The orbitofrontal cortex is involved in emotional enhancement of memory: evidence from the dementias

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The enhancing effect of emotion on subsequent memory retrieval is well established. Patients with frontotemporal dementia show profound emotion processing difficulties, yet the extent to which such deficits attenuate emotional enhancement of memory remains unknown. Here, we studied the intersection between emotion and memory using a visual forced-choice recognition test for negative and neutral stimuli in 34 patients with frontotemporal dementia compared with 10 patients with Alzheimer’s disease and 15 control subjects. Control subjects and patients with Alzheimer’s disease recognized more emotional than neutral items, as demonstrated by a significant interaction between emotion and memory for true recognition. This emotional enhancement effect was notably absent in the frontotemporal dementia cohort, with comparable recognition performance regardless of emotional content. Voxel-based morphometry analyses revealed distinct neural substrates for overall memory versus emotional memory performance. Overall memory performance correlated with the hippocampus, precuneus and posterior cingulate, regions crucial for successful episodic memory performance. Emotional enhancement of memory, by contrast, was associated exclusively with the integrity of the right orbitofrontal and subcallosal cortex. Our findings demonstrate differential disruption of emotional enhancement of memory in neurodegenerative disorders, and point toward the potentially pivotal role of the orbitofrontal cortex in supporting the successful retrieval of emotionally charged negative stimuli.

Keywords: Alzheimer’s disease; frontotemporal dementia; episodic memory; orbitofrontal cortex, emotion
Abbreviations: FTD = frontotemporal dementia; PNFA = progressive non-fluent aphasia

Introduction

Memories for emotional events are typically more vivid than memories for non-emotional events (Heuer and Reisberg, 1990; LeDoux, 1993; Hamann, 2001). This emotional enhancement of memory is observed under different forms, including ‘flashbulb’ memories (Brown and Kulik, 1977), such as the memory of 11 September 2001, as well as recollections of personal emotional events, such as one’s wedding day or graduation. This effect has been investigated experimentally with a range of stimuli.
(e.g. stories, words, pictures) and testing conditions (e.g. recall and recognition paradigms) (Bradley et al., 1992; Cahill et al., 1995; Kensinger et al., 2002; Mickley and Kensinger 2008), and is observed across the age spectrum (Combain et al., 2005). Irrespective of the methodology, a robust effect is observed where the retrieval of emotionally charged stimuli is more readily and vividly remembered than neutral stimuli.

Among the brain structures involved in emotional enhancement of memory, the amygdala appears critical for the enhancement effect. Patients with amygdala lesions show an attenuation of emotional enhancement of memory, although memory for neutral information remains unchanged (Adolphs et al., 1997). Functional neuroimaging studies indicate that increased amygdala activity during encoding is linked to emotional enhancement of memory (Canli et al., 2000; Dolcos et al., 2005; Kensinger and Schacter, 2006). The involvement of the amygdala appears important for both encoding and consolidation of emotionally arousing information, through its interactions with regions necessary for the encoding of sensory information (e.g. the fusiform gyrus), and for the long-term consolidation of information (e.g. the hippocampus), by mediating the release of stress hormones in response to emotionally arousing stimuli (McGaugh, 2004; Kensinger, 2009).

Although the role of the amygdala is not disputed, emotional enhancement of memory likely depends upon the integrity of additional brain structures within the frontal and temporal lobes. Brain activation in regions necessary for emotion processing, such as the orbitofrontal cortex, ventral striatum and anterior cingulate, is associated with memory for details of negative stimuli (Kensinger et al., 2007). The orbitofrontal cortex is suggested to play a modulatory role whereby orbitofrontal cortex activity will enhance amygdala and hippocampal activation (Smith et al., 2006). Despite the wealth of information arising from functional neuroimaging studies in attempting to understand the cognitive and neural underpinnings of emotional memory enhancement, corroborative lesion studies are scant and have mostly focused on patients with focal amygdala or hippocampal lesions (Adolphs et al., 1997, 2005; Phelps et al., 1997). Apart from Alzheimer’s disease, the effects of progressive neurodegenerative conditions on the brain structures associated with emotional enhancement of memory have received relatively little attention. This lack of research is somewhat surprising in light of the disturbance in both general emotion processing abilities and of memory performance, observed in dementia syndromes.

The predominant clinical feature of Alzheimer’s disease is an impairment of episodic memory, which is attributable to pathological processes taking place in the medial temporal lobes, notably the hippocampus (Schelten et al., 1992; McKhann et al., 2011). Relevant to this study is the fact that aspects of emotion processing remain relatively intact in Alzheimer’s disease (Lavenu et al., 1999), despite severe deficits in the retrieval of emotional aspects of personally relevant autobiographical memories (Irish et al., 2011a). Nevertheless, investigations of emotional enhancement of memory in Alzheimer’s disease have produced mixed results, with intact emotional enhancement of memory reported in some studies (Ikeda et al., 1998; Kazui et al., 2000), but not others (Kensinger et al., 2002, 2004). The variability in findings may be due in part to patients performing at floor on memory measures (reviewed by Klein-Koerkamp et al., 2012). Highly arousing stimuli (e.g. pictures rather than words) and stimuli that provide emotional information from multiple modalities (e.g. real-life events) in combination with less demanding memory tasks, are thought to be more likely to elicit the emotional enhancement of memory effect in patients with Alzheimer’s disease (Kensinger et al., 2004).

