

Effect of temporal interference electrical stimulation on phasic dopamine release in the striatum

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ABSTRACT

Background: Temporal interference stimulation (TIS) is a neuromodulation technique that could stimulate deep brain regions by inducing interfering electrical signals based on high-frequency electrical stimulations of multiple electrode pairs from outside the brain. Despite numerous TIS studies, however, there has been limited investigation into the neurochemical effects of TIS.

Objective: We performed two experiments to investigate the effect of TIS on the medial forebrain bundle (MFB)-evoked phasic dopamine (DA) response.

Methods: In the first experiment, we applied TIS next to a carbon fiber microelectrode (CFM) to examine the modulation of the MFB-evoked phasic DA response in the striatum (STr). Beat frequencies and intensities of TIS were 0, 2, 6, 10, 20, 60, 130 Hz and 0, 100, 200, 300, 400, 500 μ A. In the second experiment, we examined the effect of TIS with a 2 Hz beat frequency (based on the first experiment) on MFB-evoked phasic DA release when applied above the cortex (with a simulation-based stimulation site targeting the striatum). We employed 0 Hz and 2 Hz beat frequencies and a control condition without stimulation.

Results: In the first experiment, TIS with a beat frequency of 2 Hz and an intensity of 400 μ A or greater decreased MFB-evoked phasic DA release by roughly 40%, which continued until the experiment's end. In contrast, TIS at beat frequencies other than 2 Hz and intensities less than 400 μ A did not affect MFB-evoked phasic DA release. In the second experiment, TIS with a 2 Hz beat frequency decreased only the MFB-evoked phasic DA response, but the reduction in DA release was not sustained.

Conclusions: STr-applied and cortex-applied TIS with delta frequency dampens evoked phasic DA release in the STr. These findings demonstrate that TIS could influence the neurochemical modulation of the brain.

1. Introduction

Temporal interference stimulation (TIS) is a neuromodulation technique that could stimulate deep brain regions by inducing interfering electrical signals based on high-frequency electrical stimulations of multiple electrode pairs from outside the brain [1]. Grossman showed activation of hippocampal neurons in a rodent model without neuronal alterations in the proximity of the electrode [1]. Computer simulation

studies have been used to determine the most effective TIS parameters for stimulating deep brain regions and to understand the effect of TIS on nerves [2–7]. Lee et al. targeted the hippocampus using a human head model and evaluated the effects of anatomical structures on transcranial TIS. These authors advocated personalized transcranial TIS through the results that optimal TI parameters for delivering maximum TI currents to the target area differed by each head model [3]. TIS feasibility has also been assessed by modulating rodent and human brain. Acerbo et al.

Abbreviations: TIS, Temporal interference stimulation; STr, Striatum; MFB, Medial forebrain bundle; VTA, Ventral tegmental area; DA, Dopamine; CFM, Carbon fiber microelectrode; FSCV, Fast scan cyclic voltammetry; AP, Anterior-Posterior; ML, Medial-Lateral; DV, Dorsal-Ventral; FE, Finite element; S1J, Primary somatosensory jaw region; LPtA, Lateral parietal association cortex; M1, Primary motor cortex; V1B, Primary visual cortex binocular area.

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applied TIS with 130 Hz beat frequency to the hippocampus of mouse models with epilepsy, thereby reducing pathological fast ripple and pathological interictal epileptiform discharges [8]. Meanwhile, Missey et al. demonstrated the ability to induce seizure-like events by delivering TIS to the mouse hippocampus [9]. For humans, Ru and colleagues discovered that TIS with gamma/beta band beat frequencies increased excitability in the motor cortex [10]. In addition, it was demonstrated that using TIS to target the hippocampus increased episodic memory accuracy in human subjects [11]. Recently, TIS was applied to stimulate the human hypoglossal nerve, a peripheral nerve [12]. It was demonstrated that TIS could elicit behavioral and electrophysiological responses, unlike traditional transcutaneous stimulation, which evoked no response [12].

TIS has also been applied to deep areas of the body beyond the brain. Jabban et al. studied whether the mechanoreceptor ability to sense an electrode attached to the human upper limb was diminished and confirmed that interfering electrical stimulation reduced the sense of electrode attachment [13]. Botzanowski et al. used TIS to stimulate peripheral nerves and demonstrated that TIS could be used to target deep peripheral nerve targets (e.g., the sciatic nerve) in rodents [14]. However, few studies have investigated neurochemical changes in the brain induced by TIS. In this study, we confirmed changes in evoked phasic DA release caused by TIS through two experiments.

