

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.

Brain Dynamical Networks: Contextualizing the Function of Primary Cortices

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Review of Pais-Vieira et al.

The rodent whisker system has been a productive model to study neocortical sensory function, featuring a variety of whisker-dependent behavioral tasks, experimental accessibility to neocortical electrophysiological measurements, and well characterized neuroanatomical circuitry. The research group of Miguel Nicolelis has substantially contributed to the study of this system using multielectrode and multisite recordings from the different neuronal groups involved in whisker-dependent behaviors. These types of recordings reflect an interest in both the underlying neuronal networks and the time-dependent features, or dynamics, of these networks (Wiest et al., 2007). Using this approach, the group has shown that neural activity in the sensory thalamocortical branch of the whisker system is not only modulated by relevant external stimuli, but also by the passive or active nature of the stimulation (Krupa et al., 2004), by reward-stimuli associations (Pantoja et al., 2007), and by task learning (Wiest et al., 2010). These findings have suggested a top-down modulation of the sensory pathway independent of the incoming

stimuli, but nevertheless relevant for sensory discrimination.

In a recent report (Pais-Vieira et al., 2013), Nicolelis' group continued and extended their previous studies, aiming to better characterize the abovementioned top-down modulation. They recorded simultaneously from multiple brain areas of the vibrissae system while rats performed a behavioral task. To obtain a reward, rats had to discriminate the width of an aperture by touching the aperture's edges with their whiskers, and then deliver a response congruent with the sensed width (Fig. 1). The whisker-edge contact occurred as rats approached the aperture and poked their noses into a nose poke port located in the middle of the aperture. The group had shown previously that rats do not move their whiskers actively when discriminating correctly in this task (Krupa et al., 2001). The authors monitored neuronal activity before, during, and after whisker-edge contact, and assessed whether this activity was related to the rat's discrimination performance. They further examined the effect of pharmacological inactivation of the motor cortex (M1) on thalamocortical activity and on behavioral parameters.

Replicating their own previous findings, Pais-Vieira et al. (2013) found anticipatory modulation (both increases and decreases) of neuronal firing rates in different cortical layers of the barrel cortex (S1), during the 500 ms before whiskers' contact with the aperture edge (Krupa et

al., 2004; Wiest et al., 2010). The same kind of anticipatory activity was found in neurons of two thalamic nuclei, ventral posterior medial (VPM) and posterior medial (POM), which belong to the lemniscal and paralemniscal trigeminal pathways, respectively. This anticipatory activity was not observed in trigeminal ganglion cells (where the somata of the sensory neurons are located), nor was it likely to reflect whisker movements, because none were observed in electromyograms of vibrissae muscles and video recordings during this period. Notably, the neuronal anticipation to whisker contact was relevant for sensory processing, as the onset time of anticipatory activity in S1 and thalamus was correlated with the rat's discrimination performance. This correlation depended on M1 activity, because it was abolished after M1 inactivation with the GABA agonist muscimol, even though the anticipatory activity itself did not disappear. The only behavioral impairment caused by this pharmacological manipulation was a decrease in overall discrimination performance. No gross motor disruptions were found (no decrease in the number of trials performed and no changes in locomotion speed), and no alterations in rat's whisking ability were reported. Therefore, the motor variables presumably most relevant in this task are actions related to the animal's speed as it arrives to the aperture. All this evidence led the authors to conclude that there are important top-down modula-

Received April 27, 2013; revised May 24, 2013; accepted May 25, 2013.

We acknowledge funding by Proyecto Fondecyt Postdoctorado 3120185 (D.R.-L.) and Beca de Doctorado CONICYT (J.W.). We thank Pedro Maldonado for comments on an earlier version of the manuscript.

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DOI:10.1523/JNEUROSCI.1768-13.2013