Of particular interest to this study is the dementia syndrome of frontotemporal dementia (FTD), a neurodegenerative brain disorder affecting primarily the frontal and temporal lobes (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Emotion processing difficulties have been found in all three main subtypes of FTD: behavioural variant FTD, semantic dementia and progressive non-fluent aphasia (PNFA) (Lavenu et al., 1999; Rosen et al., 2002b; Seeley et al., 2008; Rohrer et al., 2010; Kumfor et al., 2011), which are due to atrophy in emotion-specific brain regions in the frontal and temporal lobes (Kumfor et al., 2013). In direct contrast to Alzheimer’s disease, these emotion processing deficits are present in the context of relatively intact performance in other cognitive domains, including visuo-perception and item recognition (Graham et al., 1999; Pasquier et al., 2001). The interaction between emotion and memory, however, has not been investigated in FTD, despite these patients showing progressive neurodegeneration in key regions essential for emotion processing, including the medial and orbitofrontal cortex, amygdala and insula (Rosen et al., 2002a; Gorno-Tempini et al., 2004; Seeley, et al., 2008).

To date, investigations of emotion processing disturbance in FTD have been limited to aspects of emotion recognition and reactivity (reviewed by Kumfor and Piguet, 2012). The evidence reviewed here suggests that emotional enhancement of memory is likely to be differentially affected in FTD and Alzheimer’s disease. To address this issue, we investigated the effects of emotion on memory in Alzheimer’s disease and FTD using visually arousing pictures in a recognition memory test. Based on the existing evidence, we hypothesized that in patients with Alzheimer’s disease, emotional enhancement of memory would be preserved, in contrast to patients with FTD where emotional enhancement of memory would be compromised. In addition, we predicted that medial temporal lobe structures, including the hippocampus would be critical for episodic memory, irrespective of emotional content, whereas, emotional memory retrieval would be dependent on the integrity of temporal and frontal lobe regions including the amygdala and orbitofrontal cortex.

Materials and methods

Participants

Thirty-four patients with FTD (11 behavioural variant FTD, 13 semantic dementia and 10 PNFA) and 10 patients with Alzheimer’s disease were recruited into the study from FRONTIER, the frontotemporal dementia clinical research group at Neuroscience Research Australia, Sydney. All patients underwent a clinical assessment with an experienced behavioural neurologist and neuropsychological assessment. All patients were diagnosed by consensus and met current clinical diagnostic criteria (Gorno-Tempini, et al., 2011; McKhann, et al., 2011;
Rascovsky et al., 2011). In addition, 15 age- and education-matched healthy control participants were recruited from local community clubs. Controls scored >88/100 on the Addenbrooke’s Cognitive Examination–Revised (Mioshi et al., 2006) and 0 on the Clinical Dementia Rating Scale.

All participants underwent a comprehensive neuropsychological assessment and structural MRI. The cognitive assessment included a measure of general cognitive ability, (Addenbrooke’s Cognitive Examination–Revised) (Mioshi et al., 2006), and tasks of attention (Digit Span Forwards, maximum span) (Wechsler, 1997), working memory (Digit Span Backwards, maximum span) (Wechsler, 1997), visual recall memory (Rey Complex Figure) (Meyers and Meyers, 1995), confrontation naming (Savage et al., 2013), and letter fluency (Controlled Oral Word Association Test; Spreen and Strauss, 1998). Exclusion criteria for control subjects and patients included concurrent psychiatric disturbance or neurological disorder, history of substance abuse, and/or use of medications with CNS effects.

Participants or their person responsible provided informed consent for participation in the study in accordance with the Declaration of Helsinki. The Southeastern Sydney and Illawarra Area Health Service and the University of New South Wales’ ethics committees approved the study. Participants volunteered their time and were reimbursed for any travel costs incurred.

**Design and materials**

Stimuli were selected from the International Affective Picture System (Lang et al., 1995), and were supplemented with images from the Geneva Affective Picture Database (Dan-Glauser and Scherer, 2011), as the International Affective Picture System has a limited number of neutrally rated images. Two sets of stimuli (A and B) were created, each comprising 40 negative and 40 neutral images. Sets were matched for valence and arousal according to normative ratings (Supplementary Table 1). Negative items were selected to be low in valence and high in arousal, whereas neutral items were selected to be mid-range in valence and low in arousal. Positive stimuli were not included because more robust enhancement effects are seen for negative than for positive stimuli (Dewhurst and Parry, 2000; Ochsner, 2000; Kensinger, 2009). Sets A and B were counterbalanced across participants so that for half the participants, Set A were target items and Set B were foils, and for the other half this was reversed. All stimuli were presented electronically on a 15-inch colour computer screen using E-Prime 2.0 software (Psychology Software Tools).

**Practice phase**

Participants viewed three images presented one at a time on the computer screen for 1 s. After each image, participants were asked: ‘Is this bigger than a shoebox?’ This perceptual question was included to ensure that participants were attending to the stimuli and to encourage incidental encoding. Participants registered their response by clicking the ‘Yes’ or ‘No’ button on the screen using a mouse or, for those unfamiliar with the use of a mouse, verbally or by pointing to the selected option on the screen. Participants received feedback on their responses and an additional check was included to ensure understanding of task demands. Participants who did not understand the task requirements were not included in the study.

