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Converging Evidence for Frontopolar Cortex as a Target for Neuromodulation in Addiction Treatment

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Abstract

Noninvasive brain stimulation technologies such as transcranial electrical and magnetic stimulation (tES and TMS) are emerging neuromodulation therapies that are being used to target the neural substrates of substance use disorders. By the end of 2022, 205 trials of tES or TMS in the treatment of substance use disorders had been published, with heterogeneous results, and there is still no consensus on the optimal target brain region. Recent work may

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help clarify where and how to apply stimulation, owing to expanding databases of neuroimaging studies, new systematic reviews, and improved methods for causal brain mapping. Whereas most previous clinical trials targeted the dorsolateral prefrontal cortex, accumulating data highlight the frontopolar cortex as a promising therapeutic target for transcranial brain stimulation in substance use disorders. This approach is supported by converging multimodal evidence, including lesion-based maps, functional MRI-based maps, tES studies, TMS studies, and dose-response relationships. This review highlights the importance of targeting the frontopolar area and tailoring the treatment according to interindividual variations in brain state and trait and electric field distribution patterns. This converging evidence supports the potential for treatment optimization through context, target, dose, and timing dimensions to improve clinical outcomes of transcranial brain stimulation in people with substance use disorders in future clinical trials.

Substance use disorders (SUDs) affect over 1 billion individuals worldwide, and they affect people of every age, race, gender, socioeconomic status, and nationality. Increased reactivity to drug-related cues and disrupted activity in frontal-striatal circuits are commonly observed across all SUDs. Recent technological advances in opto- and chemogenetics have further refined our understanding of the frontal-striatal circuits in reward processing and behavioral control and highlighted their causal role in drug-related behaviors (1). Until recently, however, we had no brain circuit–based intervention that could be applied to people with SUDs.

Mechanistic studies and clinical trials have provided increasing evidence for the effectiveness of noninvasive neuromodulation with transcranial electrical stimulation (tES) or transcranial magnetic stimulation (TMS) in the treatment of SUDs, including alcohol, tobacco, cocaine, cannabis, methamphetamine, and opioid use disorders (2). The enthusiasm for noninvasive neuromodulation approaches to SUD treatment is buoyed by a growing body of work demonstrating a causal relationship between noninvasive stimulation of the frontal-striatal circuits and drug-related behaviors. In a series of studies using interleaved TMS and blood-oxygen-level-dependent (BOLD) imaging, researchers have shown that it is possible to modulate the striatum via TMS to the prefrontal cortex (3, 4). Research has shown that a single session of theta burst stimulation to the frontopolar cortex can dampen cue-evoked BOLD signal in the striatum of individuals with alcohol or cocaine use disorders (5). Moreover, it has been reported that the effectiveness of modulating the striatum in individuals with cocaine use disorder depends on the integrity of the white matter pathways connecting the cortex and striatum (6).

From a mechanistic perspective, there is also a growing appreciation for the relationship between noninvasive stimulation and neurochemistry. One of the possible mechanisms derived from a series of positron emission tomography (PET) studies suggests that TMS modulates striatal dopamine release (7). Given the well-established relationship between dopamine release and drug cue seeking, this suggests that observed effects of TMS on cocaine use behavior (e.g., 8–10) could be through dopaminergic pathways, which are targeted in a variety of SUD treatments (11). However, the dopaminergic mechanism is only one of the potential pathways to modify addictive behaviors through neuromodulation. The glutamatergic pathway between the prefrontal cortex (PFC) and

the nucleus accumbens or amygdala, or intracortical GABAergic pathways, can also be modulated with neuromodulation technologies such as tES and TMS (10). However, as mechanisms of noninvasive neuromodulation continue to be conceptualized as a brain circuit–based treatment option that modifies activity in brain networks, the potential for more effective and personalized treatment for SUDs continues to grow (12).

In recent years, there has been rapid growth and expansion of noninvasive neuromodulation as a circuit-based interventional tool in the field of SUDs. At the end of 2018, only 84 reports of tES or TMS trials in the field of SUDs had been published (2). By the end of 2022, 205 tES or TMS trials had been published in the treatment of SUDs (13). Following a decade of rapid growth and expansion of the noninvasive neuromodulation tools into the SUD research field (2), the U.S. Food and Drug Administration (FDA) cleared TMS for smoking cessation in 2020. The supporting multicenter double-blind randomized controlled trial, which included 135 participants with tobacco use disorder, showed that the active repetitive TMS (rTMS) group had significantly higher smoking abstinence rates at weeks 2, 4, and 12 compared with the sham treatment group (14). Since then, the pace of new clinical trials using novel tools and protocols of noninvasive neuromodulation for SUDs has accelerated, and the list of devices and indications that have received CE marking in Europe (European Conformity, indicating compliance with the relevant European Union laws) is growing (15).

However, there is still no consensus on the optimal brain stimulation target in SUDs. As of September 2022, 18 main brain regions have been targeted in SUD trials using tES and TMS. The dorsolateral prefrontal cortex (DLPFC) has been the most commonly targeted stimulation site for SUDs, given its success as a brain stimulation target for depression and top-down models of response control (16). Within the DLPFC, the left DLPFC was by far the most frequent target, followed by the right DLPFC (2) (Figure 1). Anode/cathode electrodes over left/right DLPFC were used in 68 of 76 published tES trials in SUDs, as well as 99 of 116 published excitatory or inhibitory TMS trials. Other brain areas that have been targeted in SUD research include the frontopolar cortex, superior frontal gyrus, inferior frontal gyrus, orbitofrontal cortex, motor cortex, vertex, anterior cingulate cortex, posterior cingulate cortex, insula, temporoparietal cortex, and occipital cortex (Figure 1). However, the physiological and clinical responses to tES or TMS reported by these studies show great variability. It is important to consider that the brain region that is “targeted” (the brain region underneath the electrode or coil) may be very different from the brain region that is actually stimulated (distal areas that might be modulated through a diffuse current flow or interactions between brain regions) for each person.

When considering target selection for interventional psychiatry, two main approaches can be taken. The first is to start with the DLPFC as the target, given the extensive data supporting its efficacy and safety in treating depression, and to explore other targets only if targeting the DLPFC is not sufficient. The second approach involves using other levels of evidence, including neuroimaging, to identify specific brain regions that are disrupted in certain psychiatric disorders and have a causal relationship with symptoms. In this approach, the medial prefrontal cortex (mPFC) and frontopolar cortex emerge as a strong target for

TMS and tES montages in SUDs, while we also acknowledge the potential effectiveness of targeting the DLPFC.

To use neuroimaging to identify correlates of drug-related behaviors in individuals with SUDs, one can perform functional MRI (fMRI) during behavioral tasks (e.g., drug cue exposure or risky decision making) or during the resting state and identify neuroimaging abnormalities in patients with SUDs that can then potentially be targeted with noninvasive brain stimulation (4, 17–20). An alternative approach is to identify the underlying causal brain circuitry involved in SUDs through lesion studies (21). Understanding causal relationships between the neural substrate and drug-related behavior is critical for guiding interventional therapy (22). To achieve this, causally informative study designs try to identify brain regions that contribute to the cycle of relapse (return to substance use) or addiction remission (an extreme case of reduction of substance use) to inform the intervention efforts or target selection. For instance, it has been reported that lesions involving the insula cause a disruption of tobacco use disorder (23). Additionally, lesions disrupting addiction have been reported in brain regions other than the insula (24, 25). Recently, a new method called lesion network mapping has been applied to study brain lesions that have resulted in addiction remission (26); in the cited study, “remission” was defined as an extreme case of substance use reduction, characterized as “quitting smoking without difficulty immediately after the lesion, without relapse and in the absence of craving since quitting.”