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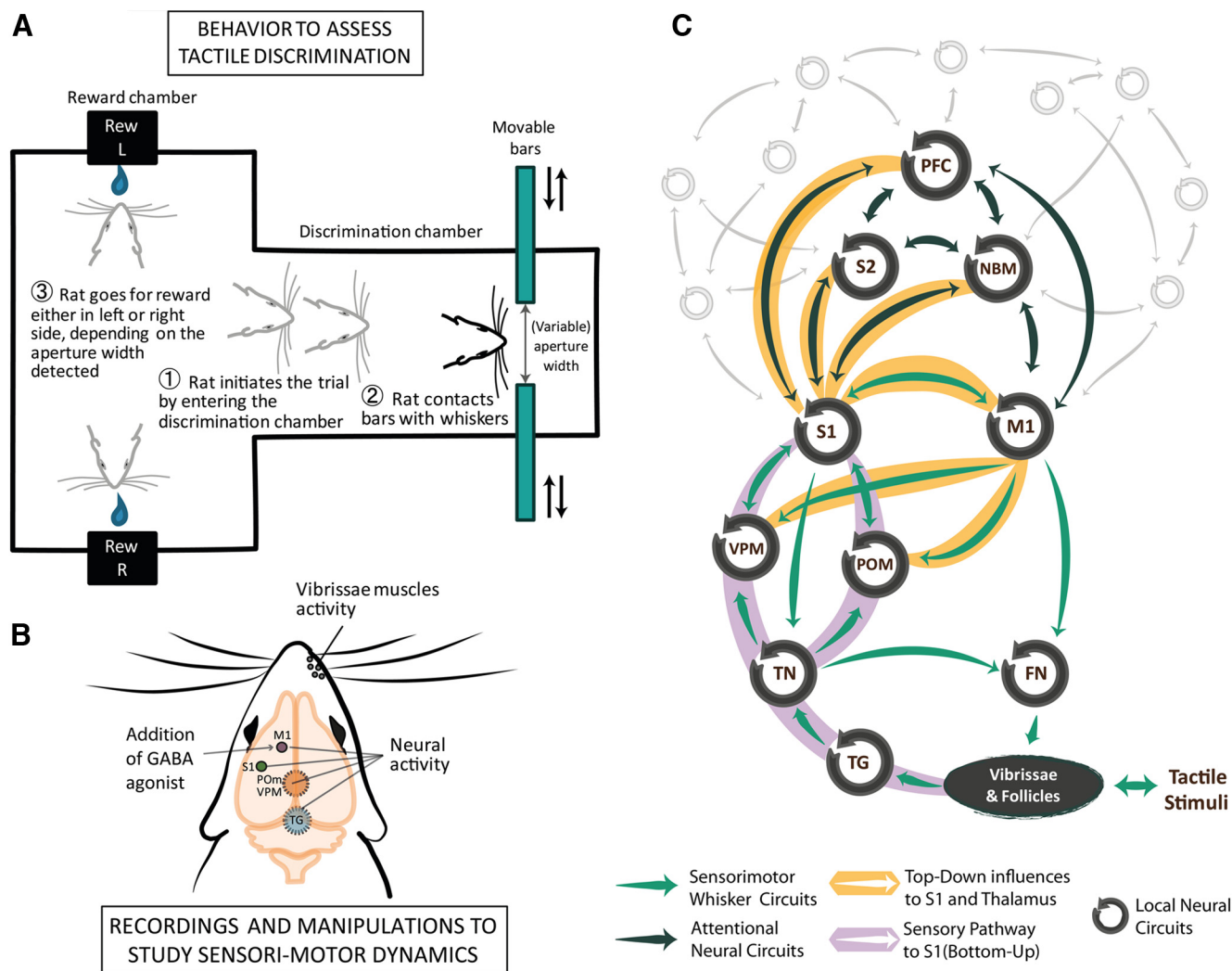


Figure 1. Experimental strategy and interpretation of findings in Pais-Vieira et al. (2013). **A**, Schematic of the behavioral task and setup. The diagram represents the behavioral chamber as viewed from above. **B**, Electrophysiological recording sites and pharmacological manipulations done during execution of the task. **C**, Cortical circuits and areas involved. Tactile stimuli elicit activation of the trigeminal pathway (trigeminal nuclei, thalamus and S1). This stimuli-driven activity reaches S1 cortex but corollary signals from M1 also modulate processing in S1, as described by Pais-Vieira et al. (2013). A wealth of other areas such as the prefrontal cortex, secondary sensory cortex and nucleus basalis magnocellularis also project to S1 and could provide contextual influence to the incoming sensory information. Whisker system neural circuits relevant to Pais-Vieira et al.'s work are represented by light green arrows. Neural circuits involved in attentional processing are represented by dark green arrows. Incoming sensory (Bottom-Up) inputs to S1 are highlighted in purple. Incoming Top-Down influences to S1 and thalamus are highlighted in orange. Local processing in each area is represented by circular arrows. Other brain circuits are shown in light gray in the background. TN, trigeminal nuclei; TG, trigeminal ganglion; FN, facial nucleus; POM, posterior medial nucleus of the thalamus; VPM, ventral posterior medial nucleus of the thalamus; S1, primary somatosensory (barrel) cortex; M1, primary somatosensory motor cortex; S2, secondary somatosensory cortex; PFC, prefrontal cortex; and NBM, nucleus basalis magnocellularis.

tions from M1 to the entire somatosensory thalamocortical loop, and that these modulations serve as a sort of motor-gating or preparatory mechanism that participates in the processing of incoming stimulus-evoked signals by thalamus and S1, thereby facilitating discrimination.

