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Neural changes associated with the generation of specific past and future events in depression

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ABSTRACT

It is well established that individuals affected by depression experience difficulty in remembering the past and imagining the future. This impairment is evident in increased rumination on non-specific, generic events and in the generation of fewer specific events during tasks tapping past and future thinking. The present fMRI study investigated whether neural changes during the construction of autobiographical events was evident in depression, even when key aspects of performance (event specificity, vividness) were matched. We employed a multivariate technique (Spatiotemporal Partial Least Squares) to examine whether task-related whole brain patterns of activation and functional connectivity of the hippocampus differed between depressed participants and non-depressed controls. Results indicate that although the depression group retained the ability to recruit the default network during the autobiographical tasks, there was reduced activity in regions associated with episodic richness and imagery (e.g., hippocampus, precuneus, cuneus). Moreover, patterns of hippocampal connectivity in the depression group were comparable to those of the control group, but the strength of this connectivity was reduced in depression. These depression-related reductions were accompanied by increased recruitment of lateral and medial frontal regions in the depression group, as well as distinct patterns of right hippocampal connectivity with regions in the default and dorsal attention networks. The recruitment of these additional neural resources may reflect compensatory increases in post-retrieval processing, greater effort and/or greater self-related referential processing in depression that support the generation of specific autobiographical events.

1. Introduction

Autobiographical memory (AM) can allow us to relive a specific moment in time in exquisite detail. However, several psychiatric disorders, including post-traumatic stress disorder (for a review see Brewin, 2011), bipolar disorder (e.g., Mansell and Lam, 2004) and depression (Williams and Broadbent, 1986), are associated with an increased likelihood of overgeneral memory. That is, when asked to describe a specific past event, individuals with depression are more likely to generate repeated or categorical events (e.g., family dinners with Aunt Elaine) rather a specific experience (e.g., Aunt Elaine's 70th birthday last September at her house). Overgeneral memory is not limited to those individuals currently in a depressive episode; individuals at high risk for depression (Young et al., 2013), in remission (Brittlebank et al., 1993; Mackinger et al., 2000; Watkins and Teasdale, 2001) or exhibiting dysphoria (MacLeod and Cropley, 1995) also exhibit decreased AM specificity.

There is increasing evidence to suggest that overgeneral AM may be related to neural changes associated with depression. Specifically, some key regions comprising the AM retrieval network (also known as default network; Andrews-Hanna, 2012; Spreng et al., 2013; Svoboda et al., 2006), that support the retrieval of memories of specific AMs, have also been implicated in studies of depressed populations. For instance, lateral prefrontal cortex (PFC) is thought to mediate the strategic search for a specific memory (Moscovitch, 1992) while medial PFC processes self-referential aspects of the memory (Cabeza and St Jacques, 2007). Neuroimaging studies have revealed that depression is associated with structural abnormalities and reduced metabolism and perfusion in both lateral and medial PFC regions (Lemogne et al., 2012; Steele et al., 2007). In line with these observations, depressed individuals consistently exhibit poorer performance on measures of executive function (for a meta-analysis see Snyder, 2013), and executive dysfunction has been linked to overgeneral AM in depression (Dagleish et al., 2007). The integrity of medial temporal lobe (MTL) function is also particularly relevant, given evidence suggesting an association of the hippocampus and the episodic richness of AMs. For instance, the vividness of AMs has been associated with the degree of hippocampal activity in healthy young (Addis et al., 2004; Addis and Schacter, 2008) and older adults

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(e.g., Addis et al., 2011; St Jacques et al., 2012). Moreover, the episodic richness of AMs is typically reduced in populations with hippocampal damage, including temporal lobe epilepsy (St-Laurent et al., 2014) and hippocampal amnesia (Hassabis et al., 2007). With respect to depression, reduced hippocampal volume in depressed individuals is well established (Campbell and MacQueen, 2004) and emerging evidence suggests that memory-related hippocampal activity may also be compromised (Fairhall et al., 2010).

To date, only a few studies have examined whether neural dysfunction may underpin overgeneral AM in depression. Zhu et al. (2012) investigated changes in resting state functional connectivity in depression, and found that the degree of overgeneral AM correlated with reduced connectivity of medial parietal regions. This observation is relevant given that medial parietal regions such as the precuneus appear to be involved in both episodic memory and visuospatial imagery (Cavanna and Trimble, 2006), and more direct evidence indicating the precuneus supports episodic memory for imageable words (Fletcher et al., 1995), visual scenes (e.g., Johnson and Johnson, 2014), imagined scenes (Hassabis et al., 2007) and vivid, contextually detailed, specific AMs (Addis et al., 2004; Gardini et al., 2006; Gilboa et al., 2004). Moreover, robust differences in resting state connectivity between non-depressed and depressed populations have led researchers to propose that hyperactivation of the default network is directly linked to greater levels of self-generated, ruminative thought (cf. context regulation hypothesis, Andrews-Hanna et al., 2014; Smallwood and Andrews-Hanna, 2013; Whitfield-Gabrieli and Ford, 2012). Crucially, this may be accompanied by a deficit in regulating the content of self-generated thought (Andrews-Hanna et al., 2014; Smallwood and Andrews-Hanna, 2013).

