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Experimental Research Article

Visual attention modulation by the dopaminergic system in the medial prefrontal cortex (mPFC)

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ABSTRACT

Introduction: Visual attention is a cognitive function that impairment in it can lead to multiple psychological and cognitive disorders such as ADHD, ADD, neglect, Alzheimer and schizophrenia. Dopamine, as a main neuromodulator of attention produced in midbrain neurons that project to the prefrontal cortex (PFC). This research aims to examine the role of dopamine in membrane potential regulation in the prefrontal region in modulating visual attention.

Methods: Eight-week-old mice of both sexes were anesthetized with urethane and then underwent cranial surgery in the mPFC area. The effects of ventral tegmental area (VTA) stimulation, PFC inhibition with muscimol, and local injection of flupentixol on visual attention were investigated using the in vivo whole-cell Patch clamp technique in both anesthetized and awake states. To demonstrate whether dopaminergic receptors in the mPFC area are involved in the observed changes under the current condition, the non-selective antagonist of dopamine receptors (flupentixol) was used.

Results: Our findings indicate that PFC inhibition significantly disrupts visual attention, as evidenced by decreased response accuracy in attention tasks. Conversely, VTA stimulation resulted in reduced neuronal firing rates, further impairing attention. Flupentixol administration resulted in reduced response accuracy and decreased neuronal spike rate, highlighting the importance of dopamine receptor activity in attention modulation

Conclusion: These results underscore the complex role of dopamine as a neuromodulator in visual attention processes and highlight the importance of the PFC in attention regulation. Understanding the interplay between the dopaminergic system and the PFC may provide insights into the pathophysiology of attention-related disorders.

Keywords:
Dopaminergic system
Visual attention
Prefrontal cortex
In vivo -whole- cell patch clamp

Introduction

Attention is a means by which relevant behavioral information is selected while the rest is ignored (Clark et al., 2015). Visual attention is one of the most important cognitive functions, especially in primates and animals where vision is the dominant sense (Corbetta et

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al., 1991; Jonikaitis and Moore 2019). Visual attention plays a crucial role in guiding behavior. It serves as a mechanism for selecting the most appropriate behavior among multiple candidates, taking into account both exogenous data from the environment and endogenous data from the subject's internal state (Kamigaki 2019). Impairments in visual processing and cognitive functions such as visual attention are significantly observed in populations with dopamine dysfunction disorders such as Parkinson's disease (PD), schizophrenia, and attention deficit hyperactivity disorder (ADHD) (Bahmani et al., 2019).

Attention, working memory, and other higher cognitive functions are dependent on the prefrontal cortex. Studies in primates have demonstrated the role of prefrontal catecholamines in controlling cognitive functions (Clark and Noudoost 2014a). It appears that the prefrontal cortex filters sensory-related information for executive control, albeit through an unknown mechanism (Anderson et al., 2011; Everling et al., 2002; McNab and Klingberg 2008; Shimamura 2000). Many of these cognitive functions are disrupted by mental disorders such as schizophrenia. Specifically, drugs that alter the signaling of catecholamines alleviate some of the psychiatric disorder symptoms. In fact, the imbalance of prefrontal catecholamines is responsible for the cognitive components of this psychiatric disorder (Clark and Noudoost 2014a).

Dopamine is also one of the major neurotransmitters in the brain, which is produced in the midbrain neurons. Dopaminergic axons reach the PFC region from the midbrain. Dopamine is not a stimulatory or inhibitory neurotransmitter, but it has a neuromodulatory effect (Seamans and Yang 2004). Dopamine indirectly regulates the transmission of synaptic information by either increasing or decreasing synaptic transmission (Noudoost and Moore 2011). Evidence suggests that dopamine affects different types of cells involved in various aspects of executive control in different ways (Mueller et al., 2020; Veit and Nieder 2013). Studies indicate that dopaminergic signals have different effects on the neural networks of the brain cortex and, more importantly, they carry out multiple functions (Thiele et al., 2016).

Both pyramidal and interneuronal cells express all dopamine receptors. The expected functional roles of dopamine vary depending on the receptor subtype, cell type, synaptic properties, and interactions with other neurotransmitters (Seamans and Yang 2004). Dopamine plays a crucial role in regulating the information flow to downstream target areas (Gazzaley and Nobre 2012; Wang 2008). Otherwise, the precise coordination of these neurons and dopamine release in executive functions like attention remains somewhat elusive. A closer examination of the various computational functions of dopamine in guiding goal-directed behavior could offer deeper insights into the workings of the dopaminergic system, particularly in the context of complex psychiatric disorders (Howe and Dombeck 2016).

Investigating the role of dopamine in cognitive control, such as visual attention, without considering the effects of reward is impossible. Dopaminergic neurons in the VTA convey reward prediction error, enabling learning (Romo and Schultz 1990). On the one hand, dopamine is a neuromodulator that plays a significant role in reward-related behavior. PFC neurons, which receive dopaminergic input from areas representing reward, have a high modulatory role in cortical activities. Both prefrontal dopamine and reward can modify the representation of goals in visual areas that mimic some of the top-down visual attention signatures (Clark and Noudoost 2014b).

So far, quantitative studies have examined the role of the dopaminergic system in controlling visual attention in the PFC region and in live animals using the whole-cell Patch clamp technique. The ability of neuroscientists to describe the neuronal mechanisms under cognitive influences has been delayed due to the difficulty of combining the anatomical and electrophysiological characteristics of neurons. By conducting this research, the pathways involved between the prefrontal cortex and the occipital region will be somewhat clarified. On the other hand, the mechanisms of dopaminergic effects in the highest brain region (mPFC) on the attention process are being investigated. Such research is a step towards identifying the etiology and treatment of attention-deficit disorders.

Materials and Methods

Behavioral Analysis

Our study commenced with the surgical implantation of a metal plate (chamber), followed by a week-long recovery period with unrestricted access to food and water (Figures 1 and 2). Subsequently, food and water intake were restricted for the duration of the training phase,

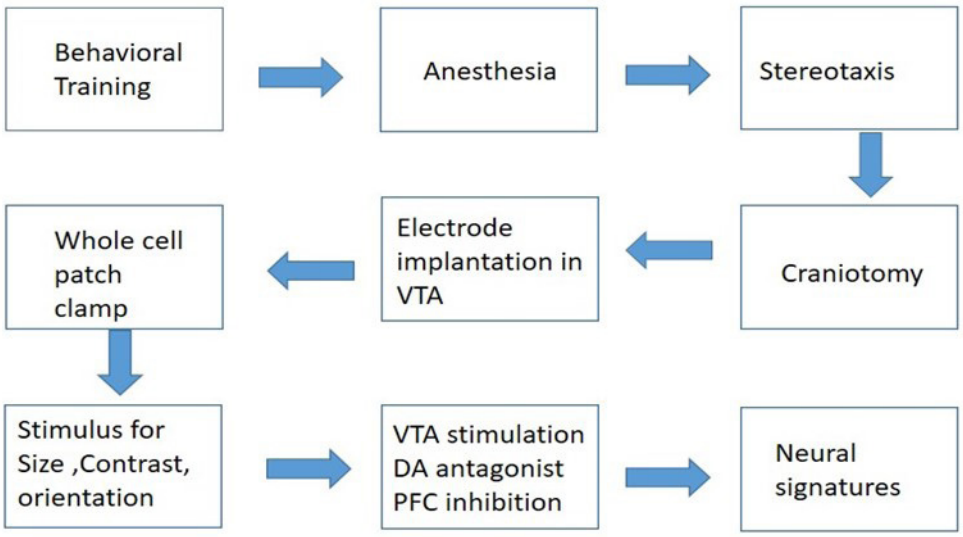

FIGURE 1. Schematic of the procedural steps related to the research protocol. This diagram outlines the ex-perimental design, including the surgical preparation of mice, the visual detection task, and the pharmacological interventions used to assess the role of the dopaminergic system in visual attention.

