Autobiographical Deficits Correlate with Gray Matter Volume in Depressed and High Risk Participants

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Abstract Word Count: 190
Manuscript Word Count: 3,500
Number of Tables: 2
Number of Figures: 3
Supplemental Information: 0
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 fMRI. 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 to 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 (Baare *et al.*, 2010, Sheline *et al.*, 2003) and parahippocampal (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 between 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 autobiographical memory recall in healthy individuals (Martinelli et al., 2013), such as the hippocampus, medial PFC, and cingulate cortices would be reduced in MDD and HR participants compared to controls, and that volumes in these regions would correlate with AM performance. Specifically, we predicted larger volumes in medial temporal and prefrontal regions 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 recall overall and did not examine different valences separately (Kim, 2012, Martinelli et al., 2013, Svoboda et al., 2006), we did not have specific predictions as to whether these regions would be correlated with the valence of recalled AMs, and thus conducted an exploratory analysis. Elucidating these relationships may facilitate our understanding of the pathophysiology underlying 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.
Methods and Materials

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), psychiatrically 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 previous 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 advertisements, underwent medical and psychiatric screening evaluations at the Laureate Institute for Brain Research, which included the Structural Clinical Interview for DSM-IV-TR disorders (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 medical or neurological disorders, exposure to any medication likely to influence cerebral function or blood flow within three weeks, and meeting DSM-IV-TR criteria for drug/alcohol abuse within the previous one year or alcohol/drug dependence (excepting nicotine) within the lifetime. Additional exclusion criteria applied to control 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 procedures, 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 version 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).

**Autobiographical Memory 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, Young et al., 2013b). Briefly, participants were presented with an emotionally valenced or neutral cue word for 12s (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 specificity and valence. AM recall was compared to a semantic example generation condition in which participants were presented with an emotionally valenced or neutral cue word for 12s (30 cues; 10/valence) and instructed to think of seven examples from the presented category, then rate the ease with which they generated examples and the number of examples generated. Cue presentation was randomized with the restriction that no two cues from the same valence could be presented sequentially. All cue words were matched for frequency of use in spoken English, and emotionally valenced words were matched on arousal ratings (Bradley and Lang, 1999). Following each cue presentation and set of ratings, participants engaged in a riser detection task (6s jittered presentation) involving non-word letter strings as a control for visual input/attention.

Following the scan, participants were presented with all AM cue words and asked to describe the memory for experimenter KY to corroborate participants’ specificity ratings.
Memories were categorized as being either specific (memory for an event that occurred at an identified place and lasted up to one day), categorical (category of events containing several episodes without reference to one specific event), extended (extended period without reference to a specific event within the time frame), semantic (fact without an associated event) (Williams et al., 2007, Williams and Dritschel, 1988), or as “can’t recall” if the participant was unable to recall the memory retrieved during fMRI. The experimenter was blind to diagnosis at the time of rating.

**Image Acquisition**

Blood-oxygenation-level-dependent (BOLD) fMRI and anatomical scans were conducted on a 3T GE Discovery MR750 scanner and eight-channel receive-only head coil (GE Healthcare, USA). The whole brain high-resolution T1 weighted anatomical MRI scans were acquired for GMV analysis with the following parameters: 120 1.2mm thick slices acquired axially, repetition time (TR)=5ms, echo time (TE)=1.93ms, flip angle=8°, matrix=256x256, field-of-view (FOV)=24cm, in-plane voxel resolution=0.94mm².

