Autobiographical deficits correlate with gray matter volume in depressed and high risk participants

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Abstract

Autobiographical memory (AM) overgenerality is a consistent neuropsychological feature of major depressive disorder (MDD) and is present in individuals at high-familial risk (HR) of developing MDD. Structural changes have been found in brain regions implicated in AM recall in MDDs and HRs. However, the relationship between selective regional gray matter volume (GMV) differences and AM recall deficits has not been examined. We examined this relationship in 27 HR, 43 unmedicated MDD and 47 low-risk healthy control participants as they completed an AM task during functional magnetic resonance imaging. FreeSurfer was used for automated anatomical image processing and volumetric quantification. Anatomical regions of interest for GMV analysis were selected based on regions most commonly activated in controls as they recall specific AMs according to a recent meta-analysis. Pearson correlations were calculated among volumetric and AM recall data. In HRs and MDDs, left hippocampal volume correlated positively with specific (HRs $r = 0.42$; MDDs $r = 0.60$) and inversely with categorical AM recall (HRs $r = -0.51$; MDDs $r = -0.35$). In MDDs, left precuneus volume also correlated positively with specific ($r = 0.49$) and inversely with categorical ($r = -0.35$) AM recall. Our results suggest selective GMV alterations within the AM network may contribute to AM impairments observed in both HR and MDD individuals.

Key words: depression; gray matter volume; hippocampus; autobiographical memory; familial risk; precuneus

Introduction

Major depressive disorder (MDD) is associated with impairments in several cognitive domains, including information processing, attention, executive function and memory (Reppermund et al., 2009). One cognitive domain in which patients with MDD consistently show impairment is that of autobiographical memory (AM; Williams et al., 2007). Patients with MDD, compared with healthy controls consistently recall fewer specific memories (memories of a single event which occurred at an identified time and place) and instead recall more categorical memories (memories of reoccurring events without reference to a single instance; Williams et al., 2007). Research suggests that AM overgenerality, particularly for positive AMs, is a trait-like marker of MDD as AM deficits exist in those remitted from depression (Spinhoven et al., 2006; Young et al., 2014), as well as in those at a high-familial risk (HR) of developing MDD (Young et al., 2013a).

Functional neuroimaging has identified a core set of brain regions involved in AM recall in healthy individuals which includes the medial temporal lobe (including hippocampus and parahippocampal gyrus), posterior cingulate cortex, precuneus and medial prefrontal cortex (PFC; Martinelli et al., 2013). Utilizing functional magnetic resonance imaging (fMRI), we recently confirmed these regions, along with the anterior cingulate cortex and dorsolateral PFC, are also recruited during specific AM recall in controls, MDD, and HR participants (Young et al., 2013a). Several of these regions show structural abnormalities in both MDD and HR participants, including decreased
hippocampal (Sheline et al., 2003; Baare et al., 2010) and parahip-
campal (Bowen et al., 1989) volumes.

While AM deficits and structural changes in brain regions implicated in AM recall have been found in these populations, the relationship between regional gray matter volume (GMV) differences and AM recall deficits has not been examined. The goal of the current study was to examine the relationship be-
tween GMV of regions recruited during AM recall and AM recall performance in HR, MDD and control participants. We predicted volumes of regions crucial for AM recall as identified in a recent meta analysis examining episodic AM recall in healthy individ-
uals (Martinelli et al., 2013), such as the hippocampus, medial PFC and cingulate cortices would be reduced in MDD and HR participants compared with controls, and that volumes in these regions would correlate with AM performance. Specifically, we predicted larger volumes in medial temporal and prefrontal re-
gions consistently implicated in AM recall would be associated with better AM performance (indicated by increased specific and decreased categorical AMs) in both the HR and MDD groups. Because available meta analyses only reported results of AM re-
call overall and did not examine different valences separately (Svoboda et al., 2006; Kim, 2012; Martinelli et al., 2013), we did not have specific predictions as to whether these regions would be correlated with the valence of recalled AMs, and thus con-
ducted an exploratory analysis. Elucidating these relationships may facilitate our understanding of the pathophysiology under-
lying MDD, and may contribute to improved diagnosis and treatment for MDD as well as to improved prediction of which HR individuals will go on to develop MDD.

