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Article

# Cortical plasticity differences in substance use disorders

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ABSTRACT

Among substances, opiates and psychostimulants are responsible for the most significant public health problems, yet few studies have characterized their similarities or differences in the cortical plasticity of individuals with these substance related problems. This investigation utilized concurrent transcranial magnetic stimulation and electroencephalography (TMS-EEG) to examine cortical plasticity characteristics of individuals with heroin and methamphetamine related substance use disorder (SUD) relative to healthy controls. TMS-EEG data were collected from healthy control subjects ($N = 35$), subjects with heroin ($N = 72$) and methamphetamine ($N = 69$) use disorder. The data were analyzed using our fully-automated artifact rejection algorithm (ARTIST). Analyses were performed separately for F3, F4 and P3 stimulation sites. Linear mixed effects models were used to examine Group (heroin, methamphetamine, healthy control) x Time (pre, post single-session rTMS) interactions. To evaluate plasticity differences across groups, we observed the changes in single pulse TMS before and after single-session of rTMS. There was no change in alpha power after stimulation of the F3 or F4 sites across groups. The alpha power of the control group was significantly decreased when stimulating the P3 site, while there was no significant change in alpha power for either drug group during the same time window. The beta power of the healthy control group increased significantly when the F3 site was stimulated. In contrast, there was no significant change in either the methamphetamine or heroin group. Following a single-session of rTMS intervention, there was a significant difference in alpha-band power between the healthy control group and the two drug groups. Taking together, the study findings identified differential plasticity effects in the two types of SUD population, and highlighted the network effects of rTMS. The findings point to an exciting future path for using rTMS to test new plasticity-based interventions for treating drug addiction.

## 1. Introduction

Substance use disorders (SUD) are among the most significant economic burdens and challenges for global health [1]. Opiates (e.g., heroin) and psychostimulants (e.g., cocaine, methamphetamine) represent two major types of substances of abuse, sharing certain clinical characteristics but differing in many behavioral and neurobiological aspects [2]. SUD is characterized by compulsive drug-seeking and persistent memory of drug abuse, which is accompanied by plasticity-like changes in the brain [3].

Synaptic plasticity represents the lasting modifications in synaptic strength and/or structures, which is considered as the cellular mechanism underlying learning and memory. The major forms of synaptic plasticity are long-term potentiation (LTP) and long-term depression (LTD), which are found to be altered and involved in different stages of drug addiction [4,5]. For instance, animal studies reported that a single exposure to cocaine and other drugs of abuse induces rapid synaptic potentiation and anti-Hebbian like plasticity in midbrain dopamine neurons [6–8], while repeated drug exposure results in abundant synaptic changes in the nucleus accumbens, amygdala, and prefrontal cortex [9–11]. However, it is unknown whether drug addiction in humans alters the capacity for induction of cortical plasticity, such as by transcranial magnetic stimulation with simultaneous electroencephalography (TMS-EEG) recording.

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**Table 1**
**Demographic and drug use characteristics (Mean ± *SEM*).**

| Variable | Meth patients ($n$ = 69) | Heroin patients ($n$ = 72) | Control group ($n$ = 35) | $F/t$ | $P$ |
|---|---|---|---|---|---|
| Age (year) | 35.83 ± 0.85 | 39.11 ± 0.91 | 35.94 ± 1.62 | 3.90 | 0.03 |
| Withdrawal time (days) | 70.99 ± 7.07 | 70.94 ± 7.79 | / | 0.00 | 0.99 |
| Intake (years) | 8.68 ± 0.43 | 12.94 ± 0.75 | / | 4.93 | 0.00 |
| Maximum dosage per time (g) | 0.90 ± 0.05 | 0.58 ± 0.05 | / | 4.37 | 0.00 |
| Maximum dosage per month (g) | 14.63 ± 1.13 | 20.62 ± 1.34 | / | 3.41 | 0.00 |

TMS provides an opportunity for focal brain region stimulation and allows cortical plasticity evaluation, such as when combined with recording of motor evoked potentials (MEPs) [12]. Recent studies reported altered motor cortical plasticity in different types of SUDs, such as for heroin, methamphetamine, and cannabis [13–15]. Yet it is unclear if the cortical plasticity alteration can be generalized to other cortical regions, especially the prefrontal cortex that controls over craving formation [16] .