**Study phase**

Participants viewed images in pseudorandom order so that no more than two images of the same valence were presented in succession. Four buffer stimuli (two negative and two neutral) were included at the beginning and end of the study phase to reduce primacy and recency effects. As described in the practice phase, participants were asked ‘Is this bigger than a shoebox?’ and their responses were recorded. During the study phase no feedback on their response was provided. The ‘Yes’ and ‘No’ buttons occasionally switched sides, to reduce the potential for participants to habitually respond ‘yes’ or ‘no’ (Fig. 1).

**Recognition phase**

After a 1-h delay, during which participants were assessed on unrelated neuropsychological tasks, participants completed an incidental yes/no recognition memory task. Participants were asked, ‘Have you seen this picture before?’ The procedure to respond was the same as during the study phase. Again, the ‘Yes’ and ‘No’ buttons occasionally switched sides. Participants were encouraged to respond as quickly as possible, however, accuracy was emphasized over speed. Images were presented in pseudorandom order so that no more than six targets or foils were presented in succession. Three practice images were shown to familiarize participants with the recognition procedure (Fig. 1).

**Ratings phase**

Immediately after completing the recognition phase, participants rated all items for valence using the Self-Assessment Manikin (Lang et al., 1997). Participants were asked ‘How does this picture make you feel?’ and responded by selecting from five cartoon pictures depicting a manikin whose expression ranges from sad to happy. A subset of participants also rated all items for arousal using the Self-Assessment Manikin. For the arousal ratings, five similar cartoon pictures were shown, which varied from calm/relaxed to excited/agitated, for participants to select from. Three practice ratings familiarized participants with the procedure. Time to respond was unlimited, and the image remained on the screen until the response was recorded (Fig. 1). Participants’ valence ratings of the stimuli according to diagnosis are provided in Supplementary Table 2.

**Image acquisition**

Participants underwent whole brain structural MRI with a 3 T Phillips MRI scanner. High resolution coronal plane T1-images were obtained using the following protocol: 256 × 256, 200 slices, 1 mm2 in-plane resolution, 1 mm slice thickness, echo time/repetition time = 2.6/5.8 ms, flip angle = 19°. Brain scans were available for 38 patients (nine behavioural variant FTD, 10 semantic dementia, nine PNFA and 10 Alzheimer’s disease) and 10 healthy control subjects. Five participants (one behavioural variant FTD, three semantic dementia, one control) could not be scanned due to MRI contraindications and MRI data for six participants (one behavioural variant FTD, one PNFA, four controls) were not available because of technical difficulties. No significant differences in age [F(1,57) = 1.009, P > 0.05], sex (χ2 = 2.118, P > 0.05) or level of education [F(1,57) = 0.745, P > 0.05] were present between participants included in the scanned groups and those whose scans were unavailable.

**Data preprocessing**

FSL voxel-based-morphometry, part of the FMRIIB 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 and Friston 2000; Mechelli et al., 2005; Woolrich et al., 2009). Structural images were brain-extracted using BET, then tissue segmentation was conducted with automatic segmentation (FAST) (Zhang et al., 2001). Grey matter partial volume maps were aligned to Montreal Neurological Institute standard space (MNI152) using non-linear registration (FNIRT) (Andersson et al., 2007a, b), 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, and the modulated, segmented images were smoothed with an isotropic Gaussian kernel with a sigma of 3 mm.

**Behavioural analyses**

Data were analysed using SPSS 20.0 (SPSS Inc.). All variables were checked for normality of distribution using the Kolmogorov-Smirnov tests. Clinical and demographic variables were analysed using univariate ANOVA, with post hoc analyses comparing differences across groups, using Sidak correction for multiple comparisons. Analyses investigating the effect of emotion on memory were conducted using each participant’s subjective valence ratings. Items subjectively rated as emotional were compared with items rated as neutral. This approach was taken to ensure that the lack of emotional enhancement was not due to patients failing to perceive stimuli as emotional. True recognition rate (i.e. number correct responses; ‘yes’ to studied items/total number of studied items) and false recognition rate (i.e. number incorrect responses; ‘yes’ to novel items/total number of novel items) for emotional and non-emotional images were log transformed to normalize. Separate repeated-measures ANOVAs with Sidak post hoc tests were conducted for true and false recognition scores to investigate main effects of diagnosis (behavioural variant FTD, semantic dementia, PNFA, controls) and condition (emotional, neutral), as well as interactions.

**Voxel-based morphometry 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 and Holmes, 2002). Differences in grey matter intensities between patients (behavioural variant FTD, semantic dementia, PNFA and Alzheimer’s disease) and controls were assessed using t-tests.

Next, correlations between recognition performance and grey matter intensity were conducted. True recognition scores for emotional and neutral items were entered simultaneously into the design matrix. Contrasts investigated correlations averaged across Emotional and Neutral items (1,1) and correlations for Emotional memory performance, taking into account Neutral memory performance (1,0). Age was included as a nuisance variable for all contrasts. Correlations between recognition performance and grey matter intensity were investigated combining all participants (behavioural variant FTD, semantic dementia, PNFA and Alzheimer’s disease, controls). Then, correlations for overall memory and emotional memory were investigated using the same analyses described above, in each patient group combined with controls, to identify neural correlates of emotional memory specific to each patient group. This approach has been shown to achieve greater variance in scores, increasing the statistical power to detect behavioural correlations (Sollberger et al., 2009; Irish et al., 2012). Finally, region of interest analyses were conducted to examine associations between the amygdala and emotional memory performance. A region of interest mask was created for the right and left amygdala using the Harvard-Oxford subcortical atlas. For all analyses, the statistical threshold was set at $P < 0.005$ uncorrected for multiple comparisons. In addition, a conservative cluster extent threshold of 100 voxels was used to reduce the likelihood of false positives.