Materials and methods

Participants

Medically healthy, right-handed individuals ages 18–55 were evaluated for their eligibility to enter one of three groups: unmedicated MDD participants in a current major depressive episode ($n = 43$) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (APA 2000), psychi-atrically healthy low-risk controls ($n = 47$), and psychiatrically healthy participants with a first-degree relative with MDD ($n = 22$). Data from a subset of these participants (16/group) was used in a pre-
vious paper identifying brain regions recruited during specific AM recall and how they differed across these populations (Young et al., 2013a). The current study includes those 16/group and an additional 27 MDD, 31 control and 6 HR participants that completed the study after the previous publication (Young et al., 2013a). Volunteers, recruited from the community via advertise-
ments, underwent medical and psychiatric screening evalua-
tions at the Laureate Institute for Brain Research, which included the Structural Clinical Interview for DSM-IV-TR disor-
ders (First et al., 2002). Family history was established via the Family Interview for Genetic Studies (Maxwell, 1992).

Exclusion criteria included current pregnancy, general MRI exclusions, serious suicidal ideation, psychosis, major physical or neurological disorders, exposure to any medication likely to influence cerebral function or blood flow within 3 weeks, and meeting DSM-IV-TR criteria for drug/alcohol abuse within the previous 1 year or alcohol/drug dependence (excluding nicotine) within the lifetime. Additional exclusion criteria applied to con-
trol and HR participants were current or past history of axis I psychiatric conditions and history of psychotropic medication use. After receiving a complete explanation of the study pro-
dures, all participants provided written informed consent to participate, as obtained according to the Declaration of Helsinki and approved by the Western IRB. Participants received financial compensation for their participation.

Intelligence testing was performed using the two-subtest ver-
sion of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Anxiety and depressive symptoms were rated using the 21-
item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), and the Profile of Mood States (POMS; McNair et al., 1971).

AM task

Participants completed a computerized version of the AM test (Williams and Broadbent, 1986) developed for use during fMRI; details of which have been reported previously (Young et al., 2013a,b). Briefly, participants were presented with an emotionally valenced or neutral cue word for 12 s (60 cues; 20/valence) and instructed to attempt to recall a specific past experience that the word reminded them of, then rate their retrieved memory on spe-
cificity and valence. AM recall was compared with a semantic example generation condition in which participants were pre-

Image acquisition

Blood-oxygenation-level-dependent fMRI and anatomical scans were conducted on a 3T GE Discovery MR750 scanner and eight-
channel receive-only head coil (GE Healthcare). The whole brain high-resolution T1 weighted anatomical MRI scans were acquired for GMV analysis with the following parameters: 120 1.2 mm thick slices acquired axially, repetition time $= 5$ ms, echo time $= 1.93$ ms, flip angle $= 8^\circ$, matrix $= 256 \times 256$, field-of-
view $= 24$ cm, in-plane voxel resolution $= 0.94$ mm$^2$.

Image processing

Volumetric analyses were performed using FreeSurfer (version 5.1; http://surfer.nmr.mgh.harvard.edu/) for automated image processing and quantification (Fischl et al., 2002). We selected regions commonly activated during AM recall in healthy individ-
uals according to a recent meta-analysis (Martinelli et al., 2013). Results are summarized in Table 1, where those brain regions and their corresponding FreeSurfer masks, along with
calculated regional volumes are shown. For the medial PFC region, the FreeSurfer mask which corresponded to the region identified in the meta-analysis (based on spatial coordinates and cluster size) was the superiorfrontal region (Figure 1). All maps were visually checked for accuracy by overlaying labels generated in FreeSurfer onto the anatomical T1 image for each subject. If accuracy was questionable, the data were not included in the final analysis. The numbers of participants removed from the group analysis due to poor FreeSurfer parcelation by subject category were 2 controls, 0 HRs and 3 MDDs leaving a final sample size of 45 controls, 22 HRs and 40 MDDs.

