Title: Do I know you? Examining face and object memory in frontotemporal dementia

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Abstract

The ability to perceive, learn and recognise faces is a complex ability, which is key to successful social interactions. This ability is proposed to be coordinated by neural regions in the occipital and temporal lobes, specialised for face perception and memory. While previous studies have suggested that memory for faces is compromised in some dementia syndromes, it remains unclear whether this simply reflects more generalised memory deficits. Here, we examined basic face perception (Identity-Matching), face recognition (Cambridge Face Memory Task) and object recognition (Cambridge Car Memory Task) in 11 semantic dementia (SD) patients (8 left-lateralised, 3 right-lateralised) and 13 behavioural-variant frontotemporal dementia (bvFTD) patients, compared with 11 controls. On the Identity-Matching task, bvFTD were impaired compared to controls, with a similar trend observed in the SD group. Importantly, both bvFTD and SD also demonstrated impaired face recognition. In contrast, only bvFTD showed impaired object recognition, with SD performing within normal limits on this task. Voxel-based morphometry analyses revealed that Identity-Matching and face recognition were associated with partly dissociable regions including the fusiform cortex and anterior temporal lobe. Object-memory was associated with thalamic integrity in the bvFTD group only. These results reveal that face perception and face memory deficits are common in bvFTD and SD, and have been previously underestimated. These deficits are due to neurodegeneration of key regions within the 'core' and 'extended' face processing system, providing convergent evidence of the neural regions supporting face perception. From a clinical perspective, impaired ability to recognise faces is common in bvFTD and SD and therefore strategies to improve face perception and memory may be beneficial for these patients.

Keywords: face perception, frontotemporal dementia, memory, fusiform cortex, temporal lobe

1 Introduction

The ability to perceive and recognise faces is arguably one of the most highly specialised skills in humans. It enables us to recognise friends or family members, as well as acquaintances or even famous individuals that we have not met before in real life. This capacity occurs with ease and requires minimal cognitive effort. In addition, the ability to learn and remember new faces appears to be virtually unlimited. Despite this ostensible simplicity, the cognitive and neural mechanisms supporting face perception and recognition are complex.

Stages involved in face perception include early perception of facial features supported by the inferior occipital gyri (Haxby et al. 2000). This is followed by extraction of invariant facial features (i.e., facial identity), while simultaneously disregarding any changeable facial information (e.g., emotional expression, age, lip movements during speech) (Bruce & Young 1986; Calder & Young 2005; Haxby, et al. 2000). This stage is supported by the inferotemporal cortex, including the lateral fusiform face area. Other neural regions including the superior temporal sulcus, purportedly involved in processing changeable face features, have also been implicated (for reviews see Calder & Young 2005; Haxby, et al. 2000). Retrieval of biographical/semantic information related to the face then involves the anterior temporal lobe (for review see Haxby, et al. 2000). Finally, successful face recognition, as well as (re-)encoding of facial information and its related contextual information may recruit additional memory systems including the medial temporal lobe and prefrontal regions (e.g., Bernstein et al. 2002). Breakdown at any of these cognitive or neural stages will compromise face perception and memory for faces.

Impaired recognition of familiar or famous faces (i.e., prosopagnosia) has received considerable interest from a cognitive and neural perspective, with a large number of studies reporting impairment, in several neurodegenerative disorders (e.g., Gefen et al. 2013; Josephs et al. 2008; Mendez et al. 1992; Snowden et al. 2004). The extent that impaired face perception and recognition of *novel* faces is present in dementia, however, is less clear.

Frontotemporal dementia (FTD) is an umbrella term, referring to a group of progressive, neurodegenerative brain disorders that affect the frontal and temporal lobes (Gorno-Tempini et al. 2011; Rascovsky et al. 2011). Three clinical subtypes are typically recognised: behavioural-variant frontotemporal dementia (bvFTD), semantic dementia (SD) and progressive nonfluent aphasia (PNFA). This study focuses on the bvFTD and SD subtypes. Individuals with bvFTD present with a marked disturbance of behaviour and personality, which is associated with degeneration of the orbitofrontal and medial prefrontal cortices (Kipps et al. 2009; Seeley et al. 2008). Episodic memory performance is often impaired, and in many cases individuals with bvFTD are as impaired as disease-matched individuals with Alzheimer's disease on standard neuropsychological tests of episodic memory (Hornberger & Piguet 2012; Hornberger et al. 2010; Irish et al. 2014b).

In contrast, individuals with SD present with a multimodal loss of general conceptual/semantic knowledge, which is usually associated with atrophy in the left anterior temporal lobe (Chan et al. 2001; Galton et al. 2001; Mion et al. 2010). Despite this profound loss of

semantic memory, non-verbal episodic memory is usually well-preserved (Hodges et al. 1992). Of relevance here, a proportion of patients (~ 30%) present with right- rather than left-lateralised temporal lobe degeneration, referred to as right SD (Chan et al. 2009). Clinically, right SD is often characterised by a change in behaviour and personality, with reports of prosopagnosia also common (Irish et al. 2013; Josephs et al. 2009; Kamminga et al. in press; Snowden, et al. 2004; Thompson et al. 2004). Although few studies have systematically examined episodic memory performance in right SD, some evidence suggests that non-verbal episodic memory and spatial navigation is compromised in this phenotype (Chan, et al. 2009; Irish, et al. 2013).