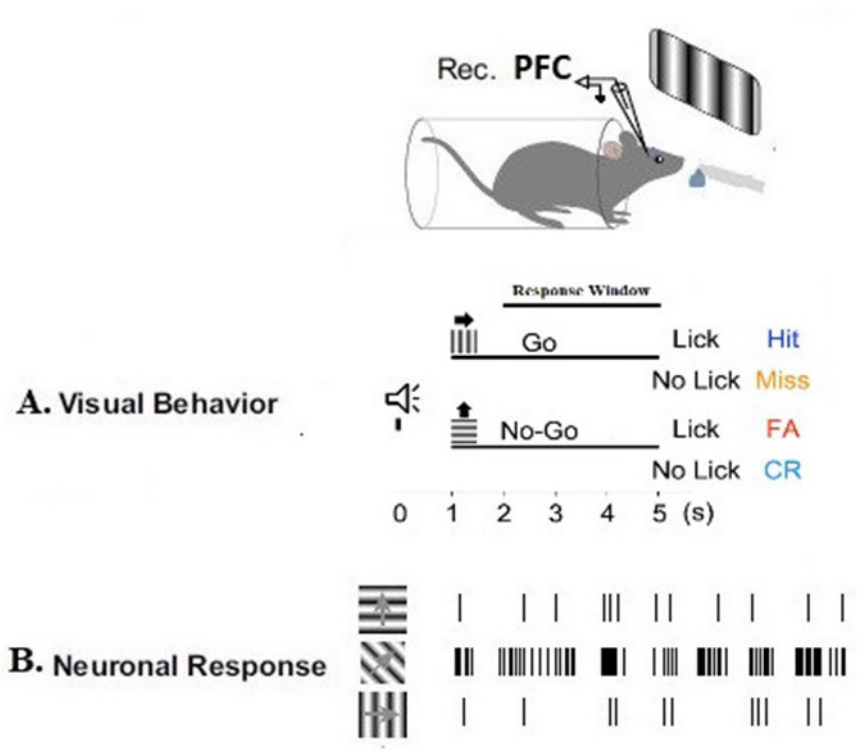

FIGURE 2. The protocol that shows visual behavior (A) and neuronal response (B). This figure illustrates the relationship between visual stimuli presentation and neuronal activity in the prefrontal cortex (PFC). It highlights the differences in neuronal firing rates during GO and NO GO trials. PFC: prefrontal cortex, FA: false alarm, CR: correct rejection.

with daily monitoring of the mice's weight during the water restriction period.

The behavioral training program began with a 1 week habituation phase, during which no visual stimuli were presented, and the mice were provided free access to water as a reward stimulus. The task involved training the mice to lick in response to a visually presented stimulus, specifically a vertically moving square wave in

conjunction with a GO stimulus. Each trial adhered to a consistent structural format: initiation with a 1.0-second tone (5 kHz), followed by the visual stimulus lasting 4 seconds, and concluding with a 5-second inter-trial interval.

Subsequently, the mice were required to discriminate between GO and NO-GO trials, with the visual stimuli randomly assigned within each trial. Licking within the designated response window of a GO trial (Hit) resulted in a water reward, while a lick during the response window of a NO-GO trial (False Alarm) led to an aversive electric shock and a subsequent 7-second timeout period. Notably, no consequences were administered for missed responses (failure to lick in a GO trial) or correct rejections (CR).

Preparing the animal (anesthesia, stereotaxis, and craniotomy)

Mice weighing between 20 to 30 grams of both genders were used in this study. Anesthetizing them with intraperitoneal injections of 10% urethane at a dosage of 1.5-2 milligrams per gram of body weight, the surgical area was shaved, an ear bar was placed in the zygomatic region, and body temperature was maintained with a temperature control device during surgery (Figure 1). Following skin and muscle removal, the mPFC area was determined by stereotactic coordinates (AP: 1.8-2 mm, DV: -2.75, and ML: 0.3 mm). A metal piece (chamber) was attached to the skull with glue and fixed with dental cement. Subsequently, a 1.5 × 2 millimeter cranial window was created with a dental drill, and the dura mater was removed, thus exposing the mPFC cortex.

Visual stimulation

The visual experiment involved the presentation of a drifting grating pattern with specific parameters: a spatial frequency of 0.04 cycles per degree, 100% contrast, and a temporal frequency of 1 Hz. A set of square-wave patterns displaying 12 different orientations at 30-degree intervals spanning from 0 to 360 degrees was shown on an LCD monitor (Eizo Nanao Flexscan L788), which was a 19-inch screen. Each pattern was displayed for 2 seconds before, 3 seconds during, and 2 seconds after each stimulus presentation, with the sequence repeated randomly three times. The LCD monitor was located at a distance of 28 cm from the animal's eyes, providing a field of vision measuring 80 by 50 degrees (Figure 2).

The dopaminergic system activation by electrical stimulation of the ventral tegmental area (VTA)

In our experimental procedure aimed at stimulating the dopaminergic projections from the ventral tegmental area (VTA) to the prefrontal cortex in mice, we employed VTA electrical stimulation. This involved the precise implantation of a bipolar tungsten electrode in the brain using a micromanipulator and a stereotaxic atlas of the mouse brain, ensuring the electrode's positioning at AP: 3.4 mm, ML: 0.4, and DV: 4.25 mm coordinates. Following the stimulation, histological validation was conducted to verify the electrode's precise placement by selectively damaging the target region, followed by slicing and microscopic observation. During the stimulation process, the VTA was electrically activated at an intensity ranging from 400 to 700 μA, with a pulse frequency set at 20 Hz, which was repeated for 10 cycles.

In vivo whole-cell patch-clamp recording

Whole-cell patch-clamp recordings were conducted on both excitatory and inhibitory neurons located within layer I at a depth ranging from 20 to 90 μm and layer II/III at a depth between 200 to 300 μm. The recording electrodes were constructed from borosilicate glass capillaries containing filaments, with an inner diameter of 0.86 mm and an outer diameter of 1.5 mm. These electrodes were filled with a specially prepared internal solution. The internal solution, with an osmolarity falling within the range of 280-290 mOsm, had its pH adjusted to mimic the intracellular environment using KOH, maintaining a level between 7.2 to 7.4. The composition of the internal solution, measured in millimolar concentrations, included CaCl2 (0.1), MgATP (4), K-Gluconate (130), Na3GTP (0.3), HEPES (10), EGTA (1), Na Phosphocreatine (10), and MgCl2 (2) (Ghaderi et al., 2018; Safari et al., 2017). The detailed methodology encompassed in this experimental approach points towards distinct layers and depths within the brain. The experiment involved measuring the resistance of electrodes within an internal solution, which ranged from 6-8 MΩ. Neuronal membrane potentials were recorded using the Axopatch 200B amplifier in current-clamp mode. Data was sampled at a rate of 20 kHz, filtered between 2 to 5 kHz, digitized at 10 kHz, and transmitted to a computer equipped with a NI-DAQ board (PCI-MIO-16E-4, National Instruments). Subsequently, custom LabVIEW software was utilized to acquire the data.