### Statistical analysis

Data analyses were performed utilizing SYSTAT 13 (Systat Software Inc.), and all analyses were corrected for multiple comparisons (Bonferroni) at $P_{\text{corrected}} < 0.05$. Gender and total GMV were included as covariates in each analysis. Gender was included as a covariate because the groups differed significantly in their gender composition, and because both regional GMV and AM performance have been shown to differ between men and women (Seiditz and Diener, 1998; Chen et al., 2013). For demographic information, clinical characteristics and GMV of the regions of interest (ROIs), a one-way analysis of variance (ANOVA) was used to compare these variables between groups. A repeated-measures ANOVA with the within subjects variables of type (specific, categorical) and valence (positive, negative and neutral) examined whether the participant groups differed on their AM performance. Only specific and categorical AMs were included as covariates because the groups differed significantly in their gender composition, and because both regional GMV and AM performance have been shown to differ between men and women (Seiditz and Diener, 1998; Chen et al., 2007). For demographic information, clinical characteristics and GMV of the regions of interest (ROIs), a one-way analysis of variance (ANOVA) was used to compare these variables between groups. A repeated-measures ANOVA with the within subjects variables of type (specific, categorical) and valence (positive, negative and neutral) examined whether the participant groups differed on their AM performance. Only specific and categorical AMs were included as covariates because the groups differed significantly in their gender composition, and because both regional GMV and AM performance have been shown to differ between men and women (Seiditz and Diener, 1998; Chen et al., 2007). Pearson correlations were performed to detect associations between GMV and AM performance (% specific, categorical, positive and negative AMs) separately for each group. Correlations found to be significant in one group were compared between groups via Fisher’s r-to-z transformation to evaluate the significance of the difference between the correlation coefficients.

### Results

#### Analysis of behavioral data

The one-way ANOVA revealed participants did not differ on demographic characteristics or control task performance (Table 2; $F(2,107) < 2.29$, $P_s > 0.16$). However, the gender distribution differed significantly between groups ($\chi^2 = 4.32$, $P = 0.04$).

Table 1. Regions recruited during specific AM recall in a recent meta-analysis, along with the corresponding FreeSurfer masks and the regional GMVs (mm$^3$) for each group

<table>
<thead>
<tr>
<th>Area</th>
<th>Episodic autobiographical recall vs control task$^a$</th>
<th>FreeSurfer Mask</th>
<th>Volume (mm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cluster size $x$, $y$, $z$</td>
<td>Structure name in FreeSurfer index</td>
<td>Controls</td>
</tr>
<tr>
<td>L medial PFC/BA10</td>
<td>432 $–50$, 6</td>
<td>Superiorfrontal cortex</td>
<td>1028</td>
</tr>
<tr>
<td>R posterior cingulate</td>
<td>672 $50$, 16, 20</td>
<td>R posterior cingulate cortex</td>
<td>2023</td>
</tr>
<tr>
<td>L middle temporal G</td>
<td>1352 $–48$, 6, 22</td>
<td>L middle temporal G</td>
<td>1015</td>
</tr>
<tr>
<td>L hippocampus</td>
<td>2512 $–26$, 0, 16</td>
<td>L hippocampus</td>
<td>17</td>
</tr>
<tr>
<td>L parahippocampus</td>
<td>760 $–42$, 6, 4</td>
<td>L parahippocampal G</td>
<td>1016</td>
</tr>
<tr>
<td>R parahippocampus</td>
<td>2776 $26$, 26, 36, 10</td>
<td>R parahippocampal G</td>
<td>2016</td>
</tr>
<tr>
<td>L precuneus</td>
<td>2080 $–6$, 58, 26</td>
<td>L precuneus</td>
<td>1025</td>
</tr>
<tr>
<td>R precuneus</td>
<td>2080 $2$, 6, 40</td>
<td>R precuneus</td>
<td>2025</td>
</tr>
<tr>
<td>L cerebellum</td>
<td>328 $–24$, 6, 20</td>
<td>L cerebellum</td>
<td>8</td>
</tr>
<tr>
<td>R cerebellum</td>
<td>2776 $22$, 30, 28</td>
<td>R cerebellum</td>
<td>47</td>
</tr>
</tbody>
</table>

BA, Brodmann Area; G, gyrus; HR, high-risk; L, left; MDD, major depressive disorder; R, right. Numbers in parentheses indicate 1 s.d.