To assess the impact of TIS on changes in neurotransmitter concentrations in the striatum (STr), two technical factors need to be considered in the experiment. First, finding the optimized position of the TIS electrode pairs on the cortex for inducing TIS to the STr target is crucial. Second, the TIS stimulation parameters, including the beat frequency and amplitude, that play a significant role in changes of actual concentrations are important. Thus, a two-step experiment was designed using a divide-and-conquer strategy. In the first step, the TIS electrode was directly inserted into the STr, positioning it next to the carbon fiber microelectrode (CFM). This approach eliminated the uncertainty associated with the TIS electrodes' position on the cortex, specifically for targeting the STr. Under this condition, we investigated the effect of various TIS parameters on the evoked phasic dopamine (DA) release, allowing to identify the most influential TIS parameters. In the second step, positioning the TIS electrodes on the cortex was optimized using simulations to target the STr precisely. Subsequently, the TIS was applied on the cortex with the identified optimal parameters from the first experiment.

2. Materials and methods

2.1. Surgical procedure

Ninety-seven healthy adult Sprague Dawley rats (300–400 g, male, Orientbio, Republic of Korea) were used in the TIS experiments. These animals were exposed to a 12 h light/dark cycle, with the lights turning on at 6:00 a.m., and provided food and water ad libitum. Before inserting electrodes, the abdominal cavity was injected with urethane (1.6 g/kg, Sigma-Aldrich, St. Louis, MO). During the surgical operation, the animals' body temperature was maintained at 37 °C using temperature maintenance equipment (TCAT-2, Harvard Apparatus, Holliston, MA 01746, USA). All experimental procedures were approved by the Hanyang University Institutional Animal Care and Use Committee (IACUC No. 2021-0242A).

2.2. Fast-scan cyclic voltammetry for DA measurement

We employed fast scan cyclic voltammetry (FSCV) to monitor evoked-phasic DA release. FSCV is an electrochemical measurement technology that obtains current signals, known as a 'voltammogram', by delivering a triangular waveform ranging from -0.4 V to $+1.3$ V to -0.4 V to the CFM. This voltammogram typically corresponds to a non-faradic current (background current) induced by ions near the CFM [15].

However, if DA is present near the CFM, an oxidative current at around $+0.6$ V and a reduction current at about -0.2 V are added to the background current. Therefore, only the redox current response to DA remains by subtracting background current, called 'background subtraction', with DA signal to a background voltammogram without DA signal. Through this background subtracted voltammogram, FSCV is available to estimate real-time DA concentration [16]. To monitor evoked-phasic DA release using FSCV, the bipolar pulse that is evoking DA release is delivered to the medial forebrain bundle (MFB) which is situated between the ventral tegmental area (VTA)-STr circuit. It is attributed to the mechanism that DA is rapidly released outside a dendrite by stimulating dopaminergic neuron fibers [17]. When MFB is stimulated, at the same time, evoked phasic DA release could be measured by subtracting the background voltammogram corresponding to the redox current of extracellular DA secreted in the STr.

In our experiment, FSCV scanning was performed at a 10 Hz repetition rate and a triangle waveform with a slope of 400 V/s and a voltage range of -0.4 V to $+1.3$ V as shown in Fig. 1A. Also, we used the WINCS Harmoni device (Mayo Clinic, USA) and WINCSware software to conduct MFB stimulation and FSCV signals simultaneously [18,19]. We delivered a bipolar pulse train (intensity: 300 μ A; frequency: 60 Hz, pulse-width: 2 ms, duration: 2 s (120 pulses)) to MFB, and at the same time, we obtained the background subtracted voltammogram corresponding to the redox current of extracellular DA secreted in the STr. The reliable evoked phasic DA responses, as shown in Fig. 1A, could be obtained when MFB stimulation was applied every 10 min. In this study, we evaluated the TIS modulation effect on DA by checking how much the MFB evoked phasic DA responses change when TIS is applied. (For more FSCV information on supplementary materials, Figs. S1, S2, S3).

2.3. Temporal interference stimulation

TIS was carried out using two function generators (Keysight Technologies, 33210A, CA, USA) and two constant current stimulators (A-M Systems, Model 2200 analog stimulus isolator, WA, USA). The function generators were used to create the beat frequency of two sinusoidal waveforms, which were transmitted to the stimulator and exited as a steady current signal. This signal was received by the twisted electrode (STr-applied TIS experiment) or screw electrode (cortex-applied TIS experiment) and was then used to stimulate the desired location. The fundamental frequency used for TIS modulation was 2000 Hz.