FTD provides a unique model to study the neurobiological basis of face perception and memory. While a large number of studies have reported impaired memory for famous faces in FTD, with divergent profiles in left SD compared to right SD (e.g., Gefen, et al. 2013; Josephs, et al. 2008; Snowden, et al. 2004; Thompson, et al. 2004), far fewer studies have examined memory for novel faces, with mixed findings. Omar et al. (2010) used the Benton Facial Recognition Test (Benton 1994), which assesses face perception by asking participants to match a target face to those in a simultaneously presented set. Patients with SD (12 left SD; 1 right SD) and bvFTD (n = 19) all performed within normal limits. Many healthy individuals, however, score in the normal range on the Benton Facial Recognition Test when only the eyebrows are visible, suggesting a piecemeal face matching approach is sufficient to complete this task successfully (Duchaine & Weidenfeld 2003). Indirect evidence from emotion processing tasks using caricatures further suggests that face perception is

abnormal in bvFTD (Kumfor et al. 2011), although this has not been studied systematically. Thus, the integrity of basic face perception in SD and bvFTD is unknown.

One of the earliest studies to examine recognition memory for novel faces in FTD used the Warrington Recognition Memory Test for Faces (Warrington 1984), an old/new test of face memory (Simons et al. 2001). Consistent with clinical reports, only the group with predominant right-lateralised SD (n = 4) were impaired, while the left-lateralised SD group (n = 4) performed within normal limits. The SD group with relatively bilateral atrophy (n = 5) was more impaired than the left-lateralised patients, but less impaired than the right-lateralised patients (Simons, et al. 2001). In contrast, no significant differences were observed between left and right SD on standard neuropsychological tests of episodic memory (e.g., Rey Complex Figure, Warrington Recognition Memory Test for Words). These results led the authors to propose that the right temporal lobe is specialised for memory for faces (Simons, et al. 2001) and therefore, apart from right SD, this function should be relatively intact in other FTD phenotypes. Importantly, however, the stimuli in the Warrington Recognition Memory Test for Faces contain substantial non-face information (e.g., hairstyles, clothing) that can be used to support recognition memory. Indeed, healthy individuals are able to score within the normal range on this test, even when all facial information is occluded (Duchaine & Weidenfeld 2003). Moreover, other evidence suggests that face memory, at least for familiar faces, is compromised in the other FTD subtypes. Individuals with left SD tend to be impaired on tests of memory for famous faces, even when only recognition and not naming is required (Gefen, et al. 2013). Thus, face recognition deficits in left SD and bvFTD may have been previously underestimated. Further,

no studies to date have directly compared faces recognition with recognition of visual non-face stimuli of similar complexity. It is therefore unclear whether any observed face memory deficits in FTD are due to the degradation of face perception, a specific recognition memory deficit, or a combination of both.

Systematic investigation of the neural correlates of face memory in FTD is also currently lacking. Existing studies investigating famous face recognition, and clinical reports of prosopagnosia in SD, highlighted the importance of the right anterior temporal lobe as a key region supporting recognition of known faces (Gefen, et al. 2013; Hsieh et al. 2011; Josephs, et al. 2008). To our knowledge, however, no studies have directly investigated the neural correlates of basic face identity perception and memory for novel faces in this population. Further, the extent that common or divergent neural correlates contribute to face memory disturbance across FTD subtypes is unknown.

Thus, the current study had two broad aims: (i) To investigate face perception and face memory in bvFTD and SD using more sensitive tasks than used in previous studies, by employing both a face memory task and a well-matched object memory task and; (ii) to identify the neural correlates underlying face perception, face memory and object memory in bvFTD and SD. Given the degradation to regions within the frontal and temporal lobes in bvFTD and SD, we hypothesised that face perception and face memory deficits would be observed in both FTD subtypes. In addition, we predicted bvFTD would show impaired object memory performance, in line with previous reports of episodic memory deficits in this syndrome.

2 Methods

2.1 Participants

Thirteen bvFTD and 11 SD patients (8 SD with predominantly left-sided atrophy, 3 SD with predominantly right-sided atrophy) were consecutively recruited from FRONTIER, the frontotemporal dementia research group in Sydney, Australia and compared with 11 healthy age- and education-matched controls. All patients were assessed by an experienced behavioural neurologist, underwent comprehensive neuropsychological assessment (Table 1) and neuroimaging, and a reliable informant was interviewed. Based on this information, patients were classified according to current consensus diagnostic criteria for bvFTD or SD (Gorno-Tempini, et al. 2011; Rascovsky, et al. 2011). In line with previous studies, individuals with SD were classified by the clinical team as either left- or right-lateralised based on their coronal MRI brain scan of the temporal lobes and their clinical presentation (e.g., Kamminga, et al. in press). The proportion of left and right SD cases in the current study is consistent with previous reports in the literature (e.g., Chan, et al. 2009). Control participants were recruited from the Neuroscience Research Australia Volunteer database and local community clubs.

For all participants, exclusion criteria were: history of significant neurological or psychological disorder, use of centrally-acting medication and limited proficiency in English. In addition, all controls were required to score > 88/100 on the Addenbrooke's Cognitive Examination-Revised (ACE-R), or the recently updated Addenbrooke's Cognitive Examination-III (ACE-III), which are general screening measures of cognition (Hsieh et al.

