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Systems Neuroscience: The Balancing Act of Behavioral Regulation

Leah H. Somerville
Department of Psychology & Center for Brain Science, Harvard University, 52 Oxford Street, Room 290, Cambridge MA 02138, USA
Correspondence: somerville@fas.harvard.edu
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In the brain, the striatum and prefrontal cortex interact to gauge the value of actions and the self-regulatory demands in a given environment. New research, involving manipulation of the neural circuitry, has revealed multiple routes by which 'imbalances' in circuit function cause regulation deficits.

In everyday life, we are constantly faced with dilemmas regarding how to select our actions to maximize positive outcomes. These are generally not so simple as finding rewards in the environment and seizing them every chance we get: context clues provide information that modifies the value of actions that have paid off in the past. For example, I might decide to pass up my favorite food (sushi, as it were) if I find out that it's from a restaurant that failed its health inspection.

Dual process theories of behavioral regulation posit that an individual ultimately selects how to behave in a situation by integrating representations of motivation and regulatory demands (for example, [1,2]). On one hand, the acquired value of a target item stimulates motivation to approach (sushi is delicious, I should eat it). On the other hand, cues in a given environment impose a regulatory signal that conflicts with this approach motivation (sushi *from this restaurant* should be avoided). Dual process theories suggest that the mind must adjudicate between these representations to guide our eventual actions [3]. However, most prior work looking at the neurobiological mechanisms of this adjudication process has been indirect and correlational (see [4,5] for reviews), often divorced from the behavioral outcomes that reveal motivation-cognition interactions.

In this issue of *Current Biology*, Meyer and Bucci [6] report significant progress toward pinpointing the neural circuit mechanisms that guide the integration of reward-approach and regulation. They took advantage of new, powerful chemogenetic techniques [7] to manipulate the functioning of subcortical-cortical brain circuitry and pair it with a clever behavioral paradigm to causally shift an organism's 'balance' toward reward-approach or regulation, given a particular neural circuit state.

Meyer and Bucci [6] targeted two regions in the rat brain: the orbitofrontal cortex (OFC) and nucleus accumbens (NAC), regions that have been implicated in regulation and reward-approach, respectively. They used chemogenetic techniques to enhance or suppress the neural functioning of these regions in real-time, while an animal had the opportunity to learn and use a cue indicating that a rewarding stimulus will actually *not* be rewarding in a particular context. This task, termed *negative occasion setting*, allows the researcher to trace the behavioral manifestations of inhibitory learning in the presence of reward-approach cues.

Meyer and Bucci's [6] results show that shifting the balance of activity between these brain regions has powerful consequences for an animal's state of behavioral regulation. Simultaneously enhancing neural firing in the NAC and reducing neural firing in the OFC created a functional 'imbalance' that caused the animal to have difficulty learning and using context cues to override approach motivation toward a previously rewarded cue. Conducting these manipulations in one region at a time — increasing NAC activity, decreasing OFC activity — resulted in a similar behavioral alteration, albeit less robustly than when both regions were manipulated simultaneously. These observations show that both NAC and OFC contribute to the balancing act of behavioral regulation, and the interactions between these regions guide an individual's propensity for reward-approach versus regulation. It will be interesting in the future to incorporate additional components of striatocortical brain circuitry to enrich their model of behavioral control from two regions to several.

Biased striatocortical circuit function has been implicated as a root mechanism

for a host of unhealthy behavioral profiles, including antisocial behavior [8], addiction [9], and other impulse control disorders [10]. At the crux of these theories lies the notion of a push-and-pull between approach motivation and attempts at control. Meyer and Bucci's [6] work shows that either an overactive NAC or an underactive OFC (prefrontal cortex in humans) — and most powerfully, both at the same time — 'tip' an organism's regulatory balance toward immediate rewards and away from contextual cues signaling the benefits of regulation. These findings show that there are multiple circuit-level manifestations of 'imbalance', and that these various 'imbalances' *cause* shifts in behavioral regulation.

This work also bears on models of human development. A predominant model for normative adolescent brain development suggests a temporary 'imbalance' between mature and strongly-signaling subcortical brain regions, including chiefly the NAC and the still-developing prefrontal cortex, which have reduced signal fidelity (for example, [11]). Key evidence in support of these models comes from studies showing exaggerated response properties in the NAC in adolescents [12], and less effective recruitment of the prefrontal cortex (with respect to behavior change) [13]. This temporary and normative adolescent 'imbalance' has been linked to a host of age-typical behaviors including high sensation seeking and reward sensitivity, difficulty inhibiting actions in the face of rewards, and risk taking in daily life [14,15]. Meyer and Bucci's [6] findings are informative to these models, given the strong inferences that can be drawn from the causal manipulations used in the study.

Although Meyer and Bucci's [6] experiments were carried out in adult animals, the behavioral profile of the 'imbalanced' animals show intriguing parallels with pubertal aged rodents tested by the same researchers in a separate study [16]. One might even be tempted to suggest that the authors' manipulations temporarily converted the adult animals into animals with 'adolescent' brain and behavioral profiles. However, we should approach such inferences with caution. Although chemogenetics can dial up and down the response sensitivity of this brain circuit, such alteration does not account for: the different mechanisms that underlie an 'imbalance'; the accumulated experience that accrues with age and shapes neural functioning and cognitive representations of contextual cues and rewards; or the neurochemical mechanisms that set apart adolescent and adult neural systems in their native state.

Like all exciting papers, Meyer and Bucci's [6] stimulates a host of new questions. Firstly, it would be exciting to examine the effect of inducing a NAC–OFC 'imbalance' in behavioral domains other than negative occasion setting. Negative occasion setting is a test of inhibition over reward, but it is also fundamentally a learning task. Parsing the contributions of NAC–OFC 'imbalance' to inhibitory processes separated from the learning process will be an important step toward specifying the necessary conditions under which NAC–OFC 'imbalance' causes changes in these complex behaviors of interest. Furthermore, while NAC and OFC are well justified regions of interest, it is important to note that they are components of much broader neural circuitry [17] and their functional profiles do not map onto reward and regulation dichotomously. The OFC of rats is roughly homologous to the human lateral prefrontal cortex, which codes not only cues signaling inhibition but also cues signaling value [18]. Such complexities have been invoked in critiques of neurobiological dual process models more generally [19]. Meyer and Bucci's [6] work, which pairs powerful causal brain manipulations with clever behavioral paradigms, is a prime example of the kind of research that is capable of tackling these open questions. More generally, this program of research is poised to reveal how we select actions to maximize positive outcomes with stunning precision.

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