The self-reference effect in dementia: Differential involvement of cortical midline structures in Alzheimer's disease and behavioural-variant frontotemporal dementia

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Highlights

- Self-referential encoding did not ameliorate source memory deficits in bvFTD or AD.
- Reduced self-reference effect (SRE) was not related to general memory deficits.
- Atrophy in different cortical midline structures was implicated in bvFTD and AD.
- Different aspects of self-referential processing may be affected in bvFTD and AD.

Abstract

Encoding information in reference to the self enhances subsequent memory for the source of this information. In healthy adults, self-referential processing has been proposed to be mediated by the cortical midline structures (CMS), with functional differentiation between anterior-ventral, anterior-dorsal and posterior regions. While both Alzheimer's disease (AD) and behavioural-variant frontotemporal dementia (bvFTD) patients show source memory impairment, it remains unclear whether they show a typical memory advantage for self-referenced materials. We also sought to identify the neural correlates of this so-called 'self-reference effect' (SRE) in these patient groups. The SRE paradigm was tested in AD (n=16) and bvFTD (n=22) patients and age-matched healthy controls (n=17). In this task, participants studied pictures of common objects paired with one of two background scenes (sources) under self-reference or other-reference encoding instructions, followed by an item and source recognition memory test. Voxel-based morphometry was used to investigate correlations between SRE measures and regions of grey matter atrophy in the CMS. The behavioural results indicated that self-referential encoding did not ameliorate the significant source memory impairments in AD and bvFTD patients. Furthermore, the reduced benefit of self-referential relative to other-referential encoding was not related to general episodic memory deficits. Our imaging findings revealed that reductions in the SRE were associated with atrophy in the anterior-dorsal CMS across both patient groups, with additional involvement of the posterior CMS in AD and anterior-ventral CMS in bvFTD. These findings suggest that although the SRE is comparably reduced in AD and bvFTD, this arises due to impairments in different subcomponents of self-referential processing.

Keywords: Self-reference effect; Source memory; Alzheimer's disease; Behavioural-variant frontotemporal dementia; voxel-based morphometry

1. Introduction

For many years, the concept of self has intrigued philosophers, psychologists and, more recently, neuroscientists. While a number of different theoretical notions and definitions of the self exist, it is accepted that the self plays an important role in memory consolidation (Northoff et al., 2006; Rogers, 1977; Symons & Johnson, 1997). According to Rogers, Kuiper and Kirker (1977), evaluating new information in relation to the self promotes deeper and more elaborate memory encoding. This so-called self-reference effect (SRE) on memory has since been demonstrated in numerous studies, where self-referentially encoded information is retrieved more accurately on a subsequent memory task, relative to information that has been encoded in relation to another person (other-reference) or based on its physical or semantic features (Rogers et al., 1977; Symons & Johnson, 1997). While the SRE paradigm typically involves encoding and retrieval of trait adjectives (Bower & Gilligan, 1979; Gutchess, Kensinger, & Schacter, 2010), the effect has also been replicated with memory for objects (Hamami, Serbun, & Gutchess, 2011; Leshikar & Duarte, 2013), actions (Rosa & Gutchess, 2011) and specific contextual details (Hamami et al., 2011; Leshikar & Duarte, 2012; Serbun, Shih, & Gutchess, 2011). As such, self-referential encoding promotes episodic memory retrieval by enhancing not only item memory, but also source memory.

The robustness of the SRE has been demonstrated across the lifespan in healthy individuals (Glisky & Marquine, 2009; Gutchess, Kensinger, Yoon, & Schacter, 2007b; Gutchess et al., 2015; Leshikar, Dulas, & Duarte, 2015). Importantly, while older individuals typically show age-related decline in source memory accuracy (Johnson, Hashtroudi & Lindsay, 1993; Yonelinas, 2002), recent work has found that these deficits are ameliorated for source information that has been encoded with reference to the self (Leshikar et al., 2015; Leshikar & Duarte, 2013). Nevertheless, it remains to be

established whether self-referencing may benefit source memory retrieval in dementia patients presenting with episodic memory impairment.

Patients with Alzheimer's disease (AD) show marked impairments in episodic memory (McKhann et al., 2011) and perform poorly on source memory tests (Haj & Kessels, 2013; Multhaup & Balota, 1997). While retrieval of self-referential episodic memories from the past are adversely affected in AD (Irish, Lawlor, O'Mara, & Coen, 2011b), notably, concept of self appears to be relatively preserved, as indexed on measures of trait self-knowledge (Klein, Cosmides, & Costabile, 2003; Rankin, 2005) and self-descriptive statements (Eustache et al., 2013). To date, evidence for the benefit of self-referential encoding on source memory retrieval in AD is mixed. Most existing studies have evaluated the self-reference *recollection* effect (SRRE) in AD using the Remember/Know/Guess paradigm, where 'remember' responses are presumed to involve episodic memory, with conscious recollection of contextual details, as opposed to 'know' responses, which reflect a 'feeling of knowing' without recollection (Tulving, 1985; 2002). While three studies in AD patients have demonstrated higher rates of 'remember' responses for self-referenced trait adjectives (Kalenzaga & Clarys, 2013; Kalenzaga, Bugaïska, & Clarys, 2013; Lalanne, Rozenberg, Grolleau, & Piolino, 2013), others have found no SRE for item recognition (Leblond et al., 2016) or both reduced SRE and SRRE (Genon et al., 2013). Nonetheless, the Remember/Know/Guess paradigm does not control for the variability of remembered contextual details for each item within and between participants. As such, a source memory experimental design would help objectively determine which, if any, specific contextual details are disproportionately enhanced by self-referencing in AD. While no prior research in AD has investigated the SRE on source memory, one study in patients with amnestic mild cognitive impairment (aMCI) showed a benefit of self-referencing in terms of reducing item and source memory errors (Rosa, Deason, Budson, & Gutchess, 2014).

Individuals diagnosed with behavioural-variant frontotemporal dementia (bvFTD) can also present with episodic memory dysfunction (Bertoux et al., 2014; Graham et al., 2005; Hornberger & Piguet, 2012; Hornberger, Piguet, Graham, Nestor, & Hodges, 2010) and show impaired performance on tests of source memory (Irish, Graham, Graham, Hodges, & Hornberger, 2012b; Simons et al., 2002). In contrast to AD however, the core clinical features of bvFTD include marked changes to personality and interpersonal conduct (Piguet, Hornberger, Mioshi, & Hodges, 2011), with declines in social cognition and empathy (Eslinger, Moore, Anderson, & Grossman, 2011; Rascovsky et al., 2011) and lack of insight (Mendez & Shapira, 2011; O'Keeffe et al., 2007). Not surprisingly, bvFTD patients show alterations in their self concept, as reflected in the striking discrepancies between patient and carer ratings of personality traits (Rankin, 2005; Ruby et al., 2007), as well as reports of dramatic changes in social, political or religious values (Miller et al., 2001). To the best of our knowledge, no study to date has explored the impact of self-referential processing on source memory in bvFTD, nor has this been directly contrasted in AD and bvFTD.