Similar to lesion-based analysis, brain stimulation sites can also help identify therapeutic targets (21). Previous neuromodulation clinical trial results involving tES (including anodal/cathodal stimulation), TMS (including single-pulse, paired-pulse, or repetitive TMS using continuous or intermittent theta burst stimulation [cTBS or iTBS], considering the stimulation frequency [low or high], with both conventional and deep TMS coils), deep brain stimulation (DBS), or transcranial focused ultrasound stimulation can be examined to identify commonly used or novel therapeutic targets, as well as the placement of the electrodes, coils, transducers, and stimulation montages. By leveraging such studies, researchers can gain valuable insights into potential targets for neuromodulation interventions. For example, neuromodulation therapies for depression revealed that functional connectivity maps from lesion-based data and from TMS and DBS studies, as three causal sources of information, converge on the same brain circuits that may serve as a refined therapeutic target to improve neuromodulation outcomes (27, 28).

Functional and structural connectomes derived from fMRI or diffusion tensor imaging data at the group level, referred to as averaged connectome maps or normative connectome, as well as group-level electric field analyses, have been shown to have potential value in target selection and stimulation dose optimization (29–31). However, group-level electric field or connectome maps cannot represent interindividual variability in terms of electric field distribution patterns or functional/structural connectivity. In this regard, personalized computational head models estimate electric field distribution patterns according to each montage/target. This approach accounts for neuroanatomical parameters and estimates the effects of each montage on various brain regions. However, electric field modeling has not been rigorously implemented in SUD studies, where it is commonly assumed

that outcomes are associated with the cortical region under stimulating tES electrodes or TMS coils. This assumption is not supported by electric field modeling, however. For example, in tES studies with diffuse current flow, electric field modeling suggests that the peak electric field (as an indicator of stimulation hotspots) may not always be under the electrodes, and the electric field spreads, covering multiple brain regions (32–34). Similar results were also reported in TMS studies, where the peak of the TMS-induced electric field was not always located directly underneath the stimulation coil (35). In addition to personalized head models, patient-specific connectivity maps, rather than a normative connectome, have also been used to identify neuromodulation targets (36, 37). These studies suggest that personalized targeting and stimulation might lead to better treatment outcomes compared with group-averaged targeting. For example, resting-state fMRI data were used to individually target the region of the left DLPFC most functionally anticorrelated with the subgenual ACC in a group of participants with major depressive disorder (36). In that study, with respect to the individualized target and based on computational head models, the depth-corrected intensity was used with the aim of delivering an equivalent stimulation dose to all personalized targets. In a similar approach, two other studies in depression (38, 39) used depth-corrected intensity based on individualized scalp-to-cortex distance measured from each patient's anatomical MRI and also utilized fMRI targeting with the highest number of sessions per day, total number of sessions, and total number of pulses. Although stimulation intensity and targeting method parameters were not systematically isolated and other variables (e.g., number of sessions per day) simultaneously changed, it remains unclear how electric field intensity and targeting method contribute to treatment response. However, other supporting evidence comes from studies that compared the therapeutic potential of target site personalization to other targeting methods and reported a better antidepressant outcome when the group-average target was closer to the personalized target (40–42).

Research conducted so far has aimed to assess the impact of brain stimulation technologies on clinical outcomes in SUDs. However, given the variability in methodology and population responses to stimulation, it has been challenging to reach a consensus on target selection. Using the approaches described above, we propose the frontopolar cortex as a highly promising target for SUDs, although it has been investigated to a lesser extent than DLPFC stimulation. Here, we synthesize converging evidence from multiple sources, including lesion-based maps, fMRI-based maps, TMS studies, tES studies, and dose-response relationships using electric field modeling, that emphasize the utility of the frontopolar cortex as a treatment target for SUDs (Figure 2).

EVIDENCE FROM LESION-BASED MAPPING

Brain lesion studies, which focus on damage that has occurred to a specific part of the brain, are used to localize human brain functions and identify causal links between symptoms and neuroanatomy (21). Combining causal mapping of human brain functions based on brain lesions and brain stimulation with modern neuroimaging techniques like fMRI provides new insights into the role of different brain areas in neuropsychiatric disease. For example, individuals with insula lesions have been shown to be more likely to quit tobacco smoking easily and to remain abstinent (23). This causal knowledge about the functions of specific brain areas (e.g., insular cortex) can be translated into therapeutic targets for

brain stimulation treatment programs. In this regard, the recent lesion network mapping study by Joutsa et al. (26) adds growing attention to the frontopolar cortex as a target area for SUD treatment. In that study, addiction remission (i.e., quitting tobacco smoking easily and remaining abstinent) was more likely after strokes in areas that had negative functional connectivity to the medial frontopolar and temporal cortices and positive connectivity to the dorsal cingulate, lateral prefrontal cortex, and insula. These brain regions could be used as neuromodulation treatment targets. The medial frontopolar cortex, the strongest negative peak, can be directly reached with transcranial brain stimulation (43–45). This suggests that high-frequency rTMS, which is usually believed to increase cortical excitability, would be expected to reduce addiction when applied to the frontopolar cortex. Indeed, this peak in the frontopolar cortex overlapped with peak electric fields of TMS coils that were effective for SUDs in multicenter trials, including the coil that is FDA cleared for smoking cessation (14). Although the primary sample of the Joutsa et al. study (26) comprised participants with tobacco use disorder, the results appeared to generalize to other SUDs. Recently, this same network was found to align with neuroimaging abnormalities across all substances of abuse (46). As lesion connectivity has been demonstrated to correlate with treatment effectiveness and has proven beneficial in identifying more successful TMS targets across various disorders (21, 27, 47), these observations support the use of excitatory noninvasive brain stimulation targeting the frontopolar cortex for the treatment of SUDs (Figure 3A).

EVIDENCE FROM fMRI-BASED MAPS

fMRI data represent a powerful experimental method to identify the optimum stimulation target while considering underlying brain function. According to fMRI findings, the frontopolar cortex is a key region for cognitive flexibility (48) and decision-making procedures (e.g., value-based [49] and unconscious [50] decision making). In addiction research, functional neuroimaging has revealed that the frontopolar cortex, along with other brain regions, such as the inferior frontal gyrus/insula, is reliably activated by drug cues (51). Additionally, its connection to other brain regions, such as the nucleus accumbens, may be altered over the course of different addiction stages (52). These frontal-striatal circuits are critical mediators of drug cue reactivity and habit formation (53), which have a well-replicated relationship with substance use outcomes and relapse (54). The medial frontopolar cortex is one of the primary hubs that mediate the valuation of drug-related stimuli during exposure to drug versus neutral cues. Moreover, modulatory network analysis has shown that the medial frontopolar area facilitates the interaction between default mode, frontoparietal, and salience networks, which are disrupted in SUDs (55, 56).