2013b; Mioshi et al. 2006). All control participants also scored 0 on the Clinical Dementia Rating “sum of boxes” (Morris 1993). All participants or their Person Responsible provided informed consent according to the Declaration of Helsinki. The South Eastern Sydney Local Health District and the University of New South Wales ethics committees approved the study.

2.2 Background demographics and neuropsychological assessment

Disease duration was measured in months from the first onset of symptoms. The Frontotemporal Dementia Functional Rating Scale (FRS) was used to determine functional severity in bvFTD and SD (Mioshi et al. 2010). In addition, all participants underwent a neuropsychological assessment to measure attention and working memory (Digit Span (Wechsler 1997), Trail Making Test (Tombaugh 2004)), visuoconstruction and non-verbal episodic memory (Rey Complex Figure Test (Rey 1941)) and language (SYDBAT (Savage et al. 2013)).

2.3 Face Perception

Aspects of basic face perception were assessed using two short non-verbal tasks, which are depicted in Figure 1 (Kumfor et al. 2014; Miller et al. 2012). In brief, on the Face-Perception task, individuals are presented with 40 face pairs, one pair at a time, showing a neutral expression, and are asked to determine whether the two images are identical or different.

For the Identity-Matching task, participants are shown pairs of faces simultaneously, which differ in emotional expression, and are asked to determine whether the two pictures are of the same person (i.e., same identity). The task consists of 42 trials.

Participants are verbally asked “Is this the same picture?” or “Is this the same person?”, depending on the task, and required to respond verbally either “yes” or “no”. For both tasks, faces were selected from the NimStim stimulus set (www.mac-brain.org). Faces were cropped so that all non-facial features including hair were removed and all images are presented in greyscale. Responding was untimed and no feedback was provided.

[INSERT FIGURE 1 ABOUT HERE]

2.4 Cambridge Face Memory Test (CFMT) (Duchaine & Nakayama 2006)

Memory for faces was assessed using the upright version of the Cambridge Face Memory Test (CFMT), shown in Figure 2 (Bowles et al. 2009; Duchaine & Nakayama 2006). During the task, participants learn to recognise six individuals, presented in grey scale, with hair and other identifying facial features (e.g., facial blemishes) removed. On each trial, the participant is required to identify the target face from two similar distractor faces. Several of the distractor faces are repeated throughout the task, so the participant cannot make a judgement based on familiarity alone. In Section 1, the target face is the identical image as shown during encoding (same images, 18 trials). In Section 2, faces are shown from different viewpoints or under different lighting conditions than seen during encoding (novel images, 30 trials). Finally, in Section 3, participants are again shown the target face from different viewpoints or lighting conditions, with additional Gaussian noise (novel image + noise, 24 trials). On each trial, participants are asked to point to the target face. Responding is untimed and no feedback is provided. Following each section, participants review the 6

target images for 20 seconds. A percent correct overall score for the 72 trials was calculated. Prior to testing, participants completed 3 practice trials and participants only progressed to the testing session after achieving 100% correct on the practice trials.

[INSERT FIGURE 2 ABOUT HERE]

2.5 Cambridge Car Memory Test (CCMT) (Dennett et al. 2012)

To assess memory for objects, we used the Cambridge Car Memory Test (CCMT), which was designed to be analogous to the CFMT, shown in Figure 3 (Dennett, et al. 2012). Similar to the CFMT, participants learn to recognise 6 target items (cars) and then recognition memory is assessed across 3 sections: Section 1 (same images, 18 trials); Section 2 (novel images, 30 trials); Sections 3 (novel images + noise, 24 trials). On each trial, participants are asked to point to the target car. The task is untimed and no feedback is provided. A percent correct overall score (/72) was calculated for subsequent analyses.

[INSERT FIGURE 3 ABOUT HERE]

2.6 Behavioural Statistical Analyses

Data were analysed using IBM SPSS Statistics version 22.0. Univariate analyses of variance (ANOVA) were conducted to examine continuous demographic and general cognitive performance variables. Chi-square analyses were used to analyse categorical variables. For the experimental variables (Face-Perception, Identity-Matching, CFMT and CCMT) univariate ANOVAs were conducted. Prior to the analyses, the suitability of variables for parametric analyses was determined using Kolmogorov-Smirnov tests. The Face-Perception and Identity-Matching tasks, did not meet the assumption of homogeneity of variance, based on Levene's test. Therefore we reanalysed the data using the non-parametric equivalent. The

pattern of results remained the same and for this reason we have reported the parametric analyses throughout, to maintain consistency. Follow-up *post hoc* analyses with Sidak correction for multiple comparisons were employed to investigate between group differences. For the analyses investigating the experimental tasks of interest (Face-Perception, Identity-Matching, CFMT and CCMT) we first compared SD with bvFTD and controls. Then, given the small number of right SD cases, we conducted the same analyses in left SD only, to investigate whether any differences in patterns of performance were observed after excluding right SD cases.

2.7 Neuroimaging

2.7.1 MRI Acquisition

Participants underwent whole-brain structural magnetic resonance imaging (MRI) with a 3 T Phillips scanner. High resolution T1-images were obtained using the following protocol: 256 x 256, 200 slices, 1mm² in-plane resolution, 1mm slice thickness, echo time/repetition time = 2.6/5.8 ms, flip angle = 19°. Brain scans were available for 30 participants (10 bvFTD, 10 SD (8 left SD, 2 right SD), 10 controls).