Evidence from neuroimaging studies points overwhelmingly to the involvement of cortical midline structures (CMS) in self-referential processing (Craik et al., 1999; Gutchess, Kensinger, & Schacter, 2007a; Northoff et al., 2006; Northoff & Bermpohl, 2004; Qin & Northoff, 2011). Drawing from this vast body of literature, Northoff et al. (2006) proposed a model in which three distinct CMS subregions (anterior-ventral, anterior-dorsal and posterior CMS) are associated with subfunctions of self-referential processing, including representation, reappraisal and evaluation, and integration (see also Northoff & Bermpohl, 2004). Specifically, the anterior-ventral CMS encompasses the medial orbitofrontal cortex (MOFC), the ventromedial prefrontal cortex (VMPFC) and the sub- and pregenual parts of the anterior cingulate cortex (PACC). This region is proposed to be involved in coding the self-relatedness of stimuli, thereby forming a self-related representation. Evaluation

and appraisal of self-referenced stimuli is associated with the anterior-dorsal CMS, which includes the dorsomedial prefrontal cortex (DMPFC) and the supragenual anterior cingulate cortex (SACC). Finally, the posterior CMS comprises the posterior cingulate cortex (PCC), the retrosplenial cortex (RSC), and the medial parietal cortex (MPC). These posterior regions are proposed to be involved in the integration of new self-referential information within the temporal context of one's emotional and autobiographical self. While each of these CMS subregions purportedly mediate specific aspects of self-referential processing, no study to date has directly contrasted the differential contributions of these subregions. One way to address this is by comparing the SRE in AD versus bvFTD patients, as these neurodegenerative disorders are characterised by predominantly posterior and anterior burdens of CMS pathology, respectively (Rabinovici et al., 2007).

To our knowledge, only one study has investigated the neural correlates of self-referential processing in dementia patients (Genon et al., 2013). In this study, AD patients did not show a significant SRE, despite showing similar activation of the VMPFC compared to controls when encoding stimuli with reference to the self. A follow-up investigation revealed a wider functional network of brain regions associated with the accurate recognition of self-referenced information, including the PCC and hippocampus in AD patients (Genon et al., 2014). In the context of Northoff's (2006) model, these findings (Genon et al., 2013; 2014) suggest that the absence of SRE in AD may not be related to impairments in the representation of stimuli as self-related by the anterior-ventral CMS, but rather, to a broader deficit in the retrieval of self-related memories, mediated by posterior CMS subregions known to be affected early in the course of the disease (Chetelat et al., 2007; Irish, Addis, Hodges, & Piguet, 2012a; Nestor, Fryer, Ikeda, & Hodges, 2003; Scahill, Schott, Stevens, Rossor, & Fox, 2002). This dovetails with previous reports of intact concept of self in AD (Eustache et al., 2013; Klein et al., 2003; Rankin, 2005).

Of particular relevance to this study is the pattern of neurodegenerative changes typically seen in bvFTD. Given that the MPFC is one of the earliest affected regions (Kipps, Hodges, Fryer, & Nestor, 2009; Rabinovici et al., 2007; Seeley et al., 2008), this neurodegenerative condition offers an excellent opportunity to examine the impact of MPFC damage on self-referenced memories. While no previous research has explored the SRE in bvFTD, evidence from studies of autobiographical memory in these patients suggests a link between MPFC atrophy and impairments in their retrieval of personally relevant memories from the past (Irish, Hodges, & Piguet, 2013; Irish, Hornberger, Wahsh, Lam, Lah, et al., 2014a). Furthermore, the MPFC represents a site of particular interest, as atrophy in this region has been associated with episodic memory dysfunction in bvFTD, which contrasts with the predominantly posterior pattern of atrophy implicated in AD (Frisch et al., 2013; Irish, Piguet, Hodges, & Hornberger, 2014b; Wong, Flanagan, Savage, Hodges, & Hornberger, 2014). Nevertheless, it remains unclear how this anterior-posterior dissociation between bvFTD and AD potentially disrupts the SRE for source memory in these patient groups.

The objectives of this study were twofold: i) to explore whether self-referential encoding would enhance source memory retrieval differentially in bvFTD and AD, and ii) to identify the CMS correlates of the SRE in these patient groups using region-of-interest voxel-based morphometry (VBM). We hypothesised that the SRE for source memory would be comparably attenuated in bvFTD and AD, but that these deficits would be associated with an anterior-posterior dissociation of CMS atrophy. Specifically, we proposed that atrophy of anterior-ventral CMS subregions would relate to the limited benefit of self-referential encoding on source memory retrieval in bvFTD. On the other hand, we predicted that the reduced SRE in AD would be associated with atrophy in the posterior CMS subregions.

2. Material and methods

2.1. Participants

Thirty-eight dementia patients (bvFTD=22; AD=16) and 17 age-matched healthy controls were recruited through FRONTIER at Neuroscience Research Australia, Sydney. All bvFTD patients fulfilled clinical diagnostic criteria for probable bvFTD (Rascovsky et al., 2011), with insidious onset, progressive decline in social behaviour and personal conduct, apathy, emotional blunting and loss of insight. To exclude potential phenocopy cases in the bvFTD cohort (Kipps, Hodges, & Hornberger, 2010), only those who showed evidence of progressive decline and atrophy on structural MRI brain scans were included. All AD patients met clinical diagnostic criteria for probable AD (McKhann et al., 2011), with worsening episodic memory impairment in the context of preserved personality and behaviour. Disease duration was estimated as the number of years elapsed since the reported onset of symptoms. The Frontotemporal Dementia Rating Scale (FRS) (Mioshi, Hsieh, Savage, Hornberger, & Hodges, 2010) and Clinical Dementia Rating Scale (CDR) (Morris, 1997) were used to determine the disease severity in bvFTD and AD patients. In addition, the Cambridge Behavioural Inventory revised (CBI-R) (Wear et al., 2008) was completed by the family or carer, to quantify symptoms of behavioural disturbance, with higher scores indicative of more severe behavioural disturbance. To determine their overall level of cognitive functioning, all participants underwent general cognitive screening using the Addenbrooke's Cognitive Examination-III (ACE-III) (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013). Age-matched healthy controls were recruited from the FRONTIER research volunteer panel and scored >88 on the ACE-III (Hsieh et al., 2013).

Exclusion criteria for all participants included current or prior history of mental illness, significant head injury, movement disorders, cerebrovascular disease (stroke, transient ischaemic attacks), alcohol and other drug abuse and limited English proficiency. Exclusion criteria for MRI scanning procedures included presence of metal fragments in the eyes, cardiac pacemaker, brain aneurysm clips, cochlear implants, other ferromagnetic implants or severe claustrophobia.

2.2. Ethics statement

All participants provided written informed consent and this study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Human Research Ethics Committee of the South Eastern Sydney Local Health District and the University of New South Wales.

2.3. Neuropsychological assessment of episodic memory

Following previously reported procedures (Irish, Piguet, Hodges, & Hornberger, 2014b; Pennington, Hodges, & Hornberger, 2011), standardised neuropsychological measures of verbal (Rey Auditory Verbal Learning Test; RAVLT) (Schmidt, 1996) and visuospatial (Rey-Osterrieth Complex Figure Test; RCFT) (Rey, 1941) episodic memory were administered to all participants. The following scores were included in our correlational analyses between episodic memory and SRE task performance: RAVLT immediate recall following interference trial (maximum score = 15); RAVLT delayed recall following 30 minutes (maximum score = 15); and RCFT 3-minute delayed recall (maximum score = 36).

