Modulation of resting connectivity between the mesial frontal cortex and basal ganglia

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Abstract

Background: The mesial prefrontal cortex, cingulate cortex and the ventral striatum are key nodes of the human mesial fronto-striatal circuit involved in decision-making and executive function and pathological disorders. Here we ask whether deep wide-field repetitive transcranial magnetic stimulation (rTMS) targeting the mesial prefrontal cortex (MPFC) influences resting state functional connectivity.

Methods: In Study 1, we examined functional connectivity using resting state multi-echo and independent components analysis in 154 healthy subjects to characterize default connectivity in the MPFC and mid-cingulate cortex (MCC). In Study 2, we used inhibitory, 1Hz deep rTMS with the H7-coil targeting MPFC and dorsal anterior cingulate (dACC) in a separate group of 20 healthy volunteers and examined pre- and post-TMS functional connectivity using seed-based and independent components analysis.

Results: In Study 1, we show that MPFC and MCC have distinct patterns of functional connectivity with MPFC–ventral striatum showing negative, whereas MCC–ventral striatum showing positive functional connectivity. Low-frequency rTMS decreased functional connectivity of MPFC and dACC with the ventral striatum. We further showed enhanced connectivity between MCC and ventral striatum.

Conclusions: These findings emphasize how deep inhibitory rTMS using the H7-coil can influence underlying network functional connectivity by decreasing connectivity of the targeted MPFC regions, thus potentially enhancing response inhibition and decreasing drug-cue reactivity processes relevant to addictions. The unexpected finding of enhanced default connectivity between MCC and ventral striatum may be related to the decreased influence and connectivity between the MPFC and MCC. These findings are highly relevant to the treatment of disorders relying on the mesio-prefrontal-cingulo-striatal circuit.

Introduction

Neuromodulation with magnetic stimulation is emerging as a valuable treatment alternative for a wide range of psychiatric and neurologic disorders[1]. Repetitive transcranial magnetic stimulation (rTMS) is a technique that can be used to apply multiple brief magnetic pulses to neuronal structures, thus transiently modulating neural excitability in a manner that is dependent mainly on the intensity and frequency of stimulation [2]. It is a non-invasive, non-pharmacological, and safe treatment, in which abnormal communication within neuronal networks can be entrained and modified. Depending on the target, the depth at which stimulation occurs appears to be a crucial factor underlying potential therapeutic efficacy in certain disorders, such as major depressive disorder[3; 4; 5]. In this study, we investigate the modulation of resting neural activity in mesial prefrontal-striatal circuits in healthy subjects by inhibitory deep wide-field stimulation with an Hesed (H-)7 coil[6; 7].

Fronto-striatal circuits are critical for the processing of reward, anticipation of outcomes, and behavioral control[8; 9; 10; 11]. Latent neural network organization and behavioral mechanisms in humans can be explored with resting state functional magnetic resonance imaging (fMRI) connectivity (rsFC), a method that measures the synchronization between intrinsic low-frequency fluctuations of brain regions in the absence of any specific task[12; 13; 14]. Since the connections identified at rest closely mirror anatomical connections[15] and predict brain activations associated with behavioral performance[16], rsFC is an important tool for characterizing in vivo circuit-level dynamics, which may support particular behavioral responses[17; 18].

Studies of substance use disorders have revealed the critical role of fronto-striatal circuits, highlighting large scale disruptions in functional connectivity between the mesolimbic

reward system and cortical regions involved in decision making and executive function (e.g. ventromedial prefrontal cortex, dorsolateral prefrontal cortex)[19; 20; 21; 22; 23; 24; 25; 26; 27]. In particular, altered rsFC between the dorsal and ventral mesial prefrontal cortex (d/vMPFC), anterior cingulate cortex (ACC) and ventral striatum (VS) is most consistently observed across disorders of addiction such as cocaine[28], heroin[29], nicotine[30; 31; 32; 33], and even internet addiction[32; 34; 35], but also in obsessive-compulsive disorder (OCD)[34]. Furthermore, vMPFC activity seems to be tightly linked to dMPFC activity[36; 37]. Thus, understanding whether and how deep rTMS targeting the MPFC influences the connected networks is critical to its potential clinical efficacy.