**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 individuals 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 both 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 parcellation 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., USA), and all analyses were corrected for multiple comparisons (Bonferroni) at $p_{corrected} < 0.05$. 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 (Chen et al., 2007, Seidlitz and Diener, 1998). For demographic information, clinical characteristics, and GMV of the 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, Neutral) examined whether the participant groups differed on their AM performance. Only specific and categorical AMs were included because there were too few occurrences of the other memory types to allow for sufficient power to detect differences, and because these are the memory types that consistently show differences between controls and MDDs (van Vreeswijk and de Wilde, 2004, Williams 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 2a; Fs(2,107)<2.29, ps>0.16). However, the gender distribution differed significantly between groups ($\chi^2=4.32, p=0.04$). With regard to clinical characteristics (Table 2a), HRs and controls did not differ from each other on POMS or HDRS scores (ts(68)<0.79, ps>0.43) while MDDs had higher scores on these measures than both HRs (ts(63)>6.18, ps<0.001) and controls (ts(81)>8.18, ps<0.001). With regard to the percent of AMs recalled for each memory type (Table 2a), the Bonferroni corrected threshold for significance was p<0.008. Groups did not differ on the percent of memories classified as extended, semantic, none, or unable to recall post-scan (Fs(2,107)<2.24, ps>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 (ts(81)>48.7, ps<0.001) or HRs (ts(68)>21.6, ps<0.001), while MDDs and HRs did not differ from each other on these measures (ts(63)<1.69, ps>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, Categorical) and Valence (Positive, Negative, Neutral) as the within-subjects variables and Group (controls, HR, MDD) as a between-groups variable (Table 2b) 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 *a priori* t-tests revealed that MDDs recalled fewer positive and more negative AMs
overall than control (ts(81)>15.9, ps<0.001) or HR participants (ts(63)>3.36, ps<0.008), but did not differ on the percent of neutral AMs recalled (controls ts(81)=1.62, ps=0.18; HRs ts(63)=1.36, p=0.25), and HRs and controls did not differ from each other on these measures (ts(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 (ts(81)=8.51, p<0.001) in left middle temporal gyrus, while 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 to both MDDs (t(81)=5.02, p<0.001) and HRs (t(68)=3.56, p<0.001) while 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-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-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 towards 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), while 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 to controls showed a trend towards different correlations between precuneus GMV and specific (p=0.08) and categorical AMs (p=0.07), while 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., 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 high-familial risk 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 (Martinelli et al., 2013), 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 unmedicated 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, Ma et al., 2012, Peng et al., 2011). 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 (Baare et al., 2010, Sheline et al., 2003). 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 taking the 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 the current study warrant discussion. While 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 (Martinelli et al., 2013). While 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 prefrontal cortex 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 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 (Rolls et al., 2008, Sander et al., 2003)) 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.
Acknowledgements

This research was supported by the Laureate Institute for Brain Research and The William K. Warren Foundation. The funders had no influence on the design or conduct of the study, collection, management, analyses, or interpretation of the data, or in the preparation, review or approval of the manuscript.

Financial Disclosures

WCD is currently an employee of Johnson & Johnson, Inc. The other authors have no financial conflicts of interest or disclosures to declare.


Figure Captions

Figure 1: Medial PFC / BA 10 region selected for volumetric analysis

The FreeSurfer superiorfrontal mask overlay is shown on an axial anatomical MRI slice. Cross hairs correspond to the locus identified by coordinates of the peak medial PFC/ BA 10 cluster identified in the meta-analysis conducted by Martinelli et al., 2013, which characterized regions where hemodynamic activity consistently increased during autobiographical memory recall tasks.

Figure 2: Relationship between hippocampal volume and autobiographical memory recall in MDD and HR participants

(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.

Figure 3: Relationship between precuneus volume and autobiographical memory recall in MDD participants

a) Sagittal anatomical MRI slice showing the FreeSurfer precuneus mask overlay. (b-c) Correlation between left precuneus gray matter volume (mm$^3$) and b) percent of AMs recalled that were considered “specific and c) percent of AMs recalled that were considered “categorical” in MDD participants.
Table 1: Regions recruited during specific AM recall in a recent meta-analysis, along with the corresponding FreeSurfer masks, and the regional gray matter volumes (mm\(^3\)) for each group.

