Brief Communications

PET Mapping for Brain-Computer-Interface-Based Stimulation in a Rat Model with Intracranial Electrode Implantation in the Ventro-posterior Medial Thalamus

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ABSTRACT

Brain-computer interface (BCI) based technology has great potential in improving the quality of life for neurological patients. This study aims to use positron emission tomography (PET) mapping for BCI-based stimulation in a rat model with intracranial electrode implantation in the ventro-posterior medial thalamus (VPM). **Methods:** PET imaging studies were conducted before and after the VPM stimulation. **Results:** Intracranial stimulation to the right VPM induced significant orienting performance. 18F-FDG accumulations were found significantly increased in the paraventricular thalamic nucleus (PVT), septohippocampal nucleus, bilateral lateral septum (LS), bilateral amygdala, bilateral piriform cortex, bilateral endopiriform nucleaus, bilateral insular cortex, olfactory bulb, and the left Crus II of the ansiform lobule of cerebellum (Crus II) after the VPM stimulation; but decreased in the bilateral somatosensory cortex (S1), right secondary visual cortex and the right simple lobule of cerebellum. **Conclusion:** This study demonstrated that PET mapping could identify specific brain regions associated with orienting performance by the VPM stimulation in rats. PET molecular imaging could be an important approach for BCI-based research and its clinical applications.

**Keywords:** Positron emission tomography (PET), brain-computer interface (BCI), electrical stimulation, ventro-posterior medial nucleus (VPM)
INTRODUCTION

Brain computer interface (BCI) systems have gained great visibility in the past years as it merges the fields of bio-robotics and neuroscience. Clinically, it is a promising new therapeutic strategy for the restoration of sensory and motor functions in patients with neurological disorders (1, 2). Owing to the technical advancement of implantable microelectrodes and processing electronics, remote control of the animal's orienting performance has been succeeded by appropriate repeated trainings after artificially introduced electrical commands into the somatosensory cortical (S1) and medial forebrain bundle (MFB) (3). During the training, the rats learned to interpret remote brain stimulation as instructions for directing their trajectory of locomotion. Recently, our group demonstrated a novel control method by direct stimulation of the ventro-posterior medial thalamus (VPM) which could initiate orienting performance in freely roaming rats without repeated training sessions (See Supplementary Video-1) (4). VPM is known as a somatosensory relay station that relays inputs sensory information from individual whiskers and projects to the primary somatosensory cortex (S1) (5), however, it is unclear which brain regions are involved in the orienting performance induced by the VPM stimulation. Thus, we hypothesized that by using positron emission tomography (PET) molecular imaging mapping approach, we could explore the intracranial VPM stimulation related orienting function and identify the specific cerebral activation pattern. In this present study, we conducted PET imaging in a freely moving rat model before and after VPM stimulation. To our knowledge, this is the first PET imaging study on the BCI-based stimulation in a rat model with intracranial electrode implantation in the VPM.

MATERIALS AND METHODS

Animals and Intracranial Stimulation Electrode Implantation

Twelve Sprague Dawley rats (male, 250-280 g) were used for this study. Bipolar electrical stimulation electrodes were constructed with insulated Nichrome wires (A-M System, bar diameter 50 μm, 0.4 mm between electrodes tips) (4). The animal was secured on a stereotaxic frame (RWD Life
Science Co.) under pentobarbital sodium anesthesia (50 mg/kg, i.p.), then the electrode was implanted to the right VPM thalamus according to the Rat Brain Atlas (6) and fixed on the skull by dental cement. The animal was given one week to recover from the above procedure. All the animal experiments were approved by the Institutional Animal Care and Use Committee at Zhejiang University.

**Electrical Stimulation and Orienting Performance**

To deliver electrical stimulation directly into the VPM, an isolated stimulator (A-M System) was connected to the implanted electrode with a flexible extension cable, allowing the animal to move freely. The stimulus paradigm was a 30-minute-block-design with 180 cycles consisting of 1 sec of stimulation ON followed by 9 sec of rest. The intracranial VPM stimulation induced orienting performance was captured by a video camera, and the “turning angle” was calculated as shown in Figure 1A. The turning angle ranges from 30° to 60° was regarded as a successful stimulus. The animals with turning angle of less than 30° or larger than 60° were excluded from this study.

**PET Imaging Protocol and Data Analysis**

All animals were food deprived overnight before PET imaging studies. Baseline and post-stimulation microPET studies were performed in a microPET R4 scanner (Siemens Medical Solutions) at 7 and 10 day after the stereotaxic surgery, respectively. In the post-stimulation microPET studies, each rat was subjected to VPM stimulation for 30 min immediately after \(^{18}\)F-FDG injection (18.5 MBq) via tail vein. PET images were acquired at 40 min after \(^{18}\)F-FDG injection and analyzed using an improved toolbox for voxelwise analysis of rat brain images on statistical parametric mapping (SPM) 8 (7). Groups were compared using a paired \(t\)-test with a significance threshold of \(P < 0.001\).