Numerous fMRI studies have demonstrated that the frontopolar cortex is involved in drug cue reactivity across different drug classes. One of the most extensive studies to date, conducted by Hanlon et al. (57), investigated the spatial topography of drug cue reactivity in a cohort of 156 individuals with tobacco, alcohol, or cocaine use disorders. The study revealed three clusters of cue-reactive activation in response to drug versus neutral cues, including the medial frontopolar cortex (Brodmann area 10) and the left and right insular cortices. Although insular cortex activity was predominantly driven by cocaine users, all three groups exhibited significant clusters of activity in the medial prefrontal cortex that extended anteriorly to the frontopolar cortex (Figure 3B). Projecting these clusters onto

the standard EEG 10–20 system that is commonly used for TMS targeting, the medial frontopolar cortex (FPz) was the location closest to the largest percentage of hotspots (Figure 4). This location overlaps strikingly well with the lesion network map identified by Joutsa et al. (4), lending further credence to the notion that the cue-induced activation in the frontopolar aspect of the medial prefrontal cortex may be a transdiagnostic endophenotype of addiction, which can also be reflected in abnormal connectivity in the resting state as well as aberrant activation during disease-relevant tasks (51, 52, 58, 59).

Expanding to other substance use disorders, in a recent study of 65 participants with methamphetamine use disorder, Ekhtiari et al. (60) demonstrated higher fMRI cue reactivity during drug versus neutral cues, which was most prominent in the medial frontopolar cortex (Figure 3B). This pattern overlaps with the drug cue reactivity findings of Hanlon et al. (57), lesion-based peaks reported by Joutsa et al. (26) (Figure 3A), and electric field maps of effective noninvasive brain stimulation targets (Figure 3C, D).

EVIDENCE FROM PREVIOUS TMS CLINICAL TRIALS

Research increasingly supports the frontopolar aspect of the medial prefrontal cortex as a promising target for transdiagnostic TMS interventions for SUDs. At least 12 TMS studies (with both inhibitory and excitatory stimulation protocols) have demonstrated that stimulating the frontopolar cortex can modulate cortical-striatal circuits involved in drug cue reactivity, leading to reductions in drug craving and/or consumption, and none of them reported negative results (4, 5, 61–70). For example, cTBS applied to the frontopolar cortex for non-treatment-seeking cocaine users and heavy alcohol users reduced neural reactivity to cocaine cues and alcohol cues (5), with the effects influenced by gray and white matter integrity (64). Another study found that cTBS to the frontopolar cortex in non-treatment-seeking chronic cocaine users and alcohol-dependent individuals decreased TMS-evoked BOLD signal in several cortical nodes that are believed to regulate salience processing and are typically activated by drug cues (62). A recent study of 74 inpatients with severe methamphetamine use disorder demonstrated that 10 sessions of active TMS to the frontopolar cortex (cTBS over Fp1), left DLPFC (iTBS over F3), or both targets significantly decreased craving, with the largest effect size observed in the group that received cTBS to the left frontopolar cortex (63). Craving scores in that study were assessed using a visual analogue scale at five time points (at baseline and twice weekly for 2 weeks). During these assessments, participants rated their cravings after being exposed to drug-related images for 5 minutes while recalling their last drug use, and the changes in craving were positively correlated with improvements in ratings of anxiety and withdrawal symptoms (63).

Furthermore, the electric fields induced by figure-eight TMS coils or deep TMS (Figure 3D) with H4 and H7 coils (intended to target the insula and the medial prefrontal/anterior cingulate cortex, respectively) overlap with the lesion locations associated with addiction remission (i.e., quitting tobacco smoking easily with no relapse) in the Joutsa et al. lesion study (Figure 3A) (26, 71). Of note, the deep TMS coil (H4), approved by the FDA for smoking cessation, is typically used to stimulate the insula and lateral prefrontal cortex, but

its peak electric field intensity intersects with this medial frontopolar cortex target (Figure 3D).

EVIDENCE FROM PREVIOUS tES CLINICAL TRIALS

Of 89 tES experiments conducted in 76 published studies that successfully modulated drug craving or consumption, 79 used either unilateral (13 trials; anode: F3/F4; cathode: Fp2/Fp1) or bilateral (51 trials; anode/cathode over F3 or F4) electrode montages “over” the DLPFC (Figure 1). However, tES produces a current that flows through different anatomical structures in a complex manner, which means that the peak induced fields may not necessarily be in the cortical areas under the stimulating electrodes (32–34). Research has shown that even when the DLPFC is targeted (with unilateral or bilateral large electrode pads over F3/F4), the frontopolar area receives the strongest electric field in both healthy participants and people with SUDs (72). As a result, modulation of the frontopolar area may mediate the efficacy of tES when “targeting” the DLPFC (Figure 3C).

EVIDENCE FROM DOSE-RESPONSE RELATIONSHIPS

The analysis of the dose-response relationship in brain stimulation studies has not been well established. To the best of our knowledge, no dose-response relationship analysis has been published to explore the association between cortical electric fields and changes in neural response in the application of TMS for SUDs. However, we have investigated the extent to which individualized electric field distribution patterns over the cortex, as an indicator of the received stimulation dose, can explain neurophysiological outcomes of tES (73). The frontopolar cortex was the area where field strength was found to be related to the neurophysiological response to bilateral transcranial direct current stimulation (tDCS) over the DLPFC. Higher electric field strength was found to be correlated with greater BOLD signal change in the drug>neutral contrast in people with methamphetamine use disorder during a standard fMRI drug cue reactivity task (74). In a cohort of 60 inpatients with methamphetamine use disorder (60), unilateral DLPFC stimulation also showed a significant correlation between the normal component of the electric fields and BOLD signal change in the drug>neutral contrast. This finding was specific to the frontopolar area, which was identified as the brain region with maximum electric field strength across the population. A significant positive correlation between the normal component of the electric field and cue reactivity in the frontopolar area (more positive electric field correlated with greater BOLD signal change) indicated that tDCS over the right DLPFC can induce excitatory effects in neural reactivity to drug cues in the frontopolar cortex.

INTERINDIVIDUAL VARIABILITY

Despite converging evidence from lesion-based, fMRI, TMS, and tES studies pointing to the frontopolar cortex as a potential target for transcranial brain stimulation in SUDs, the reliability and generalizability of the individual-level outcomes are still questionable. Accumulating evidence in various clinical populations—for example, patients with major depressive disorder—indicates that responses to neuromodulatory interventions are variable, with a substantial portion of participants considered nonresponders (75, 76). Two main

factors contribute to variation: differences in skull and brain anatomy, which affect the current flow and received stimulation dose over the cortex (32, 34, 77), and differences in brain state, function, and connectivity, which can cause variability even for the same current flow pattern (74, 78, 79). The first factor—skull and brain anatomy—is related to the estimation of the electric field magnitude and distribution patterns through the brain that interact with the underlying brain structure and should be carefully simulated using high-resolution structural images and finite element modeling (34, 80). These computational approaches were well suited to addressing anatomical variability between participants in response to the applied brain stimulation technique (77, 81). The other factor—brain state, function, and connectivity—is subject to the impact of the functional organization of local or distributed brain circuits such that the applied brain stimulation interacts with the underlying brain state (78, 82–84). To better understand how brain states affect response variations, brain mapping tools such as fMRI data can be used retrospectively to investigate differences within or between subjects (74). Variations in both brain factors could be quantified in terms of the strength and the location of a relevant measure extracted from the current flow and functional activity maps across a population. Responsiveness to frontopolar cortex stimulation may be changed, for example, according to the location and intensity of the maximum electric field within the frontopolar cortex or brain regions strongly connected to the frontopolar cortex.