2.4. In vivo experimental protocols

In the first experiment, in order to validate a direct TIS effect on evoked phasic DA response, two pairs of TIS electrodes and a CFM were located in the STr (see Fig. 1A). This eliminated the uncertainty associated with the TIS electrodes' position on the cortex, specifically for targeting the STr. As a coordination of electrodes, the TIS electrode pairs were implanted into the AP: $+1.2$ mm, ML: $+1.8$ mm (pair 1), $+2.2$ mm (pair 2), and DV: 4.4 mm. And the CFM was positioned to AP: $+1.2$, ML: $+2.0$, and DV: 4.5 from Bregma in mm [19]. The depths of these electrodes had 100 μ m difference to minimize the influence of a tissue damage on DA detection (see Fig. 4A). In order to evoke DA release, we inserted a stimulation electrode (Plastic One, MS303/3-A, Roanoke, VA, USA) into the MFB (AP: 4.6 mm; ML: $+1.4$ mm; DV: 8.0 mm $\sim$ 9.0 mm). A reference electrode (Ag/AgCl) was located to the opposite hemisphere. Electrode placement was based on the Rat Brain Atlas of Paxinos and Watson [20].

After placing the electrodes, the TIS experiment began with the measurement of the MFB-evoked phasic DA signal at 10-min intervals [19] (a total of six measurements), as illustrated in Fig. 1B. TIS was applied for 5 min after three consecutive reliable DA current measurements. In order to explore two TIS parameters (modulation beat frequency and intensity), we performed TIS with varied modulation beat frequencies (0, 2, 6, 10, 20, 60, and 130 Hz) and a fixed 400 μ A

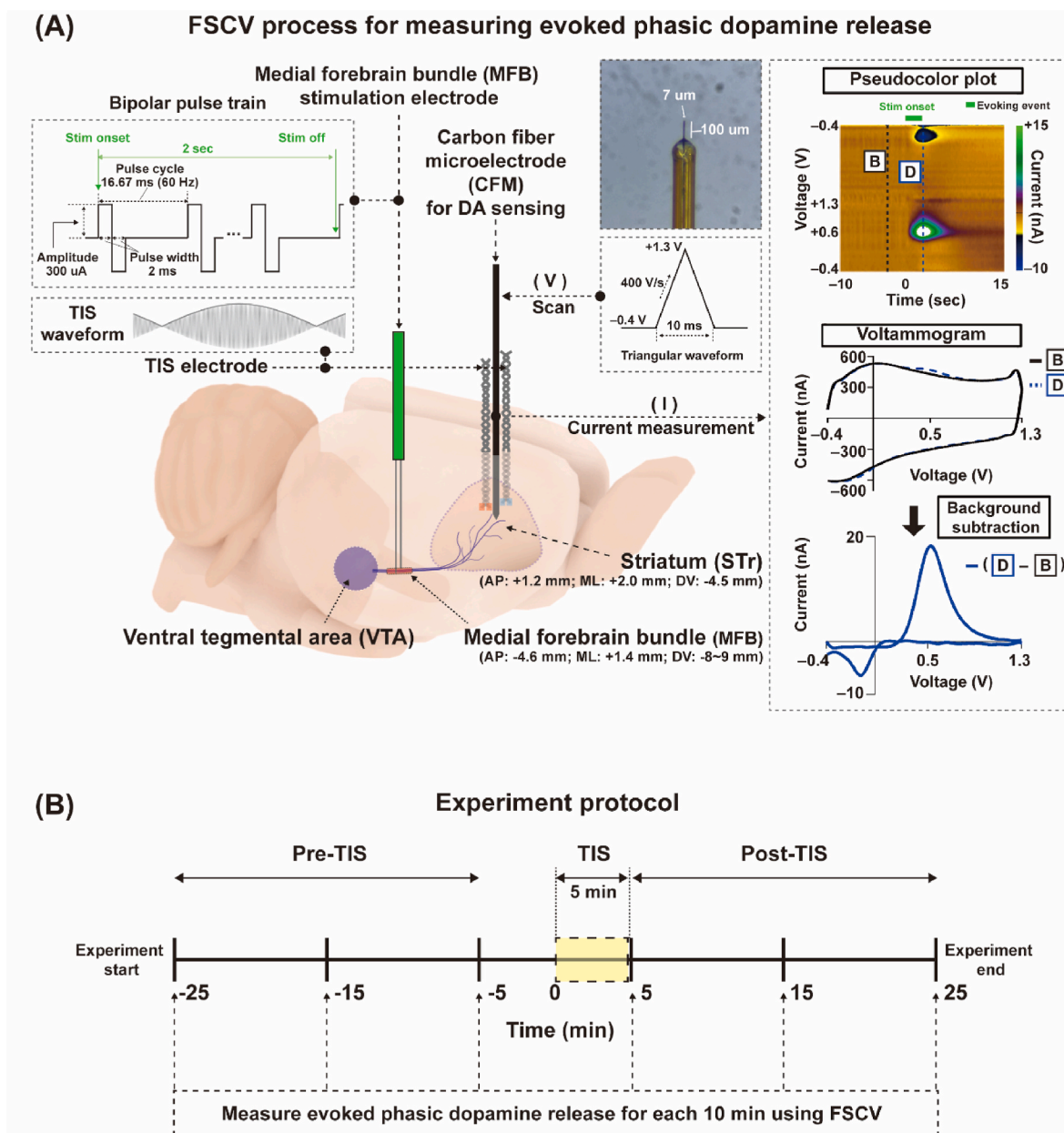


Fig. 1. Experimental protocol to monitor the effect of TIS on evoked phasic DA release. (A) Fast scan cyclic voltammetry (FSCV) process for measuring evoked phasic DA release. (B) TIS experiment protocol.