**RESULTS**
Upon completion of the last PET imaging, brain sections were stained with hematoxylin and eosin (H.E.). The pathological confirmation verified the appropriate sites of intracranial electrode implantation. A representative image of H.E staining was presented in Figure 1B.

The intracranial electrical stimulation of the right VPM induced ipsilateral orienting performance towards the right side. A representative orienting performance was presented in the Supplemental Video-2. Among the 12 tested rats, 8 showed appropriate turning angle ranged from 30° - 60° during the stimulation period, while the other 4 with turning angles less than 30° were excluded from this study.

After VPM stimulation, significantly increased $^{18}$F-FDG accumulations were found in the paraventricular thalamic nucleus (PVT), septohippocampal nucleus, bilateral lateral septum (LS), bilateral amygdala, bilateral piriform cortex, bilateral endopiriform nucleus, bilateral insular cortex, olfactory bulb, and the left Crus II of the ansiform lobule of cerebellum (Crus II ) (Table 1, Fig. 2A and 3), while significantly decreased $^{18}$F-FDG accumulations were observed in the bilateral somatosensory cortex (S1), right secondary visual cortex and the right simple lobule of cerebellum (Table 1, Fig. 2B and 4).

**DISCUSSION**

Born as highly multidisciplinary field, basic research on BCI has moved at a stunning pace since the first experiment demonstrated that electrical activity generated by ensembles of cortical neurons could directly control a robotic manipulator (8). Noninvasive neuroimaging modalities are gaining momentum in the research arena for BCI systems. Although functional magnetic resonance imaging (fMRI) is surfaced as the major tool used for noninvasive characterization of brain function with superior spatial resolution (9), PET has advantage of tracing the bio-chemical changes in cognitive or behavioral brain function during real-time tasks without the interference of ambient noise generated by the MRI scanner, and is suitable for the brain implanted with metal-based electrodes.

In the current study, by using $^{18}$F-FDG PET imaging, we found that VPM stimulation induced
increased glucose metabolism in the PVT, septohippocampal nucleus, bilateral LS, bilateral amygdala, bilateral piriform cortex, bilateral endopiriform nucleaus, bilateral insular cortex, olfactory bulb, and the left Crus II after the VPM stimulation, but significantly decreased $^{18}$F-FDG accumulations were observed in the bilateral S1, right secondary visual cortex and the right simple lobule of cerebellum. To the best of our knowledge, this is the first study using PET as a neuroimaging tool to investigate the BCI-based electrical stimulation induced orienting performance in the rat model with electrode implanted in the VMP.

One of the significant findings in our study was the increased glucose metabolism in the PVT, amygdala, hippocampus and LS after VMP stimulation. The PVT is a major source of projections to the nucleus accumbens (NAc), the bed nucleus of the stria terminalis and the central nucleus of the amygdala as well as the cortical areas associated with these subcortical regions. The PVT participates in the functional integration of limbic cortical and striatal circuitry, and is notable for providing a very dense projection to the nucleus accumbens, a part of the striatum strongly associated with the regulation of locomotion (10). Also, within the NAc, PVT profiles were found occasionally made synapses onto spines and distal dendrites (11). Consequently, the PVT with its direct and indirect projections to the nucleus accumbens forms an impressive neural network that could exert control over locomotor activity (12). The amygdala is a critical component of the neural circuitry underlying fear associations and emotional learning (13). Previous work indicates an essential role of the basolateral amygdala in stimulus-reward learning and the dorsal hippocampus in spatial learning and memory (14). Interestingly, increased glucose metabolism were observed in not only amygdala and PVT, but also in the septohippocampal nucleus and bilateral LS in this current study, which is consistent with the very recent literature on hippocampus to lateral septum pathway (15). The optogenetic stimulation of projections from LS to lateral hypothalamus decreased locomotion, suggesting that LS is crucial for control of locomotion and arousal.

The insular cortex is part of the neocortex located in the lateral temporal lobe and is highly interconnected with multiple brain networks. (16). Electrical stimulation of insula elicited body
movements in nonhuman primates, and indicated a role in sensorimotor processing (17). The mid-posterior insula has also been implicated in the processing of awareness with relation to the position, movement and sensation of the body, and thus may be necessary for coordinating movements effectively (18). The cerebellum has been implicated in the control of action and acquisition of motor skills (19), particularly, the posterolateral regions (Crus I and II) involved in adaptation to force field and visuomotor perturbation (20). Taking the above literatures and our findings together, we suggest that the insula and cerebellum may involve in movement coordination and controlling turning angle.