2.7.2 Data preprocessing

FSL voxel-based morphometry (VBM), part of the FMRIB software library package <http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html> (Smith et al. 2004) was used to analyse the MRI data (Ashburner & Friston 2000; Mechelli et al. 2005; Woolrich et al. 2009). First, structural images were brain-extracted using BET and tissue segmentation was undertaken using automatic segmentation (FAST) (Zhang et al. 2001). Then, grey matter partial volume

maps were aligned to Montreal Neurological Institute standard space (MNI152) using non-linear registration (FNIRT), which uses a *b*-spline representation of the registration warp field (Rueckert et al. 1999). A study-specific template was created and the native grey matter images were non-linearly re-registered. Modulation of the registered partial volume maps was carried out, by dividing them by the Jacobian of the warp field. The modulated, segmented images were smoothed with an isotropic Gaussian kernel (sigma = 3mm, full-width at half maximum (FWHM) = 8mm).

2.7.3 VBM analyses

A voxel-wise general linear model was applied to investigate grey matter intensity differences using permutation-based, non-parametric statistics with 5000 permutations per contrast (Nichols & Holmes 2002). In the first set of analyses, differences in grey matter integrity between patient groups and controls were investigated using *t*-tests (Supplementary material).

Next, correlations between Identity-Matching, CFMT and CCMT performance and grey matter intensity were conducted in all participants combined. Total scores on either the Identity-Matching task, the CFMT or the CCMT were entered as covariates into separate design matrices and a positive [1] correlation analysis was performed (Supplementary Material). Finally, the same covariate analysis was performed separately for each patient group combined with controls in order to identify the neural correlates subtending Identity-Matching, Face Memory and Object Memory, distinct to each patient group. This approach increases the variance in behavioural scores, without contributing towards atrophy.

Inclusion of controls therefore increases the statistical power to detect an effect, which is particularly useful in clinical populations where large sample sizes are not available (Irish et al. 2012; Kumfor et al. 2013; Sollberger et al. 2009). As for the behavioural analyses, we then repeated the same analyses excluding the 2 right SD cases, to ensure effects were not driven by this subset of SD patients (Supplementary Material).

VBM analyses were conducted across the whole brain, including the cerebellum. For all comparisons voxel-wise analyses are reported and the statistical threshold was set at $p < .001$ uncorrected. In addition, we applied a conservative cluster-extent threshold of 50 voxels to reduce the likelihood of false positives (Lieberman & Cunningham 2009).

Anatomical locations of significant results were overlaid on the Montreal Neurological Institute (MNI) standard brain, with maximum voxel coordinates provided in stereotaxic space. Anatomic labels were determined with reference to the Harvard-Oxford probabilistic cortical and subcortical atlases.

3 Results

3.1 Participants

All groups were matched for age, sex and education (all p values $> .05$). No significant difference in disease duration was observed between patient groups; however, on the Frontotemporal Dementia Functional Rating Scale (FRS) the bvFTD group was rated as more functionally impaired than the SD group (Table 1).

Examination of the cognitive performance across groups revealed profiles consistent with the clinical features typically reported (Table 1). Both bvFTD and SD patients performed worse than controls on the Addenbrooke's Cognitive Examination (ACE) measure of general cognition (both p values $< .001$). The SD group also performed significantly worse than the bvFTD group, reflecting the high language demands of this task ($p = .02$). In addition, the SD group was impaired on tasks assessing naming ($p < .001$) and comprehension ($p < .001$), performing significantly worse than both bvFTD and control participants. In contrast, bvFTD were impaired on tasks assessing attention and working memory (Trail Making Test A ($p = .008$), Trail Making Test B ($p = .001$) Digit Span Forwards ($p = .042$) Digit Span Backwards ($p = .020$)) and also performed significantly worse on the Rey Complex Figure copy ($p = .005$), likely indicating reduced planning and organisation when approaching the task. Both bvFTD ($p < .001$) and SD ($p = .015$) were impaired on the Rey Complex Figure percent retention. Given that non-verbal episodic memory is typically reported to be intact in left SD, we reanalysed performance on this task after removing the three right SD cases. These analyses indicated that left SD cases performed within normal limits ($p = .110$), suggesting that non-verbal memory is relatively preserved in left SD but is more variable in right SD, consistent with previous findings.

[INSERT TABLE 1 ABOUT HERE]

3.2 Face Perception

As shown in Figure 4, group performance did not significantly differ on the Face-Perception task ($F(2,32) = 1.175$, $p = .322$). In contrast, a significant main effect of Diagnosis was present on the Identity-Matching task ($F(2,33) = 8.263$, $p = .001$). *Post hoc* tests revealed

that the bvFTD group performed significantly worse than controls on this task ($p = .001$) with a trend also observed in the SD group (right and left SD patients combined) ($p = .055$). No difference was observed between patient groups on this task ($p = .441$) (Figure 4).

Next we conducted the same analyses, to determine whether the pattern of results remained after excluding the right SD cases. On the Face-Perception test, again no effect of Diagnosis was observed ($F(2,30) = 0.997, p = .389$). On the Identity-Matching task, a significant effect of Diagnosis was again present ($F(2,30) = 7.686, p = .002$). *Post hoc* analyses indicated that bvFTD performed significantly worse than controls ($p = .002$), whereas performance in left SD was not significantly different from controls ($p = .275$). Once again, no difference was observed between patient groups on this task ($p > .05$).