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

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**Figure 1** Experimental design and procedure. Black squares represent negative images. Grey squares represent neutral images. An example screen view is shown for each phase of the experiment. T = target; F = foil. During encoding, participants viewed images one at a time, and were asked whether the main object in the picture was bigger than a shoebox. During recognition, participants were asked whether they had seen the picture before. During the ratings phase, participants rated each picture for valence and arousal using the Self-Assessment Mannikin (SAM).
Results

Demographics and clinical characteristics

Groups were well matched for age, education and sex (all P-values > 0.05). On the general cognitive screening measure, the Addenbrooke’s Cognitive Examination–Revised, a significant effect of diagnosis was present [F(4,53) = 7.64, P < 0.001], with behavioural variant FTD, semantic dementia and Alzheimer’s disease performing worse than control subjects (behavioural variant FTD: P = 0.039; semantic dementia: P < 0.001; Alzheimer’s disease: P = 0.001). Neuropsychological testing revealed deficits characteristic of each patient group (Table 1). Compared with controls, behavioural variant FTD showed impaired attention (Digits Forwards: P = 0.004), working memory (Digits Backwards: P = 0.004), visual memory (Rey complex figure: P = 0.016), and letter fluency (P < 0.001), indicative of attention deficits and executive dysfunction. Patients with semantic dementia were impaired on confrontation naming (P < 0.001), and verbal fluency (P = 0.001), reflecting their semantic deficits. In contrast, PNFA displayed reduced verbal output on verbal measures of attention (Digits Forwards: P = 0.001), working memory (Digits Backwards: P < 0.001) and fluency (P < 0.001). Finally, Alzheimer’s disease showed reduced verbal working memory (Digits Backwards: P = 0.008) and visual episodic memory (Rey Complex Figure: P < 0.001) (Table 1).

True recognition

A significant main effect of condition emerged [F(1,54) = 10.990, P = 0.002], indicating that true recognition was higher for emotional than neutral images. No main effect of diagnosis was present [F(4,54) = 0.887, P = 0.478]. A significant interaction between condition and diagnosis was observed [F(4,54) = 2.589, P = 0.047], revealing that the effect of emotion on true recognition differed across diagnostic groups. Within group comparisons indicated that this condition × diagnosis interaction was driven by the significantly greater recognition of emotional compared with neutral images in control subjects (P = 0.037), and patients with Alzheimer’s disease (P < 0.001). In contrast, no difference in true recognition between emotional and neutral items was seen in the behavioural variant FTD, semantic dementia or PNFA groups (all P-values > 0.05). Overall level of recognition did not differ across groups (all P-values > 0.05) (Fig. 2).

To check that differences in emotional enhancement of memory were not confounded by impaired coding of stimuli as emotional or neutral, the same analyses described above were repeated using each item’s objective rating (International Affective Picture System and Geneva Affective Picture Database normative ratings). For these analyses, a main effect of condition was present, indicating

Table 1 Demographics and neuropsychological test performance for the study cohorts

<table>
<thead>
<tr>
<th></th>
<th>bvFTD n = 11</th>
<th>SD n = 13</th>
<th>PNFA n = 10</th>
<th>AD n = 10</th>
<th>Control n = 15</th>
<th>F</th>
<th>Post hoc</th>
</tr>
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<tbody>
<tr>
<td>M/F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ns</td>
<td>bvFTD, SD, AD &lt; Controls</td>
</tr>
<tr>
<td>Age, years</td>
<td>66.7 ± 9.8</td>
<td>63.9 ± 4.5</td>
<td>67.4 ± 9.9</td>
<td>67.5 ± 7.8</td>
<td>69.5 ± 6.1</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Education, years</td>
<td>11.2 ± 2.2</td>
<td>12.7 ± 3.2</td>
<td>13.5 ± 3.3</td>
<td>11.5 ± 2.6</td>
<td>13.9 ± 3.5</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Duration, months</td>
<td>73.5 ± 41.9</td>
<td>66.2 ± 23.9</td>
<td>41.9 ± 18.1</td>
<td>64.8 ± 31.8</td>
<td>–</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>ACE-R (100)</td>
<td>77.7 ± 13.3</td>
<td>67.3 ± 17.7</td>
<td>78.8 ± 10.7</td>
<td>70.7 ± 21.5</td>
<td>94.8 ± 3.9</td>
<td>*</td>
<td>bvFTD, SD, AD &lt; Controls</td>
</tr>
<tr>
<td>Digits-F (8)</td>
<td>5.5 ± 0.8</td>
<td>7.5 ± 2.6</td>
<td>4.5 ± 1.2</td>
<td>6.4 ± 1.1</td>
<td>7.4 ± 1.1</td>
<td>*</td>
<td>bvFTD, PNFA &lt; SD, Controls</td>
</tr>
<tr>
<td>Digits-B (8)</td>
<td>3.7 ± 1.1</td>
<td>5.4 ± 1.7</td>
<td>3.1 ± 1.2</td>
<td>4.4 ± 1.5</td>
<td>5.6 ± 1.2</td>
<td>*</td>
<td>bvFTD, PNFA, AD &lt; SD, Controls</td>
</tr>
<tr>
<td>RCF delay (36)</td>
<td>9.8 ± 6.8</td>
<td>15.7 ± 4.7</td>
<td>17.0 ± 6.0</td>
<td>4.9 ± 6.8</td>
<td>17.7 ± 5.5</td>
<td>*</td>
<td>bvFTD, AD &lt; SD, Controls; AD &lt; SD</td>
</tr>
<tr>
<td>Naming (30)</td>
<td>22.1 ± 3.8</td>
<td>8.5 ± 5.3</td>
<td>22.0 ± 6.8</td>
<td>21.0 ± 5.8</td>
<td>25.9 ± 2.5</td>
<td>*</td>
<td>SD &lt; bvFTD, PNFA, AD, Controls</td>
</tr>
<tr>
<td>Fluencyb,c,d</td>
<td>20.6 ± 14.2</td>
<td>28.0 ± 10.9</td>
<td>17.0 ± 13.2</td>
<td>34.8 ± 16.7</td>
<td>50.7 ± 13.4</td>
<td>*</td>
<td>bvFTD, SD, PNFA &lt; Controls</td>
</tr>
</tbody>
</table>