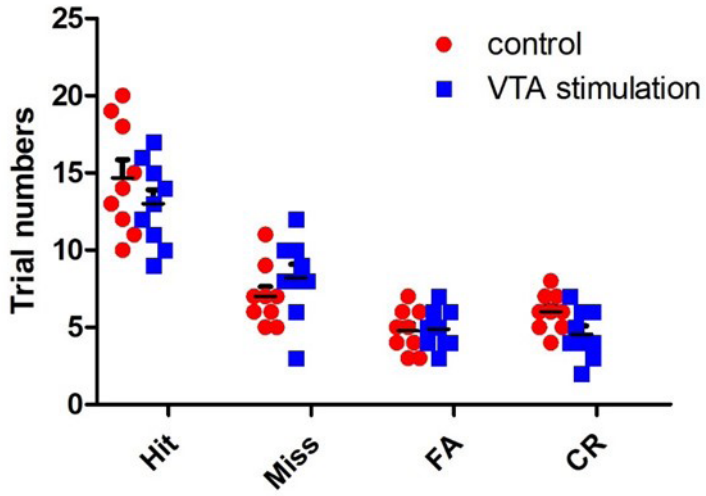

FIGURE 3. The scatter plot comparing trial numbers across different conditions: "Hit," "Miss," "FA" (False Alarm), and "CR" (Correct Rejection). The presence of error bars or means would indicate varia-bility or average performance in each condition. The difference between the four attention task variables in the control group and the VTA stimulation group was not significant (P>0.05).

The intracellular recording technique was performed blindly in anesthetized animals, predominantly focusing on neurons in the superficial layers of the visual cortex, particularly regular-spiking putative pyramidal neurons. Although the recorded data included a mix of neuron types, it primarily consisted of pyramidal excitatory neurons, which are abundant in layers II/III.

In the context of recording neural activity in awake animals, a meticulous procedure was followed to ensure optimal data collection. A mouse was positioned within a tube featuring a 2.5-centimeter inner diameter (Figure 2), with a securely affixed metal plate on its head, allowing freedom of movement for the body. Before the recording session, the mouse underwent a period of acclimatization to the head fixation process over several days. On the day of recording, a craniotomy was conducted in the prefrontal cortex (PFC) region of the mouse's brain under the influence of anesthesia, specifically ketamine and xylazine (ketamine at a dosage of 75 mg per kilogram and xylazine ranging from 5 to 10 mg per kilogram). Subsequently, the animal was allowed to recover from anesthesia, with the recording commencing approximately 1.5 hours post-recovery.

Pharmacological Analysis

The use of a drug involves adding the desired concentration of the drug to the fluid inside the chamber, taking into account the volume inside the metal plate. To demonstrate whether dopaminergic receptors in the PFC are involved in the observed changes under current conditions, the non-selective antagonist of dopamine receptors, flupentixol (Lundbeck, Denmark), was used separately. Similarly, reversible inactivation of the PFC from the GABA agonist, Muscimol (Sigma-Aldrich), was used locally applied into the chamber.

Statistical analysis

In our study, values were presented as Mean±SEM unless otherwise noted. To determine the normality of data distribution, we employed the Kolmogorov–Smirnov test. For comparing data from two conditions within the same neurons, with or without VTA stimulation, we utilized the non-parametric analysis method, the Wilcoxon signed rank test. This allowed us to statistically assess the differences between the two conditions accurately.

Results

Evaluating the behavioral test with the GO-NO GO discrimination visual task

The behavioral test in the attention task was conducted for the control group and the VTA stimulation group (Figure 3). The control group showed a higher number of hits compared to the VTA stimulation group, whereas the VTA stimulation group exhibited an increased number of misses, indicating that stimulation may negatively affect task performance. False alarm data suggested a

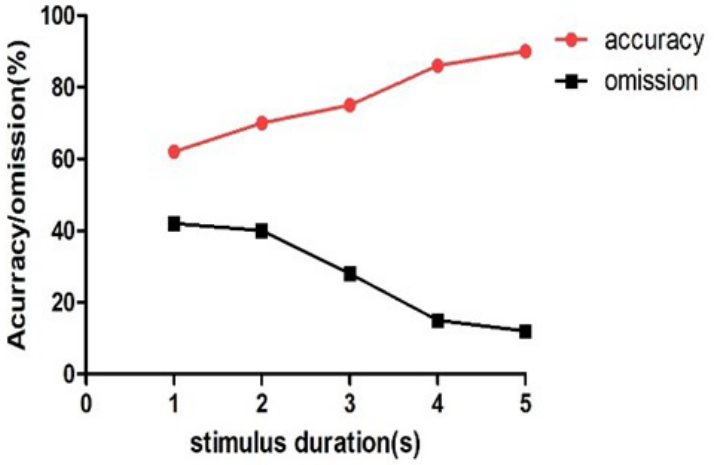

FIGURE 4. Accuracy rates and omission responses following stimulus presentation at a specific time. Stimulus duration (in seconds), ranging from 1 to 5 seconds, and accuracy/omission (%), ranging from 0 to 100%. Accuracy (red line with circles) is the percentage of correct responses and omission (black line with squares) is percentage of trials where no response was given.

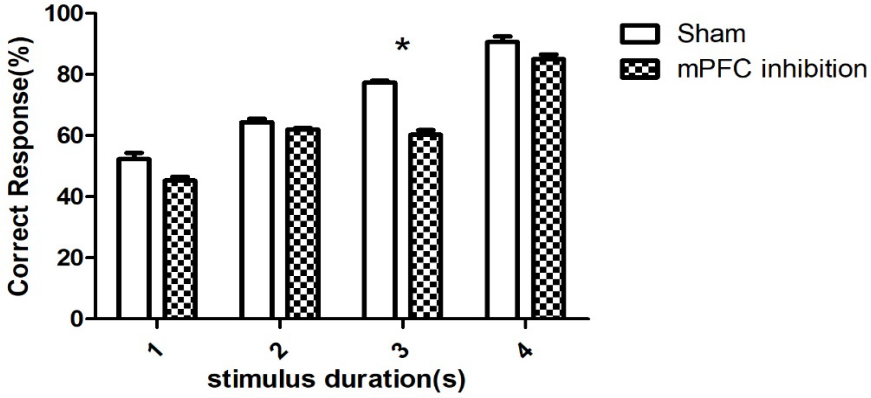

FIGURE 5. Effects of locally inactivating the mPFC region by muscimol on visual attention.
Inhibition of mPFC by muscimol (1 μM) disrupts correct responses in the visual attention task. *= $P<0.05$

possible difference in response patterns between groups. Similarly, performance in correct rejections differed, with the control group demonstrating superior ability to correctly identify non-targets. Overall, these findings indicate that VTA stimulation significantly impacts trial performance across categories, leading to reduced accuracy in target detection and non-target discrimination.