stimulation intensity firstly. There was also a control group that received no TIS. There were six animals in each frequency group. And then, the influence of stimulation intensity on MFB-evoked phasic DA release was investigated using stimulus intensities of 100/200/300/400/500 μ A with 2 Hz fixed modulation beat frequency. There was a non-stimulated control group as well. The stimulus intensity experiment involved six animals per group.

In the second experiment, the effect of TIS on DA was evaluated by delivering TIS above the cortex rather than inserting the TIS electrodes directly next to the CFM in the ST_r. Positioning the TIS electrodes on the cortex was optimized using simulations to target the ST_r precisely. Subsequently, the TIS was applied on the cortex with the identified optimal parameters from the first experiment. Based on electrode position optimization simulation (Fig. 3A) for TIS targeting of the ST_r, four titanium screw electrodes were inserted into a rat skull. The positions of TIS electrode pair 1 were set to primary somatosensory jaw region (AP: +2.75 mm, ML: +4.5 mm, DV: on the dura mater) and lateral parietal

association cortex (AP: 4.0 mm, ML: 4.5 mm, DV: on the dura mater). Also, TIS electrode pair 2 were positioned to the primary motor cortex (AP: +2.75 mm, ML: 2.25 mm, DV: on the dura mater) and primary visual cortex binocular area (AP: 8.5 mm, ML: 4.5 mm, DV: on the dura mater) (For more electrode location information on supplementary materials, Fig. S5). And applied magnitudes in the cortex were 0.95 mA (pair 1) and 1.05 mA (pair 2) based on the optimization result (Fig. 3A). An experimental protocol was identical to the first experiment (Fig. 1B).

2.5. Data processing and analysis

The maximum current value was determined from the DA oxidation current measured every 10 min during the experiment. The pre-stimulation current value, the peak DA oxidation current measured 5 min before TIS onset, was normalized using a base of 100% for the six highest oxidation current values. The nonparametric Kruskal-Wallis test was used for statistical analysis to investigate the significance of changes

in DA concentration according to all results. And Dunn's multiple comparisons test was employed as the post hoc test. Data were plotted and analyzed by using GraphPad Prism 10 (GraphPad Software, San Diego, CA).

2.6. Optimization of TIS electrode positions using a finite element model

We investigated the optimal electrode positions to maximize TIS currents delivered to the ST_r. To do this, a finite element (FE) model of the rat brain was created based on TIS-weighted magnetic resonance images. As TIS electrodes were placed on the brain surface, we extracted only the brain mask using ITK-SNAP v3.8 (www.itk-snap.org) [21], after which we created a volumetric brain model using TetGen [22]. Then, an atlas of the rat brain was registered to the FE model to capture the exact coordinates of the TIS electrodes and the target as in animal

experiments. For optimization, we employed the same approach utilized in previous studies [3,7]. We did not perform detailed calculations of electric fields or an optimization process because the main purpose of this study was to investigate how TIS affects DA response in the ST_r of rats according to the frequency of TIS. Details can be found in previous studies. Briefly, two electrode pairs (they have 500 μm for radius and 2.4×10^6 S/m for the conductivity [23]) were selected from among the electrode candidates to create TIS currents, and the amplitude of injection currents to maximize TIS currents at the target was calculated. This procedure was carried out for all possible combinations of electrode pairs. Through this exhaustive search, the optimal location and injection current for the two electrode pairs on the brain surface were determined. Compared to previous studies of human heads using the electrode candidates based on the International 10-10 EEG system, we used a manual electrode candidate for optimization because there is no reference