In Study 1, we first assess rsFC between MPFC and striatum in a relatively large sample of healthy controls. In Study 2, we then ask whether inhibitory deep wide-field stimulation with an H7-coil positioned over the MPFC (which, given the non-focal nature of the H7-coil[38; 39], we have defined here as supplementary motor area (SMA), preSMA, and dMPFC) influences rsFC with VS in a separate group of healthy controls. We focused on VS given its aberrant rsFC observed in pathological disorders as well as in our findings in Study 1 of negative connectivity of MPFC with VS and positive connectivity of mid-cingulate with VS. We hypothesize that low-frequency inhibitory rTMS will decrease rsFC of the MPFC with VS.

Methods and Materials

Protocol design and participants

In Study 1, seed to whole brain intrinsic rsFC was examined for the mesial PFC (SMA, pre-SMA and dMPFC) and the mid-cingulate. For intrinsic baseline mapping, blood-oxygenation level dependent (BOLD) fMRI data was collected during rest (10 minutes, eyes open,

watching white fixation cross on black screen) from 154 healthy volunteers (71 females; age 31±13 years) at the Wolfson Brain Imaging Centre, University of Cambridge, UK, with a Siemens Tim Trio 3T scanner and 32-channel head coil.

In Study 2, we used inhibitory, 1Hz rTMS deep wide-field stimulation with an H7-coil targeting the mesial PFC. In order to examine the effects of rTMS on neural fluctuations, we used both ROI-to-ROI analyses and confirmed findings with independent component analysis (ICA). Resting state fMRI data (10 minutes, eyes open, watching white fixation cross) was collected immediately before and after rTMS (average time between rTMS end and EPI sequence was 285±27 seconds) in a separate group of 20 healthy volunteers (15 females; age 36±12 years) at the National Institutes of Health (Bethesda, MD, USA) core fMRI Facility, with a Siemens Skyra 3T scanner and 32-channel head coil.

All subjects provided informed written consent. This study was approved by the Research Ethics Committee of the University of Cambridge and the Institutional Review Board of the National Institutes of Health.

Transcranial magnetic stimulation with the H-coil (Study 2)

To modulate the excitability of deep frontal areas in Study 2, we used a Hesed coil type 7 (H7-coil). Its design aims at stimulating frontal brain regions (i.e., the PFC) and reaching deep brain regions without increasing the electric field levels in the more superficial cortical regions [6; 40]. Deep TMS using other coils (e.g. classical double-cone coil) can be uncomfortable due to excessive stimulation of superficial structures and painful muscular contractions. The frames of the inner rim of H7-coil are also flexible to accommodate a variety of human skull shapes and allow a comfortable and closer fit of the coils to the scalp (Supplementary Figure S1).

We first found the hotspot and determined the active motor threshold (AMT) of the *Tibialis anterior muscle*, as an area situated medially at a depth similar to our regions of interest

(Figure 1A). The AMT was defined as the lowest intensity able to evoke a motor potential with an amplitude at least 200μV above the background EMG activity of a 10% maximal voluntary contraction of the left Tibialis anterior in 5 out of 10 consecutive trials. The coil was always maintained in the midline to avoid the problem of left-right anatomical and functional asymmetry, on top of the unknown exact geometrical location of the maximum field intensity of the H7-coil. In this way, the threshold determined for the left TA corresponded to an intensity strong enough to evoke action potentials in the pyramidal neurons on the mesial cortex at that depth in each individual. Repetitive TMS was delivered with a biphasic magnetic stimulator (Magstim Rapid2; The Magstim Company, Whitland, South West Wales, UK) with a frequency of 1Hz and at 110% AMT intensity. Nine hundred pulses were administered over the MPFC, 5 cm anterior to the Tibialis anterior hot-spot, for 15min. By choosing this location, we assured that the maximum field would cross areas BA 8/9, which are located in front of the peSMA [41; 42]. When administered in accordance with current international guidelines, transcranial magnetic stimulation has been shown to be safe[43; 44], with few mild adverse effects, although we acknowledge that these safety guidelines are derived primarily from studies using conventional figure-8 coils.

We used medium intensity stimulation (i.e., 110% of the active motor threshold; average effective intensity 66±8% of the maximum stimulator output) of the H7-coil, which would have penetrated effectively up to a depth of 3.5cm from the surface of the scalp (Figure 1B), corresponding to the mesial PFC region (Figure 1C).