2.4. Experimental self-reference source memory task

The self-reference source memory task was adapted from previous studies (Leshikar et al., 2015; Leshikar & Duarte, 2013). The current version assessed source memory recognition following self-

reference and other-reference encoding conditions. A perceptual condition was included as a control condition.

2.4.1. Stimuli

The stimuli consisted of 40 objects and 2 background scenes. During encoding, 30 objects were presented superimposed on 1 of the 2 background scenes. A further 10 objects were presented as novel items at the subsequent recognition memory test. The objects were colour images of common objects (e.g., saxophone, spoon, notebook, etc.) taken from the Hemera Technologies Photo-Objects DVDs (Hemera Technologies, Inc.). The 2 background scenes were colour images of landscapes (a mountain or a beach). The word frequency and familiarity of each object was calculated using the MRC Psycholinguistic Database (http://www.psych.rl.ac.uk). Ten objects were allocated to each of the 4 stimulus sets (self-reference, other-reference, perceptual and novel), which were matched for total word frequency and familiarity. Sets assigned per condition were counterbalanced across participants.

INSERT FIGURE 1 AROUND HERE

2.4.2. Procedure

Participants were first trained on a short version of the encoding and recognition tasks. Training included 12 practice encoding trials (4 trials per encoding task) and 16 practice recognition test trials, containing stimuli from the 12 practice items plus 4 novel items. Participant's understanding of the task instructions was checked before progressing from training to the experimental task. The procedures for the encoding and test phases are illustrated in Figure 1.

During the training and experimental encoding phases of the study, participants performed encoding tasks under three conditions (self-reference, other-reference and perceptual). Encoding task instructions emphasized that there were no correct answers, as judgments made during the encoding tasks were intended to be subjective.

Self-Reference Condition: Participants judged whether they liked the object-background pairing (yes/no).

Other-Reference Condition: Participants judged whether the Queen of England, Elizabeth II, would like the object-background pairing (yes/no). Importantly, a well-known but not close-other person was selected for this condition, as brain regions activated during close-other processing (e.g. one's best friend) have been shown to overlap with those activated during self-referential processing (Grigg & Grady, 2010). As previously described (Leshikar & Duarte, 2013), Queen Elizabeth II was selected as the *other* referent, under the assumption that she was well-known but not personally acquainted with any of the participants. A photograph of Queen Elizabeth II was displayed with the encoding instructions that preceded the other-reference condition. All participants demonstrated intact recognition of Queen Elizabeth II.

Perceptual Condition: Participants judged whether the object and background contained similar colours (yes/no).

The encoding phase of the study included a total of 30 trials (10 in each encoding condition). Each encoding trial lasted 4000ms, including presentation of the object-scene pair for 3500ms, followed by a 500ms central fixation. To minimize task-switching costs, trials were presented in blocks of 10 trials per encoding condition. At the beginning of each block, an instruction prompt ("Get ready for the [*self/queen/colour*] task.") was displayed. The order of the blocks was counterbalanced across participants.

The test phase of the experiment was conducted immediately following encoding. The test phase consisted of 40 test trials, where all 30 of the objects from the encoding phase were individually displayed, intermixed with 10 novel objects. Trials were self-paced and presented in a random order. For each trial, participants first made an item recognition decision by judging whether the object was "old" or "new", or whether they didn't know ("don't know"). The prompt "Old | New | Don't know" was written below the object. This was followed by a source recognition decision for those objects judged to be "old". During the source decision, the two background scenes were displayed above the object, with the prompt "Mountain | Beach | Don't know" written below the object. Following previously reported procedures (Leshikar & Duarte, 2013), the "don't know" response option was offered in order to reduce potential contamination of guessing. No feedback regarding response accuracy was provided throughout the task.

The self-reference source memory task was programmed using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA), and testing was conducted on a laptop with a 14-inch LED-backlit display. During testing, participants provided verbal responses, which were recorded by the experimenter using the programmed response keys.

2.5. Statistical analyses

Data were analysed using SPSS 20.0 (SPSS Inc., Chicago, Ill., USA). Kolmogorov-Smirnov tests were used to check for normality of distribution. Where the data were normally distributed, scores were compared across groups using ANOVAs followed by Tukey post-hoc tests. Data that were not normally distributed were analysed using Kruskal-Wallis tests followed by post-hoc pairwise comparisons, using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. A chi-squared test was used to compare sex distribution across groups. Demographic variables that differed significantly across groups were included as covariates in between-group

analyses of SRE task variables. Item and source recognition accuracy measures from the SRE task were analysed using ANCOVAs. Pairwise comparisons of the main effects were adjusted for multiple comparisons using the Sidak method. To examine differences between encoding conditions within each participant group, *post hoc* paired-samples t-tests were conducted for each group separately.

Responses from the test phase of the SRE task were converted into percentages of total items in each condition (self-reference, other-reference, perceptual, novel). Item recognition responses were classified as *studied* 'item hit' (correct recognition), *studied* 'item miss' (incorrect rejection) and *studied* "don't know" for objects previously seen during the encoding phase; and *unstudied* 'item hit' (correct rejection), *unstudied* 'item miss' (false alarm) and *unstudied* "don't know" for novel objects presented in the test phase only. Corrected item recognition was calculated by subtracting the percentage of *unstudied* 'item misses' (false alarms) from the percentage of *studied* 'item hits' (correct recognition) in each condition. Source recognition responses were classified as 'source correct', 'source incorrect' and 'source "don't know"'. Given that the source recognition question was not asked following incorrect item responses (i.e. *studied* 'item miss' and *studied* "don't know" responses), source recognition for incorrect item responses was classified as 'source incorrect'. As such, source recognition responses were assumed to be incorrect for incorrect item responses.

To investigate the source memory advantage of self-reference over other-reference encoding, a SRE magnitude score was computed for source recognition accuracy by subtracting the other-reference percentage 'source correct' scores from the self-reference percentage 'source correct' scores. Thus, larger SRE magnitude scores indicated better memory for self-reference compared to other-reference encoded source information. Within each participant group, independent samples

t-tests were conducted to determine whether SRE magnitude for source recognition was significantly greater than 0. SRE magnitude scores comparing source recognition accuracy for "self-reference" and "perceptual" encoding conditions were also computed (see Supplementary Material).