Relationship between stimulus duration and performance

The relationship between stimulus duration and task performance was evaluated using two measures: accuracy and omission rate (Figure 4). Omission rate was defined as the failure to respond to the target within the required time. Accuracy showed a clear positive relationship with stimulus duration, increasing from approximately 60% at 1 second to nearly 90% at 5 seconds, suggesting that longer exposure allows for improved stimulus processing. Conversely, omission rate demonstrated a negative relationship, decreasing from about 40% at 1 second to nearly 15% at 5 seconds, indicating that subjects were less likely to miss responding when given more time. These findings suggest that longer stimulus durations enhance decision-making by allowing for the continuous accumulation of information, resulting in improved accuracy and reduced omission rates. Optimal performance was observed at the longest stimulus duration tested (5 seconds).

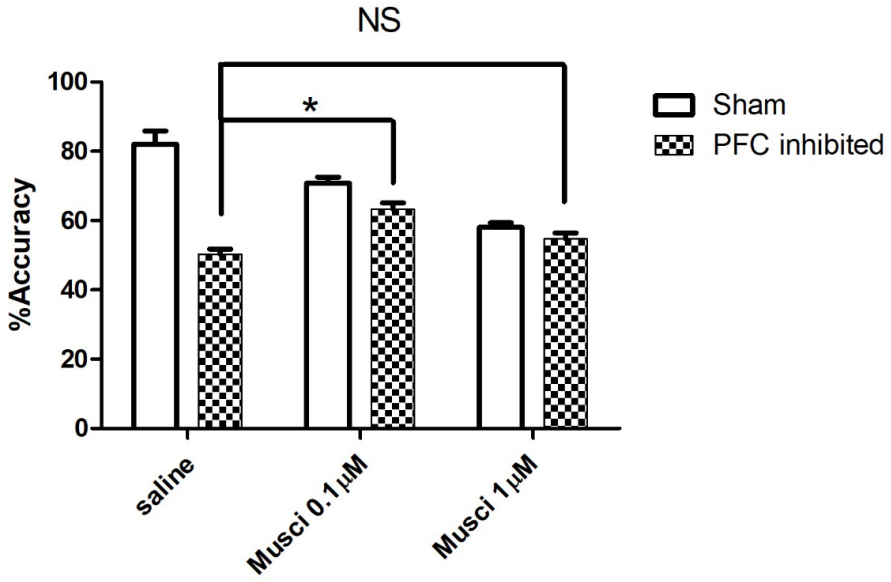

FIGURE 6. The effect of PFC inhibition with muscimol on the percentage of correct responses in the attention task, showing significant improvement with a low dose (0.1 μM). *= P<0.05, NS: Not significant

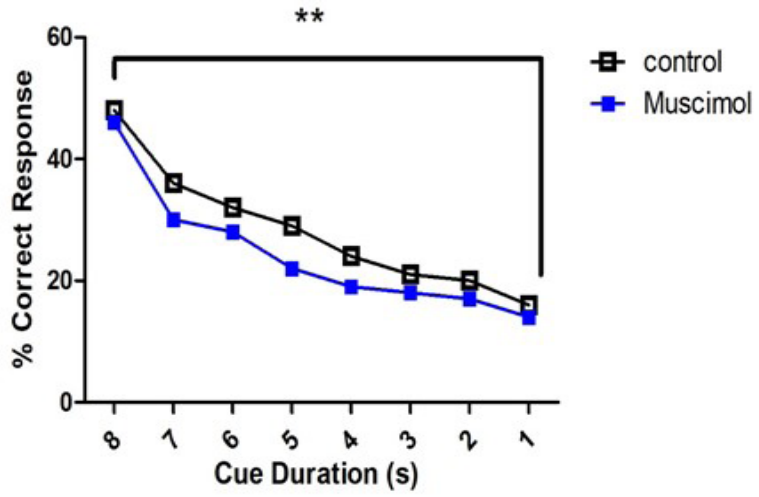

FIGURE 7. Significant reduction in correct responses is observed with mPFC inhibition by muscimol (1 μM) compared to the sham group (n=7 in each group). **= P<0.005

Effects of local inactivation of the mPFC by muscimol on visual attention

In this study, we locally added two doses of 0.1 and 1 micromolar of muscimol to the chamber to deactivate the mPFC. This dosage of muscimol can deactivate around 1 square millimeter of cortex without affecting the surrounding areas (Salkoff et al., 2019). The effects of muscimol on deactivating the cortex are reversible.

We evaluated the effect of stimulus duration on correct response rates under two conditions: sham treatment and PFC inhibition (with muscimol 1 μM) (Figure 5). Both conditions showed increased correct response rates as stimulus duration increased. However, the sham condition consistently produced higher correct response rates than the PFC inhibition condition. The difference between conditions is most pronounced at the 3-second stimulus duration ($p<0.05$), where a significant reduction in correct responses was observed in the mPFC inhibition group compared to sham ($p<0.05$). Overall, longer stimulus durations improved task performance

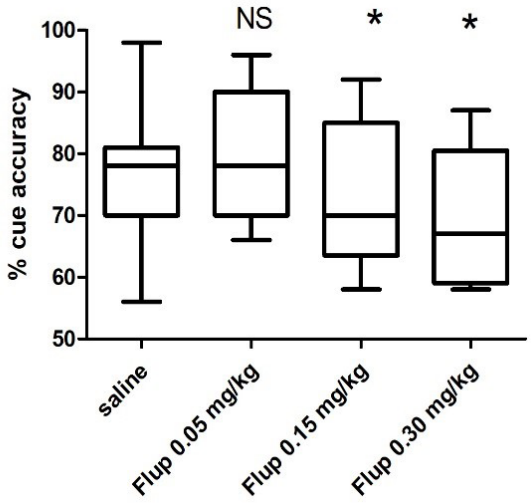

FIGURE 8. The effects of locally prescribing a flupentixol in the PFC region. The percentage of response accuracy to cue display in the attention task after administration of the non-specific antagonist flupentixol. As demonstrated, flupentixol leads to a decrease in accuracy. All doses are in milligrams per kilogram (N=9).

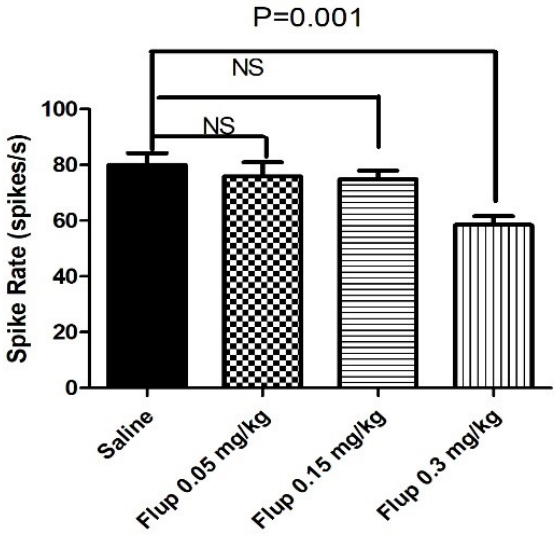

FIGURE 9. The effect of flupentixol compared to saline on spike rate. A significantly lower spike rate was observed with a dose of 0.30 milligrams of flupentixol compared to saline. (*=$P \leq 0.05$).

in both groups, but mPFC inhibition reduced correct response rates across all durations.