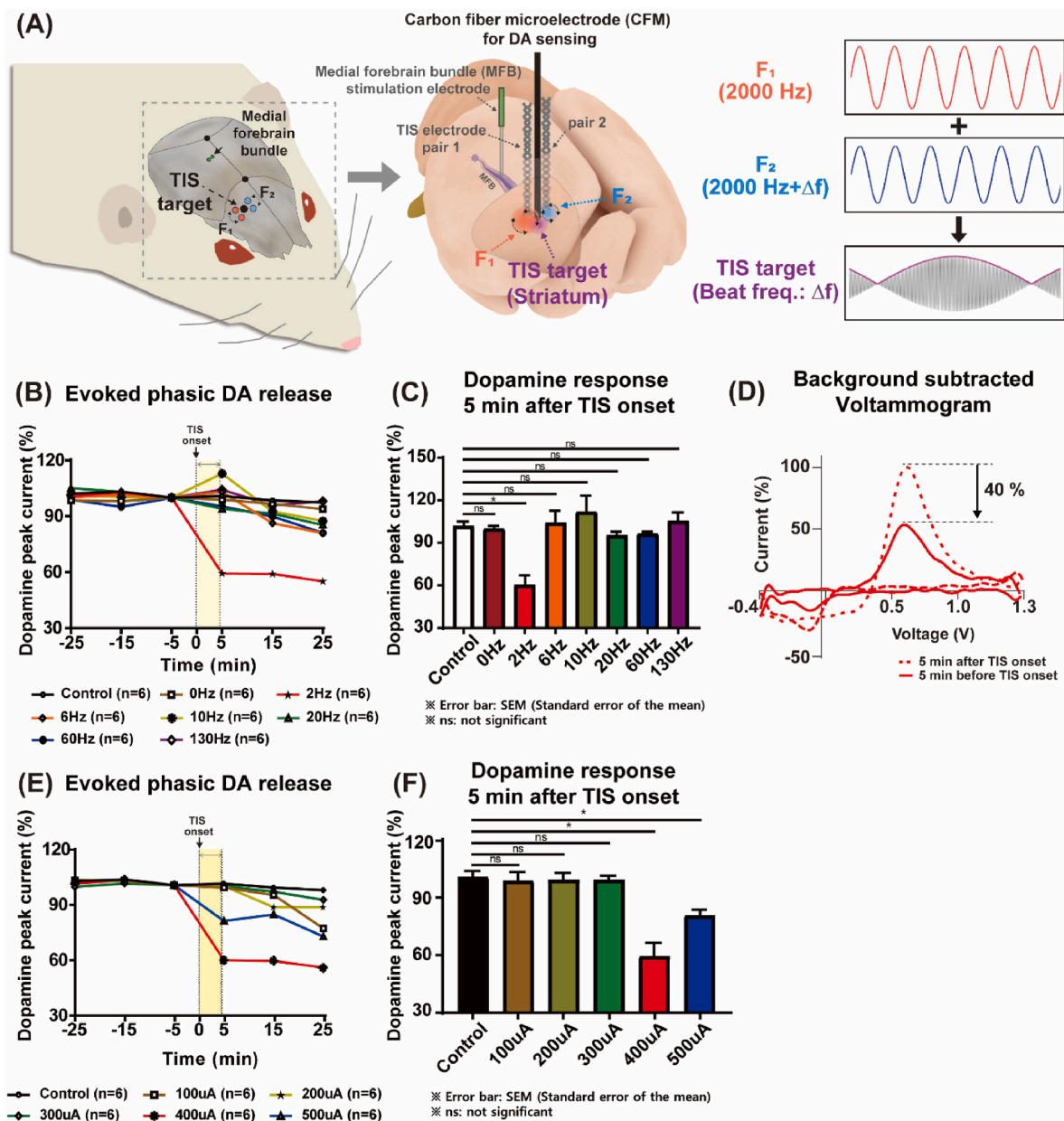


Fig. 2. Evoked phasic DA response before and after ST_r-applied TIS. (A) Overview of ST_r-applied TIS experiment. MFB-evoked phasic DA responses were obtained every 10 min for various TIS beat frequencies (B) and intensities (E). The evoked phasic DA response immediately after TIS stimulation was normalized to the TIS baseline at 5 min before the stimulation for TIS beat frequencies (C) and intensities (F). Voltammogram of phasic DA response before and after application of a TIS beat frequency of 2 Hz (D).

electrode location on the rat brain. Thus, we created 7×5 grid points on the brain surface based on bregma, with a distance between points of 2.25 mm. This resulted in 33 points covering the neocortex, which were used as electrode candidates. Two points were excluded due to their location outside the neocortex.

2.7. Histological confirmation of electrode location

To confirm the placement of electrodes (TIS electrode and CFM) within the brain, we inserted electrodes coated with DiI solution (Invitrogen, USA) into the striatum of 4 SD rats (Fig. 4A) [24]. After electrode insertion, the anesthetized rats were sacrificed when we performed transcardiac perfusion using 4% paraformaldehyde (PFA) (BIOESANG, Republic of Korea). And carefully extracting the electrodes from the brain, we fixed the brain in 4% PFA for 24 h. The fixed brain was then immersed in 30% sucrose in PBS solution for 3 days to dehydrate. After 3 days, the brain was washed with PBS and sliced into 120 μ m thicknesses. We acquired confocal images of the striatum area where the electrodes were inserted from the sliced brain tissue (Fig. 4B).