- please insert Figure 1 here -

Resting state functional MRI

The following describes the resting state acquisitions and analyses used for Study 1 and 2.

Acquisition Study 1: Functional images were acquired with a multi-echo echo planar imaging sequence with online reconstruction (repetition time (TR), 2.47s; flip angle, 78°;

matrix size 64 x 64; resolution 3.0 x 3.0 x 3.0 mm; FOV, 240mm; 32 oblique slices, alternating slice acquisition slice thickness 3.75mm with 10% gap; iPAT factor, 3; bandwidth (BW) = 1698Hz/pixel; echo time (TE) = 12, 28, 44 and 60ms).

Study 2: Functional images were acquired with a multi-echo echo planar imaging sequence (TR, 2.47s; flip angle, 70°; matrix size 70 x 60; in-plane resolution, 3.0mm; FOV, 210mm; 34 oblique slices, alternating slice acquisition slice thickness 3.0mm with 0% gap; iPAT factor, 3; bandwidth (BW) = 2552Hz/pixel; TE = 12, 28, 44, and 60ms).

For both studies, anatomical images were acquired using a T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence (76 x 240 field of view (FOV); resolution 1.0 x 1.0 x 1.0 mm; inversion time, 1100ms).

Preprocessing

The following processing and analyses apply to both resting state fMRI data unless stated otherwise. To enhance signal-to-noise ratio, we used multi-echo EPI sequence and independent component analysis (ICA), which allows data to be denoised for motion, physiological, and scanner artifacts in a robust manner based on physical principles [45]. Multi-echo independent component analysis (ME-ICA v2.5 beta6; http://afni.nimh.nih.gov) was used for data analysis and denoising. ME-ICA decomposes the functional data into independent components using FastICA. BOLD percent signal changes are linearly dependent on echo time (TE), a characteristic of the T2* decay. TE dependence of BOLD signal is measured using the pseudo-F-statistic, Kappa, with components that scale strongly with TE having high Kappa scores[46]. Non-BOLD components are TE independent and measured by the pseudo-F-statistic, Rho. Components are thus categorized as BOLD or non-BOLD based on their Kappa and Rho weightings, respectively. Non-BOLD components are removed by projection, robustly denoising data. Each individual's denoised echo planar images were coregistered to their MPRAGE and normalized to the Montreal Neurological

Institute (MNI) template. Spatial smoothing of the functional data was performed with a Gaussian kernel (full width half-maximum = 6mm).

Region of interest (ROI)-driven analysis

We performed ROI-driven functional connectivity analysis using CONN-fMRI Functional Connectivity toolbox[47] for Statistical Parametric Mapping SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), using denoised, coregistered, smoothed functional data. The time course for each voxel was temporally band-pass filtered ($0.008 < f < 0.09$ Hz). Each individual's anatomical scan was segmented into grey matter, white matter and cerebrospinal fluid. Significant principle components of the signals from white matter and cerebrospinal fluid were removed.

Study 1: Intrinsic functional connectivity mapping

For intrinsic rsFC mapping in 154 healthy volunteers, ROI-to-whole brain connectivity was computed for mesial PFC and mid cingulate ROI's. Connectivity maps were thresholded at FWE $p<0.05$ whole brain corrected. Both positive and negative functional connectivity was examined across the whole brain. Anatomically-defined ROIs were manually created or altered using MarsBaR ROI toolbox[48] for SPM (see Supplementary Methods for seed definitions)

Study 2: Effects of rTMS: ROI-based

To address the *a priori* hypothesis, ROI-to-ROI functional connectivity was first computed using Pearson's correlation between BOLD time courses for mesial PFC with ventral striatum, both pre- and post-TMS. These were entered into a paired samples t-test to compare between pre- and post-TMS. For the *a priori* ROI-to-ROI functional connectivity analysis between the mesial PFC and VS, $p<0.05$ was considered significant. On an exploratory basis, to assess the impact of rTMS on rsFC of deeper structures such as the

mid-cingulate which lies immediately below the mesial PFC, ROI-to-ROI functional connectivity of mesial PFC to mid cingulate and mid cingulate to VS were examined pre- and post-TMS. P<0.025 was considered significant (Bonferonni corrected for multiple comparisons). The VS anatomical ROI has previously been used[49] and hand drawn using MRIcro (http://www.cabiatl.com/mricro/mricro/) based on a published definition of VS[50].