TMS allows functional mapping for the whole cortex when combined with simultaneous EEG recording. TMS-EEG has emerged as a powerful tool to non-invasively probe human brain circuits, allowing the assessment of relevant cortical properties such as excitability and connectivity [17,18]. Over the past decade, this technology has been applied to a variety of clinical populations, enabling the characterization and development of potential predictors of TMS-EEG and markers for the treatment and pathophysiology of brain disorders (e.g., depression, PTSD) [19–21]. TMS-EEG detects both local and long-range cortical connectivity and allows for studying changes in oscillatory behavior of the brain, as seen in event-related spectral perturbation (ERSP).

The present study collected TMS-EEG recordings both from healthy subjects and individuals with either heroin or methamphetamine use disorders. Both baseline ERSP and plasticity-like changes induced by a 10 Hz repetitive TMS (rTMS) protocol were included for analysis using the fully-automated artifact rejection algorithm (ARTIST). We hypothesized that: (1) TMS-EEG would reveal both abnormalities in cortical functional connectivity and plasticity in SUD; (2) 10 Hz rTMS would influence cortical oscillations of healthy controls but not addiction groups; (3) the brain networks in each type of SUD may be different.

## 2. Materials and methods

### 2.1. Participants and experimental design

We calculated a priori the sample size required for the current design using G-Power version 3.1.9.2 statistical software (University of Dusseldorf, Germany), assuming a significant difference in cortical plasticity between the SUD group and healthy controls, to make a significant difference of 0.05 (two-sided test), 80% test efficacy, and considering a 10% dropout rate, each group in the study would need to recruit 35 subjects. Data were collected from heroin ($N$ = 72) and methamphetamine ($N$ = 69) use disorder subjects (in abstinence), as well as healthy controls ($N$ = 35) in Nanjing and Hangzhou, China (Table 1).

Participant's inclusion criteria. Healthy control group: (1) male volunteers (age 20–60 years old); (2) right-handed; (3) no complaints of cognitive impairment; (4) mini-mental scale examination scores greater than 27 points and less than or equal to 30 points. SUD group: (1) male volunteers (age 20–60 years old); (2) right-handed; (3) DSM-5 diagnosis: heroin or methamphetamine SUD; (4) at least 3 years drug use (no use in past 6 months); (5) no history of TMS or use of medications; (6) no neurological or mental illnesses and related medical history. Participant's exclusion criteria: (1) have a history of epilepsy, have a history of idiopathic epilepsy in first-degree relatives, and use epileptic drugs; (2) heart, lung, liver, kidney, and other important organs are hypofunction or fail; (3) severe cognitive and communication disorders and unable to cooperate; (4) wear a pacemaker, have a metal implant in the body, or have a skull defect; (5) severe damage to the cerebral cortex. (6) participating in another clinical research.

Data were collected across two sites: Nanjing and Hangzhou, China. All experimental procedures were approved by the Ethics Committee of Shanghai Mental Health Center and Nanjing Normal University. All participants signed written informed consents and participated voluntarily.

The protocol included 3 main phases: baseline single-pulse TMS was delivered to 3 cortical sites (targeted based on the International 10–20 system for EEG electrode placement: the order of the three sessions was F3 (left frontal), F4 (right frontal), and P3 (left parietal)). Following the baseline measures, a single session of 10 Hz rTMS was delivered. Finally, single-pulse TMS was repeated for each of the three stimulation sites in order to measure change elicited by the rTMS intervention.

### 2.2. TMS-EEG data acquisition

Data were collected using Visor2 ST, an integrated TMS-EEG system comprised of Power & MAG ANT Neuro 100 stimulator, P70-cool TMS coil, and a passive 64-channel EEG cap. Subjects participated in a single-session of TMS-EEG. Single-pulse TMS was delivered prior to and following a single-session of rTMS. Each single pulse condition involved 100 pulses of TMS with 5000 ms (+/- 400 ms) inter-trial interval. Three conditions of spTMS were used, targeting electrode locations: F3, F4, and P3. Between the pre and post single-pulse conditions, high-frequency rTMS stimulation was delivered to the left dorsolateral prefrontal cortex at 10 Hz frequency (5 s on, 10 s off) for 10 min (2000 pulses) as described in previous study [13]. Stimulation intensity was set to 100% resting motor threshold, as measured on the left hemisphere motor cortex. To ensure the successful application of TMS, we first had to make sure the localized target site was the correct cortical location in our study. To achieve this, the neuronavigation system was used to track the spatial position of the coil and the participant's head during stimulation, ensuring that the distance between the coil and the target site was within 5 mm and the angel was within 10°. For both single-pulse and rTMS, neuronavigation was used to target the stimulation sites (using locations identified on a template brain).

