Emotional Regulation, or: How I Learned to Stop Worrying and Love the Nucleus Accumbens

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How does the brain control emotion? In this issue of *Neuron*, Wager et al. use a novel mediation analysis of neuroimaging data to show two independent pathways for the control of emotion by the prefrontal cortex: a path through the amygdala predicts a greater negative emotional response, and a path through the nucleus accumbens/ventral striatum predicts a greater positive response.

Humans have a remarkable capacity to regulate their emotions. During the course of our lives, we encounter a variety of stressful, sad, scary, and otherwise emotional events. Nevertheless, we are capable of coping in most of these cases and controlling our emotional responses so that they do not come to dominate either our thoughts or our actions in maladaptive ways. The control of emotion can involve simply suppressing or blunting an unwanted emotional response, as in holding back tears or laughter, or in resisting disgust. In other cases, we regulate our emotions by reinterpreting the meaning of an event in order to modulate our response to it. For example, upon seeing a crying baby we can reinterpret the distressing scene, convincing ourselves that the mother will soon return. Regulating our emotions by construing an event in an alternate way is termed reappraisal.

Recent years have seen a growing interest among social cognitive neuroscientists in the neural systems that support emotional regulation, including reappraisal. Consistent with the established role of frontal cortex in cognitive control of emotion generally (Stuss et al., 1992), studies using functional magnetic resonance imaging (fMRI) have demonstrated increased activation in a number of lateral and medial frontal regions during reappraisal (Beauregard et al., 2001; Eippert et al., 2007; Ochsner et al., 2002; Ochsner and Gross, 2005; Ray et al., 2005). And reappraisal success—typically measured in terms of a change in the reported emotional response to an event—correlates with increased activation in lateral prefrontal cortex (PFC) (Ochsner et al., 2002, 2004; Ochsner and Gross, 2008).

In addition to PFC, activation associated with reappraisal is commonly observed in subcortical structures known to process affect, such as the amygdala (Levesque et al., 2003; Ochsner et al., 2004). Levels of activation in these structures appear to track the direction of emotional change. So, for example, when participants are required to reduce their emotional reaction to a negative scene, activation decreases in the amygdala. And conversely, when they are asked to enhance their emotional reaction to a negative scene, activation is increased in the amygdala (Ochsner et al., 2004). As is suggested by these patterns, activation in the amygdala is negatively correlated with behavioral measures of reappraisal success. In addition, correlations, typically negative, have been demonstrated between activation in the PFC and the amygdala in tasks that require cognitive control of emotion (Cunningham et al., 2004; Lieberman et al., 2007). Thus, to summarize, (1) increased activation in PFC has been associated with reappraisal success; (2) activation in subcortical regions known to process affect has also been correlated with reappraisal outcomes; and (3) activation in PFC has been correlated with activation in the amygdala (Ochsner and Gross, 2005, 2008) and other subcortical structures during emotional regulation. These data suggest a network model for the cognitive control of emotion, whereby PFC regulates emotion by acting on subcortical structures in order to modulate the emotional response. However, the critical piece missing from these results is direct evidence that the correlation between PFC and subcortical structures during reappraisal is what accounts for the correlation between PFC activation and changes in the emotional response.

In this issue of *Neuron*, Wager et al. (2008) apply an innovative application of mediation analysis to functional neuroimaging data to provide evidence of this missing link and specify the neural pathways that support emotional regulation. Mediation analysis is a way of statistically assessing the extent to which the correlation between an explanatory variable, X, and an outcome, Y, can be accounted for by the correlation between X and a mediating variable, M. Expressed in the terms of emotional regulation and reappraisal, mediation analysis can assess the extent to which a correlation between activation in ventrolateral PFC (vlPFC) (X) and reported reappraisal success (Y) is due to the correlation between vlPFC and subcortical structures associated with a particular affective response (M), such as the amygdala and nucleus accumbens/ventral striatum (NAC/VS) for negative and positive affect, respectively.