Effects of rTMS: Independent component analysis (Study 2)

To confirm the ROI-to-ROI findings, we then conducted ICA. While ICA has been shown to engender statistically similar results as seed based approaches in healthy volunteers[51], ICA is a multivariate data-driven approach that requires fewer *a priori* assumptions and takes into account interacting networks. Therefore, if TMS affects larger scale neural networks, ICA should succeed in highlighting this. Denoised, coregistered, and smoothed functional data was entered into ICA analysis using FSL MELODIC 3.14 software (FMRIB, University of Oxford, UK; www.fmrib.ox.ac.uk/fsl/melodic2/index.html) that performs probabilistic ICA to decompose data into independently distributed spatial maps and associated time courses to identify independent component variables[52]. A high model order of 40 was used as a fair compromise between under- and over-fitting[53]. Multi-session temporal concatenation was used to allow computation of unique temporal responses per subject/session. Comparisons between pre- and post-TMS was performed using FSL dual regression for reliable and robust[54] voxel-wise comparisons using nonparametric permutation testing with 5000 permutations and using threshold free cluster enhancement (TFCE) controlling for multiple comparisons[55]. Group differences of components that include MPFC were calculated with p<0.05 thresholds.

Results

Baseline mapping

Intrinsic resting state whole brain connectivity maps for mesial PFC and mid cingulate are displayed in Figure 2 and reported in Supplementary Table S1 and S2. Both positive and negative functional connectivity are displayed. Mesial PFC and mid cingulate showed opposite patterns of connectivity with ventral striatum: mesial PFC had negative but mid cingulate had positive functional connectivity with VS.

- please insert Figure 2 here -

Effects of TMS

Focusing on our *a priori* hypothesis, we show that after rTMS, mesial PFC had reduced functional connectivity with ventral striatum (t=2.201, p=0.043) (Figure 3). We then show an effect on mid-cingulate functional connectivity with reduced functional connectivity following rTMS between the mesial PFC and mid-cingulate (t=4.325, p=0.001) and enhanced functional connectivity between mid-cingulate and VS (t=-2.495 p=0.024).

- please insert Figure 3 here -

We conducted ICA on the resting state data pre- and post-rTMS to confirm our *a priori* hypothesis and analysis. Out of 40 components, three included prominent mesial frontal cortex (Figure 4 and Supplementary Table S3). Of the three mesial frontal network components, dual regression revealed that one of these components (IC11) was significantly decreased post-rTMS (TFCE p=0.0360). The IC00 included prominent dmPFC; the IC11 included dmPFC, preSMA, and SMA; the IC38 included prominent anterior and mid cingulate, and dmPFC. The dmPFC/ACC can be considered part of the dorsal attention network.

- please insert Figure 4 here -

196

197 Discussion

198 We characterized the effects of deep wide-field mesial prefrontal rTMS on the resting-state
199 functional network in healthy individuals. We first mapped intrinsic functional connectivity
200 of mesial prefrontal and mid-cingulate cortical regions in a large sample of healthy
201 volunteers. We found that intrinsic functional connectivity of the mesial PFC region of
202 interest with ventral striatum was negative, whereas the intrinsic functional connectivity of
203 mid-cingulate connectivity with ventral striatum was positive. Then, we show that deep
204 wide-field inhibitory rTMS targeting the mesial PFC decreases rsFC between this broad
205 mesial PFC region and the ventral striatum. These findings were further confirmed with ICA
206 analysis, a data-driven approach. Based on the modeling of the magnetic field distribution,
207 induced-electrical field decay, and the depth of the target region stimulated, we likely also
208 inhibited directly the dorsal posterior regions of Brodmann Area 32, corresponding to
209 dorsal anterior cingulate – a fact subsequently confirmed by the ICA analysis. Inhibitory
210 rTMS also decreased functional connectivity of the 'stopping' network including pre-SMA,
211 right inferior frontal cortex, and ventral caudate. This is in line with previous reports, in
212 which inhibitory rTMS (including continuous theta burst stimulation) targeting the pre-
213 SMA with standard figure-of-eight coil has been shown to enhance motor response
214 inhibition [56].