At the group level, electric field distribution patterns and functional state in response to different drug-related cues indicate that electric field and functional activity are predominantly concentrated around the frontopolar cortex across different populations with SUDs (e.g., in alcohol use disorder [85]). However, group-level maps, by definition, are unable to represent interindividual variations in electric fields and functional connectivity or activity (86). Although a few clinical trials have implemented the use of individualized data (e.g., group-level electric fields or connectome-based data) to determine the cortical target for brain stimulation studies, findings in the field of depression emphasize the need for the development of personalized target selection and stimulation optimization strategies (36, 40, 42, 87). Two examples of the importance of individual differences in a group of participants with SUDs when targeting the frontopolar cortex are 1) the widely variable location and intensity of connectivity between the frontopolar cortex and the amygdala in response to drug cues (88) (Figure 5A), and 2) the significant variability in the location and intensity of the electric field in the frontopolar cortex during DLPFC tES among individuals with methamphetamine use disorder (88) (Figure 5B). This highlights the importance of precision functional mapping at the individual level in future frontopolar cortex stimulation studies.

TYPE OF FRONTOPOLAR CORTEX STIMULATION: EXCITATORY OR INHIBITORY

After identifying a promising target for neuromodulation, the next step is to determine the optimal stimulation protocol, which involves deciding whether to increase or decrease activity in the frontopolar area. The most well-established protocols for increasing cortical excitability using tES/TMS tools are anodal tDCS and iTBS and high-frequency TMS (5–20 Hz). However, these protocols may interact with the underlying brain state or

neuronal architecture to result in inhibitory effects (89). While cathodal stimulation, cTBS, single-pulse stimulation, and low-frequency stimulation are commonly assumed to induce inhibitory effects, these protocols can also result in excitatory effects in certain doses, states, or regions. Given the differential effects of these stimulation protocols on neural excitability, it may be challenging to investigate how the type of frontopolar stimulation (e.g., high-frequency vs. low-frequency rTMS) would affect behavioral (e.g., drug consumption) or neural (e.g., BOLD signal change) outcomes.

Functional neuroimaging data are not informative per se on the directionality of neuromodulation in obtaining preferred behavior outcomes even when the basic causality of the targeted area for the preferred behavior is established (90). As an example, fMRI drug cue reactivity data usually do not provide any direction on whether activation is contributing to the craving induction and should be negatively modulated (inhibitory) or is an attempt to control craving and should be positively modulated (excitatory). In the lesion-based network derived by Joutsa et al. (26), the frontopolar cortex showed the opposite connectivity profile of lesions that led to addiction remission in terms of quitting tobacco smoking easily with no relapse (Figure 3A). They hypothesized that regions with the opposite connectivity profile (e.g., frontopolar cortex) should be good targets for excitatory brain stimulation, based on the logic that regions matching the connectivity profile of lesions leading to addiction remission should be good lesion targets (e.g., the paracingulate gyrus and anterior insula). This hypothesis seems to align well with use of the deep TMS coils, including the coil that is FDA cleared for smoking cessation, which use high-frequency stimulation over the medial prefrontal cortex, generally assumed to exert excitatory effects (in all three deep TMS studies for SUDs [61, 65, 66]). However, this proposal does not align with the figure-eight cTBS or single-pulse TMS results, which used cortical inhibition paradigms and led to a significant decrease in BOLD signal and attenuated stimulus-evoked activity in the medial prefrontal cortex (all figure-eight TMS studies for SUDs were cTBS [5, 62–64, 67] or single pulse [4]). It is also unclear whether this aligns with tES results. While the inward current (anodic effects) is thought to increase excitability, and the outward current (cathodic effects) is inhibitory, many tES studies have shown the same effect with anode and cathode switched (91). In TMS studies, as with tES, a certain percentage of participants show effects opposite to the usual direction or no effect at all (e.g., excitatory or neutral effects from an inhibitory stimulation such as 1 Hz rTMS, or showing inhibition rather than excitation in response to 10 Hz rTMS [92, 93]).

Hence, it is still unclear whether we should aim to facilitate or inhibit activity in the frontopolar area. If we increase the local field potential in the medial frontopolar cortex, which houses both glutamatergic pyramidal cells and GABAergic interneurons, the resulting effect on firing at the afferent targets remains uncertain, whether it leads to a net increase or decrease. While functional connectivity can assess the direction and strength of the temporal correlation between brain regions, a more mechanistic neurobiological inquiry is needed to evaluate the activity magnitude at each node independently. The overall effect could be influenced by several factors, including stimulation intensity (with low and high intensities tending to inhibit and facilitate, respectively), number of pulses, electric field direction (inward or outward), stimulation duration, and brain state (94–96). For example, a study on 28 individuals with refractory binge-purge eating disorders found that the outcomes of

30 sessions of 10 Hz rTMS over the dorsomedial prefrontal cortex depended on baseline functional connectivity, such that responders had lower baseline frontal-striatal connectivity than nonresponders (97). Therefore, in future studies, the state dependency of stimulation outcomes and dynamic transitions between brain states during the stimulation periods should be considered in the study design (e.g., by designing a task to optimize target engagement or the stimulation dose at the individual level).

Although brain responses to stimulation have been found to go beyond the expected "excitatory" or "inhibitory" effects of neuromodulatory protocols, the description of excitatory and inhibitory effects of brain stimulation is commonly based on motor-evoked potential (MEP) data (98). However, a direct comparison of MEP and changes in brain circuits regarding resting-state functional connectivity shows no correlation between the two measures (99). At the brain circuit level, regardless of whether excitatory and inhibitory stimulation produce opposite effects, they both have the potential to disrupt or modulate connectivity. For example, resting-state connectivity is measured based on the correlation between two time courses, meaning that excitatory or inhibitory stimulation of one region can alter its time course and decrease its correlation with other brain regions. This disruption in connectivity can occur with both excitatory and inhibitory stimulation, leading to circuit modulation. For instance, a study using deep TMS over the right insula reported disrupted connectivity between the insula and the mPFC for both 1 Hz and 10 Hz single-session rTMS compared with sham stimulation (100). Even at the MEP level, it has been shown that there is significant interindividual variability in response to cTBS; in one study, around 57% of participants showed a decrease in cortical excitability, while others showed an increase or no change (101). Therefore, it is possible that excitatory and inhibitory stimulation may not necessarily have opposite effects on the frontopolar area, and this could be explained by high rates of interindividual variability following both stimulation paradigms.

TOLERABILITY OF FRONTOPOLAR CORTEX STIMULATION

One concern regarding targeting the frontopolar area is related to tolerability and discomfort, particularly in supra-threshold techniques such as TMS. The feasibility and tolerability of TMS over the frontopolar area have been investigated, and the results showed that TMS over the frontopolar area at 110% of resting motor threshold is well tolerated and is not associated with significantly more discomfort than TMS over the DLPFC (55). Of 129 individuals who received multiple sessions of TMS over the frontopolar area, none failed to complete their treatments as a result of pain or discomfort (55). In tES studies over the frontopolar area, no adverse effects were reported by participants. For example, it has been shown that applying 1 or 1.5 mA tDCS with anode/cathode over frontopolar cortex/vertex via a 5×5 cm electrode as anode and a 10×10 cm electrode as the cathode is well tolerated, and applying tDCS via two 5×6 cm electrodes over the frontopolar cortex and forearm is also tolerable (102–104). In sum, frontopolar cortex stimulation is generally well tolerated when the ramping procedure is taken into account. Implementation of novel TMS coils or electrode placement in future studies can help improve the safety and tolerability of frontopolar cortex stimulation.