In the Wager et al. experiment, participants were presented with negative or neutral images and were asked to either "look" at the image and understand its

content or "reappraise" the image content in a way that was less negative. Following presentation of the image, participants were asked to rate their emotional reaction to the recently presented image. Consistent with previous reports, engaging in reappraisal resulted in increased activation in PFC, including vlPFC, and decreased reports of negative emotion following reappraised images. These effects were also weakly correlated. However, the mediation analysis revealed a complex story regarding the relationship between PFC and the behavioral outcome. In particular, the amygdala and the NAC/VS were both identified as reliable mediators between the PFC and the behavioral response, but in opposite ways. Increased activation in the NAC/VS was associated with reappraisal success (i.e., a reduced negative response), whereas increased activation in the amygdala was associated with a greater negative emotional response. Interestingly, vlPFC was positively correlated with both the amygdala and the NAC/VS. Thus, Wager et al. provide evidence for at least two pathways for emotional regulation, both emanating from vlPFC: a positive pathway associated with increased positive emotional response and mediated by the NAC/VS, and a negative pathway associated with an increased negative emotional response and mediated by the amygdala. This finding is important, in that it provides the strongest evidence to date that the PFC is regulating the affective response to a stimulus via limbic structures, and it associates specific pathways from PFC with particular subcortical structures. However, as with any exciting result, the identification of these pathways raises a number of important new questions.

Why Does vlPFC Enhance a Negative Emotional Response via the Amygdala When the Goal Is to Reappraise?

On first pass, it appears somewhat paradoxical that, while vlPFC is considered critical for goal-dependent emotional regulation, it is nevertheless observed in this study enhancing a negative emotional response via the amygdala, in apparent opposition to the goals of the task. A priori, one might have predicted that increased activity in vlPFC acts to reduce the amygdala response, thereby reducing the negative affective response to the scene. To resolve this apparent discrepancy, Wager et al. suggest that the PFC is not only involved in regulating emotion, as in reducing an unwanted emotional response, but also in generating the emotional response itself. Thus, vlPFC control mechanisms may not be strictly involved in "regulating emotion" per se, but rather in an appraisal process that extracts emotional meaning from a stimulus. This is a plausible interpretation of this paradoxical result; it appears related to the association of vlPFC with traditionally "nonaffective" cognitive control processes such as retrieval and selection of information from memory (Badre and Wagner, 2007), inhibitory functions (Aron et al., 2004), or both. But, because the two pathways emerged within the same reappraisal manipulation in this study, further experimentation will be required in order for this account to be fully convincing. For example, separate manipulations thought to differentially impact negative appraisal and positive reappraisal should presumably differentially impact mediator effects along the positive and negative pathways. Demonstrating such independence experimentally will be necessary to fully distinguish between these two pathways and to gain some understanding about their relative involvement and under what conditions each is deployed during emotional regulation.

Does vlPFC Directly or Indirectly Modulate Activation in Subcortical Structures?

A limitation of the mediation analysis is that it cannot rule out the existence of mediating factors or regions not tested in the model. For example, a common neurotransmitter system that innervates both the PFC and the amygdala/NAC/VS, such as the dopamine system, would not be detectable using this approach and could provide coordinated signaling to both structures. Likewise, the whole-brain analysis revealed a number of regions as reliable mediators, beyond the highlighted subcortical structures. To what extent might these regions mediate the correlation between vlPFC and the subcortical structures? Indeed, such indirect pathways seem likely given the anatomy of the frontal lobe. For example, direct corticocortical connections exist primarily between the amygdala and orbital/medial frontal cortex rather than lateral PFC regions like vlPFC (Pandya and Yeterian, 1990). Hence, there is strong motivation to further specify the route by which the PFC modulates activity in the amygdala and NAC/VS.

Further specification of these pathways will also be critical for our eventual understanding of the mechanisms by which the vlPFC regulates emotion. For example, if the vlPFC is involved in appraisal of the scene, as suggested by Wager et al., the direct object of its output may be posterior neocortical regions that support our semantic representations of meaning and perceptual representations of the outside world. Activation of representations with valenced associations in these posterior neocortical structures might result in activation of subcortical structures mediating the affective response. This is only one of many potential indirect routes between changes in PFC and changes in subcortical structures. Thus, further experimentation, using this and other functional connectivity approaches, will be required to elaborate these pathways, and determine whether vlPFC acts directly on subcortical structures or indirectly via other systems.