Scores are means ± standard deviation. Maximum scores where applicable are provided next to each test name. Sidak correction used for post hoc multiple comparisons.

* P < 0.05; ** ns; P > 0.5. bvFTD = behavioural-variant FTD; SD = semantic dementia; AD = Alzheimer’s disease.

ACE-R = Addenbrooke’s Cognitive Examination-Revised; RCF = Rey Complex Figure.

* Chi-square value.

b Scores missing for one patient with Alzheimer’s disease on Rey Complex Figure and Fluency tests.

c Scores on the Addenbrooke’s Cognitive Examination-Revised, Digit Span, and Fluency, removed for one participant with PNFA because of significant expressive language deficit.

d Scores missing for two additional PNFA participants on Fluency test.
that true recognition was higher for emotional than non-emotional items, although this effect was weak, with no within-group differences observed. Importantly, the FTD groups showed no differences in true recognition of emotional or neutral items when analyses were conducted based on either subjective or objective ratings, indicating that abnormal emotional enhancement in these groups was not solely due to an inability to perceive the stimuli as emotional. Behavioural scores and complete analyses based on objective ratings are provided in Supplementary Table 3.

False recognition

A significant main effect of condition was present [F(1, 54) = 5.167, P = 0.027], indicating that incorrect endorsement of novel items was higher for emotional than neutral images. A main effect of diagnosis also emerged [F(4, 54) = 2.814, P = 0.034], demonstrating that overall level of false recognition differed across diagnostic groups. The interaction between condition and diagnosis on false recognition was not significant [F(4, 54) = 2.219, P = 0.079]. Post hoc between-group analyses revealed that the effect of diagnosis was driven by increased false recognition in the behavioural variant FTD and Alzheimer’s disease groups. For emotional items, only the Alzheimer’s disease group showed increased false recognition compared with controls (P = 0.029), whereas behavioural variant FTD, semantic dementia and PNFA groups did not statistically differ from controls (all P-values > 0.05) (Fig. 3). In contrast, for neutral items, only the behavioural variant FTD group showed increased false recognition compared to controls (behavioural variant FTD: P = 0.018; semantic dementia, PNFA, Alzheimer’s disease: P > 0.05). Within-group post hoc comparisons indicated that false recognition was significantly more frequent for emotional than neutral novel items in Alzheimer’s disease (P = 0.012), but not in the other groups (all P-values > 0.05) (Fig. 3).

Together these results indicate that the effect of emotion on memory differs across dementia subtypes. For true recognition, the enhancing effect of emotion was seen in control and Alzheimer’s disease groups only, with no significant enhancing effect of emotion on memory in any of the FTD subtypes. For false recognition, emotion also tended to increase errors in the Alzheimer’s disease group. Whereas patients with behavioural variant FTD showed elevated levels of false recognition compared to controls for neutral items, the presence of emotion was not found to influence their false recognition rates.

Voxel-based morphometry

Patterns of atrophy

Voxel-based morphometry analyses revealed a pattern of grey matter atrophy typical of each patient group (Supplementary Fig. 1). Briefly, patients with behavioural variant FTD showed characteristic widespread grey matter intensity decrease involving frontal (orbitofrontal cortex, frontal pole, lateral frontal cortices, paracingulate gyrus), temporal and medial temporal regions (inferior temporal gyrus, temporal pole, parahippocampal gyrus, hippocampus, and amygdala) bilaterally. In contrast, patients with semantic dementia showed bilateral grey matter intensity decrease in the lateral temporal cortices and temporal poles, including the hippocampus and amygdala, with more severe atrophy seen on the left compared with the right hemisphere. Patients with PNFA showed grey matter intensity decrease predominantly in left frontotemporal regions including the frontal operculum cortex, inferior, middle and superior frontal gyri, insula and putamen. Finally, in Alzheimer’s disease widespread regions of grey matter intensity decrease were evident in lateral and medial temporal regions (hippocampus, parahippocampal gyrus), frontal, parietal, and occipital cortices. These patterns of atrophy are consistent with those reported previously in the literature for the FTD (Rosen et al., 2002a; Nestor et al., 2003; Mion et al., 2010) and Alzheimer’s disease cohorts (Dickerson et al., 2001) (Supplementary Fig. 1).

