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Regulation of Emotion in Major Depressive Disorder

Hedy Kober^{1,*} and Kevin N. Ochsner²

¹ Yale University, Departments of Psychiatry and Psychology

² Columbia University, Department of Psychology

The ability to regulate emotion is central to everyday functioning, and has been studied extensively in healthy adults in the last two decades. One conclusion supported by this research is that various cognitive strategies can be used to effectively regulate both positive and negative emotion (which is consistent with a wealth of clinical work on the efficacy of cognitive therapy). More recently, basic neuroimaging work using now-well-established experimental paradigms has increased our understanding of the neural systems involved in the cognitive regulation of emotion. The majority of this research has focused on a specific cognitive regulation strategy known as reappraisal, which involves reinterpreting the meaning of stimuli in ways that alter one's affective responses to them. Taken together, over 35 neuroimaging studies of reappraisal in healthy adults published in the past 9 years have highlighted the interaction between subcortical systems thought to generate emotion and prefrontal systems thought to implement various kinds of cognitive control processes (for reviews see (1, 2)).

More specifically, these studies have provided several insights into the specific roles that these systems play in emotion regulation. For example, 1. The dorsolateral, ventrolateral, and medial prefrontal regions implicated in reappraisal largely overlap with those generally involved in “cold” forms of cognitive control, like working memory, attentional control, and response inhibition (3), 2. These prefrontal regions are thought to modulate activity in subcortical regions implicated in generating emotion (4), 3. The particular combination of regions involved in emotion generation and regulation varies as a function of the kind of stimuli used (e.g., personalized memories, movies, images), the kinds of affective responses generated (e.g. positive or negative emotion, craving), the specific regulation strategy that is implemented (e.g., reappraisal, distraction), and the traits of the individual attempting to implement them (e.g., high trait-rumination). Together, findings like these have led to the formulation of models of the psychological and neural bases of reappraisal and the cognitive control of emotion more generally (1, 2, 5).

With these models in hand, over the past few years, researchers have begun translating this work into a clinical neuroscience context, to investigate how different patients populations may be characterized by specific patterns of dysfunction in the neural mechanisms of emotion generation and/or regulation. Such clinical investigations have examined forms of cognitive emotion regulation in patients with substance use disorders, anxiety disorders, and borderline personality disorder, among others (e.g., (6)). To date, the greatest attention has been paid to Major Depressive Disorder (MDD), in which emotion regulation is considered a core deficit. Indeed, the hallmark features of MDD diagnosis are sustained negative affect and persistent reduction in positive affect. In addition, influential

*Address correspondence to Hedy Kober PhD, Clinical and Affective Neuroscience Lab, Department of Psychiatry, Yale University, One Church St. Suite 701 New Haven, CT 06520.

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models of the neural circuitry in depression are quite consistent with basic models of emotion regulation, suggesting specific disruptions in the reciprocal cortical-limbic interactions that underlie emotion regulation (e.g., (5, 7)). Thus, studies of emotion regulation in MDD have used variants of the experimental paradigms established in studies with healthy adults. Two such studies have suggested that the regulation of negative emotion is more difficult for patients with MDD compared to healthy controls (8) but, that they are nevertheless able to reduce negative affect as well as regulate activity in amygdala and other affect-related regions (9).

In the current issue of *Biological Psychiatry*, Light et al report findings from a study of reappraisal in MDD (10). The data from this study have produced two prior reports that address related questions regarding the use of reappraisal to down-regulate negative emotions (11) and up-regulate positive emotion (12) in MDD. However, the present manuscript is the first to explore the down-regulation of positive emotion in MDD. In addition, it examines the relationship between the ability to down-regulate positive emotion pre-treatment (Time 1) and reductions in anhedonia symptoms after an 8-week pharmacological treatment (Time 2) and at a follow-up 6 months later (Time 3). This is a novel approach and such relationships have rarely been studied.

In their primary analysis, the authors compare neural activity in a regulation condition (“suppress positive”) with activity during a baseline condition (“maintain positive”), and report several findings. First, depressed participants show greater activity in right ventrolateral prefrontal cortex (rvlPFC) in the suppress vs. maintain condition, consistent with prior work. Second, although the two groups are not compared directly, healthy adults show a similar pattern in this region. Third, depressed participants with the least activity difference in rvlPFC in the suppress vs. maintain contrast exhibited the greatest reductions in anhedonia symptoms at Time 2, 8 weeks after pharmacological treatment onset (across medication types).

These results are the first of their kind, and it is exciting that neuroimaging data can be related in this way to symptom-specific changes following treatment. That being said, like many first steps in an interesting new direction, some questions are answered while others are raised, and the meaning of the results in the greater context of emotion regulation in depression is yet unclear. One question concerns the authors’ suggestion that “lower rvlPFC activity during positive suppress condition is more ‘normal,’” which is an intriguing hypothesis. However, it should be noted that healthy controls show greater rvlPFC activity in both the “positive maintain” and “positive suppress” conditions relative to the depressed group (rather than lower; as shown in their figure 2). One alternative hypothesis – given that decreased rvlPFC activity was observed in the “positive suppress” condition was *relative* to activity observed during the “positive maintain” condition – is that variability during “positive maintain” rather than “positive suppress” drives the relationship with reduced anhedonia at Time 2. A future analysis could add to our understanding of the reported finding by examining the relative contribution of each condition to the observed anhedonia change.

Another question concerns the fact that, as with many neuroimaging studies, it is possible that the observed effects hinge not only on the mechanisms that are involved in the generation and regulation of positive emotion, but also on the implementation of the regulation paradigm itself. This may be particularly salient in this case as reappraisal research has featured two broad “classes” of emotion regulation tasks that share stimuli and instructions but differ in timing. This is important, and it has been highlighted that the amount of time allotted for regulation influences the neural systems involved (1).

Furthermore, although rvIPFC activity could be a marker of regulatory effort, as the authors suggest, it may not necessarily be a marker of regulatory efficacy. Indeed, in the absence of self-reported emotion, our ability to draw strong conclusions about the efficacy of regulation is limited. While some might question the validity of self-reports, it is worth noting that they correlate with both physiological and neural markers of regulation (e.g., (6)). They are also a primary basis for the diagnosis of MDD as well as the anhedonia measure in the present report, and have been used to predict a variety of treatment outcomes (reviewed elsewhere). As such, self-reports of emotion could be used in future research to test whether changes in activity in vIPFC or other prefrontal regions really reflect reductions in affect – in conjunction with functional changes in subcortical affect-generating regions that were not reportedly modulated in the current report.

One last question concerns the way in which the present findings may relate to known abnormalities in resting metabolism as well as volume of many of the prefrontal and subcortical regions related to emotion generation and regulation. For example, it is possible that structural differences in rvIPFC volume or connectivity alter the way in which it communicates with affect-triggering regions in MDD. In turn, such differences may contribute to and further predict better or worse treatment outcomes. Future work combining methods like those used by Light et al with structural analyses may address these issues directly.

In summary, we appreciate the authors for bringing into focus questions about the regulation of positive emotion in MDD, and their relationship to pharmacological treatment outcome. Such questions are important for our developing understanding of this disorder as well as other disorders (e.g., bipolar disorder, substance-use). They also serve as the basis for future work comparing pharmacological to other forms of treatment (e.g., cognitive-behavioral, mindfulness-based treatments). Lastly, additional studies addressing these questions will be crucial to further advance our understanding of the interrelationship between negative emotion regulation, positive emotion regulation, and treatment-related change.

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