### 2.3. TMS-EEG pre-processing and source analysis

TMS-EEG data was cleaned offline using our ARTIST [22]. The 30 milliseconds of data following the TMS pulse were removed to eliminate the TMS-induced electrical artifact. Data were down-sampled to 1 kHz, and independent component analysis (ICA) was used to remove large TMS-decay artifacts. Number of ICA dimensions was determined by using principle component analysis (PCA), whereby the number of components accounted for 99.9% of the variance. A 50-Hz notch filter was used to remove line noise. Physiologically-irrelevant signal was removed using a 0.01 Hz high pass filter, and high-frequency noise was removed using a 100 Hz low-pass filter. Data were re-referenced to a common average. EEG data were then epoched with respect to the TMS stimulation (−0.5 to 1.5 s), and bad epochs were rejected. Bad channels were rejected based on spatial correlation with adjacent channels or if impedances exceeded the threshold. Spherical spline interpolation was used to interpolate over rejected channel space. A second round of ICA was used to automatically identify and remove the remaining artifacts

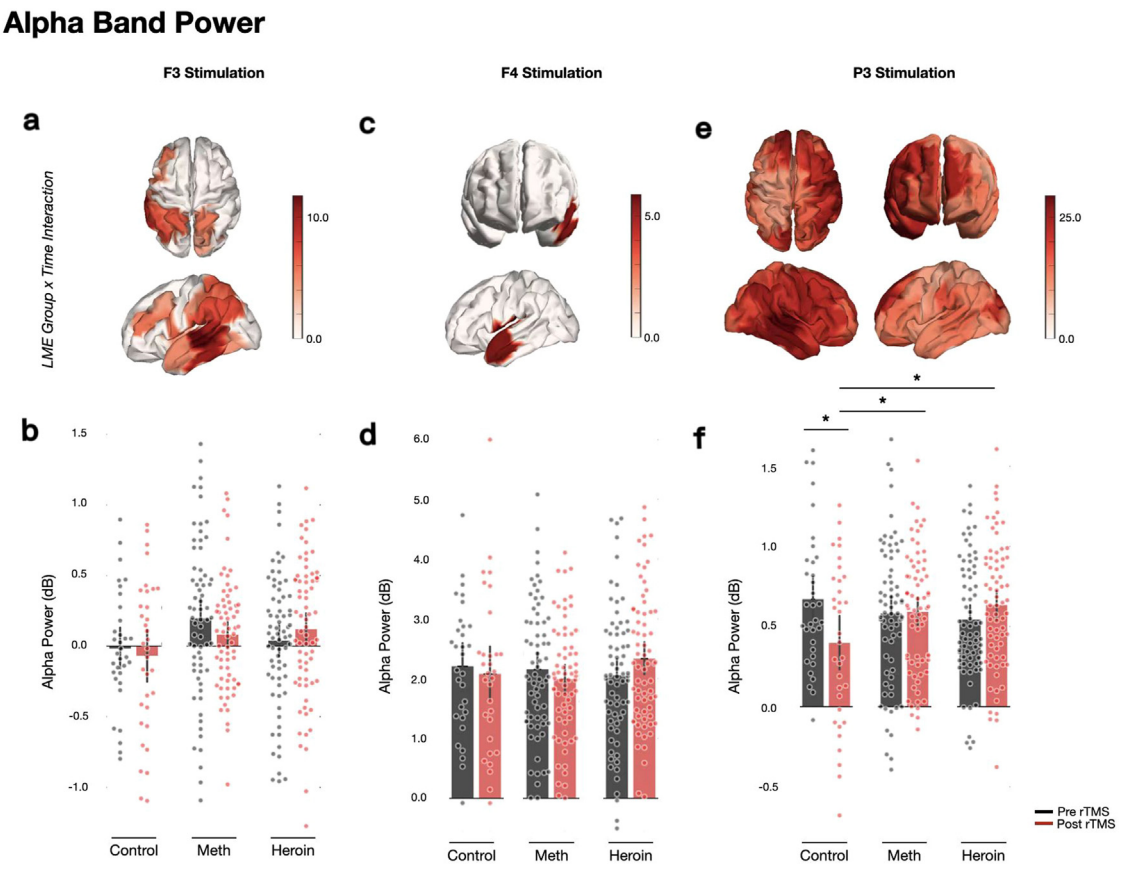


**Fig. 1. Linear mixed effect model results for alpha band power**. Group (Control, Methamphetamine, Heroin) x Time (pre, post single-session rTMS) interaction are displayed for (a) F3, (c), F4, and (e) P3 stimulation sites. F-statistic of the interaction is plotted. For each model (b, d, f), bar graphs show the pre- and post-rTMS values for each subject across groups and time. Post-hoc paired t-tests were used to identify significant effects.