<table>
<thead>
<tr>
<th>Area</th>
<th>FreeSurfer Mask</th>
<th>Volume (mm(^3))</th>
<th>F (2,107)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>HR</td>
<td>MDD</td>
<td></td>
</tr>
<tr>
<td>L Medial PFC / BA10</td>
<td>23,184 (3,550)</td>
<td>23,170 (3,068)</td>
<td>22,047 (3,202)</td>
<td>1.35</td>
</tr>
<tr>
<td>R Posterior Cingulate</td>
<td>3,464 (624)</td>
<td>3,306 (622)</td>
<td>3,116 (455)</td>
<td>2.49</td>
</tr>
<tr>
<td>L Middle Temporal G</td>
<td>11,364 (1,983)</td>
<td>11,828 (1,741)</td>
<td>10,237 (1,136)*#</td>
<td>5.86</td>
</tr>
<tr>
<td>L Hippocampus</td>
<td>3,959 (406)</td>
<td>3,603 (404)*</td>
<td>3,512 (348)*</td>
<td>12.2</td>
</tr>
<tr>
<td>L Parahippocampus</td>
<td>2,235 (351)</td>
<td>2,151 (344)</td>
<td>2,267 (357)</td>
<td>0.89</td>
</tr>
<tr>
<td>L Precuneus</td>
<td>9,894 (1,297)</td>
<td>9,817 (1,474)</td>
<td>9,444 (1,727)</td>
<td>1.03</td>
</tr>
<tr>
<td>R Cerebellum</td>
<td>33,374 (7,110)</td>
<td>36,242 (6,258)</td>
<td>34,089 (6,039)</td>
<td>1.66</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate one standard deviation. * and Bolded regions indicate a significant difference from the control group at p\(_{\text{corrected}}\) < 0.05. # indicates a significant difference from the HR group at p\(_{\text{corrected}}\) < 0.05.

a Results taken from Table 2 in (Martinelli et al., 2013). Coordinates correspond to the stereotaxic array of Talairach & 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. Abbreviations: BA = Brodmann Area; G = gyrus; HR = high-risk; L = left; MDD = major depressive disorder; PFC = prefrontal cortex; R = right;
Table 2: a) Demographic, clinical, and memory characteristics of each group in the final sample
b) Valence of the recalled memories for each group

<table>
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<tr>
<th>Demographics</th>
<th>Controls</th>
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<th>MDD</th>
<th>F(2,107)</th>
<th>p value</th>
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<tbody>
<tr>
<td>n [% female]</td>
<td>45 [51]</td>
<td>22 [70]</td>
<td>40 [63]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>31.1 (9.02)</td>
<td>30.6 (9.34)</td>
<td>35.5 (9.10)</td>
<td>2.12</td>
<td>0.24</td>
</tr>
<tr>
<td>WASI</td>
<td>113 (9.27)</td>
<td>109 (7.15)</td>
<td>109 (12.1)</td>
<td>2.29</td>
<td>0.16</td>
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<table>
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<th>Clinical Characteristics</th>
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<th>MDD</th>
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<th>p value</th>
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<tr>
<td>HDRS</td>
<td>0.42 (1.22)</td>
<td>0.63 (1.31)</td>
<td>19.2 (6.27)*#</td>
<td>295</td>
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<td>POMS total</td>
<td>-12.3 (8.77)</td>
<td>-10.5 (10.7)</td>
<td>53.0 (39.3)*#</td>
<td>87.0</td>
<td>&lt;0.001</td>
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<table>
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<th>Control Task Performance</th>
<th>Controls</th>
<th>HR</th>
<th>MDD</th>
<th>F(2,107)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td># Examples Positive Categories</td>
<td>5.89 (0.90)</td>
<td>5.59 (1.02)</td>
<td>5.63 (1.03)</td>
<td>1.36</td>
<td>0.19</td>
</tr>
<tr>
<td># Examples Negative Categories</td>
<td>5.58 (1.08)</td>
<td>5.10 (1.01)</td>
<td>5.20 (1.13)</td>
<td>1.35</td>
<td>0.19</td>
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<tr>
<td># Examples Neutral Categories</td>
<td>6.23 (0.82)</td>
<td>6.03 (0.78)</td>
<td>6.09 (1.01)</td>
<td>1.33</td>
<td>0.20</td>
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<tr>
<td>% Positive Examples Easy to Generate</td>
<td>84.7 (12.8)</td>
<td>83.8 (17.5)</td>
<td>80.9 (19.5)</td>
<td>1.53</td>
<td>0.22</td>
</tr>
<tr>
<td>% Negative Examples Easy to Generate</td>
<td>82.7 (13.4)</td>
<td>84.9 (21.0)</td>
<td>83.0 (15.0)</td>
<td>1.42</td>
<td>0.25</td>
</tr>
<tr>
<td>% Neutral Examples Easy to Generate</td>
<td>88.1 (12.3)</td>
<td>86.5 (11.8)</td>
<td>87.1 (18.7)</td>
<td>1.54</td>
<td>0.22</td>
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<table>
<thead>
<tr>
<th>AM Recall</th>
<th>Controls</th>
<th>HR</th>
<th>MDD</th>
<th>F(2,107)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Specific</td>
<td>59.7 (12.0)</td>
<td>43.7 (13.2)^*</td>
<td>40.1 (13.8)^*</td>
<td>26.0</td>
<td>&lt;0.001</td>
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<tr>
<td>Categorical</td>
<td>15.6 (6.95)</td>
<td>31.0 (10.43)^*</td>
<td>34.3 (12.0)^*</td>
<td>39.2</td>
<td>&lt;0.001</td>
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<tr>
<td>Extended</td>
<td>3.80 (3.59)</td>
<td>5.46 (3.80)</td>
<td>2.82 (2.72)</td>
<td>0.76</td>
<td>0.47</td>
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<tr>
<td>Semantic</td>
<td>7.21 (5.54)</td>
<td>8.09 (6.50)</td>
<td>6.63 (5.57)</td>
<td>0.47</td>
<td>0.62</td>
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<tr>
<td>No Memory</td>
<td>1.41 (2.13)</td>
<td>1.85 (3.18)</td>
<td>3.14 (5.22)</td>
<td>2.24</td>
<td>0.11</td>
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<tr>
<td>Can't Remember</td>
<td>12.43 (6.53)</td>
<td>10.1 (5.78)</td>
<td>12.85 (7.61)</td>
<td>1.13</td>
<td>0.33</td>
</tr>
</tbody>
</table>

