Journal Club

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Mediodorsal Thalamus and Prefrontal Cortex: Specialized Partners in Cognitive Control

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Review of DeNicola et al.

In our daily lives, the appropriate course of action depends on the context in which we find ourselves. Context is informed by a combination of internal states, including rules and goals (e.g., traffic laws and our current destination) and external cues (e.g., a pedestrian in the crosswalk or a detour sign), which we use to flexibly adapt behavior. This process is referred to as cognitive control, and is severely impaired in schizophrenia, a disease most commonly recognized for hallucinations and delusions. Current pharmacotherapies do not successfully alleviate cognitive symptoms (MacKenzie et al., 2018), leading to poorer functioning and quality of life for individuals with schizophrenia (Fett et al., 2011). To understand the etiology of cognitive control deficits, it will be necessary to delineate the neural circuits and dynamics that support cognitive control in the healthy state.

Many cognitive processes, including working memory, abstract reasoning, and cognitive control have been attributed to the prefrontal cortex (PFC), but the mediodorsal thalamus (MD), which is reciprocally connected with PFC, has increasingly

been recognized as an active partner in cognition (Wolff and Vann, 2019). Furthermore, multiple studies have documented reduced MD volume and cell number (Pakkenberg, 1990; Zipursky et al., 1992), as well as reduced MD–PFC coupling in people with schizophrenia (Minzenberg et al., 2009; Anticevic et al., 2014). This has led to the hypothesis that altered information transfer between MD and PFC contributes to schizophrenia symptoms, including cognitive control deficits. Most of what we have gleaned from nonhuman primates about the role of MD in cognitive control comes from irreversible lesion studies, which suggest that MD is important in learning new strategies to guide behavior and in adaptive decision-making, but not the maintenance of previously learned information or task rules (Mitchell et al., 2007). However, little was known about how the activity of neurons in both structures regulates cognitive control. DeNicola et al. (2020) recently investigated this question.

The authors trained monkeys to perform a dot-pattern expectancy (DPX) task, originally developed in humans (Jones et al., 2010). This task probes the following two essential components of cognitive control: the ability to represent internal states (e.g., goals or rules) and to retain and use those goals and rules to flexibly guide behavior. First, a dot pattern visual cue (A or B) is presented that indicates how the subject should respond to a subsequently presented

probe dot pattern (X or Y) to receive reward. For example, the A cue followed by an X probe indicates that the subject should make a leftward joystick movement. All other cue–probe sequences (BX, BY, AY) require a rightward joystick movement. In this way, A and B serve as contextual cues that indicate the rule (i.e., internal state) that informs the appropriate motor response when the probe appears. The frequency with which cue–probe sequences are presented can be varied to manipulate the load on cognitive control. For instance, when AX is presented more often than all other sequences, the A cue and X probe become strongly associated with a rewarded leftward joystick response. This increases the difficulty of AY and BX trials, which require subjects to make a rightward response, as the leftward joystick movement is the expected, or prepotent, response. By comparing performance in balanced (equal number of AX, AY, BX, and BY trials) versus prepotent (AX = 69% of trials, while 31% were AY, BX, or BY) trial set conditions, researchers can determine how neural activity and performance change when cognitive control load increases.

To examine how single-neuron activity in MD and PFC relates to cognitive control, DeNicola et al. (2020) used electrode arrays to simultaneously record single units in both structures while monkeys performed the DPX task. Recordings suggested that MD and PFC are specialized

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for different aspects of cognitive control. Neurons whose firing rate significantly varied as a function of cue, probe, or response were identified within MD and PFC. While both regions had a similar proportion of neurons that encoded cue information, MD contained more probe- and response-selective neurons compared with PFC. To examine the strength of information encoding at the population level in MD and PFC, the authors computed the population average proportion of explainable variance (PEV) time course for each task variable. The population average PEV attributable to cue, probe, and joystick movements were each significantly larger in MD compared with PFC during the probe period, when cue and probe information must be integrated to select the appropriate joystick movement. In addition, time-resolved decoding analysis revealed that MD populations better predicted accuracy and response time on a trial-by-trial basis. Together, these data suggest that neural signals within MD most strongly represent the integration of cue and probe information that leads to a motor decision.