2.6. Image acquisition and voxel-based morphometry (VBM) analysis

Structural MRI brain scans were available for a subset of participants (19/22 bvFTD and 15/16 AD patients and 15/17 controls). Patients and controls underwent the same imaging protocol with whole-brain T1-weighted images using a 3T Phillips MRI scanner with a standard quadrature head coil (8 channels). The 3D T1-weighted sequences were acquired as follows: coronal orientation, matrix 256 x 256, 200 slices, 1x 1 mm in-plane resolution, slice thickness 1mm, TE/TR=2.6/5.8ms. 3D T1-weighted sequences were analysed using FSL-VBM, a voxel-based morphometry analysis (Ashburner & Friston, 2000; Good et al., 2001), which is part of the FSL software package http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html (Smith et al., 2004). Following brain extraction, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool (FAST) (Zhang, Brady, & Smith, 2001). The resulting grey matter partial volume maps were aligned to the Montreal Neurological Institute standard space (MNI52) using the nonlinear registration approach with FNIRT (Anderson, Jenkinson & Smith, 2007a; 2007b) which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). To correct for local expansion or contraction, the registered partial volume maps were modulated by dividing them by the Jacobian of the warp field. Importantly, the Jacobian modulation step did not include the affine part of the registration, which means that the data was normalized for head size as a scaling effect. The modulated images were then smoothed with an isotropic Gaussian kernel with a standard deviation of 3 mm (FWHM: 8mm).

Given our strong *a priori* predictions, a single region of interest mask of CMS regions was created by combining individual masks of the relevant Harvard-Oxford cortical structural atlas regions included in the FSL software package. As the regional masks for the frontal pole, orbitofrontal cortex and superior frontal gyri include both medial and lateral portions, masks containing only the medial portions were manually traced. In accordance with Northoff et al. (2006), medial regions were defined as those falling within MNI coordinates $x < 25$ or $x > -25$ (see Figure 2). The following regions were included in the CMS mask: medial frontal pole, medial orbitofrontal cortex, medial superior frontal gyrus, medial prefrontal cortex, subcallosal cortex, paracingulate cortex, anterior cingulate cortex, posterior cingulate cortex and precuneus. These regions broadly correspond to the CMS subdivisions proposed by Northoff et al. (2006), such that the anterior-ventral CMS includes the medial frontal pole, medial orbitofrontal cortex, medial prefrontal cortex and subcallosal cortex; the anterior-dorsal CMS includes the medial superior frontal gyrus, paracingulate and anterior cingulate cortex; and the posterior CMS includes the posterior cingulate and precuneus.

INSERT FIGURE 2 AROUND HERE

A voxel-wise general linear model (GLM) was applied to investigate differences in grey matter intensity via permutation-based non-parametric testing (Nichols & Holmes, 2002) with 5000 permutations per contrast. Age and total years of education were included as nuisance variables in all imaging analyses. As a first step, differences in grey matter intensity between patients (bvFTD and AD) and controls were assessed. Group comparisons between patients and controls were tested for significance at $p < .05$, corrected for multiple comparisons via Family-wise Error (FWE) correction across space. A cluster extent threshold of 100 contiguous voxels was applied for group comparisons. Next, correlations between SRE magnitude and regions of grey matter atrophy were

investigated separately in each patient group (bvFTD, AD) combined with controls. This procedure has previously been used in similar studies including AD and bvFTD patients (Irish, Piguet, Hodges, & Hornberger, 2014b) and serves to achieve greater variance in behavioural scores, thereby increasing the statistical power to detect brain-behaviour relationships. To check for potential co-atrophy effects, diagnostic group membership was entered as an additional nuisance variable in the design matrix of the SRE magnitude covariate analyses, as per the method reported in Sollberger et al. (2009). For this co-atrophy check, we accepted a level of significance of $p<.05$ uncorrected for multiple comparisons for clusters of CMS atrophy previously identified in the SRE magnitude covariate analysis, and $p<.01$ for clusters outside these regions. Finally, inclusive and exclusive masking procedures were employed to identify regions commonly associated with SRE magnitude across both patient groups, as well as regions uniquely associated with SRE magnitude in bvFTD and AD. SRE magnitude covariate analyses and masking procedures were conducted at significance levels of $p<.01$, uncorrected for multiple comparisons. To reduce the potential for false positives, we applied a stringent cluster extent threshold of 50 contiguous voxels for the covariate analyses. Regions of significant atrophy were superimposed on T1-weighted standard brain images, and regions of significant grey matter intensity decrease were localised with reference to the Harvard-Oxford probabilistic cortical atlas. Maximum coordinates for the anatomical locations of significant results are reported in MNI coordinates.

3. Results

3.1. Demographics

Demographic and clinical characteristics of the participants are detailed in Table 1. Participant groups were matched for age ($p=.111$) and sex distribution ($p=.281$). An overall group difference was evident for total years of education ($p=.015$), driven by the fact that controls were more

highly educated than both bvFTD (p=.023) and AD (p=.039) patients. The total years of education was subsequently included as a covariate in between-group comparisons of cognitive, episodic memory and SRE task measures.

Importantly, the patient groups were matched for disease duration (p=.871) and severity of dementia symptoms on the CDR (p=.976). As expected, bvFTD patients were more impaired in comparison to AD patients on a FTD-specific measure of functional impairment (FRS; p=.016). Based on CBI-R scores, both patient groups showed significantly more symptoms of overall behavioural disturbance compared to controls (p values <.001), with more severe symptoms in bvFTD compared to AD patients (p=.006).

INSERT TABLE 1 AROUND HERE

3.2. General cognition and episodic memory assessment

Both patient groups were significantly impaired on the ACE-III cognitive screening measure, relative to controls (bvFTD, p<.001; AD, p<.001). However, performance on the ACE-III was comparable between AD and bvFTD patients (p=.202). In comparison to controls, both patient groups demonstrated significant episodic memory impairment across all measures of verbal and visual recall (p values <.01). Comparisons between patient groups revealed lower episodic memory performance in AD compared to bvFTD on the RAVLT immediate recall (p=.004), RAVLT delayed recall (p=.015) and RCFT 3-minute delayed recall (p=.003) scores.

3.3. SRE task performance

Supplementary Table 1 shows the mean percentages of each response type (hit, miss, "don't know") for items and sources from the self-reference, other-reference and perceptual encoding conditions, as well as for unstudied items.

3.3.1. Item recognition task

Supplementary Figure 1 depicts corrected item recognition accuracy for each encoding condition across the three participant groups. A three (group) by three (condition) repeated measures ANCOVA with years of education included as a covariate revealed a significant group effect ($F(2,51)=10.702$, $p<.001$) for overall corrected item recognition accuracy. This group effect reflected the fact that corrected item recognition accuracy was significantly lower in AD patients relative to controls ($p<.001$), irrespective of condition. Similarly, corrected item recognition accuracy was significantly lower in bvFTD patients compared to controls ($p=.003$). No significant condition effect ($p=.465$) or group × condition interaction ($p=.857$) was evident.

Post hoc paired-samples t-tests were conducted separately for each participant group, to explore differences in corrected item recognition for each encoding condition. In the control group, as expected, corrected item recognition accuracy was higher for the self-reference compared to perceptual condition ($t(16)=3.913$, $p=.001$) and higher for the other-reference relative to perceptual condition ($t(16)=3.118$, $p=.007$). However, corrected item recognition accuracy did not differ across self-reference and other-reference conditions ($t(16)=1.231$, $p=.236$) in this group. In the bvFTD group, corrected item recognition accuracy was lower for the self-reference compared to other-reference condition ($t(21)=-2.085$, $p=.049$). While corrected item recognition accuracy was comparable for the self-reference and perceptual conditions in bvFTD ($t(21)=0.756$, $p=.458$), this was significantly higher for the other-reference relative to perceptual condition ($t(21)=2.795$, $p=.011$). In AD patients, no significant difference in corrected item recognition accuracy was

observed between the self-reference and other-reference conditions (t(15)=0.659, *p*=.520), or between the other-reference and perceptual conditions (t(15)=0.768, *p*=.455). Nonetheless, a trend was present for higher corrected item recognition accuracy in the self-reference compared to perceptual condition (t(15)=2.085, *p*=.055).

