Functional Role of Pulvinar In the Sustained Attention

Xiaoshu Jiang and Qi Fang

***Abstract*—Sustained attention is important for survival in a challenging environment. Oscillatory activities in the pulvinar have been reported to correlate with sustained attention. However, whether pulvinar can causally establish and maintain sustained attention is elusive. To address this question, in this study, we opto-genetically activated pulvinar neurons during delay period in the five-choice serial reaction time task and measured the behavioral outputs. We found that pulvinar firing rates were significantly increased after optogenetic stimulation. Also, in the behavioral test, the correct rates were remarkably increased with decreased omission rates, but the reaction time and reward retrieval time remained the same. Together, these results deepen our understanding of the functional role of pulvinar in sustained attention.**

***Index Terms*—Cortical oscillation, five choice serial reaction time task (5-CSRTT), optogenetics, pulvinar, sustained attention, virus injection.**

I. Introduction

Sustained attention is the process of gathering cognitive resources to respond to infrequent yet task-relevant stimuli in the absence of sensory input, capacity limitation, and competition over an extended period of time [1]-[2]. It is classified as a mechanism of cognitive maintenance and differs from shifting attention or selective attention, which is the ability to select and focus on only one of the stimuli present, and dividing attention, which refers to as multi-tasking where the ability to process two or more responses to two or more stimuli simultaneously is needed [2]. Sustained attention also attaches to great importance, as attention deficit and impulsivity in many psychiatric disorders are related to the dysfunction of this process [3]-[8].

Top-down attention is a fundamental cognitive process that facilitates the detection of relative stimuli from the ever-changing environment, and cortical oscillations serve a role of a top-down control signal generated in the frontal-parietal network in attention process [9]-[11]. The cortical activity in the attention process is coordinated and synchronized by the pulvinar [12], [13], which has anatomical connections with visual cortex, prefrontal cortex and so on [14], and functionally acts as a secondary visual system [15]. These findings of the functional role of pulvinar in guiding cortical activities in attention process are contextualized by the abnormal pulvinar structures shown by people with attention deficits. Hence, we hypothesize that sustained visual attention is facilitated by high-order thalamic nucleus modulating thalamo-cortical and cortico-cortical communication. However, whether the pulvinar activation and its interaction with cortical areas represent an epiphenomenon or an actual causal mechanism remains elusive.

In behavioral studies where the procedure of an experiment should reflect a change in the process of interest [16]. specificity is very important. However, in the case of attention-related behavioral tests, this can be very hard to achieve, as other cognitive, sensorimotor, and physical processes can be confounded with attention and attention itself has several closely-interrelated aspects—selective attention, divided attention and so on. Though many protocols designed for attentional behavioral tests are highly simple and standardized, only the five-choice serial reaction time task designed by Carli *et.al* stands out from others as it establishes links between particular aspects of behavior and underlying neural substrates [17]. In this study, to prove the links between pulvinar and the sustained attention using highly specific behavioral test protocol, we opto-genetically activated pulvinar neurons during delay period in the five-choice serial reaction time task (5-CSRTT) and measured the behavioral outputs of the 5-CSRTT experiment. We found that pulvinar firing rates were significantly increased after optogenetic stimulation. Also, in the behavioral test, the correct rates were remarkably increased with decreased omission rates, but the reaction time and reward retrieval time remained the same.

II. Methods

A. Behavioral Training

Five-choice serial reaction time task (5-CSRTT) designed by Carli *et al.* was used in behavioral test and training [17]. The apparatus for 5-CSRTT testing and training included a front wall with nine holes and stimuli presented on a touch-sensitive screen located only on five of them (1, 3, 5, 7, 9) and a food receptacle which located at the opposite wall and contained automatic pellet dispenser. The holes and food receptacles were all equipped with light-emitting diode. All of the targets were visible for the subjects standing in the center and access to the receptacle was monitored via a micro-switch. Special for this experiment, an infrared (IR) beam was installed to increase the possibility of the animal facing the screen during the delay period (the delay between micro-switch in the food pellet and appearance of visual stimuli) by only initiating a trial and delay period when the IR beam was not blocked with the animal correctly facing the screen.

