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Matching cell type to function in cortical circuits

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In this issue of Neuron, Pinto and Dan (2015) performed single cell calcium imaging in the mouse dorsomedial prefrontal cortex to reveal correlated, cell-type specific responses in three major GABA-ergic interneuron subtypes during a goal-directed sensory discrimination task.

At first glance, a histological section of mammalian neocortical tissue resembles a dense mixed forest: a place where you would easily get lost without a decent map. The neocortex is populated by a wide variety of cells that exhibit heterogeneous responses during sensory processing or behavior. These features make understanding the rules of cortical information processing that underlie cognition and behavior seem like a distant goal. In the face of such diversity, an obvious strategy is to try to match functional responses with a neuron's "type," as defined by its anatomy or gene expression patterns. In the mouse neocortex, this approach is now meeting with some success.

In the last decade, researchers have identified a range of genetic markers to distinguish cortical cell types, prompting the development of mouse lines in which they can be fluorescently labeled. Cortical GABA-ergic inhibitory interneurons have received special interest. Three major non-overlapping subsets of cortical GABA-ergic interneurons are available as Cre-driver lines: parvalbumin (PV), somatostatin (SST) and vasoactive intestinal peptide (VIP), VIP neurons being a subset of a group of interneurons expressing the 5-hydroxytryptamine 3A receptor. Recent cortical slice studies have suggested that some of the features that connect these groups to each other and to excitatory pyramidal (PYR) neurons are conserved across cortical regions (Lee et al., 2013; Pfeffer et al., 2013; Pi et al., 2013). Briefly, PV neurons receive broad excitatory input from local PYR neurons and provide broad inhibitory output. SST neurons target dendrites of PYR neurons and establish a pathway for disynaptic inhibition between nearby PYR neurons. VIP neurons provide disinhibitory control of PYR neurons by inhibiting SST and a minority of PV neurons.

Recently, electrophysiological, optical and genetic tools have been used to record and manipulate the activity of all three interneuron types in vivo.

Researchers have shown interneuron-type specific patterns of activity during movement and sensory processing and suggested that interneurons may have conserved roles on local processing across cortical regions. But do PYR neurons and their neighboring interneurons have discreet functional properties during more cognitive behavioral tasks? Pinto and Dan (2015) address this fundamental question in the dorsomedial prefrontal cortex (dmPFC) (Figure 1A), a higher-order area with almost as many attributed cognitive functions and response properties as anatomical inputs and outputs (Hanks et al., 2015; Miller, 1999; Riga et al., 2014; Rigotti et al., 2013). This diversity was turned to an advantage that allowed the authors to examine the specificity of responses to a number of events during a single behavioral task.

Pinot and Dan (2015) used different mouse lines to selectively express a genetically encoded calcium fluorescent reporter (GCamP6f) in interneurons that expressed PV, SST, and VIP as well as in PYR neurons. In an acoustic discrimination task mice were trained to report one of two possible acoustic tones with licking. Licking at short latency after a target tone resulted in a water reward; but licking following a non-target tone lead to an airpuff punishment (Figure 1B). Injection of the GABA-A agonist muscimol into dmPFC reduced behavioral performance to chance level, indicating that dmPFC neurons were involved in generating the behavior. To investigate mPFC single neuron activity during the task, the authors took advantage of an imaging approach using a gradient refractive index (GRIN) lens attached to a miniature fluorescent microscope. The approach is invasive, requiring removal of superficial cortical tissue, but the mice continued to perform the task and their cells appeared healthy. The technique allowed the authors to collect simultaneous responses from the major dmPFC cell types and provided a comprehensive overview of their response properties during a cognitive task.

The results were reminiscent of electrophysiological studies in the PFC of primates (Miller, 1999): dmPFC neurons actively responded to multiple events during the task, including (i) the visual preparatory cue, (ii) the acoustic target or non-target stimulus, (iii) motor behavior (licking) and (iv) the outcome signal, the water reward or airpuff punishment. As the phases of the task were temporally close, and the calcium signal is relatively slow, a modeling

approach (generalized linear modeling, or GLM) helped establish the significance of a cell's response during a particular phase of the behavior. An analysis of the different subtypes revealed remarkable cell-type specific, highly correlated functional responses within the GABA-ergic interneuron groups, and heterogeneous response patterns in PYR neurons (Figures 1C–1F).

The two major sensory stimuli during the task were the preparatory light flash and the target or non-target acoustic tones. The preparatory cue triggered small but significant responses in PYR, PV, and VIP neurons but little response in SST neurons. Following the presentation of a tone, PV neurons showed robust responses, whereas other cell types showed no tone-triggered response. Cell-type specific responses were especially visible during licking. PV neurons responded at lick onset and offset, SST neurons at lick onset, and VIP at lick offset. PYR neurons often responded at lick onset but again in a heterogeneous way, with variable latency.