We found that the VPM electrical stimulation resulted in decreased glucose metabolism in S1, which was supported by other studies. Electrical stimulation has been shown to evoke strong and long-lasting cortical inhibition that suppressed neurons from firing (21). A recent study investigated visually evoked responses in visual cortex (22). The results showed that visual stimuli evoked fewer spikes during waking than during anesthesia and spikes evoked during wakefulness were quickly followed by a significant and long-lasting hyperpolarization, and suggests that cortical responses to sensory stimulation are dominated by synaptic inhibition in the awake cortex (22). Thus, we speculate that electrical stimulation of the VPM might lead to initial activation of cortical pyramidal neurons; subsequently, thalamocortical input recruits strong postsynaptic inhibition shunts the initial excitatory input within the course of the hyperpolarization, resulting in a long-lasting decrease in baseline activity of the S1. In the future, PET imaging study combined with electrophysiological recording and EEGs in the same subject would provide more insights into the BCI-based stimulation related brain function.

In summary, the present report presents several important findings concerning the role of specific brain regions involved in the VPM stimulation. Future study of inter-regional neural connectivity by using multi-modality imaging approaches would provide more insights into the BCI-based stimulation.

**CONCLUSION**

This study demonstrated that PET mapping could identify specific brain regions associated with orienting performance by the VPM stimulation in rats. PET molecular imaging could be an important
approach for BCI-based research and its clinical applications.

DISCLOSURE

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REFERENCES


FIGURE 1. (A) Schematic illustration for the calculation of “turning angle”. The turning angle is calculated from the different position directions between pre- and post-stimulation. (B) H.E. staining of the site of stimulation electrode placement. Arrow indicates the track of the intracranial electrode.
**FIGURE 2.** *In vivo* PET images of the rat brain. Serial coronal (A) and transverse (B) sections demonstrated significant changes of glucose metabolism after VPM electrical stimulation (*P*<0.001). Differences for brain regions have been color coded and are superimposed on MRI template.
FIGURE 3. Representative sagittal, transverse, and coronal images demonstrated increased glucose metabolism in the left (A) and right amygdala (B), and left Crus II (C) induced by VPM stimulation ($P<0.001$).
FIGURE 4. Representative sagittal, transverse, and coronal images demonstrated decreased glucose metabolism in the left (A) and right (B) S1 induced by VPM stimulation ($P<0.001$).
### TABLE 1

Significant Metabolic Changes after the VPM Stimulation (Baseline vs. Stimulation)

<table>
<thead>
<tr>
<th>Region</th>
<th>Coordinate (mm)</th>
<th>t value</th>
<th>z score</th>
<th>P&lt;sub&gt;uncorrected&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraventricular thalamic nucleus</td>
<td>0 5 -2</td>
<td>30.02</td>
<td>5.70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Septohippocampal nucleus</td>
<td>0 4 0</td>
<td>30.02</td>
<td>5.70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Right lateral septum</td>
<td>1 5 0</td>
<td>30.02</td>
<td>5.70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left lateral septum</td>
<td>-1 5 0</td>
<td>30.02</td>
<td>5.70</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Right amygdala</td>
<td>5 8 -3</td>
<td>11.16</td>
<td>4.41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Right piriform cortex</td>
<td>6 8 -3</td>
<td>11.16</td>
<td>4.41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Right endopiriform nucleus</td>
<td>6 8 -2</td>
<td>5.75</td>
<td>3.39</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Right insular cortex</td>
<td>6 8 -2</td>
<td>5.75</td>
<td>3.39</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left amygdala</td>
<td>-5 8 -3</td>
<td>6.86</td>
<td>3.67</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left piriform cortex</td>
<td>-6 9 -3</td>
<td>5.41</td>
<td>3.29</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left endopiriform nucleus</td>
<td>-6 8 -2</td>
<td>6.86</td>
<td>3.67</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left insular cortex</td>
<td>-6 8 -2</td>
<td>6.86</td>
<td>3.67</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Olfactory bulb</td>
<td>0 3 6</td>
<td>7.42</td>
<td>3.80</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left Crus II of the ansiform lobule of cerebellum</td>
<td>-4 5 -13</td>
<td>6.76</td>
<td>3.65</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Decreased</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right primary somatosensory cortex</td>
<td>5 2 0</td>
<td>9.17</td>
<td>4.12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left primary somatosensory cortex</td>
<td>-5 1 3</td>
<td>8.13</td>
<td>3.94</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Right secondary visual cortex</td>
<td>5 3 -9</td>
<td>6.30</td>
<td>3.54</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Right simple lobule of cerebellum</td>
<td>3 1 -10</td>
<td>5.13</td>
<td>3.20</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
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