In the 5-main-stage training phase, the task difficulty gradually elevated each time the animal met the criteria to advance to the next stage (high accuracy, low variation over sessions, low frequency of omissions) to ensure all animals meet the baseline performance. Before 5-CSRTT training, mice were first acclimated to the operant chamber and water reward, where the water-restricted animals got water reward.

Manuscript received August 23, 2022; revised October 24, 2022.

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DOI: 10.7763/IJET.2022.V14.1203

To advance to the next step, mice had to enter the reward tray 20 times during two 30-min consecutive sessions. For the next step, mice had to touch the white square stimulus presented randomly at one response window to get the water reward, but there was no consequence for incorrect touches. In the 5-CSRTT training phase, there was an intertrial interval (ITI) period of 5 s before the next stimulus was presented, a set stimulus duration (sequentially reduced from 32, 16, 8, 4 to 2 s in the training), and a 5-s limited-hold period when stimulus turned off, but mice were still allowed to respond. A correct response was rewarded with a water delivery while incorrect responses, omissions, and preservative (repeated) responses were punished by a 5-s time-out.

The data analyzed in the present study were retrieved from the Open Neuro online dataset. Correct percentage, percentage accuracy, percentage omission, percentage of premature responses, and so on are all indicators to assess the attention and response control, while accuracy per session (correct/all completed trials including incorrect responses, premature responses and omissions), reaction time for correct trial, or correct response latencies which measures the period between the occurrence of visual stimuli and rats' responses, and omission rates are the main dependent variables. To distinguish attention from other factors such as motivational fluctuation and sensory and motor disorders, patterns of reward-recovery time, response latencies, and omission rate are analyzed [18]. Five-CSRTT is also designed to investigate inhibitory control, which is based on two indicators: the number of premature responses (impulsive) and the number of repetitive responses (compulsive) [19]-[23].

B. Virus Injection and Electrode Implantation Surgery

The following procedures were adapted from previous literature [24]. For the anesthesia process, the animals were first injected with a ketamine/xylazine cocktail and after reassuring a stable plane of anesthesia indicated by the absence of toe-pinch response, they were intubated for ventilation with vaporized anesthetic maintenance (isoflurane and oxygen). Animals were also administered pain relief medication. To make virus injection and electrode implantation target precisely the studied regions the animals were positioned into a stereotaxic frame with heads fixed stably by a mouthpiece and ear bars, and several physiological parameters were measured to maintain the animals in a stable state. All the surgical processes were performed under aseptically. LP/Pul was injected with 0.3μL of rAAV5-CaMKII-ChR2-mCherry and implanted with optrode—microelectrode and light fibers surrounded by custom-designed plastic cylinders to anchor laser cables and prevent laser light leakage. Before the viral injection, dura and pia were removed. After the craniotomy, skin, connective tissue, and muscle were sutured together with the help of dental acrylic (dental cement), along with post-operative animals administered triple antibiotic ointment, pain medication, infection control, and headcap cleaning.

C. Animals in Vivo Recording and Optogenetics

Animals were retrained on the final level of 5-CSRTT until they reached stable criteria level performance again after recovering in the home cage from the surgery for at least a week. At the beginning of the recording session, the implanted multichannel electrode arrays in animals were connected to a data acquisition system that was, along with optic fiber cables, connected to a commutator located on the top of the box, which had another optic patch cable that connects the laser source. And, to prevent light leakage, the optic cable connection end was surrounded by a custom-made black light-proof cylindrical sheath.

