Biological Psychiatry

Commentary

Medial Prefrontal Cortex Excitation/Inhibition Balance and Schizophrenia-like Behaviors Regulated by Thalamic Inputs to Interneurons

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The prefrontal cortex (PFC) is a pivotal brain area for higher-order cognition and executive control. Functional neuroimaging studies have revealed the dysfunction of PFC in patients with schizophrenia (1). Dysfunction was also found in the mediodorsal thalamus (MD), which represents a main subcortical structure that has a strong reciprocal connection with the PFC and in thalamofrontal connectivity in schizophrenia (1). Consequently, there has been great interest in dissecting the relationship between the hypofunction of thalamofrontal circuitry and schizophrenia. However, a clear understanding of the thalamofrontal interplay in normal and disease states seems to be lacking at the neural circuit level. It remains pivotal to understand how the MD and PFC interact at the single-cell level to generate associated cognitive functions and how the alteration of their interaction may contribute to cognitive dysfunction in schizophrenia.

This understanding is addressed in this issue of *Biological Psychiatry* by Ferguson and Gao (2), who investigated two key questions: 1) How does MD communicate with different cell types within the medial PFC (mPFC) to regulate its excitation/inhibition (E/I) balance? and 2) How does suppression of MD shift the E/I balance in the mPFC to induce deficits in both cognitive abilities and social interactions? Their main approaches involve pharmacogenetic inhibition, electrophysiological recording, and behavior tests after MD inhibition. Anatomical studies have shown that MD sends mostly excitatory projections to the mPFC, to both layer III parvalbumin-expressing interneurons (PVIs) and layer V pyramidal neurons (PNs), suggesting that MD may exert a dual influence on PFC PN neurons (3). Ferguson and Gao (2) hypothesized that MD projection may be stronger onto PVIs than to layer V PNs (Figure 1); thus, decreasing the MD activity may disturb the mPFC E/I balance and cause cognitive dysfunction. To test this hypothesis, they first used inhibitory G protein–coupled designer receptors exclusively activated by designer drugs (DREADDs) to decrease MD activity and evaluated the consequences of downregulating MD activity on individual mPFC neurons with whole-cell patch clamp recordings. Indeed, dampening MD activity caused a decrease in frequency of spontaneous excitatory postsynaptic currents in both PNs and fast-spiking neurons (which are putative PVIs), and a decrease in evoked inhibitory postsynaptic currents but no change in evoked excitatory postsynaptic currents. This altered E/I balance was rescued by indiplon, a gamma-aminobutyric acid type A receptor–positive allosteric modulator. At the behavioral level, mice with MD inhibition showed impairments in working memory task, set-shifting task, and social interaction, which are schizophrenia-like. Intriguingly, by using a Gq protein–coupled DREADD to selectively activate mPFC PVIs, they were able to to normalize the E/I ratio in vitro and efficiently alleviated the behavioral deficits in vivo. These results are summarized in Figure 1.

Feedforward inhibition helps restrain the time window during which PNs integrate excitatory inputs and gate spike output. It has been shown to be a common feature of interaction between sensory thalamus and related sensory cortex (4). However, whether feedforward inhibition also exists between high order thalamus and mPFC needs to be further clarified. Delevich *et al.* (5) found earlier a feedforward inhibition in the MD to the dorsal anterior cingulate (a subregion of the mPFC) layer III PNs, mediated by PVIs. Here Ferguson and Gao (2) also found a feedforward inhibition from MD onto the mPFC layer V PNs. However, while Delevich *et al.* (5) found similar strength of thalamocortical synapses onto PVIs and layer III PNs, Ferguson and Gao's study (2) suggested that the strength of thalamocortical synapses onto PVIs may be stronger than that onto layer V PNs.