(ocular, ECG, and scalp muscle) using ARTIST's trained pattern classifier. During pre-processing, conditions were excluded if the amount of noise prohibited ICA from converging. Following artifact rejection, data were re-referenced to the common average.

The Brainstorm toolbox [23] was used to convert EEG data from channel to source space. A symmetric head model was calculated using OpenMEEG [24] using the Montreal Neurological Institute (MNI) template brain. This technique established rotating dipoles at 3003 vertices, encompassing the cortical regions of interest. Whole-brain source estimates were made from channel-space data using weighted Minimum Norm Estimate (wMNE). For each subject, a kernel was calculated to map channel-space EEG to source space current density, using the orthogonal axes at each vertex. Prior to subsequent analyses, vertices were combined to produce 100 ROIs [25]. EEGLab toolbox was used to complete frequency analysis, extracting alpha (8–13 Hz) and beta (15–22 Hz) bands of interest. Band power (dB) was calculated for each canonical band. Data were baseline corrected using −300 to −100 ms prior to TMS signal as the baseline.

### 2.4. Statistical analyses

EEG data from each stimulation site condition (F3, F4, and P3) were analyzed independently, using linear mixed effects (LME) models to look at Group x Time interactions (Group: heroin, methamphetamine, healthy control; Time: pre, post single-session rTMS). To evaluate brain plasticity of each group, pre-to-post comparisons used group as a categorical predictor, pre-vs-post rTMS as a covariate, and participant as a random intercept. Cluster-based permutation statistics were used to threshold the LME results. Using the significant ($p < 0.05$) values from the LME analysis, we identified clusters in time and space. Data labels were shuffled, and LME was re-run on the significant clusters for 150 permutations. For each cluster, the sum of F-statistics was calculated, and the maximum F-statistic across clusters of each permutation was stored. Following all permutations, a histogram was created using the maximum values. The threshold F-statistic was determined to be that which exceeded 95% of the permutation values. This new threshold was applied to the original LME clusters. Those clusters whose summed F-statistic exceeded this threshold were considered to be significant. This analysis was completed for each contrast (e.g., comparing pre-to-post rTMS alpha power during F3 stimulation). Post hoc pairwise t-tests were conducted on significant clusters (averaging over significant timepoints and regions of interest within each significant cluster). Because the first 30 ms of data post TMS stimulation is interpolated (after removal of the TMS pulse artifact), we rejected clusters within the first 40 ms post stimulation. This conservatively eliminated the findings that were due to interpolated data or the immediate transition from interpolated to recorded data.

## 3. Results

### 3.1. Linear mixed effects (Group × Time interaction)

Linear Mixed Effects models were fit for each stimulation site and frequency band independently. Clusters were found from significant ($p < 0.05$) ROIs across time and space. These clusters were thresholded using random permutations of the data to create a null distribution. Significant clusters were defined as those that exceeded 95% of the permutation distribution. At F3 stimulation site, a significant alpha cluster from 97