$^a$Results taken from Table 2 in Martinelli et al. (2013). Coordinates correspond to the stereotaxic array of Talairach and Tournoux (1988), such that each voxel is located in mm relative to the stereotaxic origin (anterior commissure), with positive $x$, $y$ and $z$ designating right, anterior and dorsal. $^b$Bolded regions indicate a significant difference from the control group at $P_{\text{corrected}} < 0.05$. $^c$Indicates a significant difference from the HR group at $P_{\text{corrected}} < 0.05$.
negative AMs overall than controls (t(81) > 0.001) and HRs did not differ from each other on these measures (Fs(2,107) > 0.008). Groups did not differ on the percent of memories categorized as extended, semantic, none or unable to recall post-scan (Fs(2,107) < 0.11). There was a difference between groups in the percent of memories categorized as specific and categorical (Fs(2,107) > 25.6, Ps < 0.001) with controls recalling significantly more specific and fewer categorical AMs than MDDs (t(81) > 4.87, Ps < 0.001) or HRs (t(68) > 21.6, Ps < 0.001), whereas MDDs and HRs did not differ from each other on these measures (t(63) < 1.69, P > 0.10). Importantly, there were no effects of gender or total GMV on any variable examined (Fs(1,107) < 1.18, Ps > 0.28).

The repeated measures ANOVA with specificity (specific and categorical) and Valence (positive, negative or neutral) as the within-subjects variables and group (controls, HR and MDD) as a between-groups variable (Table 3) resulted in a significant valence x group interaction (F(4,214) = 15.5, P < 0.001) but not a type x valence x group interaction (F(4,214) = 0.46, P = 0.76). Follow-up priori t-tests revealed that MDDs recalled fewer positive and more negative AMs overall than controls (t(81) > 15.9, Ps < 0.001) or HR participants (t(63) > 3.36, Ps < 0.008), but did not differ on the percent of neutral AMs recalled (controls t(81) = 1.62, Ps = 0.18, HRs t(63) = 1.36, P = 0.25), and HRs and controls did not differ from each other on these measures (t(68) < 0.01, Ps > 0.93). No effects of gender or total GMV were observed (Fs(1,107) < 0.821, Ps > 0.44).

**Analysis of volumetric data**

A one-way ANOVA examined group differences for each region recruited during specific AM recall (Table 1). The Bonferroni corrected threshold for significance was P < 0.005. Importantly, total (whole brain) GMV did not differ between groups (F(2,107) = 0.48, P = 0.62). There were significant group differences in the GMV of the left middle temporal gyrus and left hippocampus (Fs(2,107) > 4.86, Ps < 0.01). Follow-up t-tests revealed that MDDs had smaller GMV than both HRs (t(63) = 5.17, P < 0.001) and controls (t(81) = 8.51, P < 0.001) in left middle temporal gyrus, whereas controls and HRs did not differ from each other in middle temporal gyrus volume (t(68) = 1.16, P = 0.25). Controls had larger left hippocampal volumes compared with both MDDs (t(81) = 5.02, P < 0.001) and HRs (t(68) = 3.56, P < 0.001) whereas MDDs and HRs did not differ from each other (t(63) = 1.03, P = 0.31).

**Correlation between behavioral and volumetric data**

Pearson correlations were performed between the GMV of each region identified in Table 1 and measures of AM recall (percent
specific, categorical, positive and negative) separately for each group. The Bonferroni corrected threshold for significance was $P < 0.001$. No significant correlation was found between GMV and AM performance within the control group. Within the HR group, the left hippocampal volume correlated positively with the percent of specific ($r = 0.42, P < 0.001$) and inversely with the percent of categorical ($r = -0.51, P < 0.001$) AMs recalled (Figure 2b and c). The MDD group also showed significant correlations in the same direction between left hippocampal volume and the percent of specific ($r = 0.60, P < 0.001$) and categorical ($r = -0.35, P < 0.001$) AMs recalled (Figure 2d and e). In addition, in the MDD group the left precuneus volume also correlated positively with the percent of specific ($r = 0.49, P < 0.001$) and inversely with the percent of categorical ($r = -0.35, P < 0.001$) AMs recalled (Figure 3). There was no significant correlation identified in any group between the GMV of any region examined and the percent of positive or negative AMs recalled (largest $r$ value of any valence correlation $= 0.27$, uncorrected $P = 0.17$).