Conversely, certain features of PFC activity suggest that it represents cognitive load to a greater extent than MD. For example, during prepotent trials, cue-related PEV signals emerged earlier in PFC than in MD. Additionally, during prepotent trials, the cue could be better decoded from the activity of PFC neurons than from MD neurons, and this was exaggerated for B cues. This is notable because monkeys most frequently made errors on BX trials, indicating that this trial type was the most cognitively demanding. During BX error trials, PEV attributable to cue was significantly suppressed in PFC and MD compared with correct trials, suggesting that weak encoding of the B cue was associated with failure to inhibit the prepotent response to the X probe. Finally, neurons in PFC but not MD showed selectivity for Y probes over X probes, consistent with a bias for representing stimuli associated with the infrequent joystick response. Together, these data suggest that PFC does not represent all task information equally, but rather emphasizes cue and probe encoding on trials in which the prepotent response must be overridden. This pattern of engagement may reflect the response of PFC to increased cognitive control load and result in better performance. How do MD and PFC work together to mediate cognitive control? Functional coupling between MD and PFC, assessed by how

neural representations of task variables covaried in time, was bidirectional and most prominent among neurons that encoded the probe at the time when cue and probe stimulus representations had to be integrated to guide the motor response. The authors conclude that MD is specialized for decision-making and response selection, whereas PFC represents task space by responding to changes in cognitive load.

These experiments complement several recent studies in rodents regarding the role of reciprocal interactions between MD and PFC in cognitive control and flexibility. For example, Schmitt et al. (2017) used a crossmodal cognitive flexibility task to demonstrate that MD neurons pool input from PFC neurons to help PFC learn task rules and cueing contexts in mice. MD neurons also provide excitation to GABAergic fast-spiking (FS) interneurons to suppress cue-selective neurons in PFC that represent the irrelevant context (Schmitt et al., 2017; Rikhye et al., 2018). These data lend support to the conclusion in the study by DeNicola et al. (2020) that the PFC provides important state information within the DPX task and raises the question of whether MD helps PFC represent the relevant internal state (or suppress distracting or irrelevant state information) through the recruitment of local FS interneurons in primates, a mechanism previously characterized in rodents (Delevich et al., 2015; Ferguson and Gao, 2018b).

Finally, the conclusions from this study provide new opportunities to explore how MD and PFC function under pathologic conditions. Individuals with schizophrenia exhibit deficits in the DPX task only when cognitive load is high (Jones et al., 2010), and alterations in both MD and PFC structure and function feature prominently in schizophrenia. Additionally, FS interneuron pathology has been documented widely in postmortem studies (Lewis et al., 2012), as well as in a range of animal studies modeling cognitive endophenotypes of the disease (Ferguson and Gao, 2018a). Together, these data motivate a model in which abnormal FS interneuron activity in PFC and dysregulated MD–PFC circuit function converge to give rise to cognitive control deficits in schizophrenia. NMDA receptor antagonists powerfully regulate prefrontal FS interneuron activity in rodents (Homayoun and Moghaddam, 2007) and produce cognitive control deficits in both animal models and humans (Morris et al., 2005). Thus, incorporating NMDA receptor antagonists

in future studies could relate changes in physiological signatures of DPX task performance to deficits in cognitive control and FS interneuron hypofunction. For example, suppressing FS interneuron firing may degrade the ability of PFC neurons in PFC to encode the cue stimulus, leading to incorrect response encoding within MD and behavioral errors on trials that require a high degree of cognitive control (e.g., BX). Furthermore, recording PFC FS interneurons could reveal how their activity relates to the encoding of task variables and cognitive control.