215 We also found effects of deep rTMS on connectivity between deeper structures such as the
216 mid-cingulate cortex, which was unlikely to be directly stimulated with our stimulation
217 parameters: decreased rsFC between the broad mesial PFC and mid-cingulate cortex, and,
218 unexpectedly, enhanced rsFC between mid-cingulate cortex and ventral striatum. These
219 findings suggest that while deep wide-field mesial prefrontal inhibitory rTMS might directly

decrease the functional connectivity between the stimulated and the connected structures, the decreased influence from superficial cortical regions might indirectly enhance the intrinsic connectivity between remote structures (i.e., the mid-cingulate cortex and ventral striatum).

Application of rTMS to superficial cortical regions with the strongest negative functional connectivity with subgenual ACC has already been shown to be most clinically efficacious in reducing depression[57]. Thus, based on the deep cortical or subcortical structure of interest for a given disorder, appropriate superficial sites for rTMS can be selected based on intrinsic functional connectivity strengths and patterns. Since we demonstrate in our second study that there is an exaggeration of intrinsic functional connectivity strengths with deep inhibitory rTMS, detailed mapping of baseline connectivity patterns will inform the selection of rTMS targets with the aim to 'normalize' aberrant underlying functional connectivity in disease states. The outcome of this modulation could be of interest in the treatment of disorders relying on the mesioprefrontal-cingulo-striatal circuit.

The H-coil series was originally designed to have a significant impact on deep structures, like the anterior cingulate cortex[6; 7]. It has been used with different degrees of success to treat depression[58; 59], alcohol use disorders [60], nicotine addiction[61], and even as adjunctive therapy in Parkinson's disease[62], blepharospasm [63], and chronic migraine [64]. Due to the quick drop in TMS efficacy with increasing target depth[65], it has been proposed that any stimulation outside the primary motor cortex should be referenced to motor cortex excitability and adjusted to the target depth[66; 67]. The original assertion that the H-coil can modulate the activity of deep structures has been based mainly on calculating the intensity of the induced electrical field at different depths for a given stimulation intensity[40]. However, other factors can significantly influence the efficacy of rTMS, including the orientation of the coil[68; 69; 70] and the configuration of the subjacent

245 and/or target cortex[71; 72; 73; 74; 75], as well as the secondary electrical fields generated
246 at the boundary between the cerebrospinal fluid and the gray matter [76]. Subsequent
247 studies of the distribution of the magnetic field generated by the H-coil revealed that the
248 largest field intensity variation and hence, the functional effect covers first the mesial
249 neuronal structures in close proximity to the coil, i.e., superior MF areas, like dMPFC, pre-
250 SMA, SMA[40; 77; 78; 79], and only secondarily deeper structures such as the cingulate
251 cortex if stimulation intensity is high enough[7; 40]. In order to reach the stimulation
252 threshold of neurons, a total field of 30–100 V/m is needed, depending on the neurons [80].
253 Since focal coils, like flat 8-shaped or double-cone coils, produce very strong fields that
254 decay fast as a function of distance, 500 V/m would be induced at 1 cm depth (i.e. scalp) for
255 50 V/m at 5cm, which would be very uncomfortable due to superficial muscle contraction
256 under the stimulated site[6]. According to our simulations (Figure 1B) using a spherical
257 head model, the structure of the H7-coil induces only 150V/m at 1cm in the same
258 conditions, albeit at the cost of focality, making it more tolerable. In this study, we used
259 medium intensity stimulation (i.e., 110% of the active motor threshold; average effective
260 intensity 66±8% of the maximum stimulator output), which would have stimulated a region
261 of interest corresponding to the mesial PFC. This allowed us to influence directly the output
262 of these areas and indirectly the activity of functionally linked structures[81; 82; 83; 84; 85;
263 86]. Based on the simulated model of the target and depth reached using our stimulation
264 parameters, we likely directly stimulated down to dorsal posterior regions of Brodmann Area
265 32 corresponding to dorsal anterior cingulate. However, it is unlikely that we directly
266 stimulated the mid-cingulate; thus any change in connectivity observed in the mid-cingulate
267 would likely be an indirect effect via changing the functional output of connected areas.
268 Here, we extend the understanding of the effects of magnetic stimulation over the middle
269 frontal areas, following previous TMS studies investigating more superficial stimulation of

the lateral frontal areas[57; 87; 88; 89]. Subsequent studies are indicated to investigate the influence of higher intensities and higher frequencies[90] on rsFC of frontal superficial and deep structures, when applied with coils designed to reach broader regions. The magnetic field generated by an H7-coil is covering a much wider area of the frontal lobe, but as with the classical double-cone coil, which has a similar shape but smaller, the magnetic field generated at the edges of the coil is assumed to be non-focal and weak enough as not to induce a meaningful neuronal depolarization.