OTHER APPROACHES AND EFFECTS IN TARGETING THE FRONTOPOLAR CORTEX

While targeting the frontopolar area and circuits will have some direct effects, recent studies have demonstrated the possibility of indirectly targeting subcortical areas through cortico-subcortical connections (105, 106). For example, the ventromedial prefrontal network comprises cortical, subcortical, and striatal nodes, and targeting the frontopolar cortex as a part of this network with transcranial brain stimulation technologies can indirectly modulate other parts of the network (107). In the same vein, indirect targeting of the frontopolar area is also possible through other cortical brain regions that are structurally or functionally connected to it. Previous studies have identified robust connections between the frontopolar area and other cortical regions in the temporal lobe, such as the superior temporal gyrus and the medial temporal cortex (108, 109). The addiction remission circuit derived from lesion studies also included both positively connected (insula, cingulate, DLPFC) and negatively connected (frontopolar) regions (26). Consequently, while the frontopolar cortex is one of the most promising noninvasive brain stimulation targets, it may only serve as a gateway to the entire network, and multisite stimulation might boost the effect further by modulating connected brain areas. For example, it has been found that the combined stimulation of the DLPFC and frontopolar cortex (combination of iTBS over the DLPFC and cTBS over the ventromedial PFC) reduced cravings more effectively than stimulating the DLPFC (using iTBS) or frontopolar cortex (using cTBS) alone in the treatment of patients with severe methamphetamine use disorder (63).

BEHAVIOR/BRAIN STATE

There is an increasing recognition of the significance of brain “state” on the directionality and amplitude of tES/TMS effects. This can be seen in the contrast between collecting an active versus resting motor threshold with TMS, where even a slight muscle engagement can significantly enhance the TMS-evoked response. Although this is more difficult to measure outside the motor system, it has also been shown in conditions such as PTSD (110), obsessive-compulsive disorder (OCD) (111), and addiction (112). In such scenarios, participants are often given a provocation script to engage a particular brain state (e.g., imagining their greatest trigger for craving, listening to an audio script with instructions to handle a cigarette and a lighter, and viewing pictures of tobacco-related cues [14]), and the targeted brain regions appear to be more responsive to the induced electric fields. The idea is that certain brain networks are triggered by a particular task, such as provocation, and as a result of their existing activation, they are more susceptible to modulation by tES or TMS (79, 113). For instance, Dinur-Klein et al. (112) found that in a group of participants with tobacco use disorder, TMS with and without provocation was more effective when the stimulation was delivered after the presentation of tobacco-related cues. Similarly, FDA-approved protocols for OCD and smoking cessation also include symptom provocation to elicit a moderate level of obsessional distress or craving before each stimulation session, and it is anticipated that the use of provocation-based brain stimulation studies will continue to increase (14, 114). Thus, designing an appropriate task to optimally target the desired brain region, such as the frontopolar cortex, during neuromodulation may be crucial.

FUTURE DIRECTIONS

Future research directions in neuromodulation for SUDs could include network-level dose-response studies that integrate data at both the individual and group levels. By manipulating intrinsic or extrinsic variables, such as ongoing brain state and stimulation parameters, it may be possible to delineate dose-response relationships and characterize response profiles for the targeted brain networks (115). Furthermore, brain-wide mapping of lesions/fMRI/PET, collection of tES/TMS-evoked BOLD signal changes, and integration of the results with computational head models can help identify network origins of changes in behavioral task performance or clinical outcomes such as drug craving or consumption (116).

Future trials tailored to individuals, such as Stanford Neuromodulation Therapy (36), and closed-loop tES, TMS-fMRI, or EEG (117, 118) can help to rapidly and effectively target specific brain regions with optimal stimulation doses for each person. Addressing between-subject variations in targeting the frontopolar cortex and finding methods to reliably measure brain response/target at the individual level should be prioritized in future studies. Recording the exact location of the stimulation coil or electrode montage for each person in future clinical trials can help map heterogeneity in response/target, ultimately establishing the optimal target site at the individual level and leading to pragmatic improvements in treatment designs for SUDs.

CONCLUSIONS

The evidence based on brain lesion maps, fMRI drug cue reactivity studies, and simulations of the electric field in previously successful transcranial brain stimulation converge and support the frontopolar cortex as a target for transcranial stimulation across various substance use disorders. Additionally, our evidence suggests that the frontopolar cortex may be mediating the observed clinical effects of tES/TMS protocols even when the frontopolar cortex is not necessarily the intended stimulation target. However, further research is needed to pinpoint the optimal individualized frontopolar coordinates and stimulation dose and pattern over the targeted region to maximize clinical benefits at both the individual and group levels.

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on scientific advisory boards, or has invention assignment agreements with Allergan (AbbVie), Apple, Biovisics, Boston Scientific, Ceragem, GlaxoSmithKline, Google X, Halo Neuroscience, Humm, i-Lumen, Lumenis, Mecta, SafeToddles, and Ybrain; he is an inventor on a patent on brain stimulation held by City University of New York; and he has equity in Soterix Medical. Dr. Paulus has served as an adviser for Hoffmann–La Roche and Spring Care, and he has received royalties from UpToDate. Dr. Fox holds intellectual property on the use of brain connectivity imaging to analyze lesions and guide brain stimulation; he has served as a consultant for Abbott, Boston Scientific, Magnus Medical, and Soterix; and he has received investigator-initiated research funding from Neuronetics. Dr. Hanlon is employed by and has financial interests in BrainsWay. Dr. Ekhtiari has received honoraria from Indivior for speaking at educational events. The other authors report no financial relationships with commercial interests.

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Examination Questions for “Converging Evidence for Frontopolar Cortex as a Target for Neuromodulation in Addiction Treatment”

1. What are the converging levels of evidence provided in this paper to support frontopolar cortex as a target for neuromodulation in addiction treatment?
   - **A.** Pharmacological trials, quantitative EEG mapping, animal models, gene manipulation
   - **B.** Lesion based maps, functional maps, brain stimulation trials, dose-response relationship
   - **C.** Epidemiologic studies, quasi-causal modeling, electric field manipulation, effective connectivity
   - **D.** Optimization trials, safety studies, adherence measurement, gene linkage mapping
2. What are the two main factors that contribute to the variations in response to a neuromodulation in the individual level (making some patients response and some non-responsive)?
   - **A.** Differences in skull and brain anatomy and differences in brain state, function, and connectivity
   - **B.** Differences in the neuromodulation technology and differences in duration of stimulation
   - **C.** Differences in the level of education in the staff and differences in patients’ adherence

D. Differences in selected targets and differences in post stimulation management

3. To address “state dependency” in response to brain stimulation in people with substance use disorders and to increase the efficacy of the intervention, which of the following strategies were most effectively implemented:

   A. Structural MRI

   B. Priming with medications

   C. Drug cue provocation

   D. Electric field modeling

Data availability:

fMRI data and computational head models related to the 65 participants with methamphetamine use disorder are available on request from the corresponding author. The fMRI drug cue reactivity task and its codes are available at https://github.com/rkuplicki/LIBR_FDCR_Dynamic. The data associated with cue reactivity in participants with cocaine, alcohol, and tobacco use disorders are available on request from Dr. Hanlon. More details on lesion maps can be found in the supplement to reference 26.