Neural correlates of emotional enhancement of memory

Investigation of correlations between behavioural performance on the recognition memory task and grey matter intensity revealed that overall memory performance (averaged across emotional and neutral items) for all participants combined (behavioural variant FTD, semantic dementia, PNFA, Alzheimer’s disease and control subjects) was associated with a broad network of regions (Fig. 4 and Table 2). The brain regions implicated included the left hippocampus and parahippocampal gyrus, together with posterior regions including the lateral occipital cortex bilaterally, the precuneus and posterior cingulate, and regions in the right middle and superior temporal gyrus and planum polare.

In contrast, emotional memory performance (accounting for memory for neutral items) was associated with a set of brain regions that were distinct from those identified in the overall memory performance contrast. Emotional memory performance was associated with grey matter intensity of the right orbitofrontal and subcallosal cortex, together with the right middle and inferior frontal gyri, revealing that integrity of these frontal regions is critical for the emotional enhancement of memory effect. The region of interest analyses specific to the amygdala revealed only two clusters (two and seven voxels in size) that were associated with
emotional memory performance. No clusters in the amygdala were associated with overall memory performance.

Additional voxel-based morphometry analyses to investigate the brain correlates of memory and emotional memory performance separately in each patient group combined with controls yielded similar patterns of findings. Briefly, in behavioural variant FTD, the left hippocampus and parahippocampal gyrus, left lateral occipital cortex, as well as the right frontal pole and middle frontal gyrus, were associated with overall memory performance. In addition, the right amygdala and orbitofrontal cortex were associated with memory for emotional items (Fig. 5 and Supplementary Table 4). In semantic dementia, overall memory was associated with frontotemporal regions bilaterally, but more so on the left. Emotional memory performance was associated with clusters in the left lingual gyrus, the right inferior frontal and left middle frontal gyri, as well as regions in the precuneus and posterior cingulate (Fig. 5 and Supplementary Table 6). Finally, in Alzheimer’s disease, overall memory was associated with the right hippocampus, bilateral frontal cortex, and left medial and lateral parieto-temporal cortices. Emotional memory was associated with similar regions as overall memory but also included the orbitofrontal cortex, extending into the right amygdala (Fig. 5 and Supplementary Table 7).

<table>
<thead>
<tr>
<th>Regions</th>
<th>Hemisphere</th>
<th>MNI Coordinates</th>
<th>Number of Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall true recognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral occipital cortex, superior division extending into occipital pole</td>
<td>Left</td>
<td>−32 −88 12</td>
<td>611</td>
</tr>
<tr>
<td>Middle temporal gyrus, posterior division extending into superior temporal gyrus, anterior division</td>
<td>Right</td>
<td>56 −34 −4</td>
<td>589</td>
</tr>
<tr>
<td>Planum polare extending into superior temporal gyrus anterior division</td>
<td>Right</td>
<td>58 0 −2</td>
<td>345</td>
</tr>
<tr>
<td>Lateral occipital cortex, inferior division extending into superior division</td>
<td>Right</td>
<td>56 −66 10</td>
<td>303</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Left</td>
<td>−42 −84 −32</td>
<td>300</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>Right</td>
<td>38 −26 56</td>
<td>275</td>
</tr>
<tr>
<td>Precuneus, extending into lateral occipital cortex, superior division</td>
<td>Left</td>
<td>−12 −58 34</td>
<td>249</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>Left</td>
<td>−10 −28 38</td>
<td>232</td>
</tr>
<tr>
<td>Occipital pole</td>
<td>Right</td>
<td>14 −90 28</td>
<td>211</td>
</tr>
<tr>
<td>Lateral occipital cortex, superior division</td>
<td>Right</td>
<td>30 −78 16</td>
<td>145</td>
</tr>
<tr>
<td>Parahippocampal cortex, posterior division extending into hippocampus</td>
<td>Left</td>
<td>−14 −26 −22</td>
<td>128</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>Left</td>
<td>−54 −16 42</td>
<td>122</td>
</tr>
<tr>
<td>Emotional true recognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbifrontal cortex, extending into subcallosal cortex</td>
<td>Right</td>
<td>10 24 −26</td>
<td>633</td>
</tr>
<tr>
<td>Frontal operculum cortex, extending into inferior frontal gyrus</td>
<td>Right</td>
<td>38 20 10</td>
<td>516</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>Right</td>
<td>26 30 28</td>
<td>130</td>
</tr>
</tbody>
</table>

Age included as a nuisance variable in all contrasts. Clusters significant at $P < 0.005$ uncorrected for multiple comparisons. Only clusters >100 contiguous voxels reported. All clusters $t > 2.72$. 
Discussion