We further investigated the impact of muscimol at different doses (Figure 6). Muscimol treatments (a GABA agonist) at different concentrations produced varying effects. The sham condition showed high accuracy (~90%), whereas mPFC inhibition significantly reduced accuracy to about 50%. In muscimol treatment with a dose of 0.1μM, the sham condition showed reduced accuracy compared to saline (~75%). The mPFC inhibition condition shows improved accuracy compared to saline (~65%). At 1μM muscimol, both sham and mPFC inhibition conditions showed similar accuracy levels (~60%), suggesting that this higher dose eliminated the difference between the groups. Dose-dependent effects were observed, with increasing muscimol concentration progressively reducing the difference between sham and mPFC inhibition conditions. A significant difference was found only in the saline condition, and the overall effect of mPFC inhibition was not statistically significant. Low-dose muscimol (0.1μM) exerted differential effects on sham and mPFC inhibition conditions.

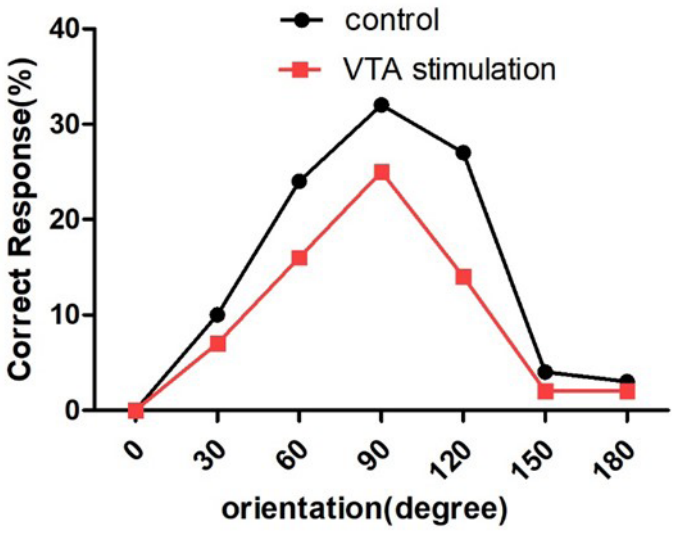

FIGURE 10. Role of orientation of visual stimulus on correct response of the neurons under VTA stimulation. This figure displays the decrease in correct response in the group that received VTA stimulation compared to the control group.

To assess attention in mice under mPFC inhibition, we manipulated the duration of stimulus presentation. The results indicated that as the stimulus presentation duration decreased, the average correct response rate also decreased (Figure 7). A repeated measures ANOVA revealed significant main effects of both stimulus presentation duration and mPFC inhibition. The administration of muscimol significantly reduced the percentage of correct responses compared to the control group, particularly as cue duration decreased. Both conditions showed increasing correct response rates with longer cue durations, but the difference between conditions was most pronounced at intermediate cue durations (3-7 seconds). Muscimol treatment reduced correct response rates across most cue durations, and the interaction between cue duration and treatment indicated that muscimol's effect was strongest at intermediate durations.

The effects of local application a flupentixol in the mPFC on visual attention

In this study, we investigated three doses of flupentixol (0.05, 0.15, and 0.30 mg/kg). Response accuracy to cues decreased in the presence of flupentixol (Figure 8). Figure 8 shows a box plot comparing the percentage cue accuracy across different conditions in a behavioral experiment. The saline (control) condition showed a median accuracy of ~78-80%. As the dose increased, a progressive decline in cue accuracy was observed. The two higher doses (0.15 and 0.30 mg/kg) produced statistically significant reductions in accuracy compared to the control, while the lowest dose (0.05 mg/kg) did not. Variability, as reflected by the box plots, appeared greater in the control and lowest dose conditions than in the higher dose groups.

Additionally, the impact of flupentixol on the spike rate of neurons in the mPFC during visual attention tasks was assessed (Figure 9). A dose-dependent decrease in spike rate was observed, with the 0.30 mg/kg dose producing a significant reduction compared to saline ($p = 0.001$). The 0.05 and 0.15 mg/kg doses did not significantly alter spike rates relative to control. These findings indicate that higher doses of flupentixol exert a pronounced inhibitory effect on mPFC neuronal firing.

Effects of VTA Stimulation on Neuronal Firing Rates

In this study, we examined the impact of ventral tegmental area (VTA) stimulation (AP = 3.4, ML = 0.4, DV = 4.25) on the firing rate of neurons with different preferred orientations (Figure 10). The data showed a decrease in correct responses in the VTA stimulation group compared to the control group. Specifically, neurons with a preferred orientation of 90° exhibited correct response rates of 32% in the control group and 25% in the VTA stimulation group. The results also highlight that the orientation of the stimuli significantly influences neuronal correct responses. Overall, these findings sug-

gest that VTA stimulation leads to a reduction in correct responses in the mPFC, which may contribute to impaired visual attention. This underscores the intricate relationship between dopaminergic activity and attentional processes in the brain. Both conditions showed a clear orientation preference, with peak correct responses occurring around 90°. VTA stimulation generally resulted in lower correct responses compared to the control condition, while maintaining the overall shape of the tuning curve. The effect of VTA stimulation was not uniform across all orientations. It's most pronounced at the preferred orientations. Baseline activity in both conditions showed very low correct responses at certain orientations (e.g., 0°, 180°).

Discussion

There are studies that have explored the use of Go/No-Go tasks to investigate attention in rodents (Dolzani et al., 2014; Muñoz-Redondo et al., 2024; Oakeshott et al., 2013). These studies highlight the versatility of this paradigm in investigating various aspects of rodent cognition, including attention, while also providing insights into neurological disorders and potential platforms for preclinical screening. In our study, Similar to previous findings in humans, mice respond to valid cues with higher speed and accuracy (Kamigaki 2019; Squire et al., 2013). In the present study, analysis of the visual attention task showed that VTA stimulation may impair the ability to correctly identify or respond to targets (Figure 3). Stimulation may negatively affect performance. VTA stimulation affects the ability to correctly identify non-targets. The results suggest that VTA stimulation has a significant impact on trial performance across different categories.

In the present study, inactivating mPFC with muscimol provides a framework for understanding the interaction controlling attention and visual information encoding (Figures 5 and 6). The key issue is the nature of the attention deficit, its characteristics, and the associated functional impairments.

In a previous study, it has been shown that inactivating the PFC by muscimol reduces preference-based orientation selectivity (Paneri and Gregoriou 2017). In our study, local muscimol application (adding to the chamber) disrupted the performance of an attention task in the mPFC even when the animal had been well trained. This suggests that the mPFC is essential for the acquisition and successful execution of attention tasks (Rossi et al., 2012). Data from electrophysiological and inactivation of PFC in primates suggest that the PFC plays a role in suppressing distractors and thus improves visual attention (Gregoriou et al., 2014). Kahn and colleagues' study (Kahn et al., 2012) demonstrates that inactivating the PFC in rats impairs visual attention, which is consistent with our study results. Damage or inhibition of the mPFC region leads to decreased attention accuracy, increased omissions, and premature responses (Pezze et al., 2009).

There was a significant difference between sham and mPFC inhibition conditions at 3 seconds (Figure 5). This highlights the critical role of mPFC at this particular stimulus duration. The time-dependent effects imply that mPFC's contribution may vary depending on the amount of time available for processing. The result demonstrates that mPFC inhibition impairs performance on a stimulus-based task, particularly at intermediate stimulus durations. The effect of stimulus duration on performance is preserved under mPFC inhibition, but at a reduced level.