In the final phase of the trial, Pinot and Dan (2015) discovered that dmPFC GABA-ergic interneurons exhibited distinct responses depending on whether the outcome was a reward or a punishment, consistent with previous studies (Courtin et al., 2014; Kvitsiani et al., 2013). Once again, PYR neurons behaved heterogeneously while PV neurons non-selectively responded to both the reward and punishment. The activity of SST neurons, however, was mostly lick-related and exhibited little response to trial outcome. VIP neurons were more selective and responded more to airpuff punishment than to water reward, in line with a recent study of these cells in auditory cortex (Pi et al., 2013). Intriguingly, the outcome of the trial affected both behavior and dmPFC coding in the subsequent trial. Following a punishment but not a reward, Pinto and Dan (2015) observed a larger response to the preparatory visual cue in PYR and VIP neurons and a significant enhancement of the mouse's behavioral performance. The neural mechanisms underlying the adaptive control of behavioral outcome and dmPFC coding will be a fascinating target for future experiments in which the probability of a reward/punishment is manipulated.

The cross-correlation of neuronal activity is a classic analysis tool to assess putative functional connectivity (Fujisawa et al., 2008) and to highlight synchronized or rhythmic firing during information processing. As expected from the response patterns during the task, the calcium responses of PYR neurons were weakly correlated whereas GABA-ergic neurons displayed high levels of correlated activity within their respective groups, even for cells separated by a distance of 200 μm. A recent study in dmPFC using extracellular electrophysiological recordings showed that PV and SST neurons displayed distinct firing patterns during a reward behavior at relatively slow timescale (Kvitsiani et al., 2013). Interestingly, Kvitsiani et al. (2013) found that at a faster time scale (< 5 ms) significant correlations were present in PV but not in SST neurons. Thus, although Pinto and Dan (2015) observed consistent intra-type tuning curves in GABA-ergic interneurons on long time scales, distinct processing strategies may exist between groups at time scales as yet undetectable by calcium imaging.

Previous work in PFC has shown the importance of local inhibition in regulating PFC processing and behavioral output (Constantinidis et al., 2002; Courtin et al., 2014; Kvitsiani et al., 2013). The study by Pinto and Dan (2015), to our knowledge, represents the first time that the functional calcium responses of 3 major subclasses of interneurons have been directly compared in mPFC to cover sensory, motor and motivational aspects of behavior through a single trained behavioral task. The dataset permitted a comprehensive comparison of the responses of different interneuron types during the same behavior. Interneuron responses were correlated remarkably strongly within subgroup and exhibited some response features similar to that observed in other cortical regions. PV neurons had homogenous, non-selective responses to almost all phases of behavior. This resembles the broad tuning of PV neurons to sensory input in sensory cortices and their homogeneous responses during the initiation of voluntary arm movements in the motor cortex (Isomura et al., 2009). VIP neurons showed an enhanced response to aversive stimuli, resembling their activity in auditory cortex (Pi et al., 2013). The cortex-wide punishment response suggests that neuromodulators may be important regulators of VIP neuron firing, which is

correlated even when cells lie at some distance from each other; more evidence comes from the hallmark expression of nicotinic cholinergic and serotonergic receptors on VIP neurons. In sensory cortex, SST neurons show reduced firing during movement (Gentet et al., 2012; Lee et al., 2013), thus the strong activation of SST neurons during licking sequences reported by Pinto and Dan (2015) comes as a surprise. This suggests that local factors may influence SST responses. The next step will be to measure the impact of these subtypes on local neural computation and behavioral output in the dmPFC using simultaneous recordings and optogenetic manipulations.

In sharp contrast to GABA-ergic neurons, PYR neurons showed heterogeneous responses across all task-related phases. This diversity of responses may reflect differences in the wiring of subtypes of glutamatergic excitatory neurons that can be distinguished at a molecular level. Recent studies using cre-driver lines, axonal anatomy and levels of immediate early gene expression (Jouhanneau et al., 2014) have categorize functional differences in pyramidal neuron subsets. Taking similar approaches to dmPFC may reveal whether the association of cell types with specific responses extends beyond GABA-ergic neurons.

Thus Pinto and Dan (2015) provide a new window into the neural machinery of sensory-based decisions in dmPFC. The next years will see manipulations of these cell types and a growth of comparative data from other PFC and cortical regions. Such work will be a key step along the path to defining the mechanisms in cells and networks that underlie sensory-triggered decisions, and determining the impact of GABA-ergic interneurons on local processing and behavior.