III. Results

A. Increased Evoked Firing Rates in the Pulvinar after Optogenetic Stimulation

To examine whether optogenetic stimulation can increase evoked firing rates in pulvinar neurons expressing ChR2, we delivered blue light and measured the evoked firing rates of the pulvinar neurons before and after optogenetic stimulation. We found that blue light delivery significantly increased evoke spiking responses in the pulvinar neurons (pulvinar firing rates: OFF: 0.62 Hz ± 0.62 Hz, ON: 14.27 Hz ± 3.27 Hz, n = 10, p < 0.0001, paired t-test) (Fig. 1). These results suggest that our stimulation paradigm effectively activated the pulvinar nucleus.

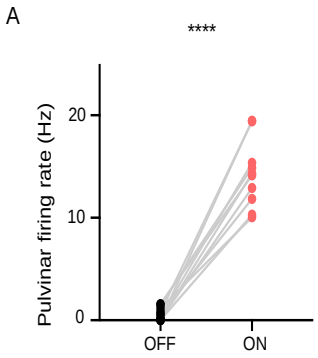

Fig. 1. Pulvinar firing rate without and with optogenetic stimulation of pulvinar nucleus. (A) Pulvinar firing rate: OFF = 0.62 ± 0.62 Hz, ON =14.27 ± 3.27 Hz, n = 10, p < 0.0001, paired t-test. ****, p < 0.0001.

B. Behavioral Changes before and after Pulvinar Optogenetic Stimulation

To further study the role of the pulvinar in sustained attention, we delivered bule light during the delay period of the 5CSRTT to activate the pulvinar nucleus and quantified the behavioral outputs with and without the optogenetic stimulation. We found that the correct rates were statistically significantly increased after pulvinar activation while the omission rates were significantly reduced (correct rate: OFF: 70.25% ± 3.86%, ON: 77% ± 4.97%, n = 4, p = 0.0029, paired t-test; omission rate: OFF: 11.50% ± 1.29%, ON: 4.75% ± 1.71%, n = 4, p = 0.0029, paired t-test; premature rate: OFF: 9.25% ± 0.96%, ON: 9.25% ± 0.96%, n = 4, p > 0.9999, paired t-test; incorrect rate: OFF: 6.75% ± 1.26%, ON: 6.75% ± 1.71%, n = 4, p > 0.9999, paired t-test) (Fig. 2). We further measured the latency to response and latency of reward retrieval and found that the reaction time and reward retrieval time had no significant change after the stimulation of pulvinar. (Reaction time: OFF: 1.13 s ± 0.05 s, ON: 1.14 s ± 0.06 s, n = 4, p = 0.7308, paired t-test; reward retrieval time: OFF: 0.87 s ± 0.02 s, ON: 0.85 s ± 0.05 s, n = 4, p = 0.5990,

paired t-test) (Fig. 3). Together, these data indicated that stimulating pulvinar can significantly improve animal's performance by increasing the accuracy while reducing the omission rate, without changing the general motor function or motivation level.