PFC appears to play a crucial role in task accuracy under normal conditions. GABA agonist (via muscimol) seems to modulate mPFC function and can partially mimic PFC inhibition effects. High-dose muscimol (1μM) appears to overwhelm the effects of mPFC inhibition, possibly by globally increasing inhibitory signaling. The result showed complex interactions between mPFC function, GABA signaling, and visual attention task performance. mPFC inhibition significantly impairs performance under normal (saline) conditions, but this effect is modulated by muscimol in a dose-dependent manner. The results suggest that GABAergic signaling plays a crucial role in mPFC-dependent cognitive processes, and that pharmacological manipulation of this system can have varying effects depending on the functional state of the mPFC.

In this study, it was demonstrated that the local administration of the non-selective dopamine D1/2 receptor antagonist (flupentixol) led to a decrease in spike rate and reduced accuracy in response. A reduced spike rate is a key signature of attention. A study showed that the D1 antagonist (SCH 23390) selectively reduced attention accuracy, while the D2 antagonist (sulpiride) had no significant effect on attention task variables (Granon et al., 2000). Flupentixol is a typical antipsychotic drug.

Antipsychotic medications interact with monoamine receptors in the PFC and thereby exert their therapeutic effects (Artigas 2013; Santana and Artigas 2017). In our study, application of the flupentixol led to attention disruption, a result similar to the findings of Burk and colleagues (Burk et al., 2018) (Figure 8). In the study by Burk and colleagues (Burk et al., 2018), local infusion of the D1 agonist in the mPFC region improved attention in the 5CSRTT task at high and medium doses of the drug. However, lower doses of the agonist had no impact on attention performance (Chudasama and Robbins 2004). In the study by Burk and colleagues (Burk et al., 2018), systemic and intra-mPFC administration of dopamine agonists alleviated ADHD symptoms. Systemic administration of the antagonist flupentixol, commonly prescribed to reduce brain dopamine in schizophrenic individuals, resulted in side effects such as reduced working memory and attention (Phan et al., 2024).

This experiment investigates the effects of different doses of flupentixol on some form of cue-based task performance, related to attention processing. The results suggest that higher doses of flupentixol significantly impair performance on this task. Flupentixol appears to have a dose-dependent effect on neuronal activity and behavior. The drug also decreases spike rate in a dose-dependent manner, indicating a general suppression of neuronal activity. The lowest dose (0.05 mg/kg) generally does not produce significant effects, suggesting a threshold for the drug's impact. These results collectively suggest that flupentixol, a dopamine antagonist, modulates neuronal activity and behavior, with higher doses leading to more pronounced effects on both electrophysiological measures and task performance. These results could be relevant for understanding the role of dopamine in attention processes, the dose-dependent effects of dopamine antagonists, and potential clinical applications in conditions characterized by dysregulation of the dopaminergic system.

The results of the current research highlight the significance of dopaminergic signaling within the PFC for visual attention. The reduction in spike rate following flupentixol application suggests that dopamine plays a critical role in facilitating neuronal firing that is necessary for optimal attention performance. The decrease in spike rate may correlate with impaired attention, as reduced neuronal firing in the PFC can lead to diminished processing of relevant visual stimuli. This aligns with the broader understanding that dopamine modulation is essential for cognitive control and attentional processes in the mPFC, emphasizing the critical role of dopamine in modulating visual attention. The result effectively illustrates the dose-dependent inhibitory effects of flupentixol on neuronal spikes significant reduction in spike rate at higher doses highlights the importance of dopaminergic signaling for maintaining optimal cognitive function, particularly in attention.

In our study, we demonstrated how activation of VTA projections to the mPFC influences attention. Our findings indicated that electrical stimulation of dopaminergic neurons in the VTA region disrupts visual attention, with the mechanism involving a decrease in correct responses in attention tasks (Figures 3 and 10). It is well known that the main source of dopaminergic inputs to the mPFC is the VTA (Lammel et al., 2012). These findings are consistent with previous studies (Boekhoudt et al., 2017; Flores-Dourojeanni et al., 2021; Thiele et al., 2016) in which optogenetic activation of the VTA reduced visual attention without producing significant alterations in sensorimotor behavior during attention tasks (5-CSRTT). Furthermore, optogenetic stimulation of the VTA resulted in decreased accuracy and an increased number of incorrect responses. Omissions and premature responses were not affected by the stimulation (Flores-Dourojeanni et al., 2021).In rodents completing attention tasks, increased activity of the midbrain dopaminergic system is detrimental to attention performance but has no effect on response inhibition. Additionally, when the VTA or substantia nigra (SN) regions are stimulated, a noticeable decrease in attention occurs, consistent with the findings of Boekhoudt and colleagues (Boekhoudt et al., 2017). The study by Thiele and Bellgrove (Thiele and Bellgrove 2018), showed that increased dopaminergic activity in the midbrain impairs attention performance, similar to our study results. The intricate relationship between the VTA and mPFC in behaving animals has garnered significant attention in neuroscience research. Layer 5 pyramidal neurons of the PFC provide inputs that greatly modulate VTA activity, which in turn influences PFC activity (Santana and Artigas 2017). Dopaminergic neurons in the VTA may burst fire in response to prominent environmental stimuli (Buchta et al., 2017; Schultz 2002). All of the data from Buchta and Mahler's study (Buchta et al., 2017) collectively suggest that activation of VTA

terminals reduces intrinsic inhibition in PFC cells. Neuronal firing patterns in the VTA are also correlated with dopaminergic levels in the PFC. This work puts forth the theory that VTA controls PFC function by releasing dopamine from axonal terminals. This intricate interplay between these brain regions sheds light on the neural mechanisms underlying complex behaviors and cognitive processes in animals.

Research has shown that dopamine in the PFC directly and indirectly modulates excitatory pyramidal cells through its effects on local GABAergic neural circuits (Gorelova et al., 2002). The mPFC receives dopaminergic inputs from mesocortical dopaminergic projections of the midbrain VTA. It appears that dopamine activates the inputs of GABAergic interneurons to restrict the firing discharge of pyramidal neurons. Activation of dopaminergic neurons in the VTA disrupts attention by increasing the omission of trial ignoring. Interestingly, dopaminergic neuronal activity does not affect impulsive action (Boekhoudt et al., 2017). These results indicate that midbrain dopaminergic activity induces attentional deficits but does not influence impulsive behavior. Findings by Ott and colleagues (Ott and Nieder 2019) have shown that dopaminergic input to the PFC is essential for executive functions. In our study, inactivation of the mPFC led to clear alterations in the activity of downstream target regions (Granon et al., 2000) , accompanied by behavioral deficits in attention tasks. Our findings indicate that normal mPFC activity is essential for successful performance in attention-related tasks. Our study focused on dopamine signaling in the target regions (mPFC). The functioning of the mPFC is closely tied to dopamine signaling in the midbrain dopaminergic system, particularly in the VTA.