[INSERT FIGURE 4 ABOUT HERE]

3.3 Cambridge Face and Car Memory Test Performance

As shown in Figure 5, on the CFMT a significant effect of Diagnosis was observed ($F(2,34) = 14.255, p < .001$) with bvFTD ($p < .001$) and SD ($p < .001$) performing worse than controls. No difference was observed between patient groups ($p = .805$). On the CCMT, again a significant effect of Diagnosis was present ($F(2,34) = 3.742, p = .035$). Here, however, only the bvFTD group were impaired compared to controls ($p = .032$), with no significant difference in performance between SD and controls ($p = .255$). The difference between bvFTD and SD was not significant ($p = .750$) (Figure 5).

To investigate whether the findings were driven by the 3 right SD cases, we reanalysed the data including left SD cases only. Importantly, the significant effect of Diagnosis previously observed was again present on the CFMT ($F(2,31) = 12.765, p < .001$), with both bvFTD ($p < .001$) and SD ($p = .001$) performing worse than controls. Results on the CCMT also showed the same pattern as the initial analyses with an overall effect of Diagnosis ($F(2,31) = 4.481, p = .020$). Again the bvFTD group only, performed worse than controls ($p = .021$), with left SD demonstrating relatively intact object memory on the CCMT ($p = .856$). Individual patient profiles are reported in the Supplementary Material.

[INSERT FIGURE 5 ABOUT HERE]

3.4 VBM Analyses

3.4.1 *Patterns of grey matter intensity changes*

Compared with controls, the SD group demonstrated striking changes in the anterior temporal lobe, encompassing the temporal pole, temporal fusiform gyrus, amygdala and parahippocampal gyrus which extended into the orbitofrontal cortex. Although the grey matter intensity decrease was present bilaterally, it was somewhat more extensive in the left than the right hemisphere (See Supplementary Material for figure). When we reanalysed the pattern of change in left SD cases only, we again found significant changes encompassing the left temporal pole, extending into the left orbitofrontal cortex, amygdala, hippocampus and left fusiform cortex. A smaller cluster was also identified in the right hemisphere including the right inferior temporal gyrus, and right temporal pole, confirming

the disproportionate left-lateralisation of brain changes in these patients. The bvFTD group showed relatively circumscribed grey matter intensity decrease compared with controls. Significant clusters were identified in the frontal pole, as well as the left orbitofrontal cortex and small regions in the left insula and temporal pole (See Supplementary Material for figures depicting patterns of atrophy in each group).

3.4.2 Neural correlates of face processing, face memory and object memory

As shown in Figure 6, in the SD group, Identity-Matching performance (shown in red) was predominantly associated with integrity of the right temporal lobe. This cluster encompassed the right anterior portion of the fusiform cortex and extended into the right inferior temporal gyrus, amygdala and temporal pole. In addition, Identity-Matching performance was associated with integrity of the left temporal pole, left inferior temporal gyrus and left parahippocampal gyrus, extending into the amygdala (Table 2).

Neural correlates of face memory performance in the SD group (shown in yellow) tended to be left lateralised and were associated with integrity of the left fusiform cortex and temporal pole as well as the anterior portion of the left middle temporal gyrus. In addition, a cluster was identified in the right temporal lobe which encompassed the anterior portion of the middle temporal gyrus, extending into the right temporal pole and the right orbitofrontal cortex. No regions significantly correlated with object memory in SD (Figure 6, Table 2). When we reanalysed the data excluding the 2 right SD cases with available MRI scans, the results remained largely the same (Supplementary Material).

In contrast, in bvFTD, Identity-Matching performance (shown in red) was associated with integrity of the left orbitofrontal cortex extending into the left temporal pole, which is shown in Figure 6. In addition, performance was significantly associated with integrity of the left fusiform gyrus. Memory for faces (CFMT performance) (shown in yellow) was associated with integrity of the left temporal pole, extending into the left orbitofrontal cortex, with a second region identified in the left insula. Notably, object memory (CCMT performance) (shown in blue) in this group was associated with a distinct set of brain regions including the right frontal opercular cortex extending into the insula, together with the left thalamus (Figure 6, Table 2).

VBM analyses for the Face-Perception task were not conducted because both patient groups performed within normal limits. VBM analyses in all participants combined are reported in the Supplementary Material.

[INSERT FIGURE 6 ABOUT HERE]

4 Discussion

In this study we used novel experimental tasks, in combination with voxel-based morphometry, to investigate face perception, face memory and object memory in individuals with SD and bvFTD. Our results revealed that patients with SD showed circumscribed deficits on tasks assessing face memory, even in individuals with disproportionate left-lateralised temporal atrophy. Crucially, these deficits were associated

with degradation of regions within the temporal lobes bilaterally, brain regions that are thought to play a key role in face processing. In contrast, individuals with bvFTD showed deficits in face perception, as well as face *and* object memory. Notably, these impairments were associated with degradation of distinct regions involved in face processing (i.e., the fusiform cortex, anterior temporal lobe) and memory (i.e., the thalamus). In the following sections we consider the current findings in light of our understanding of these FTD phenotypes, and current models of face processing.