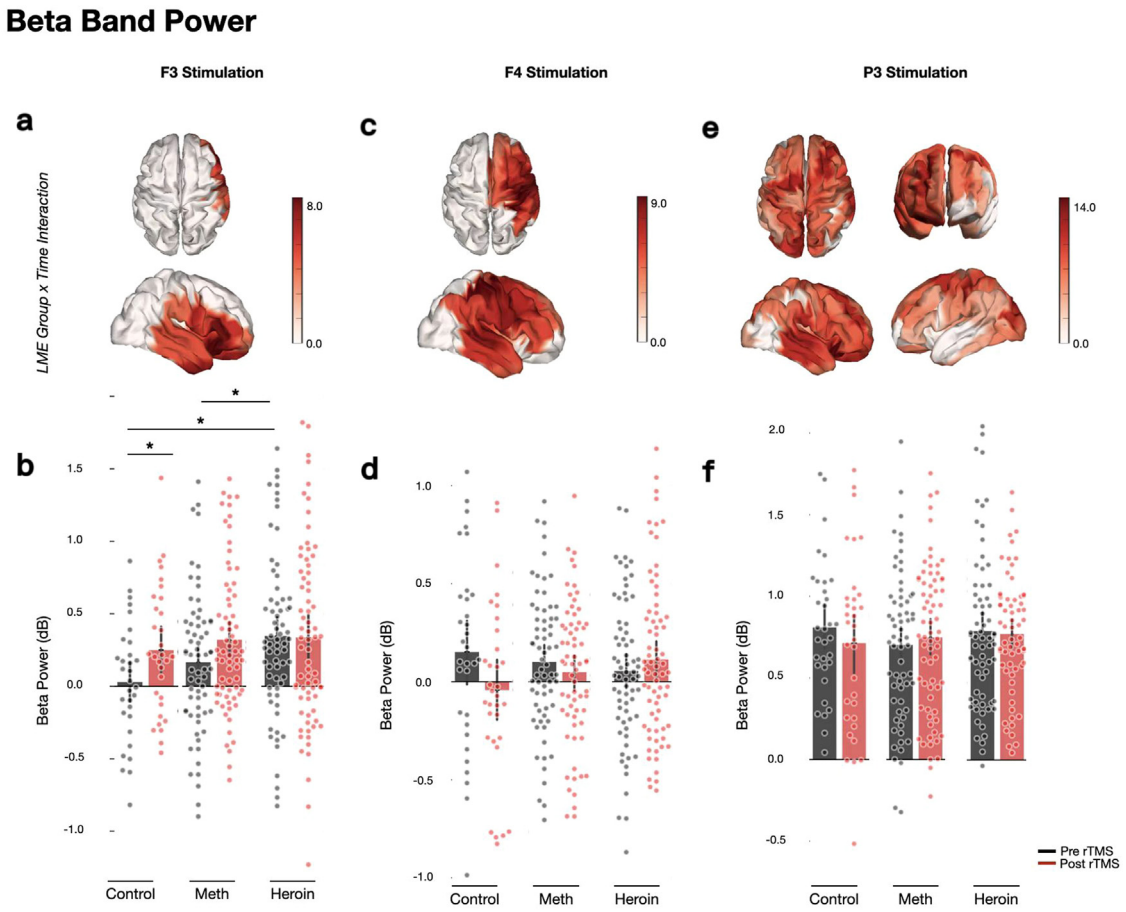


**Fig. 2. Linear mixed effect model results for beta band power**. Group (Control, Methamphetamine, Heroin) x Time (pre, post single-session rTMS) interaction are displayed for (a) F3, (c), F4, and (e) P3 stimulation sites. F-statistic of the interaction is plotted. For each model (b, d, f), bar graphs show the pre- and post-rTMS values for each subject across groups and time. Post-hoc paired t-tests were used to identify significant effects.

to 132 ms, largely encompassing the left dorsal attention network, left default mode network, as well as parts of the left ventral attention and control networks was found (Fig. 1a).

Looking at the beta frequency power, the results showed a significant cluster across the right ventral attention, right default mode, and right limbic regions, from 63 to 73 ms post stimulation (Fig. 2a). At the F4 stimulation site, we found a significant alpha cluster across the left somatosensory motor region and left default temporal region from 43 to 55 ms (Fig. 1c). There was a significant interaction effect for beta frequency from 138 to 143 ms in the somatosensory motor, dorsal attention, ventral attention, control, and default mode networks (all right lateralized) (Fig. 2c). Following the P3 stimulation site, the results confirmed a significant full brain interaction effect for alpha frequency from 43 to 139 ms (Fig. 1e). For beta frequency, there was a similarly global effect from 48 to 92 ms (Fig. 2e). (For the complete region list for each cluster, see Tables S1-S3).

To evaluate plasticity differences across groups, we looked at changes in single-pulse TMS before and after a single-session of rTMS. The results showed no change in alpha power during F3 or F4 stimulation sites across the groups (Fig. 1b, d). During P3 stimulation site, there was a significant decrease in alpha power globally in the control group from 43–139 ms ($p < 0.05$), whereas there was no significant change in alpha power for either of the two drug groups during the same time window (Fig. 1f). We found an increase in beta power for the healthy control group during F3 stimulation site ($p < 0.05$, Fig. 2b). There was no significant change in either the methamphetamine or heroin groups. These results indicated that the cortical plasticity in both SUD groups were impaired.