Cognitive neuroscience benefits from the study of functional networks. This is particularly the case in the study of complex cognitive functions like cognitive control, whether of emotion, memory, or action. By definition, cognitive control involves the representation of contextual or goal information in order to modulate processing elsewhere in the system, a network function. But often this influence is assumed rather than demonstrated. Using a mediation analysis, Wager et al. (2008) not only provide evidence for such a network in the case of emotional control, but also specify which cortical and subcortical structures are influenced by the PFC, under which circumstances, and the way in which they may be grouped into distinct pathways. Such a dynamic network approach will likely benefit other areas of cognitive neuroscience investigation and provide similar insights into the functional networks supporting cognitive function.

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Drosophila Olfaction: The End of Stereotypy?

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Recent work has demonstrated substantial wiring and functional stereotypy in the fly olfactory system. In this issue of *Neuron*, Murthy et al. demonstrate that in the mushroom body, a site of olfactory associative learning, this initial peripheral stereotypy gives way to functionally nonstereotyped circuits.

In the study of the circuit basis of behavior, it is often interesting to examine the extent to which genetically specified connectivity may underlie species-specific behavior. Equally interesting (and perhaps even more challenging) is the circuit basis of differences in the behavior of individuals within a species, which may represent experience-dependent processes such as learning. Fruit flies are being used to address both of these issues as they have a range of innate and learned behaviors. Because both types of behaviors coexist in the same individual, it is conceivable that the nervous system will include stereotyped as well as nonstereotyped elements. The latter could result from differences in neuronal connectivity or more subtle differences in synapse function, raising the possibility that anatomically identical circuits could produce different behavioral outputs. Both scenarios, differences in connectivity or function, prompt the question of where along the path from sensory input to motor output interindividual differences lie. In the present issue of *Neuron*, Murthy et al. (2008) identify the first nonstereotyped element in the olfactory system of *Drosophila*.

During the last decade great insight has been gained into the structure and function of the first two relays of the olfactory system in *Drosophila* (Figure 1). Perhaps the defining feature of these results has been the demonstration of extensive anatomical and functional stereotypy. This stereotypy first becomes evident in the invariant projection of each type of olfactory receptor neuron from the antenna to specific glomeruli in the antennal lobe, which produces an invariant spatial map of odor space (Vosshall et al., 2000; Couto et al., 2005; Fishilevich and Vosshall, 2005). Within each antennal lobe glomerulus, olfactory receptor neuron axons form connections with the dendrites of a specific group of projection neurons (PNs), the principal output cells. In addition both excitatory and inhibitory local neurons connect multiple glomeruli.

The wiring of olfactory receptor neurons and PNs is under precise genetic control (reviewed by Jefferis and Hummel, 2006) such that there appears to be a hard-wired transfer of information across each glomerulus that may be required for innate olfactory behavior. Consistent with this, olfactory responses of PNs are highly stereotyped (Ng et al., 2002; Wang et al., 2003; Wilson et al., 2004). On leaving the antennal lobe, PNs send axons to the lateral horn, where they form highly stereotyped axon terminals. On their way to the lateral horn, PNs also send axon collaterals to the mushroom body calyx. The mushroom body is composed of some 2500 neurons called Kenyon cells (KCs). While there is consensus about the anatomical stereotypy of PN axonal arborizations in the lateral horn (Marin et al., 2002; Wong et al., 2002), a unified image has not yet emerged for the synapses of PNs on the KCs. Although initial studies were inconclusive, more recent reports show a significant level of stereotypy in PN-KC projections (Tanaka et al., 2004; Jefferis et al., 2007; Lin et al., 2007); this stereotypy can be described as a zonal bias for the termination site of PN axons and KC dendrites. At the functional level, Wang et al. (2004) used Ca^{2+}