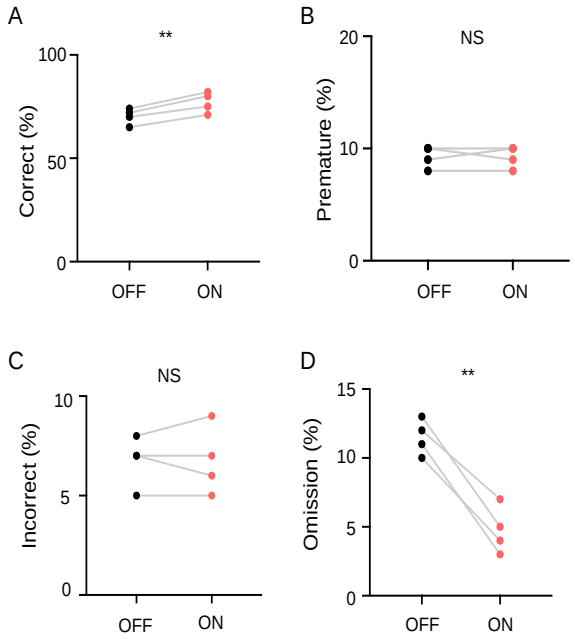

Fig. 2. Behavioral changes without and with optogenetic stimulation of the pulvinar nucleus. (A) Correct rate: OFF = 70.25% ± 3.86%, ON = 77.00% ± 4.97%, n = 4, p = 0.0029, paired t-test. **, p < 0.01. (B) Premature rate: OFF = 9.25% ± 0.96%, ON = 9.25% ± 0.96%, n = 4, p > 0.9999, paired t-test. NS, not significant. (C) Incorrect rate: OFF = 6.75% ± 1.26%, ON = 6.75% ± 1.71%, n = 4, p > 0.9999, paired t-test. (D) omission rate: OFF = 11.50% ± 1.29%, ON = 4.75% ± 1.71%, n = 4, p = 0.0029, paired t-test.

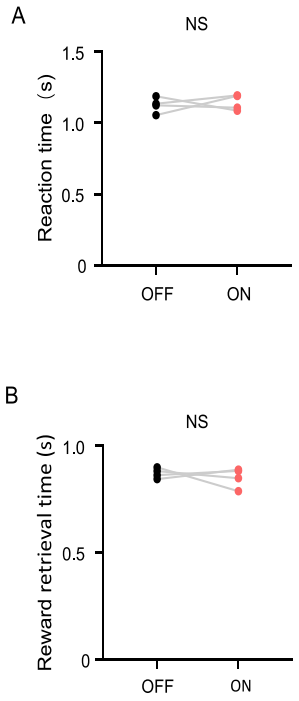

Fig. 3. General motor function and motivation level without and with optogenetic stimulation of pulvinar nucleus. (A) Reaction time. OFF = 1.13 s ± 0.05 s, ON = 1.14 s ± 0.06 s, n = 4, p = 0.7308, paired t-test. NS, not significant. (B) Reward retrieval time. OFF = 0.87 s ± 0.02 s, ON = 0.85 s ± 0.05s, n = 4, p = 0.5990, paired t-test.

IV. Discussion

Pulvinar-cortical (temporo-occipital area and a higher-order visual area) synchrony is required in a selective attention task [13]. Deactivating pulvinar with muscimol decreases visual responsiveness and high-frequency synchrony within V4 [25]. It has also been shown that pulvinar rhythmically engages or disengages in frontal-parietal network based on its theta phase during a spatial attention task [26]. As demonstrated by numerous attentional studies, pulvinar, which connects to multiple cortical regions and forms cortical-pulvinar-cortical input-output loops, serves a central role in modulating interactions between cortical regions and pulvinars especially during attention-related task [13].

High-order thalamo-cortical visual circuit is a candidate circuit for the network-level substrate of sustained attention [12]. Cortical oscillations, which serve the role of a top-down control signal generated in the frontal-parietal network in attention [9]-[11], may be driven by subcortical structures including higher-order visual thalamus. As anatomically, primate pulvinar has highly specialized subdivisions connected to visual cortex, superior colliculus, temporal lobe, and so on [14] ,and functionally acts as a secondary visual system [15] and coordinates cortical activity during visual attentional behavior [12], [13], it is a major hub and potential synchronizer of cortical activity. Findings about pulvinar activity affecting visual responsiveness in attentional task and synchronous activity in V4 and temporo-occipital cortex [13], [25] are confirmed by the abnormal pulvinar-cortical functional connectivity observed in patients with ADHD [27]. Overall, it has been suggested that in attention-related tasks, pulvinar activities are the fundament in maintaining and guiding cortical activity.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Qi Fang directed the paper's topic; Xiaoshu Jiang wrote the paper; Qi Fang and Xiaoshu Jiang analyzed the data; all authors had approved the final version.

Acknowledgment

Xiaoshu Jiang would like to thank the guidance and help offered by Qi Fang.

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