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Marmosets confirm that context is king

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Neural responses to vocalizations are expected to depend on the sensory features of the stimulus. In this issue of *Neuron*, Jovanovic and colleagues show that call-responsive neurons in the prefrontal cortex of marmosets signal not only the auditory stimulus but also the social-behavioral context.

Nobody calls the police when the teenager says, "My parents will kill me if I get home late," because the context of this statement conveys the true meaning of the words. In this issue of *Neuron*, Jovanovic and colleagues (Jovanovic et al., 2022) report that marmosets, too, perceive the same social call differently in different contexts. Various circumstances that require changing a response to the same sensory stimulus qualify as context. Context can be external, such as a location in space, the presence or absence of social partners, or an internal state, such as pain, fatigue, or awareness of one's mental or physical limitation. What makes the work of Jovanovic and colleagues exciting is that they chose for context the subject's freedom to move. Specifically, they compared the perception of vocal signals and their neural representation in premotor and prefrontal cortices while marmosets were restrained or free to move, and when the timing of the calls was set (or not) to match the pace of natural marmoset conversations. Shifting from the restrained to the freely moving context represents a commendable shift from a traditional, reductionistic to a naturalistic paradigm. This approach brought to light new and exciting findings. Not only did most cortical neurons respond differently to the same calls in each situation, but information about context could be recovered from the baseline activity of these call-responsive neurons. This outcome warrants a reassessment of two assumptions on which many neurophysiological studies rest.

The first assumption, which has been often challenged (for review see Buzsáki, 2019) but survived due to its intuitive explanatory power, is that neural responses evoked by external sensory stimuli are faithful to the features of the stimulus. In more general terms, behavioral responses to sensory stimuli are often assumed to be more tightly related to specific stimulus features than to internally organized brain states that set the behavioral agenda of the organism. Based on such assumptions, individuals who are unable to ignore minor sensory inputs, such as a small wrinkle in their socks, are diagnosed with sensory hypersensitivity, rather than a deficit of executive function, that should allow them to ignore minor, irrelevant stimuli. The essence of executive functions, emerging mainly from the prefrontal cortex, is context-dependent behavioral (and cognitive) flexibility. Context blindness, as often seen in autism, is a clear illustration of what happens when the same stimulus elicits the same response in all circumstances.

Neurophysiological studies often ignore context for practical and technical reasons. For traditional neural recordings in awake animals, which require the acute insertion of microelectrodes, the head (and the brain therein) often must remain immobile to avoid slight movements of the microelectrodes relative to the monitored neurons. Under these conditions, neurons may differentiate between multiple stimuli, respond to operant behaviors, and signal even abstract variables such as value or desirability. Moreover, the more varied the stimuli and the task demands, the more diverse and complex the neural responses become (Gothard, 2020). By extension, an imaginary census of all the neurons in the brain subjected to multiple, unrelated tasks would likely show that most neurons are multidimensional (i.e., show mixed selectivity) (Rigotti et al., 2013) rather than specialized for a narrow range of stimuli or behaviors. The question is what proportion would respond to context, such as the freedom to move, or some other form of contextual information? Neurophysiologists knew for a long time that even non-motor areas of the brain, such as the hippocampus, stop responding to the external stimuli when movements are not possible (Foster et al., 1989). Jovanovic and colleagues show us that both social context and the freedom to move (or lack thereof) are incorporated in the responses of individual neurons in the premotor-prefrontal areas of the marmoset brain. They remind us that the advantages of reduced and movement-restricted preparations, aimed at isolating a particular mental operation, must be balanced against the advantages (and disadvantages) of exploring behaviors in their full complexity, despite the "messy data" they produce. One might argue that the more naturalistic the behavior, the better it captures the solution that evolution converged on to solve the messy problems of real life. It may be that the real difficulty of understanding how the brain solves these problems does not stem from the difficulty of decoding the information contained in neural activity but from insufficient understanding of how these signals are used to inform behavior (Krakauer et al., 2017).

The second assumption that has been successfully challenged by Jovanovic and colleagues is that the period immediately following the presentation of a stimulus is the most important segment of neural activity. They show that this segment of time does not contain all the information we need to understand how neurons process sensory stimuli. Rather, background neural activity in the marmoset prefrontal cortex preceding and following a perceived vocalization predicted the likelihood of a reciprocating response. Traditionally, neuronal responses triggered by a stimulus are quantified by the difference between prestimulus baseline and the immediate post-stimulus activities. The firing rate of neurons during the baseline period, or during the inter-trial interval, has been only rarely scrutinized. Nevertheless, the baseline period is fertile ground to explore how the brain might integrate stimuli and events across multiple timescales, how it predicts—rather than reacts to—external events, and how it creates persistent affective states. Indeed, affective states, such as anxiety, persist longer than an emotional reaction to the anxiogenic stimulus. A state of anxiety can be "kept alive" over long periods in the elevated baseline firing rate of neurons in the amygdala that broadcast this information to multiple brain areas (Lee et al., 2017). Likewise, during an associative learning task, monkeys form expectations for aversive outcomes, and the baseline firing rate of neurons in the anterior cingulate cortex and the amygdala predict the strength of the learned association (Taub et al., 2018). A few other investigators, like Histed and colleagues (Histed et al., 2009), also struck gold when they explored the baseline. They found that baseline activity in the cortex and multiple areas of the basal ganglia retains information about the outcome of multiple preceding trials to inform the animal's future strategy to maximize rewards. It appears, therefore, that task-relevant information may be represented by baseline firing rates of neurons in multiple brain areas. Indeed, thousands of simultaneously recorded neurons across a wide range of structures in the mouse brain signaled during inter-trial intervals the animal's engagement with a task and predicted what the mouse would do in response to upcoming stimuli (Steinmetz et al., 2019).

Future work, focused on the baseline activity of neurons from multiple areas, will have to determine how this often-ignored feature of brain activity holds specific information about the social state of the brain, the engagement of the animal with its environment, the freedom to move, an echo of the past, or a premonition of the future. The link between context and baseline activity that this study brought to light may explain the dynamic switches in brain states that alter the responses of individual neurons to the same stimulus. Social and emotional stimuli, which can trigger prolonged internal states instantiated in the baseline activity of diverse types of neurons, are the mostly likely candidates to operate these switches.

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DECLARATION OF INTERESTS

The author declares no competing interests.

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