Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Representations of Distinct Salience Signals in the Nucleus Accumbens

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Review of Zaehle et al.

Introduction

Processing salient events is an essential component of adaptive behavior. To navigate a changing world, organisms must learn which events are meaningful and determine the appropriate behavioral response. Many regions throughout the brain, including affective subcortical and executive cortical networks, have been implicated in processing salience. In particular, the nucleus accumbens (NAcc) in ventral striatum has been associated with anticipating and responding to saliency in a variety of domains, including reward, novelty, and violations of expectation. Many of the paradigms investigating NAcc function, however, confound these cognitive processes, making it difficult to characterize how the NAcc contributes to these dissociable forms of salience processing.

In a recent study published in *The Journal of Neuroscience*, Zaehle et al. (2013) used intracranial recordings in human epilepsy patients to analyze NAcc activity during a behavioral task designed to parse distinct forms of saliency processing. Researchers presented participants with four classes of stimuli. The standard stimulus was a frequently repeated scene, while the neutral scene (one familiar, repeated scene), target scene (one familiar scene that indicated a button press), and novel scenes (trial-unique, new scenes) were oddball stimuli that appeared rarely. This afforded the opportunity to isolate neural responses to item novelty (novel > neutral), contextual deviance/violation of expectation (neutral > standard), and targetness (target > neutral). Interestingly, the authors found unique responses in NAcc to different classes of salient events. Specifically, they found significantly increased local field potentials (LFPs) for targetness, but not for contextual deviance or item novelty. Although LFPs did not discriminate between novelty and contextual deviance, these forms of salience exhibited differential NAcc oscillatory activity. Local decreases in theta (4–8 Hz) power were related to item novelty, while local decreases in beta (13–30 Hz) power reflected contextual deviance. Thus, three unique neural signatures marked distinct forms of salience processing in the NAcc. The findings are particularly interesting because they suggest that the same neural structure can support the representation of multiple types of information through synchronous neural activity at different frequencies. Beyond characterizing distinct forms of salience within the NAcc, these findings highlight a more general value of using electrophysiological methodologies to investigate effects that may not be distinguishable at the coarse temporal scale of fMRI.

A role for the NAcc in the initiation of adaptive behavior

Zaehle et al. (2013) provide a unique contribution to the existing literature characterizing saliency processing in the NAcc. This study, however, does not directly address one core function of the NAcc: the translation of basic salience signals into contextually appropriate behaviors. The NAcc has a diverse set of sensory, affective, and motivational afferents and motor efferents, making it well positioned to translate environmental salience signals into motor action plans (Goto and Grace, 2008). Additionally, the NAcc has been demonstrated to modulate response vigor, locomotion, and exploration (McGinty et al., 2013). To fully characterize the function of the NAcc it is critical to understand its role in promoting adaptive behavior. In the Zaehle study, however, neither novel nor contextual violation stimuli were behaviorally relevant: when an item in these categories was identified as a nontarget, no further action was necessary. In contrast, in a previous intracranial study that investigated NAcc salience signaling in response to contextual violations (Axmacher et al. 2010), participants were required to plan an action response to each contextual violation; and Axmacher and colleagues found increased LFPs in the NAcc in response to contextual violations. Zaehle et al. (2013) address this discrepancy in findings as failure to repli-

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cate, but an alternative explanation is that the critical factor driving differences in NAcc LFP responses across these two studies was whether or not the environmental salience necessitated participants to initiate a behavioral response. The NAcc LFP signal could therefore represent behaviorally relevant salience.

