. 2011. Episodic retrieval and the cortical binding of relational activity. *Cogn Affect Behav Neurosci* **11:** 277–291. doi:10.3758/s13415-011-0031-4

Simons JS, Spiers HJ. 2003. Prefrontal and medial temporal lobe interactions in long-term memory. *Nat Rev Neurosci* **4:** 637–648. doi:10.1038/nrn1178

Smith SM. 2002. Fast robust automated brain extraction. *Hum Brain Mapp* **17:** 143–155. doi:10.1002/hbm.10062

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, et al. 2004. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* **23:** S208–S219. doi:10.1016/j.neuroimage.2004.07.051

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, et al. 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* **31:** 1487–1505. doi:10.1016/j.neuroimage.2006.02.024

Squire LR, Zola-Morgan S. 1991. The medial temporal lobe memory system. *Science* **253:** 1380–1386. doi:10.1126/science.1896849

Thakral PP, Madore KP, Schacter DL. 2017. A role for the left angular gyrus in episodic simulation and memory. *J Neurosci* **37:** 8142–8149. doi:10.1523/JNEUROSCI.1319-17.2017

Tomita H, Ohbayashi M, Nakahara K, Hasegawa I, Miyashita Y. 1999. Top-down signal from prefrontal cortex in executive control of memory retrieval. *Nature* **401:** 699–703. doi:10.1038/44372

Tulving E. 2002. Episodic memory: from mind to brain. *Annu Rev Psychol* **53:** 1–25. doi:10.1146/annurev.psych.53.100901.135114

Upadhyay N, Suppa A, Piattella MC, Di Stasio F, Petsas N, Colonnese C, Colosimo C, Berardelli A, Pantano P. 2016. Gray and white matter structural changes in corticobasal syndrome. *Neurobiol Aging* **37:** 82–90. doi:10.1016/j.neurobiolaging.2015.10.011

Vilberg KL, Rugg MD. 2008. Memory retrieval and the parietal cortex: a review of evidence from a dual-process perspective. *Neuropsychologia* **46:** 1787–1799. doi:10.1016/j.neuropsychologia.2008.01.004

Vincent JL, Snyder AZ, Fox MD, Shannon BJ, Andrews JR, Raichle ME, Buckner RL. 2006. Coherent spontaneous activity identifies a hippocampal-parietal memory network. *J Neurophysiol* **96:** 3517–3531. doi:10.1152/jn.00048.2006

Wagner AD, Shannon BJ, Kahn I, Buckner RL. 2005. Parietal lobe contributions to episodic memory retrieval. *Trends Cogn Sci* **9:** 445–453. doi:10.1016/j.tics.2005.07.001

Whitwell JL, Jack CR, Boeve BF, Parisi JE, Ahlskog JE, Drubach DA, Senjem ML, Knopman DS, Petersen RC, Dickson DW, et al. 2010. Imaging correlates of pathology in corticobasal syndrome. *Neurology* **75:** 1879–1887. doi:10.1212/WNL.0b013e3181feb2e8

Wong S, Irish M, Leshikar ED, Duarte A, Bertoux M, Savage G, Hodges JR, Piguet O, Hornberger M. 2017. The self-reference effect in dementia: differential involvement of cortical midline structures in Alzheimer's disease and behavioural-variant frontotemporal dementia. *Cortex* **91:** 169–185. doi:10.1016/j.cortex.2016.09.013

Zhang YY, Brady M, Smith S. 2001. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *Ieee T Med Imaging* **20:** 45–57. doi:10.1109/42.906424