Fisher’s $r$-$z$ transformations were performed to determine if significant correlation coefficients in one group significantly differed from those in the other groups. The Bonferroni corrected threshold for significance was $P < 0.004$. When examining the hippocampal correlation coefficients, controls and HRs showed a trend toward a different correlation between hippocampal GMV and specific AMs ($P = 0.07$), and a significant difference in the correlation between hippocampal GMV and categorical AMs ($P < 0.001$). MDDs and controls had significantly different correlations between hippocampal volume and both specific ($P < 0.001$) and categorical AMs ($P < 0.001$), whereas MDDs and HRs did not differ from each other in the correlation between hippocampal GMV and specific AMs ($P = 0.35$) or categorical AMs ($P = 0.45$). Controls and HRs did not differ in the correlation coefficient between precuneus and specific ($P = 0.24$) or categorical AMs ($P = 0.67$). MDDs compared with controls showed a trend toward different correlations between precuneus GMV and specific ($P = 0.08$) and categorical AMs ($P = 0.07$), whereas MDDs had marginally significantly different correlation coefficients than HRs for precuneus GMV and specific ($P = 0.008$) and categorical AMs ($P = 0.049$).

**Discussion**

In this study, we investigated the relationship between AM performance and GMV in brain regions recruited during AM recall in low-risk healthy control, HR and unmedicated MDD participants. Behaviorally, we replicated the overgeneral AM phenomenon in MDD (van Vreeswijk and de Wilde, 2004; Williams et al.,

![Fig. 2. Relationship between hippocampal volume and AM recall in MDD and HR participants.](http://scan.oxfordjournals.org/)

(a) Coronal anatomical MRI slice showing the FreeSurfer hippocampal mask overlay. (b–e) Correlations between left hippocampal volume (mm$^3$) and the (b) percent of AMs recalled that were considered ‘specific’ in HR participants, (c) percent of AMs recalled that were considered ‘categorical’ in HR participants, (d) percent of AMs recalled that were considered ‘specific’ in MDD participants and (e) percent of AMs recalled that were considered ‘categorical’ in MDD participants.
2007) with MDDs recalling fewer specific and more categorical AMs than control participants. Additionally, we confirm our original findings of fewer specific and more categorical AMs in a sample at HR for developing MDD (Young et al., 2013a) to a larger subject sample (i.e. the subject sample studied herein included 16 HR and 16 MDD subjects who participated in the previous study). Our results support the hypothesis that AM impairment is part of a stable underlying neuropsychological vulnerability to MDD.

In regions found to be consistently recruited during AM recall according to a recent meta-analysis (Martineili et al., 2019), we examined regional differences in GMV between groups as well as correlations between GMV in these regions and AM performance in a sample of control, HR and unmediated MDD participants. MDD participants had smaller mean GMVs than controls and HRs in left middle temporal gyrus. Reduced gray matter in MDD relative to control participants previously has been reported in this region (Drevets et al., 2008; Peng et al., 2011; Ma et al., 2012). In addition to being part of the medial temporal lobe memory system which research indicates is critical for memory recall (both semantic and episodic; Tranel et al., 1997), this region also forms part of the default mode network (Buckner et al., 2008), which is involved in self-referential thought and is hypothesized to be related to increased rumination evident in depression (Berman et al., 2011), and shares extensive anatomical connections with the medial prefrontal network implicated in the pathophysiology of mood disorders by neuropathological and neuroimaging studies (Price and Drevets, 2010). The finding of reduced GMV in this regions in MDD but not HR participants, along with a lack of significant correlation with measures of AM performance, suggests that volumetric abnormalities in this temporal structure is an illness marker of depression more related to the development of MDD than to AM performance.