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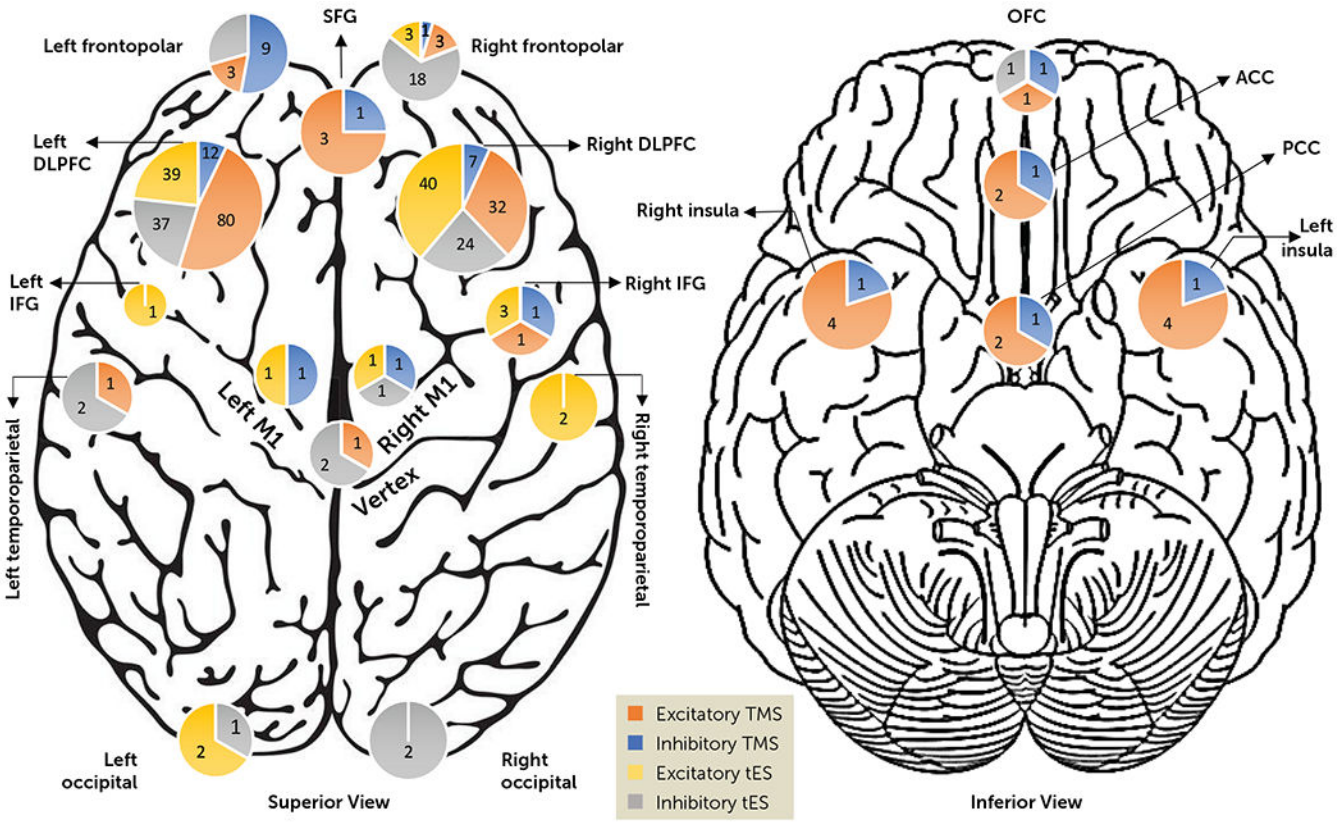

FIGURE 1. Brain targets for TMS/tES trials in substance use disorders[a]

[a] Studies were categorized according to their assumed stimulation effects. TMS with frequency >5 Hz and iTBS studies were considered “excitatory TMS”; TMS with frequency ≤5 Hz and cTBS studies were considered “inhibitory TMS”; anodal tES was considered “excitatory tES”; and cathodal tES was considered “inhibitory tES.” In 20 tES studies, one of the electrodes was placed on the right or left supraorbital area (counted as frontopolar). The insula and frontopolar cortex were targeted bilaterally in deep TMS studies with both stimulatory and inhibitory frequencies. ACC=anterior cingulate cortex; DLPFC=dorsolateral prefrontal cortex; IFG=inferior frontal gyrus; OFC=orbitofrontal cortex; PCC=posterior cingulate cortex; SFG=superior frontal gyrus; tES=transcranial electrical stimulation; cTBS or iTBS=continuous or intermittent theta burst stimulation; TMS=transcranial magnetic stimulation.

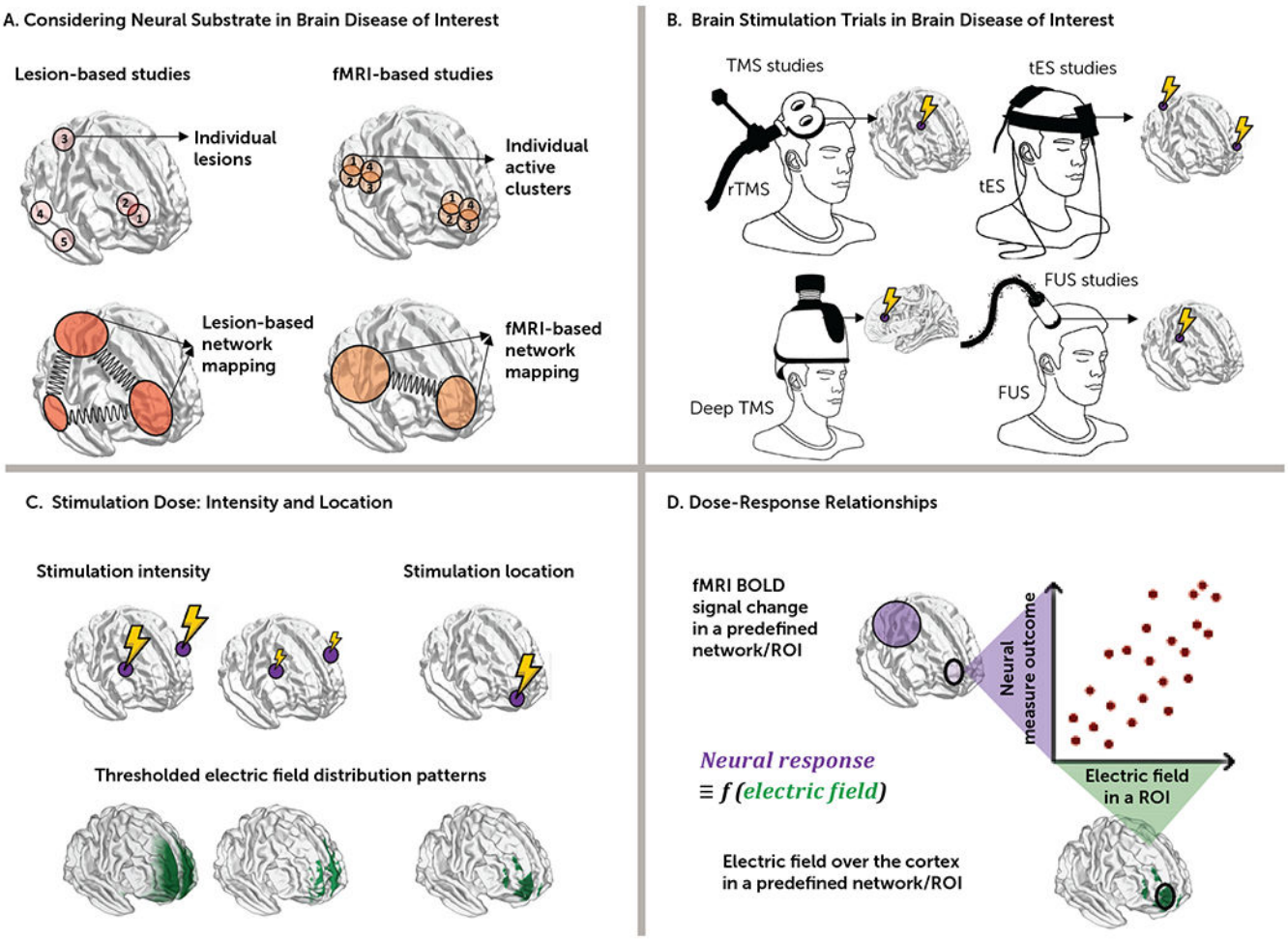

FIGURE 2. Converging evidence for therapeutic brain stimulation targets[a]