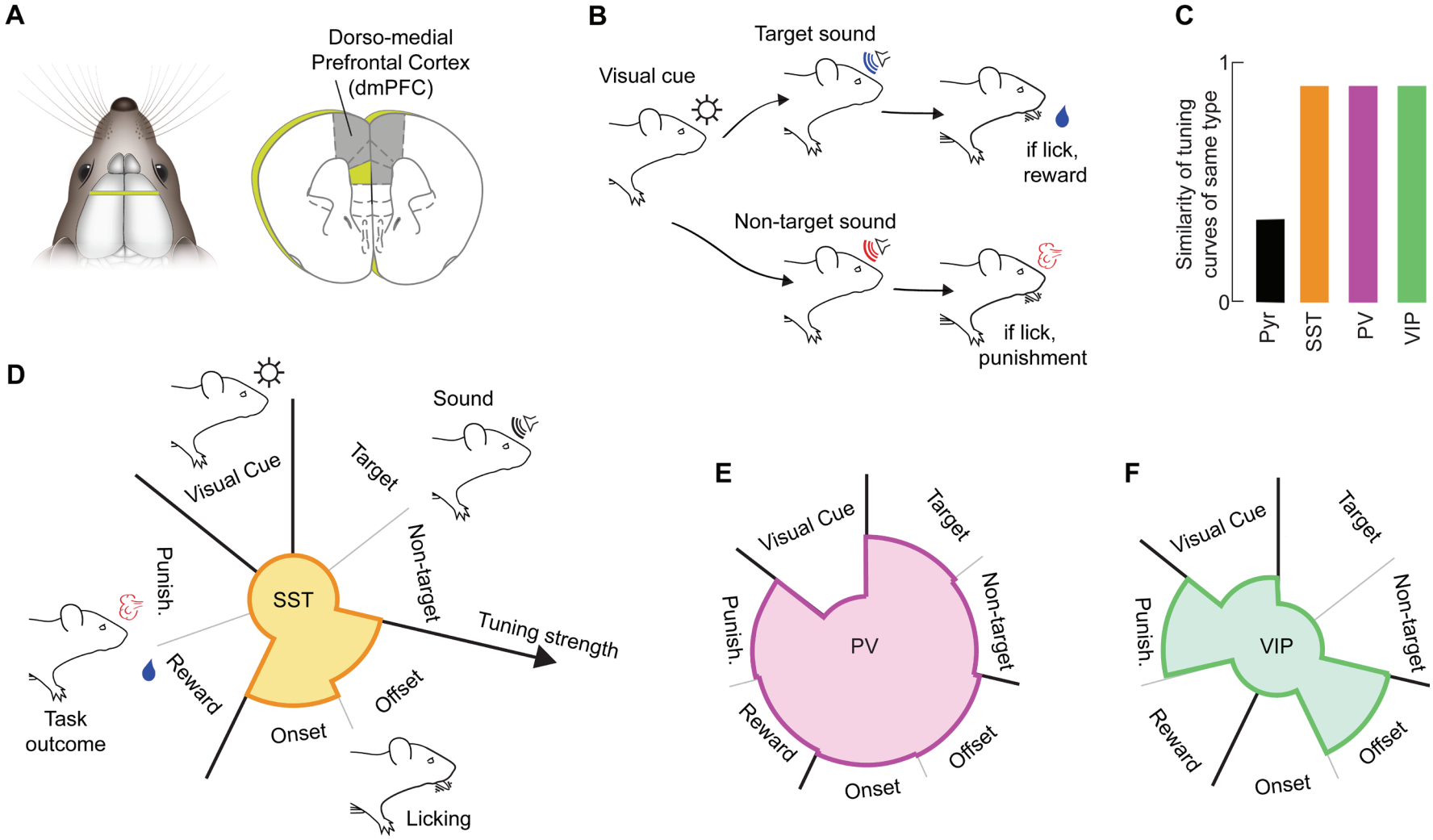
A
Dorso-medial
Prefrontal Cortex
(dmPFC)
B
Visual cue
Target sound
if lick,
reward
Non-target sound
if lick,
punishment
C
Similarity of tuning
curves of same type
1
0
Pyr
SST
PV
VIP
D
Visual Cue
Target
Sound
Non-target
Tuning strength
Offset
Onset
Licking
Reward
Punish.
Task
outcome
SST
E
Visual Cue
Target
Non-target
Offset
Onset
Reward
Punish.
PV
F
Visual Cue
Target
Non-target
Offset
Onset
Reward
Punish.
VIP

FIGURE LEGEND

Figure 1. Cell type-specific functional response tuning in dmPFC to task related events in a GO / NO-GO sensory discrimination behavior.

(A) Left: cartoon mouse brain with coronal slice of recording site highlighted in yellow. Right: cartoon of the slice showing the dorso-medial prefrontal cortex (gray area). Highlighted yellow section shows imaging site, the right prelimbic cortex.

(B) GO / NO-GO behavioral task. Following a visual cue, the mouse was exposed to a sound with either a target or a non-target frequency. Licking in a 1.5-s response window after the target tone was rewarded by water, while licking following the non-target tone was punished with an air puff. If the mouse failed to lick there was no reward or punishment.

(C) Schematic showing the similarity of the response tuning of neurons of the same subtype. Note the high correlation among interneuron subtypes versus the difference of activity between PYR neurons.

(D) Schematic showing functional response tuning of calcium signal in SST interneurons to sensory, motor and motivational features of a GO / NO-GO behavior.

(D) Same as D but for PV interneurons.

(E) Same as D but for VIP interneurons.

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