3. Results

3.1. Modulation of evoked phasic dopamine release by temporal interference stimulation near the striatum

Experiments were performed to investigate the impact of TIS on neurotransmitter concentrations by directly applying TIS to the CFM at beat frequencies of 0, 2, 6, 10, 20, 60, and 130 Hz and intensities of 100, 200, 300, 400, 500 μ A (see Fig. 2A). To investigate how TIS evoked phasic DA release depending on beat frequency, we applied TIS at different modulation frequencies (0, 2, 6, 10, 20, 60, 130 Hz) at a fixed intensity of 400 μ A. As a result, TIS with a beat frequency of 2 Hz decreased evoked phasic DA release by 40% (see Fig. 2B, D), and reduced response was maintained through the end of the protocol. In

contrast, the other beat frequencies group (0, 6, 10, 20, 60, 130 Hz) did not affect evoked phasic DA release. Statistical analysis revealed that only the 2 Hz group showed a significant difference from the control group (Kruskal-Wallis test, $p = 0.0083$; Dunn's multiple comparisons test, $p = 0.0073$ for the 2 Hz group vs. control group) (see Fig. 2C).

To examine the impact of TIS intensity on DA release, intensities of 100 μ A ($n = 6$), 200 μ A ($n = 6$), 300 μ A ($n = 6$), 400 μ A ($n = 6$), and 500 μ A ($n = 6$) were evaluated and compared to results from a non-stimulated control group ($n = 6$). The TIS beat frequency was set to 2 Hz based on the ability of this frequency to reduce MFB-evoked phasic DA in the previous experiment significantly. Evoked phasic DA release was substantially reduced in the 400 μ A and 500 μ A groups (see Fig. 2E). However, no differences were observed between the control (non-stimulated) group and groups stimulated with 100–300 μ A intensities. Statistical analysis revealed significant differences between the 400 μ A and 500 μ A groups compared to the control group (Kruskal-Wallis test, $p = 0.0007$; Dunn's multiple comparisons test, $p = 0.0018$ for 400 μ A vs. control group, $p = 0.0393$ for 500 μ A vs. control group).

3.2. Effect of cortex-applied TIS on evoked phasic DA release

Rather than placing the TIS electrodes next to the CFM, they were placed above the cortex to stimulate the ST_r. TIS electrode positions (pair 1: right S1J–left LPT_a, pair 2: right M1–left V1B) and intensities (pair 1: 0.95 mA, pair 2: 1.05 mA) were optimized using computer simulation to ensure that the ST_r was targeted when using TIS above the cortex (see Fig. 3A and S5). The experiment was carried out in the same manner as the first experiment protocols. As previously, a 2 Hz beat frequency significantly reduced evoked phasic DA release compared to the 0 Hz and control groups (see Fig. 3B). However, this reduction was not sustained, unlike the prior experiment when TIS was applied next to the ST_r. Statistical analysis revealed significant differences between the 2 Hz group compared to the 0 Hz and control groups, as shown in Fig. 3C (Kruskal-Wallis test, $p = 0.0006$; Dunn's multiple comparisons test, $p =$