### 3.2. Baseline comparison (pre-rTMS) and post single-session rTMS

There were no significant differences in alpha power and beta power across three groups prior to rTMS stimulation ($p > 0.05$). Following a single session of rTMS, a significant difference in alpha band power between the healthy controls and both drug groups during P3 stimulation site was found (control vs meth, $p < 0.05$; control vs heroin, $p < 0.01$) (Fig. 1f).

## 4. Discussion

The present study for the first time systemically compared the cortical plasticity differences in two typical types of SUD, based on analyses of TMS evoked oscillatory responses before and after a single session of high-frequency rTMS at the left dorso-lateral PFC. Notably, the plasticity protocol applied at F3 induced remote network effects, as evidenced by alpha power decrease and beta power increase in response to P3 and F3 TMS pulses in healthy control participants. However, this decrease in alpha and increase in beta power was not seen in either the heroin or methamphetamine group, highlighting the possibility of impaired synaptic plasticity in SUD. These findings are highly relevant in designing effective treatments for SUD, where impaired frontal cortical

plasticity may implicate in targets and frequency for neuromodulation protocols.

Preclinical studies reported the induction of anti-hebbian synaptic plasticity on midbrain dopamine neuron following a single dose of cocaine exposure, and the occlusion of LTP induction on NAc D1-MSNs following repeated cocaine injections [6-8,11]. Prolonged drug-seeking training (e.g., methamphetamine) induced impaired synaptic plasticity at motor cortical synapses, as well as synaptic changes at PFC synapses [13]. Our previous TMS studies translated these findings to clinical populations, and confirmed the state of impaired motor cortical plasticity in heroin and methamphetamine use disorder subjects, respectively [13,15]. The current findings are in line with these prior findings and the synaptic plasticity theory underlying drug addiction. Alteration in cortical plasticity may be a common aspect across different addiction disorders.

Synaptic occlusion is considered as one important mechanism underlying the reduced synaptic plasticity hypothesized in SUD. That is, the potentiation evoked by drug exposure precludes the insertion of more AMPARs at the given region of synapses. Our results did not detect baseline differences in TMS induced oscillatory changes among the three groups. This may be due to the fact that AMPARs mediate the early phase of TMS evoked potentials (TEPs) (e.g., within 20 milliseconds) and is not included in present analysis. Future studies combing analyses on synaptic transmission and plasticity would offer more mechanistic insight to the plasticity changes observed on SUD individuals. Still, the present observation may accompany both low cortical excitability [26] and altered functional connectivity [27] of SUD.

Notably, the 10 Hz rTMS trains applied at L-DLPFC induced remote network effects, e.g., parietal network connectivity reflected by the observed oscillatory changes. This is in line with recent findings that rTMS induces long-distance network effects [28]. The 10 Hz-L-DLPFC protocol is the standardized FDA-approved treatment procedure for depression treatment and has been found to be effective in reducing craving and drug seeking behavior in different type of SUDs [29–32]. It will be critical to associate the network dynamic changes and the therapeutic effects of prefrontal targeted rTMS treatments in SUD.

The study has several limitations. First, the TEPs were not included in analysis and therefore the synaptic transmission comparison is lacking. However, TEP-based analyses have been criticized recently due to the inability to confidently separate somatosensory artifact from more clinically pertinent signal. By focusing our analyses on later latency signals and ERSP, we hoped to mitigate these problems. Secondly, the early phase of the signals contained residual decay artifact even after data cleaning. To conservatively avoid making conclusions based on artifactual signal, we excluded data prior to 40 ms post stimulation. Thirdly, while this study identified impaired plasticity in SUD groups, future work should evaluate how these findings relate to the therapeutic effects of rTMS treatments.

## 5. Conclusion

In conclusion, the present study identified impaired cortical plasticity in two most common types of SUD population. The findings might offer mechanistic insights for craving, and highlight the therapeutic importance for cortical plasticity in SUD.

## Author contributions

Q.L., W.W., A.E. and T.Y. conceived and designed the study. Q.L., M.L. and T.Y. collected the data. Q.L., M.L., F.B., W.W., A.E., and T.Y. analyzed the data and wrote the manuscript together.

## Data and materials availability

Original data are available upon request to the corresponding authors.

## Declaration of competing interest

The authors declare that they have no conflicts of interest in this work.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.fmre.2023.02.015.

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