SD is typically characterised as a language disorder, with prominent anomia and loss of general conceptual knowledge. Increasingly, however, it is recognised that deficits in social cognition and emotional functioning are also present in this syndrome (Hsieh et al. 2013a; Irish et al. 2014a; Kumfor, et al. 2013; Kumfor, et al. 2011; Kumfor & Piguet 2012; Rankin et al. 2009; Rosen et al. 2002). The precise mechanisms and neural substrates subtending these deficits, however, are relatively poorly understood. Our results provide new evidence that face recognition is disproportionately affected in SD. Consistent with previous studies (e.g., Simons, et al. 2001), qualitative examination of patient profiles of individuals with predominantly right-lateralised temporal atrophy suggest that these patients do indeed show worse face recognition performance than those with the typical left-lateralised profile. Importantly, using a well-matched object recognition task, we have demonstrated circumscribed face recognition deficits are present in SD, even in cases with predominantly left hemisphere damage.

Our neuroimaging analyses revealed both common and distinct brain regions subtending face perception and memory in SD. Basic face perception, as measured by the Identity-Matching task, was associated with a predominantly right-lateralised network including the fusiform cortex, inferior temporal gyrus, amygdala and temporal pole. Haxby (2000) proposed that the fusiform cortex is the key node involved in identity recognition within the core face processing system. Our results provide additional support for this model using a neuropsychological paradigm to elucidate brain-behaviour relationships. Interestingly, regions within the extended face processing system, including the anterior temporal pole, were also significantly associated with identity recognition. The anterior temporal pole is commonly implicated in aspects of biographical retrieval, and thus its association with identity perception of novel rather than familiar faces, was somewhat unexpected. Recent evidence, however, indicates that the anterior temporal lobe is also involved in aspects of face recognition. For example, two individuals who had undergone unilateral anterior temporal lobe resection, were found to experience impaired performance on a face matching task similar to the identity matching task we used here (Olson et al. 2014). The authors proposed that these deficits were due to disruption in the role of the anterior temporal lobe, including the perirhinal cortex, in high-level face processing, specifically the coding of face patches to enable identification across individuals. This proposition is in line with fMRI findings demonstrating sensitivity of the ventral anterior temporal lobe for processing identity in both healthy adults and macaques (reviewed by Von Der Heide et al. 2013). In addition, recent studies have revealed that abnormal functioning of the anterior temporal lobe node of the 'extended' face processing system is present in congenital prosopagnosia (Avidan et al. 2014; Rivolta et al. 2014). This emerging evidence, together

with the current findings, therefore provides important support for the role of the anterior temporal lobe in face perception and recognition.

Memory for faces in SD was also associated with regions within the temporal lobe, although the neural correlates identified appeared more bilateral than those associated with identity matching. These regions included the left anterior fusiform gyrus, extending into the left temporal lobe as well as the left middle temporal gyrus. Atrophy of the left superior temporal sulcus/medial temporal gyrus has also been previously associated with poor face identity recognition in developmental prosopagnosia (Choi et al. 2012), indicating that this brain region contributes to abnormal face recognition across different clinical populations. In addition to these left-lateralised structures, a region within the right middle temporal gyrus, extending into the orbitofrontal cortex and right temporal pole was associated with face memory performance in the SD group.

Evidence supporting the lateralisation of face memory to the right temporal lobe is mixed. Some researchers have suggested that recognition of non-verbal information, including recognition of familiar/famous faces, is right-lateralised whereas recognition of familiar names and similar verbal information appears left-lateralised (Gainotti 2013). Others, however, have proposed that recognition of familiar faces is left-lateralised, while recognition of novel faces only, is right-lateralised (Von Der Heide, et al. 2013). Our findings indicate that both the left and right temporal lobes are involved in recognition of novel faces. We were unable to investigate whether different mechanisms contribute to face memory deficits in left and right SD, given the small number of right SD cases. Nevertheless,

it is plausible that divergent neurocognitive mechanisms subtend face memory in left and right SD. Finally, it should be explicitly noted that deficits in face memory in SD were observed despite object memory remaining relatively intact. Although non-verbal memory is variable in right SD (Kamminga, et al. in press; Thompson et al. 2003), it is typically well preserved in left SD (Tan et al. 2014). The finding of intact object memory in our SD cohort therefore provides corroborative evidence that deficits in face recognition in these patients, is specific to faces, rather than just a general episodic memory deficit.

The behavioural and neuroimaging findings in the bvFTD group were distinct from those observed in SD. Individuals with bvFTD showed reduced ability to accurately discriminate facial identity across pairs of faces. Crucially, this impairment in identity recognition was correlated with integrity of the anterior portion of the left fusiform gyrus, a region which is known to be critical for face perception, specifically the perception of unique facial identity (Haxby, et al. 2000). In addition to the fusiform gyrus, reduced identity recognition correlated with the left orbitofrontal cortex extending into the left temporal pole, as well as a region within the anterior cingulate. These regions have been previously implicated in bvFTD with regards to social cognition more generally (Ibañez & Manes 2012). Our findings suggest that like other aspects of social cognition, including emotion processing and theory of mind, face processing is also affected in bvFTD, and this appears to be due to degradation to key nodes within the Social Context Network (Couto et al. 2013; Ibañez & Manes 2012) as well as core brain regions in the face processing system (Haxby, et al. 2000).