3.3.2. Source recognition task

Figure 3A depicts source recognition accuracy for each encoding condition across the three participant groups. A three (group) by three (condition) repeated measures ANCOVA with years of education included as a covariate revealed a significant group effect ($F(2,51)=25.372$, $p<.001$) for overall source recognition accuracy. This group effect indicated that source recognition accuracy was significantly higher in controls compared to both bvFTD ($p<.001$) and AD ($p<.001$) patients, irrespective of condition. Furthermore, AD patients scored significantly lower than bvFTD patients ($p=.003$) on overall source recognition accuracy, regardless of condition. No significant condition effect ($p=.937$) or group × condition interaction ($p=.977$) was detected.

To explore differences in source recognition for each encoding condition*, post hoc* paired-samples t-tests were conducted separately for each participant group. In controls, source memory recognition accuracy was significantly higher for the self-reference compared to the other-reference condition (t(16)=3.357, *p*=.004), and higher for the self-reference compared to the perceptual condition (t(16)=3.067, *p*=.007). In contrast, source memory accuracy did not differ between the other-reference and perceptual conditions in controls (t(16)=0.803, *p*=.434). That is, controls showed a significant SRE for source recognition accuracy. In the patient groups however, none of the pairwise comparisons between self-reference, other-reference and perceptual conditions reached significance (all *p* values >.1). Therefore, only control participants showed a

significant source memory benefit for self-referenced compared to other-referenced and perceptually encoded stimuli.

3.3.3. SRE magnitude for source recognition

Figure 3B shows the mean SRE magnitude for source recognition accuracy across participant groups. Independent samples t-tests were conducted to determine whether SRE magnitude for source recognition was significantly greater than 0, indicating a positive memory advantage for self-referenced information. While SRE magnitude was significantly greater than 0 in the control group ($t(16)=3.357$, $p=.004$), this did not reach statistical significance in either bvFTD ($t(21)=-0.576$, $p=.571$) or AD ($t(15)=0.496$, $p=.627$). As such, only control participants showed a significant SRE, whereas both AD and bvFTD patients showed no source memory enhancement effect for self-referenced information.

INSERT FIGURE 3 AROUND HERE

3.4. Correlations between SRE magnitude and episodic memory impairment

Spearman rank correlations were used to examine the relationship between SRE magnitude and performance on neuropsychological tests of episodic memory. Across all participants, SRE magnitude scores did not correlate significantly with the RAVLT immediate recall ($R=.114$, $p=.449$), RAVLT delayed recall ($R=.178$, $p=.238$) or RCFT 3-min recall ($R=.238$, $p=.097$) scores. Similarly, correlations between SRE magnitude scores and episodic memory scores within each participant group did not reach statistical significance (all p values >.1). This suggests that the benefit of self-reference over other-reference encoding was not related to episodic memory performance per se.

3.5. Voxel-based morphometry results

3.5.1. CMS grey matter atrophy profiles across patient groups

Figure 4 displays the patterns of CMS grey matter atrophy evident in each patient group relative to controls. BvFTD patients showed a predominantly anterior profile of CMS atrophy, encompassing the bilateral subcallosal cortex, orbitofrontal cortex, medial prefrontal cortex, frontal pole, anterior cingulate cortex, paracingulate cortex and superior frontal gyrus, as well as bilateral regions of the posterior cingulate cortex (see Figure 4A, Table 2). In contrast, the AD group showed a predominantly posterior profile of grey matter atrophy, including the bilateral posterior cingulate cortex and precuneus. To a lesser extent, bilateral anterior cingulate and paracingulate and right frontal polar grey matter atrophy was also evident in AD patients (see Figure 4B, Table 2).

Direct comparison of the two patient groups revealed a predominantly anterior burden of atrophy in bvFTD, in contrast to a predominantly posterior burden of atrophy in AD. Bilateral regions in the subcallosal cortex, orbitofrontal cortex, medial prefrontal cortex, anterior cingulate cortex and paracingulate cortex showed greater atrophy in bvFTD compared to AD (see Figure 4C, Table 2). The reverse contrast revealed significantly greater atrophy in the bilateral posterior cingulate cortex and precuneus in the AD group (see Figure 4D, Table 2). These grey matter atrophy profiles are consistent with previously reported patterns of atrophy in bvFTD (Seeley et al., 2008) and AD (Karas et al., 2004; Rabinovici et al., 2007).

INSERT FIGURE 4 AROUND HERE

INSERT TABLE 2 AROUND HERE

3.5.2. Grey matter correlates of SRE magnitude

SRE magnitude (indicating source memory advantage of self vs. other-referencing) scores were entered into two separate general linear models, to investigate correlations between SRE magnitude and regions of grey matter atrophy in each patient group (bvFTD, AD) combined with controls. In bvFTD, SRE magnitude covaried with grey matter intensity decrease in predominantly anterior CMS regions including the anterior cingulate cortex, paracingulate cortex, medial prefrontal cortex and subcallosal cortex, bilaterally (see Figure 5A, Table 3). In AD, SRE magnitude covaried with grey matter intensity decrease in bilateral anterior cingulate and paracingulate cortices, right posterior cingulate cortex and precuneus, and right frontal pole and orbitofrontal and medial prefrontal cortices (see Figure 5B, Table 3). Analysis of potential co-atrophy effects revealed that these regions remained significant (p<.05, uncorrected) when controlling for diagnostic group effects (see Table 3), and no significant clusters outside the regions of CMS atrophy identified in the SRE magnitude analyses emerged (p<.01, uncorrected). As a final check, mean cluster intensity values were extracted for each significant cluster in the anterior-dorsal CMS, anterior-ventral CMS and posterior CMS and plotted against SRE magnitude scores for bvFTD patients and controls (see Supplementary Figure 3A) and AD patients and controls (see Supplementary Figure 3B).

INSERT FIGURE 5 AROUND HERE

INSERT TABLE 3 AROUND HERE

To identify the regions significantly associated with SRE magnitude in both bvFTD and AD, we conducted an overlap analysis (see Figure 6, Supplementary Table 2). This analysis revealed the bilateral anterior cingulate and paracingulate cortices to be commonly implicated across both patient groups. Next, exclusive masking was used to identify the regions that uniquely contributed to SRE magnitude in each patient group (see Figure 6, Supplementary Table 2). In bvFTD, integrity

of the right medial prefrontal and subcallosal cortices, as well as left anterior cingulate cortices correlated exclusively with SRE magnitude. In contrast, SRE magnitude in AD patients was exclusively associated with integrity of the right posterior cingulate cortex, as well as regions in the right frontal pole and orbitofrontal cortex and right anterior cingulate cortex. Thus, in relation to the three CMS subregions proposed by Northoff et al. (2006), anterior-dorsal CMS atrophy was associated with reduced SRE magnitude across both bvFTD and AD. In bvFTD, there was additional involvement of anterior-ventral CMS atrophy only. By contrast, SRE magnitude was exclusively associated with posterior CMS atrophy in AD patients, as well as atrophy in an OFC/frontal polar region within the anterior-ventral CMS.

