Remember the Good Times? Biased Autobiographical Memory in Depression

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We live most of our lives looking through rose-colored glasses, preferentially recalling positive over negative memories, to maintain a more positive and resilient mood (1). This bias breaks down in depression, such that negative information is favored over positive—a shift that may maintain the illness (2). The depressive recall bias extends as well to the nature of memories, such that positive memories are less specific (i.e., overgeneral). As any clinician can attest, the pervasiveness of this shift can become a major impediment to effective therapy. Despite the frequency with which this clinical observation is made, how these biases are implemented in the brain has not been clear. Also unclear is whether these biases reflect the acute illness, persist despite remission of symptoms, or represent a vulnerability to depression (e.g., due to family history). In addressing these questions, we can not only learn about the biology of depression, but we can also draw important lessons about neuroimaging approaches in psychiatry and develop a heuristic that could help patients understand their own memory biases.

In this issue of the *Journal*, Young and colleagues take on this challenge (3), extending their earlier work in this area. They asked study participants undergoing functional MRI to retrieve positive, negative, or neutral memories in response to a cue, and to rate the specificity of these memories. Brain activity was compared with a condition in which participants were instructed to generate example emotional scenarios. The sample comprised an impressive 160 unmedicated participants—a large sample for clinical neuroimaging studies—in four groups: healthy control subjects, individuals with a high risk of depression (due to family history), patients with remitted depression, and patients with current depression. Although sample sizes for individual groups were similar to those of other imaging studies, including all of these groups greatly increased the authors' ability to draw conclusions about whether findings reflected the acute illness, trait abnormalities (i.e., in current and remitted depression), or a vulnerability state (i.e., in the high-risk participants). This reflects a significant improvement over their previous studies, which did not include all four groups and had only 16 participants per group (4, 5). Herein lies the first lesson for psychiatric neuroimaging, namely, that comparisons across multiple groups are necessary for understanding the specificity of findings (be it across phases of illness or across different diagnoses), and conclusions are difficult to draw in the small sample sizes that are still common in the field. Such studies with large sample sizes raise expectations of the field as a whole and will result in findings that are more likely both to have an impact and to be replicated.

For positive memories, patients with current and remitted depression recalled fewer positive specific memories than either the healthy control subjects or the high-risk participants, suggesting a persistent abnormality at the behavioral level, but not one reflected in familial risk alone. Depressed patients also recalled more specific negative memories than did healthy control subjects, while the other groups had intermediate scores.

The authors' primary focus for functional MRI activation analyses was the amygdala, in light of its role in emotion-biased memory encoding (6). Only currently depressed patients failed to activate the amygdala during positive memory recall, and those patients whose amygdala response was more blunted reported greater depressive symptoms and less specific memory recall. Hence, while amygdala activity may help explain the positive memory recall deficit in depressed patients, it cannot by itself explain the similar behavioral deficit in patients with remitted depression. One answer may come from looking at the amygdala's network context, as investigated through functional connectivity. While currently depressed patients were characterized by decreased amygdala connectivity to the dorsal anterior cingulate and posterior cingulate, the nearby precuneus was underconnected to the amygdala in both the current and remitted depression groups. Thus, either failure to engage the amygdala or activation that is normal but occurs in the context of under-connectivity to medial parietal regions implicated in memory may account for the decreased recall of positive memories in patients with both current and remitted depression. Activation in the hippocampus was not directly assessed in the authors' analysis, but it may also be important for understanding emotional memory.

With respect to negative memories, the authors found that amygdala activity was increased in all groups relative to the control group, but that only the depressed group reported significantly greater recall of negative memories than the

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control group. Depressed patients' amygdalae, however, were overconnected to the dorsal cingulate, posterior cingulate, precuneus, and several other regions relative to all other groups. Thus, simple overactivation of the amygdala (which thus may reflect a familial risk for depression) does not result in preferential recall of negative memories unless it is accompanied by greater engagement of medial parietal putative memory-related regions. Herein lies the second lesson for psychiatric neuroimaging, namely, that studying brain activation within network contexts is critical for understanding neural mechanisms, and that having a behavioral measure may greatly facilitate interpretation of findings.

This work also highlights the importance of positive memories in depression, emphasizing the fact that amygdala hypoactivity reflects a current depressive state (although behavioral reports were more consistent with a persistent abnormality). This finding parallels work in healthy individuals showing that short-term antidepressant administration increases amygdala responses to positive stimuli and recall of positive words (7). In depression, early improvements in recognition of positive stimuli with antidepressant treatment predict ultimate mood improvement (7). In animal models, optogenetically triggered replay of positive memories through hippocampal stimulation specifically increased animals' resilience to stress-induced behavioral abnormalities, along with activity in the amygdala and ventral striatum (8). Interestingly, in both the human emotional bias work and animal optogenetic memory replay lines of research there was also an asymmetry such that effects on positive material was not the opposite of changes in negative material, suggesting a potentially unique utility to our ability to remember the good times.

Young et al. focus on amygdala-dorsal cingulate connectivity as a potential mechanism for biased memory recall, which they argue is due to altered salience signals during recall (decreased for positive and increased for negative). It is important to note that this is an interpretation of the findings, but not one that the data can directly prove. However, it provides an organizing hypothesis that may inform future work, including targeting of memory recall for therapeutic purposes. The authors have already reported on one potential avenue for this using neurofeedback trained on amygdala activity during positive memory recall (9). Their pilot study found that training resulted in reduced depressive symptoms compared with a control neurofeedback condition. Salience, when considered with respect to memory, is also not a unitary phenomenon. For example, both perceptual and semantic (conceptual) salience interact to influence memory recall (10). The framework of blunted salience for positive material (resulting in fewer specific positive memories), and exaggerated salience for negative material (resulting in more specific negative memories) also provides a useful heuristic

explanation for a common clinical phenomenon. It may help patients understand their own experiences of depression, take them in context, and explicitly target them during therapy. Important for both clinicians and patients, the effects shown in this study reflect biases and not absolute inabilities to recall positive memories. Thus, this capacity is likely something that can be improved. As such, understanding the source of altered salience in depressed patients, in the context of research or clinical care, may provide alternate means to increase it for positive memories and decrease it for negative memories (2), including through conventional cognitive-behavioral therapy techniques.

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