The Pais-Vieira et al. (2013) study provides additional evidence for the hypothesis that an animal's sensory function, assessed in this case by discrimination performance, does not rely solely on stimulus-triggered activity. Their results suggest the operation of a corollary discharge mechanism, in which the dynamics of the arrival of the M1 signal to S1 and thalamus is critical. This top-down signal

would be expected to coordinate the animal's movements with the afferent information the sensory system is receiving. In this regard, the behavioral task was particularly well chosen by the authors because rats had to use their whiskers to discriminate, but did not need to actively move them. Inactivation of M1 in a task requiring active whisking would probably have precluded task execution altogether, without allowing an experimental dissection of the underlying neural processes.

Intriguingly, although M1 silencing by muscimol caused a decrease in average overall performance, discrimination performance exceeded 80% in several muscimol sessions (Pais-Vieira et al., 2013, their

Fig. 9C). If we assume an important role for the described top-down modulation, how can we interpret this result? The authors showed that both the animal's running speed and the timing of anticipatory activity were directly correlated with performance, and noted that different speeds could elicit different whisker-edge contact signals. Interestingly, the pharmacological inactivation of M1 disorganized the normal dynamics of S1 and thalamic anticipatory activity, but did not abolish it. Correlation between running speed and performance was not altered either. Considering these experimental results, we propose two possible underlying mechanisms: First, that M1 is not the only region

exerting influences over S1, that is, other top-down inputs help S1 to accurately interpret the internal and external contextual conditions at which afferent information is acquired. And second, that rats can sense running speed through sensory cues other than M1 corollary discharge to S1, and thus could continue to run faster to enhance peripheral receptor stimulation. M1 corollary discharge would then be one of several contributions to the preparatory activity in S1 required to discriminate stimuli.

Where might this additional anticipatory activity come from? Recent research shows that brain areas that support context-dependent activity do influence sensory function. Attentional circuits, for example, operate through modulation of thalamocortical sensory networks. This modulation, as has been shown in rats, humans and monkeys, is driven by network activity from a variety of cortical and subcortical areas that can include the nucleus basalis magnocellularis, secondary somatosensory cortex, prefrontal cortex, and brain circuits related to motor control (Chiba et al., 1995; Steinmetz et al., 2000; Corbetta and Shulman, 2002). Another source of corticothalamic modulations is the brainstem reticular formation, whose activity is related to the state of arousal of the system and which serves as a filter for incoming stimulus-triggered signals, influencing sensory function (Sherman and Guillery, 2002).

Top-down modulations are of course not a specific feature of the rodent whisker system. Similar to the findings by Pais-Vieira et al. (2013), it has been reported that corollary activity related to eye movements reaches primary visual cortex (V1), where it seems to inform the neocortex of the status of the animals' sampling mode before the arrival of visual inputs (Maldonado et al., 2008; Ito et al., 2011). Furthermore, it has been shown that visually evoked signals do not determine activity in V1, but only modulate it (Fiser et al., 2004), and that V1 is also modulated by

contextual influences and task type (Crist et al., 2001).

The picture of primary sensory cortex that emerges is that of a node in a highly dynamical network, rather than an isolated receiver/decoder of sensory inputs (Fig. 1C). Traditional explanations of the role and function of primary sensory cortices are based mainly on a relatively simple representation of the sensory stimulus to be conveyed to higher cortices for more complex processing, interpretation, and integration. As sensory neurophysiology started to move from anesthetized-animal, simple stimuli experimental models to behaving-animal, natural stimulation models, this picture has begun to change. Although relevant stimuli of course elicits activity in primary sensory cortices, this activity does not depend exclusively on the stimulus' features, but on a wealth of context-dependent factors such as attentional state, previous experiences, task type and sampling mode.

From a broader point of view, the abovementioned considerations imply that activity in primary cortices, which show correlations with some stimulus features, reflects the integration of multiple cortical and subcortical regions which modulate prestimulus cortical state and primary cortex responses, highlighting the notion that sensory stimulation, and the associated perceptual processes, always occurs in the context given by the animal's history and current state. This seemingly reasonable statement is frequently overlooked in sensory research, and is an excellent take-home message brought by the article by Pais-Vieira et al. (2013).

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