INSERT FIGURE 6 AROUND HERE

4. Discussion

A vast body of work highlights the preferential encoding of information related to the self. In the current study, we investigated how damage to regions in the CMS, crucial for self-referential processing, impact the SRE in neurodegenerative disorders with divergent anterior versus posterior CMS pathology. In bvFTD, where the burden of pathology is overwhelmingly anterior, we found that the reduced SRE was related to atrophy in the anterior-ventral CMS. In contrast, atrophy in the posterior CMS was uniquely associated with the attenuated SRE in AD, consistent with the predominantly posterior burden of atrophy in this patient group. Furthermore, atrophy in the anterior-dorsal CMS was implicated across both patient groups. Our findings therefore highlight important similarities and differences in the contribution of these CMS subregions and corresponding subcomponents of self-referential processing, in mediating the SRE in bvFTD and AD.

This is the first study, to our knowledge, to explore the mechanisms underpinning SRE disruption in AD and bvFTD. In line with our predictions, bvFTD patients did not show an enhancement effect of self-referential processing. Our findings mesh well with previous work showing impaired retrieval of autobiographical memory, which is inherently self-referential, in these patients (Irish et al., 2011a; Piolino et al., 2003). Importantly, the reduced benefit of self- versus other-referential encoding did not correlate with performance on standardised tests of episodic memory, suggesting that the absence of SRE in these patients could not be explained by a general memory deficit per se. Rather, our results indicate that self-referencing has no appreciable influence on source memory retrieval in bvFTD. One potential explanation is that alterations in self concept influence the degree to which self-related information is preferentially encoded in this syndrome. In his original study, Rogers (1977) described the self as a cognitive structure that plays an active role in memory, such that new information that is consistent with one's self is organised and remembered more easily than information that is incompatible with one's self. This raises the possibility that alterations to the self, as documented by changes in personality (Rankin, 2005; Ruby et al., 2007) and personal values (Miller et al., 2001) in bvFTD, impact on its stability and reliability as a cognitive structure that facilitates the encoding of self-related information. Nonetheless, the precise mechanisms underlying this effect require further investigation.

On a behavioural level, our findings in AD are comparable with bvFTD, where there was no self-referential enhancement of source memory. The absence of SRE in our AD group corroborates results from previous reports of attenuated SRE and SRRE in AD (Genon et al., 2013; Leblond et al., 2016), but extend these findings by using a source memory experimental design, showing neither item nor source memory enhancement. While a number of existing studies have demonstrated significant SRE and SRRE in AD (Kalenzaga et al., 2013; Kalenzaga & Clarys, 2013; Lalanne et al.,

2013), the apparent disparity in results may be related to differences in methodological approaches. Whereas all previous self-referential encoding tasks conducted in AD patients have involved making judgments regarding the self-relevance of trait adjectives, reports of significant SRE or SRRE appear to be driven by the effect in positive (Lalanne et al., 2013) or negative (Kalenzaga et al., 2013; Kalenzaga & Clarys, 2013) trait adjectives only. Thus, it is plausible that self-referencing alone is not sufficient to provide a memory advantage in AD, unless the to-be-remembered stimuli are emotional in nature. Indeed, evidence suggests that a significant emotional enhancement effect persists in AD patients, despite their profound episodic memory impairments (Kalenzaga, Piolino, & Clarys, 2014; Kumfor, Irish, Hodges, & Piguet, 2013; 2014). Given that we included relatively neutral objects and background stimuli in our SRE paradigm, it is unlikely that emotional valence had any appreciable impact on memory performance. Taken together, our findings contribute to a growing body of research which indicates that self-referential processing alone is insufficient to enhance memory retrieval in AD.

Importantly, while the absence of source memory enhancement for self-referential information was comparable in bvFTD and AD, the neural correlates differed markedly between groups. In line with evidence from neuroimaging studies that have highlighted the importance of the MPFC for SRE (D'Argembeau et al., 2005; Moran, Heatherton, & Kelley, 2009; Northoff et al., 2006; Philippi, Duff, Denburg, Tranel, & Rudrauf, 2012), atrophy in this region was associated with reductions in SRE magnitude in bvFTD. In the context of Northoff's (2006) model, damage to this anterior-ventral CMS region disrupts the initial coding of stimuli as self-related, thus compromising downstream self-referential processes in more posteriorly located CMS regions. In conjunction with findings from MPFC lesion patients, who do not show any significant SRE (Philippi et al., 2012), our results support the notion that disruption to the initial stages of self-referential processing in the anterior-ventral CMS may impact the extent to which memory for self-related

information is enhanced. On a broader level however, the anterior-ventral CMS has also been proposed to function as a 'valuation' centre, where subjective value is assigned to incoming stimuli (D'Argembeau, 2013; Northoff & Hayes, 2011). As such, this region appears to be involved in processing and integrating features that contribute to the subjective value of a stimulus, such as self-relatedness (D'Argembeau, 2013; Northoff & Hayes, 2011), reward value (Kringelbach, 2005; Levy & Glimcher, 2012) and emotional value (Winecoff et al., 2013), which determines whether it is preferentially encoded. Of particular relevance, bvFTD patients do not show the typical memory advantage for emotional information, and this has been associated with atrophy in the OFC, which forms the most ventral part of the anterior-ventral CMS (Kumfor et al., 2013; 2014). In the same vein, the reduced memory enhancement effect for personally 'valuable' information was related to anterior-ventral CMS atrophy in our bvFTD patients. Damage to this anterior-ventral CMS region in bvFTD may therefore be particularly disruptive to the early processing of self-referential information, during which personal value is assigned.

In contrast, integrity of the posterior CMS regions (including the PCC and precuneus) was exclusively associated with the degree of self-referential enhancement of memory in AD. This contrasts with results from Genon et al. (2013; 2014), where PCC activity was associated with the accurate recognition of self-referentially encoded information, rather than the SRE magnitude per se. Instead, SRE magnitude was associated with lateral PFC atrophy, which presumably mediates the interaction between self-referential and higher order cognitive processes (Genon et al., 2013; Northoff et al., 2006). Nonetheless, our results extend existing findings by using a targeted region-of-interest approach to identify specific CMS correlates of the SRE in AD, primarily involving the posterior CMS but also an OFC/frontal polar region in the anterior-ventral CMS. Notably however, this anterior-ventral CMS subregion implicated in AD was located more laterally and did not overlap with the anterior-ventral CMS subregion implicated in bvFTD. Whether this lateral-ventral

distinction reflects further functional subdivisions within the anterior-ventral CMS, requires further investigation. Nonetheless, our results in AD are compatible with previous reports of both posterior and anterior-ventral CMS activity during the retrieval of self-referenced relative to non-self-referenced stimuli in healthy adults (Fossati et al., 2004; Leshikar & Duarte, 2013; Yaoi, Osaka, & Osaka, 2015). On a broader level, the involvement of both posterior and anterior-ventral CMS subregions is also consistent with the pattern of CMS activity during inherently self-related memory processes such as autobiographical memory retrieval (Addis, McIntosh, Moscovitch, Crawley, & McAndrews, 2004; Maguire, 2001; Svoboda, McKinnon, & Levine, 2006). In the context of Northoff's (2006) model, involvement of the posterior CMS in AD, but not bvFTD, suggests that the reduced SRE in AD may be further impacted by specific deficits in the ability to integrate newly coded self-referential information within the context of existing autobiographical memories (Cavanna & Trimble, 2006). Our findings therefore point to the unique contribution of posterior CMS atrophy to self-referential memory processes in AD, corroborating previous work emphasizing the role of the posterior CMS regions in the retrieval of past, and simulation of future, self-referential events in this patient group (Irish et al., 2012a; 2013).