Unlike in SD, individuals with bvFTD were impaired on both the face and object memory tasks. Interestingly, however, divergent neural correlates were associated with performance on these tasks. Similar to SD, performance on the face memory task was associated with integrity of the left anterior temporal pole in bvFTD, confirming the role of this region in face recognition. Conversely, performance on the object memory task was associated with integrity of the left thalamus. The thalamus is a key relay station with white matter projections to the prefrontal, temporal, premotor, primary motor, sensory, occipital and posterior parietal cortices (Behrens et al. 2003). Notably, individuals who have suffered a thalamic stroke frequently present with an amnesic syndrome, together with executive dysfunction and behavioural change (reviewed by Carlesimo et al. 2011), a profile which is remarkably consistent with that seen in bvFTD. The role of the thalamus in supporting memory in bvFTD has only recently been recognised, with disproportionate atrophy in this region evident on both neuroimaging and at post-mortem in bvFTD compared to Alzheimer's disease and healthy controls (Hornberger et al. 2012). Moreover, bvFTD patients with memory impairment show greater anterior thalamic atrophy than those with less memory impairment (Hornberger, et al. 2012). Additional examination of the potential role of the thalamus in cognition in bvFTD is certainly warranted. Importantly, our findings demonstrate that non-verbal object memory is impaired in bvFTD and this is due to degradation of the thalamus, a key node within the episodic memory network.

The identification of divergent neural correlates underpinning face and object memory, together with the impaired Identity-Matching performance in bvFTD, provides important evidence that face perception, rather than more general cognitive or memory deficits,

contribute to the identity recognition deficits observed behaviourally in this clinical syndrome. Studies examining face memory have reported variable results to date, with several studies suggesting that this ability is relatively preserved in bvFTD and left SD (e.g., Omar et al. 2010). Nevertheless, indirect evidence using caricatured facial expressions has indicated that abnormal face processing may in part contribute to the facial emotion recognition deficits in this group (Kumfor, et al. 2011). Importantly, the CFMT task employed here precludes the potential for participants to use a piecemeal approach or non-facial features to successfully perform the task (Duchaine & Nakayama 2006; Duchaine & Weidenfeld 2003). Under these conditions we have demonstrated that both individuals with bvFTD and SD show deficits in aspects of face and identity processing, which impact on the ability to learn and recognise novel faces. Given the current findings, systematic examination of face perception ability, such as whether holistic face processing is preserved in bvFTD and SD, is warranted.

From a clinical perspective, the CFMT and CCMT appear to offer novel, well-validated and psychometrically sound tasks to assess face and object memory in neurodegenerative syndromes. Notably, in other clinical populations (e.g., developmental prosopagnosia), face perception ability predicts face memory performance (Huis in 't Veld et al. 2012). While we were not able to investigate this potential relationship here, due to the limited sample size, this will be an important area for future studies to address. Nevertheless, the impaired ability to recognise and process faces as demonstrated here, likely contributes to the pervasive social deficits observed in bvFTD and SD, although to our knowledge this has not yet been investigated. This relationship warrants attention, as strategies to improve face

perception and face memory may help to improve the quality of life of patients and their interpersonal relationships with their carers and families.

In summary, our results demonstrate that both face perception and memory is abnormal to various degrees in SD and bvFTD, and is due to the degradation of key regions within the core and extended face processing system. Individuals with bvFTD exhibit additional deficits in object memory that is due to degeneration of memory processing brain regions, namely the thalamus. Importantly, these results highlight that abnormalities in face perception and memory are not exclusive to right SD. Finally, while our results provide additional evidence from a neurobiological perspective supporting current models of face processing, they raise important questions about the laterality of face processing, which will be crucial for future studies to consider.

5 Figure Captions

Figure 1: Example trial for the Face-Perception and Identity-Matching tasks.

Note. For both examples, the correct answer is yes.

Figure 2: Examples of stimuli and design of the CFMT.

Note. Panel A shows study views of a target face. These are presented one at a time for 3 seconds each. Panel B shows a test panel from Section 1 (face 3 is the target) Panel C shows a test panel from Section 2 (face 1 is the target). Panel D shows a test panel from Section 3 (face 3 is the target). Reprinted from: *Neuropsychologia*, 44, Duchaine & Nakayama, The Cambridge Face Memory Test: Results for neurologically intact individuals and an investigation of its validity using inverted face stimuli and prosopagnosic participants, p. 576-585 (2006), with permission from Elsevier.

Figure 3: Format and design of the CCMT.

Note. Panel A shows study views of a target car. These are presented one at a time for 3 seconds each. Panel B shows a test panel from Section 1 Panel C shows a test panel from Section 2. Panel D shows a test panel from Section 3. Panel E shows an example of the type of actual stimuli used. Reprinted from: *Behaviour Research Methods*, 44, Dennett et al., The Cambridge Car Memory Test: A task matched in format to the Cambridge Face Memory Test, with norms, reliability, sex differences, dissociations from face memory, and expertise effects. p. 587-605 (2011) with permission from Springer.

Figure 4. Performance on the Face-Perception and Identity-Matching tasks in bvFTD and SD compared with healthy controls.

Note. Markers represent individual scores. Left SD cases represented with filled circles, right SD represented with open circles. Lines represent the mean and standard deviation. Missing

data for 1 bvFTD case on the Identity-Matching task and 1 left SD case on the Face-Perception and Identity-Matching tasks. * $p < .05$ compared to controls, T $p = .055$ compared to controls.