Both MDD and HR participants had smaller GMVs than controls in the left hippocampus, consistent with previous neuroimaging studies (Sheline et al., 2003; Baare et al., 2010). Furthermore, left hippocampal GMV was correlated with AM performance in both HR and MDD groups, but not in controls. It is possible that reduced variance in both hippocampal volume and in the percentage of specific AMs recalled in the control group prevented the detection of such a relationship between these variables. In HRs and MDDs, larger hippocampal volume was associated with a higher percentage of specific AMs and fewer categorical AMs recalled, indicating improved AM performance with larger hippocampal volume. The hippocampus is critically involved in AM retrieval (Svoboda et al., 2006), and the results of the current study suggest that structural alterations within the hippocampus are functionally significant and directly related to AM overgenerality in depressed and high-risk participants. We cannot unequivocally infer causality from correlational data, however, and longitudinal studies are needed to examine the temporal relationship between the onset of reduced hippocampal volume and that of AM overgenerality. Furthermore, longitudinal studies would allow direct testing of the hypothesis raised by our results that reduced hippocampal volume combined with reduced AM specificity may further predict which HR participants ultimately will develop MDD.

Left precuneus GMV correlated positively the percent of specific and negatively with the percent of categorical AMs recalled in MDDs but not in HRS or controls. This region is involved in the task-first-person perspective and during self-referential processing (Cavanna and Trimble, 2006), as well as during the retrieval of specific relative to general AMs (Addis et al., 2004). That the correlation between precuneus GMV and AM overgenerality was evident only in the MDDs suggests that the impairment in specific AM recall involves a broader network of structures during the active disease state. Like the middle temporal gyrus, the precuneus also forms an integral part of the default mode network (Buckner et al., 2008).

Several limitations of this study warrant discussion. Although FreeSurfer performs valid and reliable parcellations of sub-cortical structures that were pertinent to our study goals, parcellations of prefrontal structures do not correspond to regions typically reported in the AM literature (medial PFC), and therefore the FreeSurfer structure was selected which corresponded most closely to the cluster reported in the meta analysis (Martineili et al., 2013). Although the selected superiorfrontal region in FreeSurfer clearly incorporates the peak of the cluster reported in Martinelli et al. (2013), it is possible that the anatomical distribution of this cluster was not entirely confined to the corresponding FreeSurfer region. This limitation conceivable may have reduced our sensitivity for detecting correlations between this prefrontal region and AM performance. It could also be the case, however, that mesiotemporal lobe structures, such as the hippocampus, are more important for AM recall than prefrontal structures. Better parcellation routine of the PFC within FreeSurfer is necessary to better test whether a relationship exists between AM recall performance and prefrontal structures. Additionally, our sample size was relatively small for a volumetric study, and the groups were not balanced for gender. Our use of gender as a covariate in the analyses mitigated this limitation by reducing possible confounding effects of gender. Nevertheless, larger studies with balanced numbers of males and females would allow for examination the interaction between gender and diagnosis on these correlations. Finally, we did not detect a significant correlation between GMV and the valence of recalled AMs. Our sensitivity for detecting

Fig. 3. Relationship between precuneus volume and AM recall in MDD participants. (a) Sagital anatomical MRI slice showing the FreeSurfer precuneus mask overlay. (b–c) Correlation between left precuneus GMV (mm³) and (b) percent of AMs recalled that were considered ‘specific’ and (c) percent of AMs recalled that were considered ‘categorical’ in MDD participants.

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such a relationship may have been reduced by the limitation that available meta-analyses addressed AM recall more broadly and did not separately examine different emotional valences of AMs. It is conceivable that regions which play more prominent roles in emotional regulation or experience [such as the amygdala and anterior cingulate cortex (Sander et al., 2003; Rolls et al., 2008)] would be associated with the ability to recall differently valenced memories, and future studies may benefit from selecting ROIs which include regions critical for emotional AM recall to investigate this construct.

This is the first study directly associating impairments in AM recall with neuromorphometric abnormalities found in unmedicated, early-onset MDD and HR participants. The results from this study allow us to elucidate brain structures involved in the pathophysiology of and risk for depression and provide insight into how these structural differences affect cognition. The finding that both MDD and HR participants recall fewer specific AMs and that the ability to recall these AMs is correlated with left hippocampal volume may impact efforts to address AM deficits faced by MDD and HR participants.

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