COMMENTARY

The Ups and Downs of Emotion Regulation

Cameron S. Carter

In the article by Kross *et al.* (1) in this issue of *Biological Psychiatry*, the authors report results from a functional magnetic resonance imaging study that focuses on the use of cognitive strategies for affect regulation. Although the study was conducted in healthy individuals, the results as well as the general approach—which draws upon a body of work from basic social, cognitive, and affective neuroscience—are likely to have important implications for understanding of major depression and how to treat it. A growing body of evidence implicates excessive activity and/or responsiveness in a limbic circuit that includes the subgenual anterior cingulate cortex (sgACC), medial prefrontal cortex (PFC), and the amygdala in depression. This systems neuroscience perspective has led to a number of imaging studies that suggest that excessive limbic activation is an illness biomarker and that, although different treatments (e.g., pharmacological vs. cognitive behavioral therapy [CBT]) have differential impact on this circuitry, successful outcomes are associated with reduction or elimination of limbic over-activity (2).

The present study uses a modified emotion regulation paradigm to investigate the impact of different affect-regulation strategies on activity in a depression-related limbic circuit. Previous studies of emotion regulation have mostly used normative pictures such as the International Affective Picture System (IAPS) picture collection or aversive stimuli such as electric shock to elicit negative affect. The authors note that these approaches might have limited relevance to depression where negative affect is often associated with personal memories and internal rumination related to these memories. The authors also note that previous imaging studies of emotion regulation have not often shown either engagement or modulation of the sgACC, which—as noted in the preceding text—has been shown to closely track depression across a wide range of studies and has become a target for deep brain stimulation in treatment refractory cases (3). Hence in the present study the authors elicited individualized painful autobiographical memories from a group of healthy volunteers and then trained the subjects to use three distinct strategies after retrieving these memories in the scanner. Subjects were trained to: 1) focus and ruminate on the feelings associated with the memories, 2) mindfully accept them as passing mental events not connected to or controlling the self, or 3) analyze the causes and reasons for their feelings in response to the memories.

The authors found that, compared with an active baseline cognitive task, implementing all three strategies activated the left dorsolateral prefrontal cortex (DLPFC) (Brodmann area [BA] 46), consistent with the role for this region in many forms of cognitive control (4). The cerebellum and several visual regions were also differentially activated across conditions. Differences in activity across the three different affect-regulation strategies were seen in a network of regions that included medial PFC and the sgACC. Importantly, activity was highest in these regions for the "feel"

instruction and lowest for the "accept" instruction, with the "analyze" condition showing intermediate levels of activity. This modulation of limbic activity closely tracked subject's reports of negative affect during scanning, with the highest negative affect reported during "feel", the lowest during "accept", and intermediate levels being seen during "analyze". In the direct comparison of the "accept" and "feel" conditions there were positive correlations between an observed increase in negative affect and increased activity in medial PFC and sgACC as well as positive correlations with decreases in negative affect and activity in the caudate, medial frontal gyrus, and precuneus.

These results suggest that by using autobiographical memories it is possible to engage sgACC and other depression-related regions in healthy subjects and that activity in this circuitry can be modulated by strategies such as mindful acceptance and analytic thinking that are intended to disrupt ruminative processes in the brain. They also support an important role for DLPFC in normal emotion regulation and suggest that mindfulness might be a more generally effective strategy for emotion regulation in this context than analytical thinking, although this might be just a matter of degree.

The present result is important because of the successful engagement of depression-related regions such as sgACC as well as the demonstration that emotion regulation strategies of the type used in psychotherapy for depression can be shown to have an impact on the function of this circuitry as well as on the associated affective responses in healthy subjects. As the authors suggest, the work does indeed have implications for translational research in mood disorders. However, translating tools and constructs from social cognitive and affective neuroscience to the investigation of clinical disorders is not without its challenges (see review, by the senior author of the present study, for a detailed discussion) (5). This includes limitations to our understanding of the basic mechanisms underlying social and emotional processes as well as the technical challenges of taking social and emotional paradigms into clinical and translational research.

The present study established a novel paradigm for studies of depression, due to its use of autobiographical memories and subsequent engagement of sgACC, while also providing evidence for differential effects of different emotional regulation approaches. The present study focused on healthy subjects and did not explore individual differences in emotion regulation or the effects of individual differences in mood on these processes. Furthermore the procedure used in the present study was a complex one, involving extensive training and a high level of subject cooperation. Implementing an approach such as this in depressed or anxious patients might be challenging. An additional challenge for the translation of this approach is that emotion regulation studies such as the present one do not provide an on-line performance measure, which is generally essential in cognitive activation studies in patients to ensure adequate engagement with the task (in this case both emotional memory retrieval and the application of specific emotion regulation strategies) as well as to constrain the interpretation of changes and/or group differences in brain activity (6) across different experimental conditions. In the present study, affect ratings were obtained at the end of each block. The tracking of

From the University of California at Davis, Sacramento, California.

Address reprint requests to Cameron S. Carter, M.D., University of California at Davis, UC Davis Imaging Research Center, 4701 X Street, Sacramento, CA 95817; E-mail: cameron.carter@ucdmc.ucdavis.edu.

changes in brain activity and these ratings seen in the present study is impressive and does help constrain the interpretation of the brain activity changes seen during different emotion regulation strategies, but it is unclear whether this would be observed in patients who have both increased baseline activity and increased reactivity in the limbic system. Behavioral studies using emotion regulation paradigms in patients would help determine the degree to which such a design would be feasible and informative in depression.

In addition to informing our understanding of the neural mechanisms underlying emotion regulation and the potential differential impact of different strategies used during the psychotherapy of depression, it is interesting to speculate as to whether the approach used in the present study might predict treatment or outcome or even help guide who is likely to benefit from treatment such as CBT and who might not. For example, inability to activate left DLPFC during procedures such as the present one might indicate a limited ability to engage the necessary cognitive control to participate in CBT. Perhaps transcranial magnetic stimulation targeting this region could be shown to enhance the function of this region and hence the ability of patients to engage in affect-regulation strategies during CBT.

Previous studies have suggested that sgACC and/or ventromedial PFC activity levels predict response to both pharmacotherapy and CBT (7,8). Perhaps the ability to modulate activity in these areas with affect-regulation strategies might be an even stronger predictor of treatment response, particularly to CBT. Alternatively, the ability to learn to modulate limbic activity during the course of therapy might better predict positive outcome with this approach. Finally, additional approaches, such as functional magnetic resonance imaging biofeedback (9), targeting activity in sgACC and other elements of limbic overactivity in depression, might be seen as homologous to the present approach and used either to "jump start" cognitive

therapy or as a stand-alone approach. Future studies using appropriately adapted affect-regulation paradigms such as those in the study by Kross et al. should help us to investigate these possibilities and take us closer to a more targeted approach to treating major depression.

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