In the present study, electrical stimulation of the VTA inhibited PFC activity and induced attentional disturbances. Moreover, VTA stimulation influenced the balance of excitation and inhibition in PFC neurons by enhancing the excitability of parvalbumin-positive interneurons while exerting a more modest effect on principal neurons. This modulation appears to be mediated by dopamine receptors, particularly through effects on inhibitory transmission system (Zhong et al., 2020). Dopamine can raise the signal-to-noise ratio (SNR) of PFC neurons by lowering spontaneous discharge levels and boosting evoked responses, as shown by earlier research on VTA-PFC in anesthetized rodents (Lavin et al., 2005). Our research demonstrated how PFC output is influenced by dopamine cell activation.

Given the absence of a fovea in the mouse retina, attention in rodents is primarily expressed through head and body movements, rather than the eye movements commonly observed in primates. Although mice generate eye movements resembling saccades, it remains unclear to what extent these are visually driven or under voluntary control (Sakatani and Isa 2007). Moreover, mice lack the frontal eye field (FEF), a brain region critical for eye movement control in primates (Thiele and Bellgrove 2018). In our study, the animal's head was fixed with a chamber, which may have induced stress, whereas human studies of attention are not typically conducted under such conditions (Li et al., 2021).

Based on our findings, we propose that the role of the dopaminergic system in regulating visual attention should be further investigated in the primary visual cortex (V1). In addition, future studies should explore the functional interaction between V1 and the prefrontal cortex (PFC) in mediating visual attention.

Conclusion

The present study demonstrates that the dopaminergic system, particularly through its interactions with the prefrontal cortex (PFC), plays a crucial role in modulating visual attention in mice. Our findings indicate that both the inhibition of the PFC and the stimulation of the ventral tegmental area (VTA) significantly impact attention performance, underscoring the complexity of dopamine's role as a neuromodulator. The results reveal that PFC inhibition leads to decreased accuracy in attention tasks, while VTA stimulation reduces neuronal firing rates, further impairing attentional processes. These insights contribute to a deeper understanding of the neural mechanisms underlying visual attention and suggest that dysregulation of dopaminergic signaling in the PFC may be implicated in attention-related disorders such as ADHD and schizophrenia. Future research should continue to explore the intricate relationships between the dopaminergic system, the PFC, and visual attention to develop targeted therapeutic strategies for these conditions.

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Conflict of interest

The authors declared no conflict of interest.

Ethics approval

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References

Anderson J C, Kennedy H, Martin K A. Pathways of attention: synaptic relationships of frontal eye field to V4, lateral intraparietal cortex, and area 46 in macaque monkey. Journal of Neuroscience 2011; 31: 10872-10881. https://doi.org/10.1523/JNEUROSCI.0622-11.2011

Artigas F. Serotonin receptors involved in antidepressant effects. Pharmacology & Therapeutics 2013; 137: 119-131. https://doi.org/10.1016/j.pharmthera.2012.09.006

Bahmani Z, Clark K, Merrikhi Y, Mueller A, Pettine W, Vanegas M I, et al. Prefrontal contributions to attention and working memory. Processes of Visuospatial Attention and Working Memory: Springer, 2019: 129-153. https://doi.org/10.1007/7854_2018_74

Boekhoudt L, Voets E S, Flores-Dourojeanni J P, Luijendijk M, Vanderschuren L J, Adan R A. Chemogenetic activation of midbrain dopamine neurons affects attention, but not impulsivity, in the five-choice serial reaction time task in rats. Neuropsychopharmacology 2017; 42: 1315-1325. https://doi.org/10.1038/npp.2016.235

Buchta W C, Mahler S V, Harlan B, Aston-Jones G S, Riegel A C. Dopamine terminal from the ventral tegmental area gate intrinsic inhibition in the prefrontal cortex. Physiological Reports 2017; 5: e13198. https://doi.org/10.14814/phy2.13198

Burk J A, Blumenthal S A, Maness E B. Neuropharmacology of attention. European Journal of Pharmacology 2018; 835: 162-168. https://doi.org/10.1016/j.ejphar.2018.08.008

Chudasama Y, Robbins T W. Dopaminergic modulation of visual attention and working memory in the rodent prefrontal cortex. Neuropsychopharmacology 2004; 29: 1628-1636. https://doi.org/10.1038/sj.npp.1300490

Clark K, Squire R F, Merrikhi Y, Noudoost B. Visual attention: Linking prefrontal sources to neuronal and behavioral correlates. Progress in Neurobiology 2015; 132: 59-80. https://doi.org/10.1016/j.pneurobio.2015.06.006

Clark K L, Noudoost B. The role of prefrontal catecholamines in attention and working memory. Frontiers in Neural Circuits 2014a; 8. https://doi.org/10.3389/fncir.2014.00033

Clark K L, Noudoost B. The role of prefrontal catecholamines in attention and working memory. Frontiers in Neural Circuits 2014b; 8: 33. https://doi.org/10.3389/fncir.2014.00033

Corbetta M, Miezin F M, Dobmeyer S, Shulman G L, Petersen S E. Selective and divided attention during visual discriminations of shape, color, and speed: functional anatomy by positron emission tomography. Journal of Neuroscience 1991; 11: 2383-2402. https://doi.org/10.1523/JNEUROSCI.11-08-02383.1991

Dolzani S D, Nakamura S, Cooper D C. A novel variable delay Go/No-Go task to study attention, motivation and working memory in the head-fixed rodent. F1000Research 2014; 2: 125. https://doi.org/10.12688/f1000research.2-125.v1

Everling S, Tinsley C J, Gaffan D, Duncan J. Filtering of neural signals by focused attention in the monkey prefrontal cortex. Nature Neuroscience 2002; 5: 671-676. https://doi.org/10.1038/nn874

Flores-Dourojeanni J P, van Rijt C, van den Munkhof M H, Boekhoudt L, Luijendijk M C, Vanderschuren L J, et al. Temporally specific roles of ventral tegmental area projections to the nucleus accumbens and prefrontal cortex in attention and impulse control. Journal of Neuroscience 2021; 41: 4293-4304. https://doi.org/10.1523/JNEUROSCI.0477-20.2020

Gazzaley A, Nobre A C. Top-down modulation: bridging selective attention and working memory. Trends in Cognitive Sciences 2012; 16: 129-135. https://doi.org/10.1016/j.tics.2011.11.014

Ghaderi P, Marateb H R, Safari M-S. Electrophysiological profiling of neocortical neural subtypes: a semi-supervised method applied to in vivo whole-cell patch-clamp data. Frontiers in Neuroscience 2018; 12: 374322. https://doi.org/10.3389/fnins.2018.00823

Gorelova N, Seamans J K, Yang C R. Mechanisms of dopamine activation of fast-spiking interneurons that exert inhibition in rat prefrontal cortex. Journal of Neurophysiology 2002; 88: 3150-3166. https://doi.org/10.1152/jn.00335.2002

Granon S, Passetti F, Thomas K L, Dalley J W, Everitt B J,

Robbins T W. Enhanced and impaired attentional performance after infusion of D1 dopaminergic receptor agents into rat prefrontal cortex. Journal of Neuroscience 2000; 20: 1208-1215. https://doi.org/10.1523/JNEUROSCI.20-03-01208.2000

Gregoriou G G, Rossi A F, Ungerleider L G, Desimone R. Lesions of prefrontal cortex reduce attentional modulation of neuronal responses and synchrony in V4. Nature Neuroscience 2014; 17: 1003-1011. https://doi.org/10.1038/nn.3742