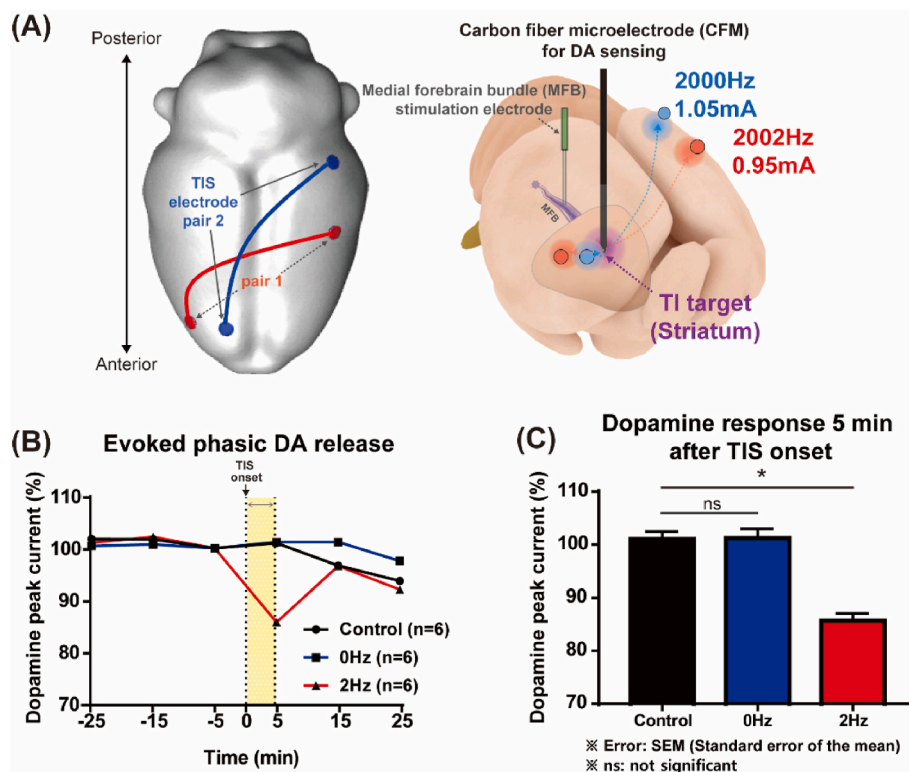


Fig. 3. Evoked phasic DA response to cortex-applied TIS. (A) Computer simulation of TIS targeting the ST_r. (B) Time-dependent changes in evoked phasic DA response. (C) The rate of change in evoked phasic DA release after TIS.

0.007 for the 2 Hz group vs. control group).

3.3. Histological confirmation of electrode location

We successfully confirmed the traces of electrodes (TIS electrodes and CFM) implanted in the ST_r of all four animals through histological verification. In our experiment, CFM was precisely inserted for the DA hotspot targeting within ST_r (AP: +4.5, ML: +2.0, DV: 4.5 from bregma in mm) via a stereotaxic frame (see Fig. S2B). TIS electrode pairs were positioned 100 μ m above the Carbon fiber to allow TIS to be delivered as close to the DA measurement location as possible (Fig. 4A). As a result of confocal imaging, as shown in the four red circles of Fig. 4B, we found that the CFM was located around at a depth of 4.5 mm from the brain surface, which is the DA hotspot. In the case of the TIS electrode pairs, it was verified that pairs were also positioned in the ST_r through the electrode tracks indicated by the red markers on the confocal image (see Fig. 4B). In each of the confocal images on the right side of Fig. 4B, the location of the TIS electrode pair and CFM could be confirmed in the slice corresponding to AP 1.2 mm through the electrode tracks with red markers. Also, we confirmed the part of TIS electrode pairs was located on ST_r in the slice corresponding to AP 1.08 mm.

4. Discussion

This study aimed to determine how TIS affected MFB-evoked phasic DA release. To achieve this, we monitored evoked phase DA release in the ST_r by applying bipolar pulses to the MFB that the evoked phasic DA release through an electrochemical measurement technique called FSCV. However, to investigate the impact of TIS, we first need to confirm that the DA signal being measured by FSCV is indeed detecting DA. Additionally, it's crucial to verify that the MFB-evoked phasic DA response, measured at 10-min intervals, is reliable within the experimental protocol. Therefore, to ensure the accuracy of our findings, we carried out post-calibration and pharmacological confirmation experiments separately. In general, to validate that the signals measured by FSCV are indeed attributable to DA, an *in vivo* pharmacological test involving an administration of a DA reuptake inhibitor and a post *in vitro* calibration for 1 μ M DA are conducted [25–29]. We administered GBR-12909 (10 mg/kg, Sigma-Aldrich, St. Louis, MO), the DA reuptake inhibitor, to three rats to verify the MFB-evoked phasic DA release in ST_r every 10 min (see Fig. S4A). After the drug injection, we confirmed an increase in the evoked phasic DA response by over 290% within 1 h (see Fig. S4B). Subsequently, for post-calibration, we carried out an *in vitro* test for 1 μ M DA (see Fig. S4A). This test was performed using the same CFM used in the *in vivo* experiment. We noticed that both the phasic DA signal obtained from the *in vivo* experiment before 20 min and from the post-calibration had a significant correlation ($R^2 = 0.924$) (see Fig. S4C).

These two experimental results demonstrated that the voltammograms - the phasic DA signals measured via FSCV - indeed detect DA. Based on this established reliability, we conducted two TIS experiments to verify the efficacy of TIS using the MFB-evoked phasic DA signal.

In the first experiment, we used TIS electrodes next to the CFM to assess the effect of TIS and found that TIS with a beat frequency of 2 Hz decreased evoked phasic DA release. Furthermore, we found a substantial decrease in evoked phasic DA release at intensities greater than 400 μ A. In the second experiment, we positioned the TIS electrodes on the cortex instead of next to the CFM to explore the effect of TIS with a beat frequency of 2 Hz. TIS electrode locations on the cortex were optimized using computer simulations to target the ST_r. Similar to the previous experiment, TIS with a beat frequency of 2 Hz decreased the evoked phasic DA release. However, the decrease in DA release was not sustained through the experimental protocol.