While we identified divergent CMS contributions to the SRE specific to each patient group, our analyses also implicated the anterior-dorsal CMS, particularly the anterior cingulate cortex, as a common neural correlate of SRE magnitude in bvFTD and AD. With respect to its role in self-referential processing, Northoff (2006) proposed that the anterior-dorsal CMS is involved in the reappraisal and evaluation of self-related information. Indeed, a recent meta-analysis of functional neuroimaging studies contrasting self- and other-judgments revealed a spatial gradient in MPFC activation, such that self-referential judgments were associated with greater ventral MPFC activity, whereas other-referential judgments were related to greater activity in the dorsal MPFC (Denny, Kober, Wager, & Ochsner, 2012). The finding that dorsal MPFC supports judgments about

others is unsurprising, given its role in perspective taking tasks, such as those involving theory of mind (ToM) (D'Argembeau et al., 2007; Gallagher & Frith, 2003). Crucially, bvFTD patients show impairments in perspective taking and empathy (Cerami et al., 2014; Dermody et al., 2016; Eslinger et al., 2011), which have been proposed to be associated with underlying difficulties in inhibiting their own perspective when required to adopt another person's perspective (Le Bouc et al., 2012). It is therefore possible that bvFTD patients tended to encode all stimuli in relation to the self, thereby reducing the SRE magnitude. Importantly however, our findings from the perceptual encoding condition do not support this position, as we did not find enhanced source memory retrieval for both the self- and other-reference conditions compared to the perceptual condition. Furthermore, while perspective taking and ToM deficits have been widely reported in bvFTD patients (Adenzato, Cavallo, & Enrici, 2010; Bertoux, Funkiewiez, O'Callaghan, Dubois, & Hornberger, 2013; Kipps & Hodges, 2006), recent work has delineated between cognitive (attribution of intention) and affective (attribution of emotion) ToM, showing comparable deficits in cognitive ToM across both bvFTD and AD patients (Dermody et al., 2016; Dodich et al., 2016). Against this background, the anterior-dorsal CMS involvement in SRE magnitude across both bvFTD and AD patients may be related to deficits in their ability to evaluate information from the perspective of another person. Nonetheless, the relationship between perspective taking ability and self-referential enhancement of memory in these patient groups remains to be established, and represents an important area for future research.

From a theoretical viewpoint, the current findings suggest that attenuation of the self-referential enhancement effect in bvFTD and AD may reflect the breakdown of discrete facets of self-referential processing, which in turn rely upon the integrity of different subregions of the CMS. Our results in bvFTD confirm the importance of prefrontal cortex contributions to episodic memory function (Simons & Spiers, 2003; Wong et al., 2014) and complement a growing body of

literature, which views the anterior-ventral CMS as a core 'valuation' hub by assigning subjective value to personally-, affectively- and motivationally-salient information (D'Argembeau, 2013; Northoff & Hayes, 2011). On the other hand, our findings in AD confirm the prominence of the PCC in mediating all aspects of self-related memory impairments in this syndrome (reviewed by Irish & Piolino, 2015). While our findings are in line with the notion that different CMS subregions mediate discrete aspects of self-referential processing, functional neuroimaging studies employing targeted experimental paradigms that directly contrast the different aspects of self-referential processing are necessary to support this proposal.

A number of methodological issues warrant consideration. Firstly, as our SRE task only assessed source memory accuracy for background images, it is unclear how this compares to accurate retrieval of other source details (e.g. encoding context). Nonetheless, our findings demonstrate that self-referential processing in AD and bvFTD does not ameliorate impairments on an objective measure of source memory. A second point to consider is the use of background image, rather than encoding context, as the source recognition question, as this precluded us from distinguishing between false alarms for 'new' items incorrectly assigned as self, other or perceptually referenced. Of particular relevance, recent studies (Rosa & Gutchess, 2013; Rosa, Deason, Budson, & Gutchess, 2015) have indicated that the SRE may also impact false alarm rates, such that 'new' items that are subsequently judged to be highly self-relevant are more likely to be falsely recognized as 'old'. Given that false recognition rates on clinical measures of episodic memory are elevated in both bvFTD and AD patients (Flanagan et al., 2016), future studies should investigate the potential impact of self-referential processing on false alarm rates in these patient groups. Thirdly, due to time constraints and patient fatigue, it was necessary to limit the number of trials in our SRE encoding task. Given the small number of responses, item-only hits and item misses were collapsed into the same response category (i.e. source-unrecollected) to contrast

against item-and-source hits (i.e. source-recollected). Hence, our source memory recognition accuracy measure only allowed us to draw conclusions regarding source memory effects, which were not conditionalised based on item memory effects. Similarly, the small number of responses also precluded us from correcting for lucky guesses in source recognition performance, as per previously reported procedures in healthy adults (Leshikar & Duarte, 2013). As such, the impact of such response biases on source recognition memory following self-referential encoding in these patient groups represents an important area of future enquiry. Additionally, we were not able to contrast subsequent item and source recognition accuracy for items positively or negatively judged for pleasantness during encoding. Given that greater MPFC activation is observed in relation to stimuli judged to be self-relevant (D'Argembeau et al., 2005; Moran et al., 2009), comparison of memory for stimuli according to degree of self-relevance may further elucidate mechanisms underlying the reduced SRE in bvFTD and AD. Likewise, the relationship between the SRE and alterations in concept of self represents an important area of future enquiry, especially considering the marked changes to personality and interpersonal conduct in bvFTD (Piguet et al., 2011). While previous studies in AD have used self-rated measures of identity valence and certainty (Lalanne et al., 2013; Leblond et al., 2016), inclusion of measures that allow comparison between self and informant responses is necessary, as loss of insight is a prominent clinical characteristic in bvFTD (Piguet et al., 2011). Furthermore, given that we employed a region-of-interest approach in our VBM analyses, we could not exclude the possibility that atrophy of regions beyond the CMS may have also contributed to the reduced SRE in bvFTD and AD. In particular, the lateral prefrontal cortex has been proposed to support interactions between self-referential and higher-order processes, especially during tasks with a strong cognitive component (Northoff et al., 2006). Comparison of the SRE on tasks with a low versus high cognitive load may help further elucidate the role of the lateral prefrontal cortex in self-referential processing in these patient groups. Nonetheless, given that the lateral prefrontal cortex shows a similar degree of

atrophy (Rabinovici et al., 2007) and contributes to episodic memory deficits (Wong et al., 2014) in both bvFTD and AD, it is unlikely that this region differentially contributes to the reduced SRE in these patient groups. Finally, future investigations of self-referential processing in bvFTD and AD would benefit from incorporating resting-state functional connectivity metrics to clarify the impact of CMS pathology on the SRE in, the context of large-scale network dysfunction characteristic of these disorders.