In summary, converging evidence highlights the MD–PFC circuit as a key hub in cognitive control and schizophrenia pathophysiology. DeNicola et al. (2020) lay additional groundwork for understanding how alterations in MD–PFC circuit function lead to specific cognitive impairments. By directly translating a well validated human task to nonhuman primates, they bridge psychiatry and systems neuroscience approaches to reveal circuit mechanisms of clinically relevant aspects of cognition.

References

- Anticevic A, Cole MW, Repovs G, Murray JD, Brumbaugh MS, Winkler AM, Savic A, Krystal JH, Pearlson GD, Glahn DC (2014) Characterizing thalamo-cortical disturbances in schizophrenia and bipolar illness. *Cereb Cortex* 24:3116–3130.
- Delevich K, Tucciarone J, Huang ZJ, Li B (2015) The mediodorsal thalamus drives feedforward inhibition in the anterior cingulate cortex via parvalbumin interneurons. *J Neurosci* 35:5743–5753.
- DeNicola AL, Park MY, Crowe DA, MacDonald AW, Chafee MV (2020) Differential roles of mediodorsal nucleus of the thalamus and prefrontal cortex in decision-making and state representation in a cognitive control task measuring deficits in schizophrenia. *J Neurosci* 40:1650–1667.
- Ferguson BR, Gao WJ (2018a) Pv interneurons: critical regulators of E/I balance for prefrontal cortex-dependent behavior and psychiatric disorders. *Front Neural Circuits* 12:37.
- Ferguson BR, Gao WJ (2018b) Thalamic control of cognition and social behavior via regulation of gamma-aminobutyric acid signaling and excitation/inhibition balance in the medial prefrontal cortex. *Biol Psychiatry* 83:657–669.
- Fett AK, Viechtbauer W, Dominguez MD, Penn DL, van Os J, Krabbendam L (2011) The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: a meta-analysis. *Neurosci Biobehav Rev* 35:573–588.
- Homayoun H, Moghaddam B (2007) NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. *J Neurosci* 27:11496–11500.

- Jones JA, Sponheim SR, MacDonald AW 3rd (2010) The dot pattern expectancy task: reliability and replication of deficits in schizophrenia. *Psychol Assess* 22:131–141.
- Lewis DA, Curley AA, Glausier JR, Volk DW (2012) Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends Neurosci* 35:57–67.
- MacKenzie NE, Kowalchuk C, Agarwal SM, Costa-Dookhan KA, Caravaggio F, Gerretsen P, Chintoh A, Remington GJ, Taylor VH, Müller DJ, Graff-Guerrero A, Hahn MK (2018) Antipsychotics, metabolic adverse effects, and cognitive function in schizophrenia. *Front Psychiatry* 9:622.
- Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC (2009) Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch Gen Psychiatry* 66:811–822.
- Mitchell AS, Baxter MG, Gaffan D (2007) Dissociable performance on scene learning and strategy implementation after lesions to magnocellular mediodorsal thalamic nucleus. *J Neurosci* 27:11888–11895.
- Morris BJ, Cochran SM, Pratt JA (2005) PCP: from pharmacology to modelling schizophrenia. *Curr Opin Pharmacol* 5:101–106.
- Pakkenberg B (1990) Pronounced reduction of total neuron number in mediodorsal thalamic nucleus and nucleus accumbens in schizophrenics. *Arch Gen Psychiatry* 47:1023–1028.
- Rikhye RV, Gilra A, Halassa MM (2018) Thalamic regulation of switching between cortical representations enables cognitive flexibility. *Nat Neurosci* 21:1753–1763.
- Schmitt LI, Wimmer RD, Nakajima M, Happ M, Mofakham S, Halassa MM (2017) Thalamic amplification of cortical connectivity sustains attentional control. *Nature* 545:219–223.
- Wolff M, Vann SD (2019) The cognitive thalamus as a gateway to mental representations. *J Neurosci* 39:3–14.
- Zipursky RB, Lim KO, Sullivan EV, Brown BW, Pfefferbaum A (1992) Widespread cerebral gray matter volume deficits in schizophrenia. *Arch Gen Psychiatry* 49:195–205.