Figure 5. Performance on the CFMT (face memory) and CCMT (object memory) tasks in bvFTD and SD compared with healthy controls.

Note. Markers represent individual scores. Left SD cases represented with filled circles, right SD represented with open circles. Lines represent the mean and standard deviation. * $p < .05$ compared to controls.

Figure 6. Neural correlates of Identity-matching (red), CFMT (face memory) (yellow) and CCMT (object memory) (blue) in semantic dementia and behavioural-variant frontotemporal dementia, combined with controls. *Note.* Coloured voxels indicate regions that are significant at $p < .001$ uncorrected for multiple comparisons. L = left, R = right. y values are MNI coordinates

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Face-Perception

"Is this the same picture?"

Identity-Matching

"Is this the same person?"

(A)

Examples

(B)

Introduction:
Test item with
identical images

(C)

Test item with
novel images

(D)

Test item with
novel images
with noise

a Learn target in three views

b Discriminate target from two distractors (same image as study)

c Discriminate target from two distractors (novel image)

d Discriminate target from two distractors (novel image + noise)

e Example stimulus from the CCMT

Table 1. Demographic characteristics and neuropsychological test performance of the study sample.

	bvFTD n = 13	SD n = 11	Controls n = 11	F	p	Post hoc
Sex (M:F)	8:5	5:6	8:3	1.725 [#]	ns	
Age	62.5±9.4	63.7±7.5	68.6±4.7	2.124	ns	
Education	12.0±3.3	13.0±3.0	14.8±2.9	2.959	ns	
FRS (Rasch Score)	-0.6±0.8	1.1±1.7	-	10.106	.005	bvFTD < SD
Disease duration (months)	65.8±45.4	78.9±23.8	-	.741	ns	
ACE Total Score (/100) ^a	77.0±10.3	66.4±11.2	96.7±2.3	32.459	<.001	Patients < controls; SD < bvFTD
Digits Forwards (max. span)	6.1±1.0	6.7±1.7	7.5±1.1	3.362	.047	bvFTD < controls
Digits Backwards (max. span)	4.1±1.0	5.6±1.8	5.7±1.3	5.474	.009	bvFTD < SD, controls
Trails A Time (sec)	47.6±15.2	42.3±19.5	28.3±5.8	5.518	.009	bvFTD > controls
Trails B Time (sec)	142.7±59.7	91.0±36.8	66.5±20.1	9.448	.001	bvFTD > SD, controls
RCF Copy (/36)	27.9±5.9	33.0±1.9	33.8±3.3	7.132	.003	bvFTD < controls
RCF % Retention	31.9±20.2	41.3±14.8	65.8±21.5	9.761	<.001	bvFTD, SD < controls
Naming	20.0±6.5	8.2±4.2	28.5±1.6	55.579	<.001	SD < bvFTD < controls
Comprehension	25.5±2.5	20.2±4.8	29.8±0.4	24.896	<.001	SD < bvFTD < controls

Note. Values are mean ± standard deviation. [#]Chi-square value. Abbreviations: ns = non-significant; FRS =Functional Rating Scale (higher scores denote higher functioning); ACE = Addenbrooke's Cognitive Examination; RCF = Rey Complex Figure. Missing data: Trails B: 1 bvFTD; Naming: 5 bvFTD, 2 SD; Comprehension: 5 bvFTD, 1 SD.

Table 2. Neural correlates of identity matching, face memory and object memory (memory for cars) in semantic dementia and behavioural variant frontotemporal dementia.

Regions	Hemisphere	MNI			Voxels
		X	Y	Z	
Semantic dementia + controls					
Identity-Matching – Total Score					
Inferior temporal gyrus (anterior) extending into temporal fusiform gyrus (anterior), temporal pole, planum polare, amygdala	Right	42	-2	-48	1961
Parahippocampal gyrus extending into amygdala	Left	-26	-4	-34	242
Superior temporal gyrus (posterior)	Right	66	-36	6	191
Temporal pole	Left	-24	18	-40	182
Putamen	Left	-30	-6	-4	89
Inferior temporal gyrus (anterior)	Left	-44	-8	-46	72
CFMT (Face Memory) –Total Score					
Temporal fusiform cortex (anterior), temporal pole extending into parahippocampal gyrus, orbitofrontal cortex and insula	Left	-20	-4	-44	2033
Middle temporal gyrus (anterior), temporal pole, orbitofrontal gyrus	Right	54	4	-36	820
Middle temporal gyrus (anterior)	Left	-54	0	-36	307
CCMT (Object Memory) – Total Score					
No significant clusters ≥ 50 voxels					
Behavioural-variant FTD + controls					
Identity-Matching – Total Score					
Orbitofrontal cortex extending into temporal pole	Left	-28	16	-26	222
Temporal fusiform cortex (anterior)	Left	-34	-8	-44	68
Anterior cingulate, (posterior portion)	Left	-10	2	40	63
Orbitofrontal cortex	Left	-38	34	-10	50
CFMT (Face Memory) –Total Score					
Temporal pole, orbitofrontal cortex	Left	-52	18	-24	205
Insula	Left	-40	4	0	140
CCMT (Object Memory) – Total Score					
Insula, frontal opercular cortex	Left	-36	2	2	184
Thalamus	Left	-10	-12	2	112

Note. Clusters significant at $p < .001$ and with a cluster-extent threshold of 50 voxels.