[a] In panel A, target selection is informed by network-based lesions or fMRI maps at the individual or group level. In panel B, previously reported results in clinical trials with different noninvasive brain stimulation methods inform future experimental designs. In panel C, different factors affect stimulation dose over the cortex, such as stimulation location and intensity; head models can illustrate the effects of these factors on stimulation dose. In panel D, the relationship between outcome measures from neural substrates (e.g., fMRI in panel A) and stimulation dose to a particular network (e.g., electric fields in panel C) aids our understanding of how noninvasive brain stimulation–induced electric fields or magnitude of stimulation site connectivity to a network ultimately modulate brain functions (for example, do larger electric fields in a predefined region of interest or network cause stronger neural response?). BOLD=blood-oxygen-level-dependent; FUS=focused ultrasound stimulation; ROI=region of interest; rTMS=repetitive transcranial magnetic stimulation; tES=transcranial electrical stimulation.

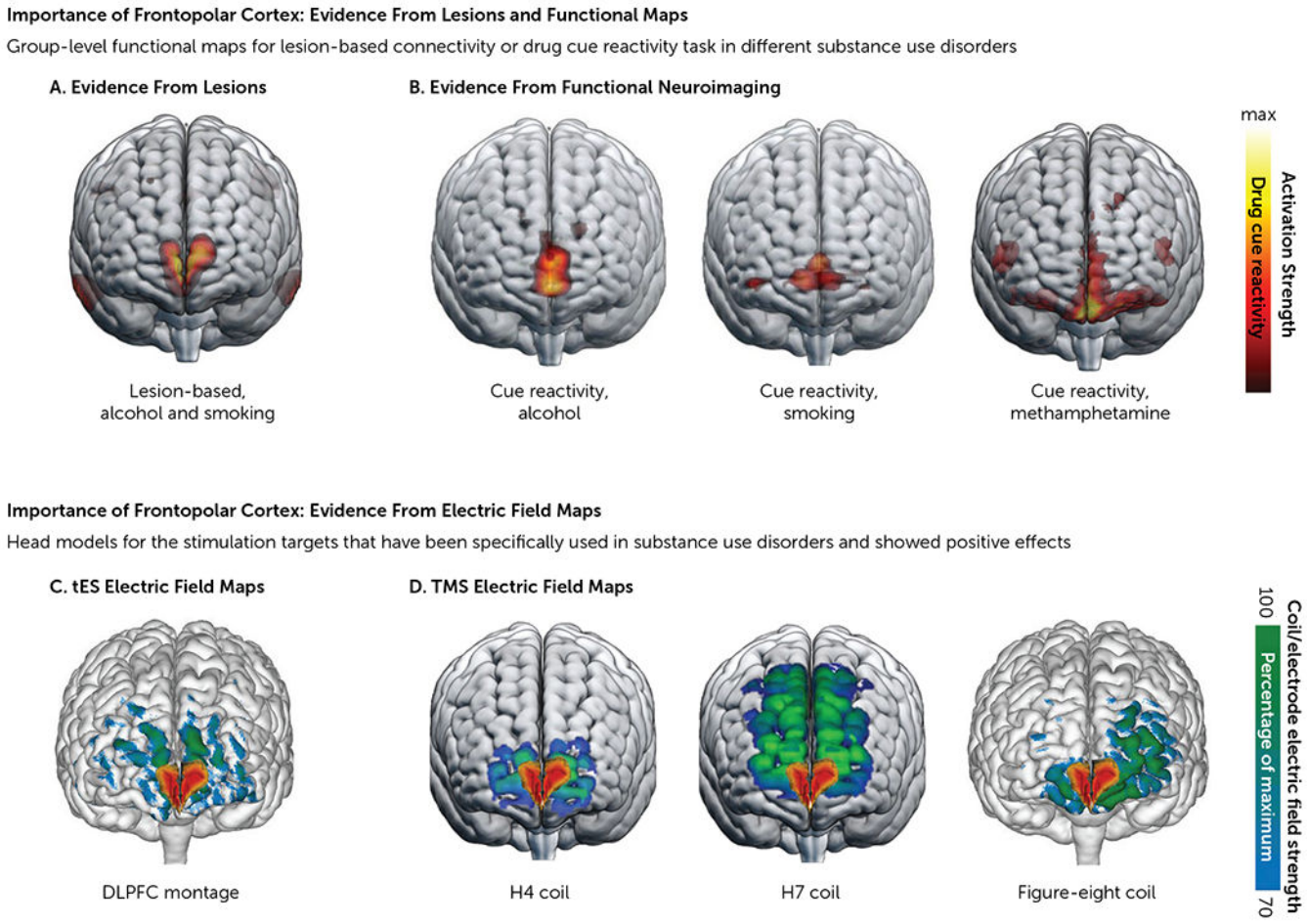

FIGURE 3. Evidence from brain imaging maps highlights the role of the frontopolar cortex as an optimal treatment target in addiction[a]

[a] The upper half of the figure illustrates evidence from lesions and functional mapping. Panel A is lesion-based map illustrating functional connectivity of lesions that lead to addiction remission, as reported by Joutsa et al. (26). Panel B illustrates functional neuroimaging maps showing active voxels obtained from a whole-brain response to a standard fMRI drug cue reactivity task in three studies: in heavy alcohol users (N=53), reported by Hanlon et al. (57); in participants with tobacco use disorder (N=48), reported by Hanlon et al. (57); and in participants with methamphetamine use disorder (N=65), reported by Ekhtiari et al. (119). The lower half of the figure illustrates evidence from electric field maps of transcranial brain stimulation protocols that have been used in substance use disorders with positive outcomes. Note the overlap between the functional map in the lesion-based study in panel A and the electric field distribution patterns in panel C, with the commonly used tES montage (target/reference electrodes: over F3/Fp2, 5×7 cm, with 2 mA intensity [e.g., 72]) and deep TMS (including H4 [e.g., 120] and H7 coils [e.g., 61] and conventional TMS with a figure-eight coil over Fp1 [e.g., 62]). DLPFC=dorsolateral prefrontal cortex; tES=transcranial electric stimulation; TMS=transcranial magnetic stimulation.