Additional findings from Zaehle et al. (2013) further support the notion that NAcc LFP responses underlie a more general role in initiating behavioral responses. First, across participants NAcc LFPs were correlated with individuals' reaction times to target stimuli. This finding is especially notable because NAcc LFPs were not associated with the mere presence of target items, but rather the speed at which individuals were able to initiate a motor response to these targets. Second, it appears that there was a sustained novelty LFP response in the right NAcc (Zaehle et al. 2013, their Fig. 3), which the authors did not address because of their epoching approach (100–500 ms after stimulus onset, rather than the full stimulus duration of 1500 ms). While no task-specific actions were necessary in response to novel items, previous research in animals and humans has demonstrated that novelty in the environment may intrinsically induce prolonged exploratory behaviors (Lisman and Grace, 2005). Prolonged LFPs to novel stimuli may thus reflect activation of visual exploratory behaviors. Future studies could use a combination of eye-tracking and electrophysiology methods to test this specific hypothesis. In our view, the findings from Zaehle et al. suggest that discrete forms of salience in the environment are signaled by different oscillatory firing rates, while the need for behavioral activation is signaled by increased LFP responses.

The source of NAcc salience signals

While the findings from Zaehle and colleagues' experiment provide much insight into how information processing differs within the NAcc across varying salience signals, the paper does not explore where or why these different signals emerge. Although the use of intracranial EEG allotted the researchers opportunity to characterize salience-processing signals in the NAcc, the method limited analyses exclusively to the NAcc. However, findings from studies in other fields using a diverse array of methodologies provide insight into how these distinct set of salience signals within the NAcc may emerge.

Given that distinct brain networks are thought to code different salience signals, and that the NAcc is a locus of convergence for a diverse set of inputs (Goto and Grace, 2008), we speculate that the observed frequency-specific oscillatory patterns in the NAcc might arise from interactions with separate brain networks. This hypothesis is consistent with emerging evidence suggesting that while high-frequency oscillations (for example gamma, 30–90 Hz) index local neural computations, lower frequency oscillations (<30 Hz) may be the product of longer-range interactions (for review, see Donner and Siegel, 2011). Thus, we speculate that change in theta and beta oscillations (both <30 Hz) in response to item novelty and contextual deviance in the NAcc may index long-range interactions between NAcc and other brain regions.

Numerous studies, have characterized dissociable networks that separately contribute to the processing of novelty and expectancy violation (i.e., contextual deviance), as well as the initiation of adaptive behavior. Previous research has demonstrated that lesions to the medial temporal lobe, particularly the hippocampus, disrupt novelty related signals in the NAcc as well as novelty-related behaviors (Lisman and Grace, 2005). This research suggests that memory-related signals from the hippocampus may drive changes in theta power in the NAcc during novelty processing. Indeed, theta oscillations generated in the hippocampus have been shown to be crucial for successful memory for novel information (Buzsáki and Moser, 2013). In line with this interpretation, Zaehle et al. demonstrated that theta-power in the NAcc was predictive of later memory for novel stimuli. Previous research has also demonstrated that the lateral prefrontal cortex is sensitive to maintenance of contexts and deviations of those maintained contexts, and lesion studies have further demonstrated that an intact lateral prefrontal cortex is necessary for processing expectancy (Kishiyama et al., 2009). Given that there are direct connections of the PFC to the NAcc, these findings suggest that inputs from the lateral PFC could result in decreases in beta-power in the NAcc during deviations of expectations. Finally, a large literature has shown that engagement of the mesolimbic dopamine system, specifically midbrain projections to the NAcc, is critical in initiating motivated/adaptive behavior. In fact, VTA/dopaminergic signaling has been demonstrated to modulate both LFPs in the NAcc and the initiation of goal-directed behavior (Goto and Grace, 2008). Thus, these broader literatures provide indirect evidence that distinct cortical and subcortical afferents may mediate the diverse saliency signals in the NAcc. Future studies should further investigate these relationships to better characterize what cortical and subcortical networks contribute to distinct salience signals in the NAcc.

Summary

Zaehle and colleagues (2013) characterize a novel mechanism by which discrete NAcc signals carry information about distinct forms of salience. The authors demonstrate that in the NAcc theta power is reduced in response to novel items, beta power is reduced in response to contextual deviants, and LFPs are increased in response to targetness. Building upon previous literature, however, we propose an alternative interpretation that the NAcc LFPs may reflect a more general signal to initiate adaptive behaviors. While the current study was informative, it opens many avenues of future research addressing the nature and source of these NAcc salience signals.

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