The most intriguing finding of this study is that TIS with a delta band frequency reduces evoked phasic DA release. Several studies have investigated the relationship between DA release and the delta frequency of neural activity. First, it was discovered that DA deficits induce delta oscillation. For example, rodent models of Parkinson's disease showed spike firing rates with delta frequencies when DA concentration was decreased with 6-OHDA [30]. Similarly, DA transporter knock-out mice displayed an increase in the relative spectral power of delta oscillation, which decreased DA release [31]. Second, an increase in DA concentration has been shown to decrease the power of delta oscillation. For example, a mouse model demonstrated a decrease in delta oscillation of LFP when DA concentration was increased using a D2R agonist [30]. Another possibility we could consider is that TIS with a delta frequency might affect striatal GABA-interneurons, reducing DA release [32]. These findings suggest a link between the regulation of DA release and changes in the electrophysiological properties of neural activity [33]. Our research is the first, to our knowledge, to demonstrate that DA release is regulated by directly applying the delta frequency of TIS.

Another interesting finding is that the change in evoked phasic DA release was not maintained when TIS with a beat frequency of 2 Hz was applied to the cortex (see Fig. 3B) in contrast to the application of TIS near the ST_r, which decreased evoked phasic DA release for 30 min after stimulation. This may be due to the attenuation of the electric field by the skull and cerebrospinal fluid [34] between the cortex and the target area of the ST_r. Another thinkable explanation for this finding could be the variance in the types of stimulation electrodes utilized. A fundamental distinction between the two experiments conducted in this study lies in the different types of stimulation electrodes. In the first experiment, we employed an electrode designed to penetrate the brain, placing the stimulation electrode close to the measurement electrode. However, in the second experiment, we aimed for minimally invasive deep brain stimulation using screw-type electrode pairs. In future studies, we will

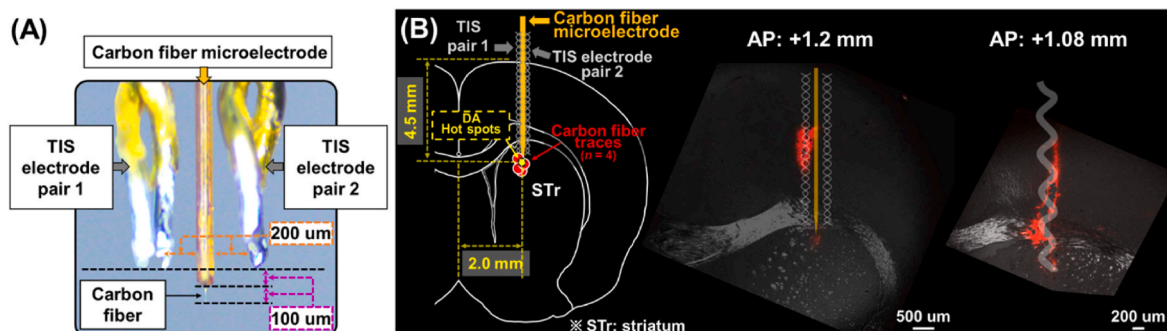


Fig. 4. Histological validations for electrodes (TIS electrode and CFM) position. (A) TIS electrode and CFM were used in TIS applied to the ST_r directly (the first experiment). In order to deliver TIS to ST_r directly, the TIS electrode was placed 100 μ m above the CFM. (B) Confocal image was demonstrated that the tip of the CFM was placed in the ST_r (AP: +1.2 mm; ML: +2.0 mm; DV: 4.5 mm) as indicated by the trace marked in red circle ($n = 4$). The trace of the CFM tip (AP: +1.2 mm) and TIS electrode's track (AP: +1.2 mm and +1.08 mm) were confirmed as red marker on the confocal image. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

investigate if TIS of increased intensity and duration delivered to the cortex can sustain the MFB-induced decrease in phasic DA response.

5. Conclusion

In summary, this study demonstrates that both STR-applied and cortex-applied TIS with a delta frequency (2 Hz) modulates evoked phasic DA release in the STR. These findings demonstrate that TIS could influence the neurochemical modulation of the brain.

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CRedit authorship contribution statement

Youngjong Kwak: Conceptualization, Methodology, Software, Data curation, Validation, Visualization, Writing – original draft. **Seokbeen Lim:** Conceptualization, Methodology, Software, Data curation, Validation, Visualization, Writing – original draft. **Hyun-U Cho:** Methodology. **Jeongeun Sim:** Methodology. **Sangjun Lee:** Methodology, Software. **Suhyeon Jeong:** Validation. **Se Jin Jeon:** Validation. **Chang-Hwan Im:** Methodology, Software. **Dong Pyo Jang:** Conceptualization, Methodology, Software, Visualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2023.09.012>.

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