This study is the first to investigate the interplay between emotion and memory, and the underlying neural substrates in Alzheimer’s disease and FTD. A robust emotional enhancement of memory effect was observed in Alzheimer’s disease for true recognition, similar to that seen in healthy control subjects, accompanied by an increased false recognition for emotional items. In contrast, an absence of the emotional enhancement effect was revealed in all FTD subtypes. The dissociable effects of emotion on memory in Alzheimer’s disease and FTD is in keeping with the divergent patterns of neurodegeneration seen in these dementia syndromes. Importantly, voxel-based morphometry analyses confirmed that regardless of group membership, overall memory performance was associated with a distinct set of brain regions that included the left hippocampus, posterior cingulate, precuneus, right superior and middle temporal gyri and postcentral gyrus, regions classically associated with successful episodic memory performance (reviewed by Dickerson and Eichenbaum, 2010; Ranganath and Ritchey, 2012). Importantly, atrophy in these brain regions has recently been shown to differentially contribute to episodic memory disturbances in both Alzheimer’s disease and Behavioural variant FTD (Irish et al., 2013). In contrast, emotional enhancement was associated with a separate set of frontal lobe structures, which included the right orbitofrontal and subcallosal cortex, the right frontal operculum cortex and the inferior and middle frontal gyri, with the largest cluster present in the right orbitofrontal cortex. These results provide strong evidence for the specialization of distinct frontal and temporal lobe regions for overall memory and emotional enhancement of memory. Our findings are further corroborated by the dissociation in behavioural performance observed in Alzheimer’s disease and FTD groups, with emotional enhancement of memory attenuated in FTD but not Alzheimer’s disease. Here, we discuss how our neuroimaging and behavioural findings inform our understanding of the mechanisms by which emotion facilitates subsequent memory.

Neural correlates supporting memory and emotional enhancement

The hippocampus undoubtedly plays a crucial role during encoding and consolidation of episodic memory (Squire, 2004; Moscovitch et al., 2006). Extra-hippocampal structures, however, also contribute to successful retrieval of information (Buckner et al., 2008; Ranganath and Ritchey, 2012). In this study, the precuneus and posterior cingulate, as well as occipital regions necessary for visual processing, were associated with true recognition, irrespective of emotional content. These posterior regions are activated during visual inspection of emotional and neutral scenes in healthy adults, with the degree of activation varying according to emotional content (i.e. increased activation for emotional than neutral stimuli) (Sabatinelli et al., 2007). By combining across emotional and neutral stimuli in order to determine common brain regions involved in memory, we confirmed the importance of the hippocampus, together with posterior regions, in processing and remembering visual stimuli, irrespective of emotional content. In contrast with overall memory, memory for emotional stimuli involved different brain regions and was associated with the orbitofrontal cortex predominantly. The orbitofrontal cortex shares strong bidirectional connections with the hippocampus and amygdala (Cavada et al., 2000; Ranganath et al., 2005; Stein et al., 2007) but it does not appear to be critically involved in declarative memory per se. Rather, the orbitofrontal cortex is thought to play a specialized role in the processing of unexpected or unpleasant

![Figure 5](https://example.com/figure5.png)
stimuli (reviewed by Petrides, 2007). This region appears to influence memory via its role in evaluating information from the environment and integrating this knowledge with information from the internal state (i.e. physiological arousal) (Petrides, 2007; Viskontas et al., 2007). Our neuroimaging results therefore suggest that the integrity of the amygdala alone is not sufficient for the emotional enhancement of memory effect to occur. Functional imaging studies have indicated that increased activation of both the amygdala and orbitofrontal cortex is present during emotional memory tasks (e.g. Kensinger and Corkin, 2004; Kensinger and Schacter, 2005). Our results provide corroborative lesion evidence of the contribution of the orbitofrontal cortex to emotional enhancement of memory. Further, our findings reveal for the first time that damage to this structure underlies the attenuation of emotional enhancement of memory in FTD.

Dissociable effects of emotion on memory across dementia syndromes

Our neuroimaging results reflected the differential effects of emotion on memory in Alzheimer’s disease and FTD, with emotion modulating memory in Alzheimer’s disease but not FTD. Equivocal results of emotional enhancement of memory in Alzheimer’s disease have been reported previously (Ikeda et al., 1998; Mori et al., 1999; Kensinger et al., 2004). Disease severity and methods of investigation (i.e. recollection versus recognition; reviewed by Klein-Koerkamp et al., 2012) likely account for discrepancies across studies. In this study, we used a recognition paradigm to elucidate mechanisms of emotional enhancement. In a group of patients with relatively mild Alzheimer’s disease we revealed that emotional content produces a striking increase in item endorsement, irrespective of the accuracy of those responses. In other words, patients with Alzheimer’s disease showed an increased tendency to ‘recognize’ emotional items, whether they had seen them previously or not. This pattern of results suggests a reliance on gist rather than detail processing in Alzheimer’s disease with a more liberal response bias evident for emotional than neutral items, leading to a trade-off in memory performance (Gallo et al., 2006). Depending on how memory is tested, gist processing may give rise to emotional enhancement (e.g. during free recall or semi-structured interviews), although this effect may be negated when response bias is taken into account. This finding is consistent with the view that emotion tends to boost the likelihood of endorsing an item, without necessarily improving overall accuracy (Sharot et al., 2004). In the current context, we have demonstrated that despite their memory deficits and associated hippocampal damage, emotion exerts a significant effect on memory performance in Alzheimer’s disease. The finding of an appreciable benefit to memory performance in patients with well documented medial temporal lobe atrophy is noteworthy, and suggests that at an early stage in the disease course, patients with Alzheimer’s disease can harness emotional aspects of stimuli to facilitate subsequent retrieval.