Howe M W, Dombeck D A. Rapid signalling in distinct dopaminergic axons during locomotion and reward. Nature 2016; 535: 505-510. https://doi.org/10.1038/nature18942

Jonikaitis D, Moore T. The interdependence of attention, working memory and gaze control: behavior and neural circuitry. Current Opinion in Psychology 2019; 29: 126-134. https://doi.org/10.1016/j.copsyc.2019.01.012

Kahn J B, Ward R D, Kahn L W, Rudy N M, Kandel E R, Balsam P D, et al. Medial prefrontal lesions in mice impair sustained attention but spare maintenance of information in working memory. Learning & Memory 2012; 19: 513-517. https://doi.org/10.1101/lm.026302.112

Kamigaki T. Prefrontal circuit organization for executive control. Neuroscience Research 2019; 140: 23-36. https://doi.org/10.1016/j.neures.2018.08.017

Lammel S, Lim B K, Ran C, Huang K W, Betley M J, Tye K M, et al. Input-specific control of reward and aversion in the ventral tegmental area. Nature 2012; 491: 212-217. https://doi.org/10.1038/nature11527

Lavin A, Nogueira L, Lapish C C, Wightman R M, Phillips P E, Seamans J K. Mesocortical dopamine neurons operate in distinct temporal domains using multimodal signaling. Journal of Neuroscience 2005; 25: 5013-5023. https://doi.org/10.1523/JNEUROSCI.0557-05.2005

Li S, May C, Hannan A, Johnson K, Burrows E. Assessing attention orienting in mice: a novel touchscreen adaptation of the Posner-style cueing task. Neuropsychopharmacology 2021; 46: 432-441. https://doi.org/10.1038/s41386-020-00873-8

McNab F, Klingberg T. Prefrontal cortex and basal ganglia control access to working memory. Nature Neuroscience 2008; 11: 103-107. https://doi.org/10.1038/nn2024

Mueller A, Krock R M, Shepard S, Moore T. Dopamine receptor expression among local and visual cortex-projecting frontal eye field neurons. Cerebral Cortex 2020; 30: 148-164. https://doi.org/10.1093/cercor/bhz078

Muñoz-Redondo C, Parras G G, Andreu-Sánchez C, Martín-Pascual M Á, Delgado-García J M, Gruart A. Functional states of prelimbic and related circuits during the acquisition of a GO/noGO task in rats. Cerebral Cortex 2024; 34: 271. https://doi.org/10.1093/cercor/bhae271

Noudoost B, Moore T. The role of neuromodulators in selective attention. Trends in Cognitive Sciences 2011; 15: 585-591. https://doi.org/10.1016/j.tics.2011.10.006

Oakeshott S, Farrar A, Port R, Cummins-Sutphen J, Berger J, Watson-Johnson J, et al. Deficits in a simple visual Go/No-go discrimination task in two mouse models of Huntington's disease. PLoS Currents 2013; 5. https://doi.org/10.1371/currents.hd.fe74c94bdd446a0470f6f905a30b5dd1

Ott T, Nieder A. Dopamine and Cognitive Control in Prefrontal Cortex. Trends in Cognitive Sciences 2019; 23: 213-234. https://doi.org/10.1016/j.tics.2018.12.006

Paneri S, Gregoriou G G. Top-down control of visual attention by the prefrontal cortex. functional specialization and long-range interactions. Frontiers in Neuroscience 2017; 11: 545. https://doi.org/10.3389/fnins.2017.00545

Pezze M A, Dalley J W, Robbins T W. Remediation of attentional dysfunction in rats with lesions of the medial prefrontal cortex by intra-accumbens administration of the dopamine D 2/3 receptor antagonist sulpiride. Psychopharmacology 2009; 202: 307-313. https://doi.org/10.1007/s00213-008-1384-4

Phan J H, Ugwu K, Fong S L E. A Case of overlapping extrapyramidal side effects and neuroleptic malignant syndrome. BJPsych Open 2024; 10: S286-S287. https://doi.org/10.1192/bjo.2024.683

Romo R, Schultz W. Dopamine neurons of the monkey midbrain: contingencies of responses to active touch during self-initiated arm movements. Journal of Neurophysiology 1990; 63: 592-606. https://doi.org/10.1152/jn.1990.63.3.592

Rossi M A, Hayrapetyan V Y, Maimon B, Mak K, Je H S, Yin H H. Prefrontal cortical mechanisms underlying delayed alternation in mice. Journal of Neurophysiology 2012; 108: 1211-1222. https://doi.org/10.1152/jn.01060.2011

Safari M-S, Mirnajafi-Zadeh J, Hioki H, Tsumoto T. Parvalbumin-expressing interneurons can act solo while somatostatin-expressing interneurons act in chorus in most cases on cortical pyramidal cells. Scientific Reports 2017; 7: 12764. https://doi.org/10.1038/s41598-017-12958-4

Sakatani T, Isa T. Quantitative analysis of spontaneous saccade-like rapid eye movements in C57BL/6 mice. Neuroscience research 2007; 58: 324-331. https://doi.org/10.1016/j.neures.2007.04.003

Salkoff D B, Zagha E, McCarthy E, McCormick D A. Move-

ment and performance predict widespread cortical activity in a visual detection task. bioRxiv 2019: 709642. https://doi.org/10.1101/709642

Santana N, Artigas F. Laminar and cellular distribution of monoamine receptors in rat medial prefrontal cortex. Frontiers in Neuroanatomy 2017; 11: 87. https://doi.org/10.3389/fnana.2017.00087

Schultz W. Getting formal with dopamine and reward. Neuron 2002; 36: 241-263. https://doi.org/10.1016/S0896-6273(02)00967-4

Seamans J K, Yang C R. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Progress in Neurobiology 2004; 74: 1-58. https://doi.org/10.1016/j.pneurobio.2004.05.006

Shimamura A P. The role of the prefrontal cortex in dynamic filtering. Psychobiology 2000; 28: 207-218. https://doi.org/10.3758/BF03331979

Squire R F, Noudoost B, Schafer R J, Moore T. Prefrontal contributions to visual selective attention. Annual Review of Neuroscience 2013; 36: 451-466. https://doi.org/10.1146/annurev-neuro-062111-150439

Thiele A, Bellgrove M A. Neuromodulation of attention. Neuron 2018; 97: 769-785. https://doi.org/10.1016/j.neuron.2018.01.008

Thiele A, Brandt C, Dasilva M, Gotthardt S, Chicharro D, Panzeri S, et al. Attention induced gain stabilization in broad and narrow- spiking cells in the frontal eye-field of macaque monkeys. Journal of Neuroscience 2016; 36: 7601-7612. https://doi.org/10.1523/JNEUROSCI.0872-16.2016

Veit L, Nieder A. Abstract rule neurons in the endbrain support intelligent behaviour in corvid songbirds. Nature Communications 2013; 4: 1-11. https://doi.org/10.1038/ncomms3878

Wang X-J. Decision making in recurrent neuronal circuits. Neuron 2008; 60: 215-234. https://doi.org/10.1016/j.neuron.2008.09.034

Zhong P, Qin L, Yan Z. Dopamine differentially regulates response dynamics of prefrontal cortical principal neurons and interneurons to optogenetic stimulation of inputs from ventral tegmental area. Cerebral Cortex 2020; 30: 4402-4409. https://doi.org/10.1093/cercor/bhaa027