In summary, this study reveals the differential involvement of CMS subregions in facilitating the SRE, by contrasting neurodegenerative disorders with a predominantly anterior versus predominantly posterior burden of pathology. Absence of the SRE in bvFTD is associated with underlying pathology in the anterior-ventral CMS, which potentially mediates the early stages of self-referential processing, during which personal value is assigned to stimuli. In contrast, pathology in the posterior CMS uniquely contributes to the attenuated SRE in AD, likely reflecting breakdown in integrative processes that link newly encoded self-related information with existing self-referential, autobiographical memories. In addition, anterior-dorsal atrophy appears to contribute to reductions in SRE across both bvFTD and AD, pointing to deficits in the evaluative aspects of self-referential processing in both syndromes. Our results provide important insights into the mechanisms underlying self-referential memory and point to clinically relevant similarities and differences in the interaction between self and memory in bvFTD and AD. Exploring the relationship between alterations in self concept and the memory benefit conferred by self-referential processing will be an important next step for future studies to address.

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

	Control	bvFTD	AD	Group effect	Post hoc test
Sex (M:F)	9:8	14:8	6:10	n.s.	
Age (y)	67.21 (6.35)	62.10 (6.78)	64.81 (9.13)	n.s.	
Education (y)	14.38 (2.38)	11.90 (2.64)	11.91 (3.42)	*	Controls > bvFTD, AD
Disease duration (y)	-	5.54 (3.80)	5.51 (4.67)	n.s.	
CDR Sum of Boxes [18]	0.25 (0.38)	5.45 (2.83)	4.10 (1.79)	***	Controls < bvFTD, AD
FRS Rasch score	-	-1.06 (0.99)	0.06 (1.48)	*	bvFTD < AD
CBI-R total frequency score [100]	3.06 (3.06)	39.57 (13.44)	27.08 (13.36)	***	Controls < AD < bvFTD
ACE-III [100]	96.31 (2.87)	75.82 (12.14)	67.50 (7.67)	***	Controls > bvFTD, AD
RAVLT immediate recall [15]	10.8 (2.48)	5.69 (4.01)	2.07 (1.98)	***	Controls > bvFTD > AD
RAVLT delayed recall [15]	10.67 (2.99)	5.63 (3.26)	1.27 (1.33)	***	Controls > bvFTD > AD
RCFT 3-min recall [36]	22.21 (6.86)	9.80 (6.15)	4.32 (4.99)	***	Controls > bvFTD > AD

[a] Standard deviations in parentheses, maximum score for tests shown in brackets.

Clinical Dementia Rating Scale (CDR); Frontotemporal Dementia Rating Scale (FRS); Cambridge Behavioural Inventory-Revised (CBI-R); Addenbrooke's Cognitive Examination (ACE-III); Rey Auditory Verbal Learning Test (RAVLT); Rey-Osterrieth Complex Figure Test (RCFT).

*p<.05, **p<.01, ***p<.001, n.s. = non-significant

Table 2. Voxel-based morphometry results showing regions of significant grey matter intensity decrease for bvFTD and AD groups compared to controls.

Regions	Hemisphere (L/R/B)	MNI coordinates			Number of voxels
		X	Y	Z	
bvFTD < Controls					
Medial prefrontal cortex, subcallosal cortex, orbitofrontal cortex, frontal pole, anterior cingulate cortex, paracingulate cortex, superior frontal gyrus	B	6	32	-16	7462
Posterior cingulate cortex	L	-14	-34	38	104
AD < Controls					
Posterior cingulate cortex, precuneus	B	-8	-46	2	3669
Anterior cingulate cortex, paracingulate cortex	B	12	14	34	699
Frontal pole	R	16	50	-22	113
bvFTD < AD					
Subcallosal cortex, orbitofrontal cortex, medial prefrontal cortex	B	10	14	-20	1426
Paracingulate cortex, anterior cingulate cortex	B	6	34	32	867
AD < bvFTD					
Precuneus, posterior cingulate cortex	B	2	-68	40	3196

All results FWE-corrected at p<.05; only clusters with at least 100 contiguous voxels included. All clusters reported t>1.99. Age and years of education were included as covariates in all contrasts. L = Left; R = Right; B = Bilateral; MNI = Montreal Neurological Institute.

Table 3. Voxel-based morphometry results showing regions of significant grey matter intensity decrease that covary with SRE magnitude scores

Regions	Hemisphere (L/R/B)	MNI coordinates X	Y	Z	Number of voxels
bvFTD combined with controls					
Anterior cingulate cortex, paracingulate cortex†	B	0	32	28	152
Medial prefrontal cortex, subcallosal cortex†	R	4	38	-14	122
AD combined with controls					
Anterior cingulate cortex†	B	2	28	26	311
Frontal pole, orbitofrontal cortex, medial prefrontal cortex†	R	12	42	-20	240
Posterior cingulate cortex†	R	16	-36	38	68

All results uncorrected at p<.01; only clusters with at least 50 contiguous voxels included. All clusters reported t>3.36. Age and years of education were included as covariates in all contrasts.

† Clusters significant (p<.05) when diagnostic group included as an additional covariate for co-atrophy check.

L = Left; R = Right; B = Bilateral; MNI = Montreal Neurological Institute.

Figure captions

Figure 1. Encoding and test phase procedures for the SRE task. Screens were separated by a fixation cross (500ms) not represented here.

Figure 2. Representation of brain regions included in the CMS mask used in VBM analyses

Figure 3. A) Mean percentage correct source recognition responses for self-reference, other-reference and perceptual encoding conditions across participant groups. B) SRE magnitude (self-reference source accuracy - other-reference source accuracy) across groups. * = significant difference between encoding conditions. # = SRE magnitude significantly different from 0. Error bars represent standard error of the mean.

Figure 4. VBM analyses showing CMS regions of greater reduction in (A) bvFTD patients in comparison with controls (B) AD patients in comparison with controls (C) bvFTD patients in comparison with AD patients and (D) AD patients in comparison with bvFTD patients. Coloured voxels show regions that were significant in the analysis with $p<.05$, Family-Wise Error corrected, and a cluster threshold of 100 contiguous voxels. Clusters are overlaid on the MNI standard brain.

Figure 5. Regions of CMS grey matter atrophy correlating with self-other SRE magnitude in A) bvFTD patients and B) AD patients. Coloured voxels show regions that were significant in the analysis with $p<.01$, uncorrected and a cluster threshold of 50 contiguous voxels. Clusters are overlaid on the MNI standard brain.

Figure 6. Regions of CMS grey matter atrophy that correlate with SRE magnitude scores across both bvFTD and AD (overlap shown in green), and regions that correlate exclusively in bvFTD patients (red) and exclusively in AD patients (blue). Coloured voxels show regions that were significant in the analysis with $p<.01$, uncorrected and a cluster threshold of 50 contiguous voxels. Clusters are overlaid on the MNI standard brain.