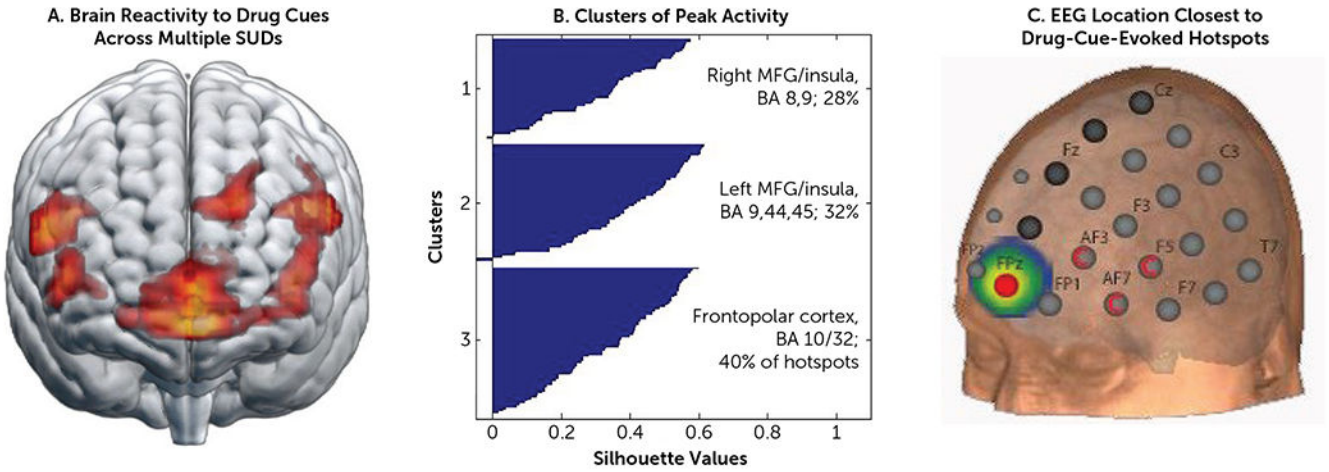

FIGURE 4. Target selection based on brain-state clustering across multiple substance use disorders[a]

[a] Brain reactivity to drug cues versus non-drug cues was acquired from 156 non-treatment-seeking chronic cocaine users (N=55), heavy alcohol users (N=53), and participants with current tobacco use disorder (N=48) (57). Analyses were done at the group level (panel A) and at the individual level (panel B). For k-means clustering, the K++ algorithm, 1000 repetitions, and random seeding were used. Of the entire sample of 156 individuals, 103 had at least one cluster that was significantly elevated to the drug versus neutral cues. As illustrated in panel C, for the group as a whole, the EEG 10-10 coordinate FPz had the largest percentage of hotspots within 2 cm (11%), 3 cm (19%), 4 cm (32%), and 5 cm (49%). FPz was also the best location for alcohol cues and tobacco-related cues. The hotspots associated with cocaine cue reactivity were closest to AF3, AF7, and AF5, likely driven by points in the anterior insula. BA=Brodmann area; MFG=middle frontal gyrus; SUD=substance use disorder.

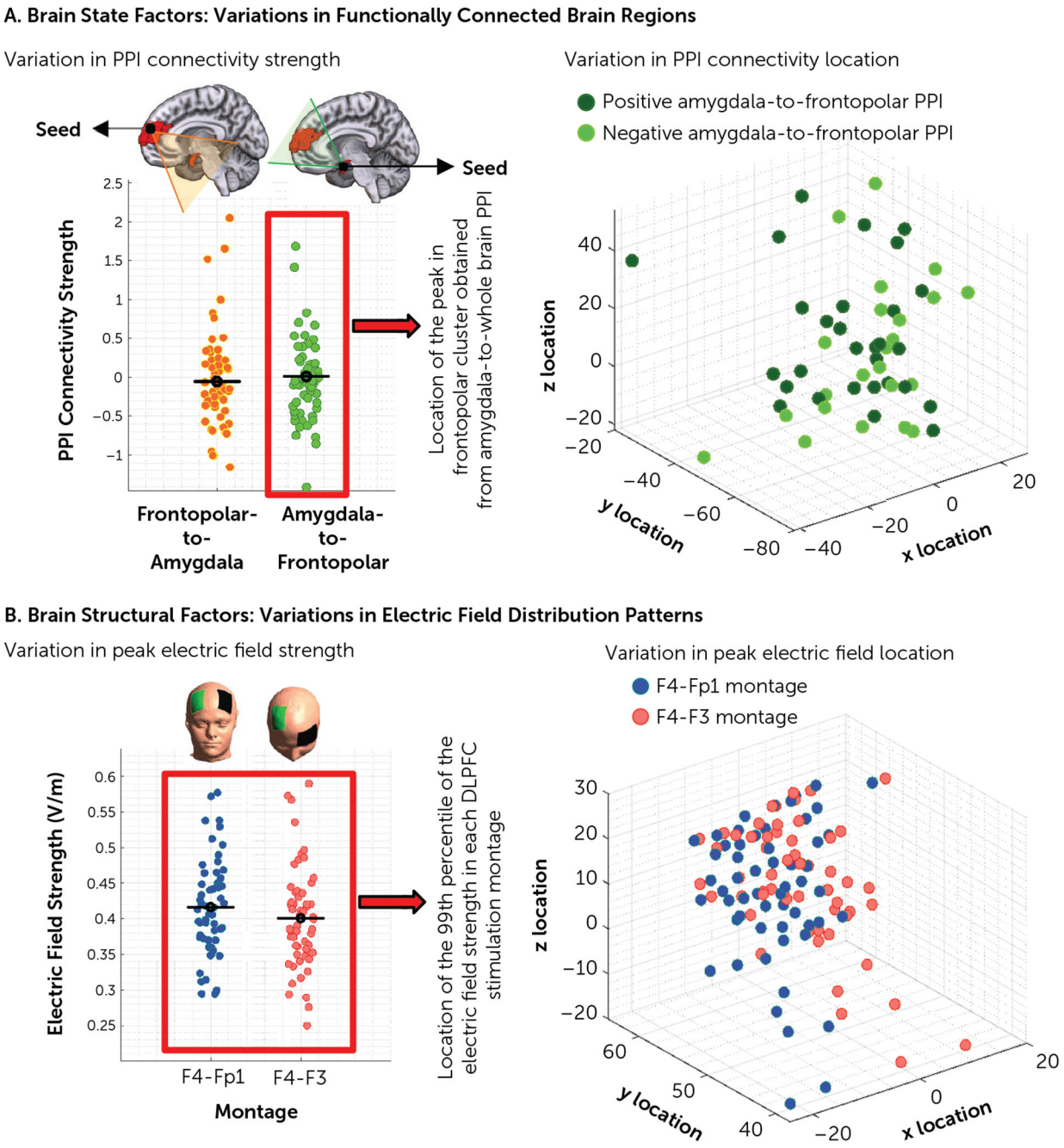

FIGURE 5. Interindividual variability in targeting the frontopolar cortex[a]

[a] Between-individual differences are visualized in terms of strength and the location of two main sources of variations (dots represent the data for individual subjects). Panel A illustrates brain state factors. Group-level frontopolar cortex-to-whole brain psychophysiological interaction (PPI) analysis showed a significant cluster in the amygdala, and group-level amygdala-to-whole brain PPI analysis showed a significant cluster in the frontopolar area. In the left-hand panel, PPI strength in each direction is presented for each subject. In the right-hand panel, the amygdala-to-whole brain peak location of the connected

brain region in MNI space is represented for each subject; positive PPI connections are in dark green and negative PPI connections are in light green. Panel B illustrates brain structural factors. The left-hand panel shows electric field distribution patterns that were simulated for two of the most commonly used electrode montages, F4-Fp1 and F4-F3. The individualized strength of the 99th percentile of the electric field (which is commonly located in the frontopolar area) is presented for each montage; F4-Fp1 in red and F4-F3 in blue (left-hand panel). The location of the peak electric field in Montreal Neurological Institute space for each subject is also reported (right-hand panel). Results are reported for 60 participants with methamphetamine use disorder. DLPFC=dorsolateral prefrontal cortex.