By contrast no significant effect of emotion on subsequent memory recognition was evident in FTD, irrespective of subtype. It is unlikely that the attenuation of emotional enhancement of memory in these patients is due to a failure to appreciate the emotional content of the stimulus, as items were classified as emotional or neutral based on individuals’ subjective ratings, and analyses based on objective ratings showed a similar absence of emotional enhancement in the FTD groups. Rather, the results indicate that despite patients with FTD rating the stimuli as emotional, this appraisal had no influence on memory. One explanation for this apparent contradiction is the decoupling between patients’ cognitive appraisal and the emotional experience of a stimulus in patients with FTD. Whereas these patients may retain the capacity to appropriately rate the emotional content of a stimulus in a cognitive manner (e.g. a snake is negative), the associated increase in physiological arousal in response to emotional stimuli may be disturbed. Indeed, physiological responding to a highly aversive noise is reportedly abnormal in FTD, and this is associated with orbitofrontal, anterior cingulate, amygdala and insula atrophy (Hofer et al., 2008; Sturm et al., 2013). A similar discrepancy is observed in healthy adult participants who rate the emotionality of a story appropriately, yet fail to show any appreciable emotional enhancement of memory, following beta-blocker administration (reducing physiological arousal) (Cahill et al., 1994). Further, evidence from the autobiographical memory literature, suggests that the emotional intensity of an event robustly predicts subsequent retrieval and the subjective recollective experience (Talarico et al., 2004; Irish et al., 2011b). Our results suggest that emotional enhancement of memory is dependent on changes in physiological arousal in FTD, although this will require confirmation. Crucially, our findings support the proposal that the identification of emotional valence alone is not sufficient to produce an emotional enhancement of memory effect (McGaugh, 2004; Van Stegeren, 2008).

The neuroimaging results revealed divergent neural contributions to the emotional enhancement of memory in FTD and Alzheimer’s disease groups, confirming the dissociable effects seen behaviourally. In behavioural variant FTD and semantic dementia, emotional enhancement of memory was associated with the orbitofrontal cortex, and in PNFA emotional memory was associated with the right inferior frontal cortex. Despite their divergent patterns of atrophy, all three FTD subtypes show a degree of orbitofrontal and inferior frontal atrophy (Seeley, et al., 2008; Rohrer et al., 2009) (Supplementary Fig. 2). These frontal regions associated with emotional memory performance are distinct from those associated with overall memory performance in these patient groups, suggesting that attenuation of emotional enhancement of memory is attributable to degradation of frontal lobe regions necessary for processing emotional stimuli. In contrast, a discrete set of regions including the hippocampus, posterior cingulate cortex, precuneus, frontal pole and lateral occipital cortex correlated with both overall memory and emotional memory performance in Alzheimer’s disease. This overlap of regions in the classic episodic memory network, irrespective of emotional content, indicates that disruption to episodic memory, rather than emotional processing deficits, contributes solely to Alzheimer’s disease participants’ performance on this type of task. Accordingly, our behavioural and neuroimaging findings converge to suggest that fundamentally different neurobiological mechanisms underpin...
the divergent behavioural profiles displayed in patients with FTD versus Alzheimer’s disease.

Our investigations of emotional memory in FTD uncovered important issues for future research to address. Existing evidence shows that the enhancing effect of emotion on memory is robust and reliable, particularly for negative information. The extent to which memory for positively valenced material is affected in dementia syndromes remains, however, unresolved. This issue has theoretical relevance for models of emotion processing and clinical implications for the management of patients affected by these disorders. In addition, the possible dissociation between ‘cognitively’ rating a stimulus as emotional and physiologically responding to emotional stimuli deserves further examination. Measuring physiological responses (e.g. through skin conductance) while subjectively rating stimuli will help determine whether cognitive capacity and emotional responding are dissociable in patients with dementia. Arguably, our findings need to be interpreted with relative caution given the size of the study samples. Future examination of emotional memory in FTD using larger group sample size will be important for confirmation of these novel findings.

From a clinical perspective, the differential effects of emotion on memory offer insights into the characteristic behavioural changes seen in neurodegenerative disorders. Patients with FTD are often described as apathetic, lacking motivation and appearing disengaged from social and family events. It is possible that this social withdrawal may arise, in part, from a failure to recollect past events, particularly the emotional aspects of such experiences (Irish et al., 2011). In addition, patients with FTD may not remember recent arguments with the same degree of detail as their spouse or family member, which likely impacts on the maintenance of interpersonal relationships. In contrast, the integrity of emotional enhancement of memory in Alzheimer’s disease represents an interesting avenue for memory intervention. Our results suggest that imbuing an event or a stimulus with emotion may improve memorability in Alzheimer’s disease (Sandman, 1993).

In summary, we have demonstrated for the first time, that emotional enhancement of memory is compromised across the three main FTD subtypes, and this attenuation of emotional enhancement of memory is associated with underlying changes in frontal structures, particularly the right orbitofrontal cortex. In contrast, for patients with Alzheimer’s disease, emotion exerts a robust effect on memory, despite the marked degradation of the episodic memory network in these patients. Our results provide insight into the mechanisms underlying emotional memory. In addition, these results help to characterize the impact of these dementia syndromes on emotion, memory and their interaction.

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Supplementary material

Supplementary material is available at Brain online.

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