Ferguson and Gao's findings (2) also underscore the importance of thalamocortical activation of mPFC gamma-aminobutyric acidergic interneurons in an extensive range of mPFC-dependent behaviors. Two key sets of symptoms of schizophrenia were evaluated here: the cognitive symptoms, including working memory and behavioral flexibility, were tested by a delayed nonmatch to sample paradigm and a set-shifting task; and the negative symptoms, including lack of social motivation and abnormalities in social interaction, were tested by the social preference and social novelty tests. In the delayed nonmatch to sample paradigm task, they found that reduction of MD activity did not affect the acquisition but did worsen the performance only at the 60-second delay interval, which suggests that MD is specifically involved in the maintenance of representations critical for working memory instead of general task learning. These results are consistent with previous publications [for review, see Parnaudeau *et al.* (3)]. For example, Scott *et al.* (6) demonstrated that MD to mPFC helps working memory retention during the delay period and that mPFC to MD guided subsequent choice. In the set-shifting task, they found that MD inhibition induced deficits in performance of initial association that was reversed by maintaining the original E/I balance through DREADD activation of PVIs. However, deficits in reversal learning could not be rescued by

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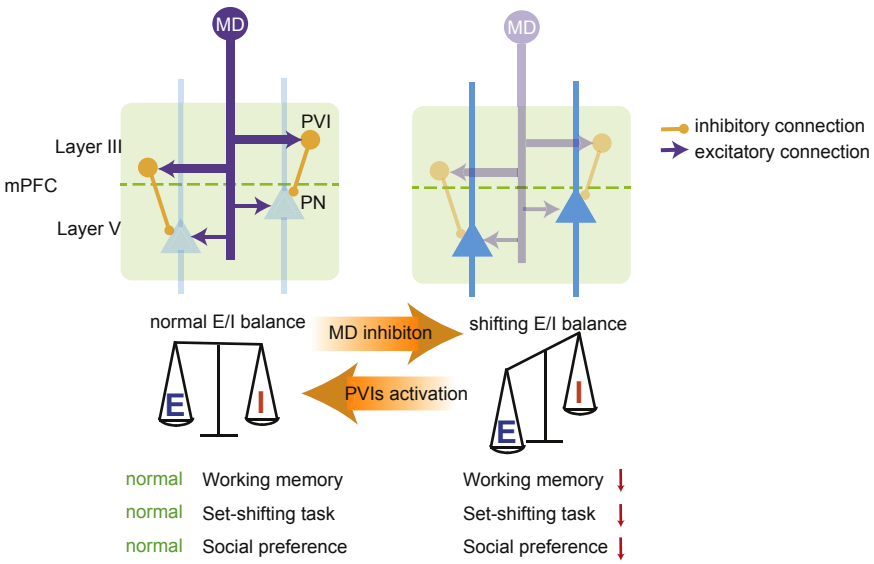

Figure 1. Illustration of the main findings from Ferguson and Gao (2). Dampening activity of the mediodorsal thalamus (MD) causes a remarkable decrease in parvalbumin-expressing interneurons (PVIs) activity, resulting in an altered excitation/inhibition (E/I) balance in the medial prefrontal cortex (mPFC). Mice with MD inhibition show impairments in working memory task, set-shifting task, and social preference. Blue triangles and orange circles represent pyramidal neurons (PNs) and PVIs in the mPFC, respectively. Purple circles represent MD neurons.

activation of PVIs in mPFC, which makes sense because reversal learning has been linked to the MD and the lateral orbitofrontal cortex (3) but not the mPFC. As for the negative symptoms of schizophrenia, Ferguson and Gao (2) found that MD inhibition abolished the preference to social object in the three-chamber test. This defect is in line with accumulating data showing the function of the MD in social behavior: social interaction activates a large portion of MD neurons (7). Synaptic weakening of the MD–dmPFC pathway in social defeated mice paralleled the development of social avoidance (8). Conversely, synaptic strengthening of the MD–dmPFC pathway increased winning possibility in social competitions (9). Again, Ferguson and Gao (2) found that the social preference deficit could be reversed by activation of PVIs to maintain the origin E/I balance in mPFC. Together with earlier lines of evidence (10), these data suggest that an appropriate E/I ratio in the PFC is required for social motivation in mice.

In conclusion, Ferguson and Gao (2) provide a comprehensive set of data regarding a PVIs-mediated feedforward inhibition mechanism from the MD to the mPFC, which is important for regulating E/I balance and improving mPFC-dependent behaviors. The results are likely to inspire more studies to further explore the nature of the communications between the thalamus and cortex. Understanding how dysfunction in this circuit leads to cognitive and social impairments in psychiatric diseases will be of high clinical relevance.

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Article Information

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