Examining task-related neural differences, Whalley et al. (2012) found that while depressed individuals engaged many regions in the AM network, they also exhibited reduced activity in lateral PFC relative to control participants. However, no MTL activity was evident in this study, likely due to the use of a paradigm involving recognition of words taken from participants' transcripts of traumatic AMs rather than the elaborative retrieval of specific AMs. Young et al. (2013, 2012) have reported reduced prefrontal activity in depression during the retrieval of specific AMs. Moreover, the authors also reported that the engagement of the MTL during AM retrieval was reduced in depressed relative to control individuals (Young et al., 2012). Notably, however, the group difference in MTL activity was not evident when the analysis was restricted to only specific AMs, suggesting that the group difference may reflect an increased number of generic AMs for the depressed group, and/or differences in the vividness of the AMs retrieved. Therefore, one aim of this study was to examine whether depression is associated in differences in neural activity and connectivity even when specificity and vividness of AMs is matched.

In addition to lowered specificity in AM, the ability to imagine simulations of future events is similarly affected. Depressed individuals tend to generate future events that are generic in nature (MacLeod and Byrne, 1996; MacLeod et al., 2005; Williams et al., 1996) and are reduced in episodic detail (King et al., 2011) and vivid mental imagery (Holmes et al., 2008) compared to non-depressed controls. These observations are consistent with the notion that access to episodic AM is important for constructing future simulations and that past and future events rely on similar cognitive processes and neural networks (cf. constructive episodic simulation hypothesis; Schacter and Addis, 2007; Schacter et al., 2012, 2013). Indeed, the default network is robustly engaged by future simulation as it is during AM retrieval (Addis et al., 2007; Schacter et al., 2012). As with AM for past events, the PFC and MTL are thought to mediate the strategic generation of a future event and its episodic richness, respectively. However, whether the reduced specificity of past and future autobiographical events in depression is associated with similar patterns of neural dysfunction remains unclear. Interestingly, however, some key neural differences between AM retrieval and future simulation also exist. For example, MTL and PFC regions are often more engaged during future thinking than past remembering (Addis et al., 2011; Addis and Schacter, 2008; Okuda et al., 2003; Schacter et al., 2012), possibly reflecting the fact that future simulation recruits additional processes such as intentional thought (Okuda et al., 2003) and the recombination of details into a coherent simulation (Gaesser et al., 2013). Therefore, it is possible that group differences in neural activity may be more apparent during future simulation than AM retrieval.

To address whether the specificity of past and future events in depression reflects neural dysfunction, particularly in default network regions linked to the specificity of autobiographical events, depressed individuals and matched control participants completed an fMRI study during which they generated specific past and future events. Using Partial Least Squares (PLS; McIntosh and Lobaugh, 2004), we assessed whether group differences in neural activity during AM retrieval were evident even when the specificity and the vividness of past events were matched across groups. Moreover, we investigated whether neural differences were also evident during the generation of future events and if so, whether group differences were more apparent during the future condition than the past condition. Using PLS also allowed us to explore whether task-related connectivity of key regions, such as the MTL, differed across groups.

2. Materials and methods

2.1. Participants

A total of 33 right-handed participants were included in the study. Seventeen participants comprised the depression group, all of whom had a history of depression and nine of whom scored in the mild to severe range of depression on the Beck Depression Inventory II (BDI-II; Beck et al., 1961) at the time of testing (see Table 1). Fifteen had received a diagnosis from a health professional. The remaining two participants self-reported a history of depression, but importantly they both scored in the moderate to high severity ranges of depression on the BDI-II at the time of testing. Eight of the seventeen participants in the depression group were currently taking medication for depression.

The control group comprised 16 participants without a history of depression who all scored below the cut-off for mild depression on the BDI-II. Table 2 provides a summary of the demographic and psychological characteristics of the depression and control groups. The groups did not differ significantly in terms of age, $F(1, 31)=2.81$; $p=.104$, sex, χ^2 $(1, N=33)=.004$; $p=.948$, education, $F(1, 31)=.35$; $p=.556$, or IQ as estimated by performance on the North American Adult Reading Test (NAART), *Welch's* $F(1, 20.24)=.61$; $p=.453$. Importantly, however, participants in the depression group reported having experienced on average 3 episodes of depression, while non-depressed controls had never been depressed. Moreover, scores on the BDI-II and BAI confirmed that the depression group presented with significantly lower mood than controls in the two weeks prior to taking part in the study, *Welch's* $F(1, 19.07)=24.80$; $p<.001$, as well as greater anxiety one week prior to testing, *Welch's* $F(1, 18.21)=18.74$; $p<.001$.

History of traumatic brain injury, alcohol or substance dependency, psychiatric illness (other than depression or comorbid anxiety), claustrophobia, current pregnancy and presence of pacemaker or any other metal implants constituted exclusion criteria for both groups. The study was approved by the local ethics committee

Table 1
Depression, anxiety and medication status of the depression group.

Depression status	*N*	Mean BDI-II (range)	Mean BAI (range)	Mean number depressive episodes (range)	Number currently/ previously medicated
Severe	4	35.00 (32–40)	18.50 (12–33)	4 (2–5)	2/1
Moderate	3	23.67 (22–26)	18.00 (12–25)	3 (1–5)	0/0
Mild	2	16.00 (15–17)	13.50 (5–22)	2.5 (2–3)	2/0
Minimal	8	8.25 (1–13)	9.13 (3–24)	3.5 (1–9)	4/3

Note: BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory II.