b) Memory Type | Valence | Controls | HR  | MDD  | F(2,107) | p value |
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<tbody>
<tr>
<td>Specific</td>
<td>Positive</td>
<td>58.7 (13.2)</td>
<td>57.2 (11.7)</td>
<td>48.2 (12.5)</td>
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<tr>
<td></td>
<td>Negative</td>
<td>30.3 (9.82)</td>
<td>31.7 (12.1)</td>
<td>37.6 (13.9)</td>
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<tr>
<td></td>
<td>Neutral</td>
<td>11.0 (8.66)</td>
<td>11.2 (8.06)</td>
<td>14.2 (9.98)</td>
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<tr>
<td>Categorical</td>
<td>Positive</td>
<td>60.5 (20.3)</td>
<td>59.4 (14.4)</td>
<td>49.5 (14.1)</td>
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<tr>
<td></td>
<td>Negative</td>
<td>18.9 (13.2)</td>
<td>22.0 (12.2)</td>
<td>30.9 (14.5)</td>
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<tr>
<td></td>
<td>Neutral</td>
<td>20.5 (19.3)</td>
<td>18.6 (13.4)</td>
<td>19.6 (15.2)</td>
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<tr>
<td>Overall</td>
<td>Positive</td>
<td>59.0 (10.9)</td>
<td>58.1 (10.4)</td>
<td>50.0 (8.47)#</td>
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<td></td>
<td>Negative</td>
<td>27.2 (8.40)</td>
<td>28.3 (9.88)</td>
<td>33.0 (10.4)#</td>
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<tr>
<td></td>
<td>Neutral</td>
<td>13.6 (8.87)</td>
<td>13.4 (9.54)</td>
<td>16.8 (11.3)</td>
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</tr>
</tbody>
</table>

Numbers in parentheses indicate one standard deviation of the mean.
* indicates a significant difference from the control group at $p_{\text{corrected}} < 0.05$
# indicates a significant difference from the HR group at $p_{\text{corrected}} < 0.05$
Abbreviations: AM = autobiographical memory; HDRS = Hamilton Depression Rating Scale; HR = high-risk; MDD = major depressive disorder; POMS = Profile of Mood States; WASI = Wechsler Abbreviated Scale of Intelligence