We delivered magnetic pulses at 1Hz for 15 minutes. This frequency can induce a long term depression (LTD)-like effect in the targeted neuronal networks that outlasts the stimulation for a sufficient duration to assess the influence on resting-state fMRI[91; 92; 93; 94]. By using low stimulation intensities, we effectively depressed the excitability of the superior mesial prefrontal areas and possibly also the dorsal posterior region of Brodmann Area 32 corresponding to dorsal anterior cingulate cortex. An LTD-like effect would thus decrease neuronal excitability in the mesial PFC, rendering it less responsive to incoming information. Decreased responsiveness would functionally decouple this region from both neighboring and deeper structures. Indeed, we found reduced functional connectivity of the broad mesial PFC with mid-cingulate, and between the broad mesial PFC and ventral striatum, with ICA confirming decreases in the network including mesial PFC, dorsal anterior cingulate and ventral caudate/ventral striatum. Since the fronto-striatal network relies on a dynamic equilibrium between its different parts[11; 95; 96], functionally "nudging" one part should entrain a reconfiguration of all functional connections, including functional connectivity between remote regions receiving projections from the stimulated region. This seems to be the case in our study: we found increased functional connectivity between the mid-cingulate area and ventral striatum after inhibiting the mesial PFC.

The outcome of this modulation could be of interest in treatment of disorders relying on the mesioprefrontal-cingulo-striatal circuit. In healthy humans, this circuit is involved in cognitive and emotional control, error and conflict monitoring[97; 98; 99], response inhibition[100], and positive and negative prediction error and anticipation[101; 102; 103]. Abnormal cortico-ventro striatal hyperconnectivity has been OCD[104; 105; 106] and addictions (for a review see[107]). In disorders of addiction, decreased functional connectivity between the ventral striatum and the cingulate cortex bilaterally is commonly observed[29; 32], with enhanced dorsal cingulate and ventral striatal activity in the context of drug cues[108]. Numerous targets had been proposed for invasive deep brain stimulation aimed at correcting these imbalances, including the anterior limb of the internal capsule[109], subthalamic nucleus[110], and ventral striatum/nucleus accumbens[111]. In order to avoid the risks of an invasive procedure, studies have explored stimulating other nodes of these networks that are accessible to TMS at the surface of the brain. Stimulation of the dorsolateral prefrontal cortex, is (arguably[58; 59]) successful in treatment-resistant major depressive disorder[4; 112], with modest results in OCD[113]. On the other hand, stimulation of the dorso-medial prefrontal cortex [114] or preSMA/SMA complex[115; 116; 117] seems slightly more encouraging. Notably, there is no gold standard yet for the frequencies to be used. The stimulation frequencies used thus far in most studies cover a wide range including continuous delivery at 1Hz, or intermittently at 10 or 18Hz in 5s trains separated by breaks of 10s. While 1Hz stimulation is known to induce LTD-like effects, the mechanism of action and the eventual outcome of other multiple medium-frequency trains is still open to debate and investigation[118; 119].

Wide inhibitory stimulation of the dorso-mesial areas of the frontal lobe might have both clinical and mechanistic benefit. Wider superficial stimulation has a clear clinical benefit allowing a reduction in the intensity of the stimulation with deeper stimulation, thus

319 increasing patients' comfort and adherence by decreasing superficial muscle contraction,
320 and minimizing risks. Aberrant activity in networks in psychiatric disorders may affect
321 broader regions that can be targeted via wide inhibitory stimulation. We show that
322 stimulation that is both wide and deep is associated with decreased connectivity between
323 the mesial prefrontal areas and deeper structures (like the mid-cingulate areas and ventral
324 striatum), with possibly a secondary effect of increasing connectivity between cingulate and
325 ventral striatum. Wider stimulation will also have a broader effect on multiple neural
326 regions, impacting a wide range of cognitive functions. Using the H7-coil with inhibitory
327 rTMS is thus consistent with both inhibition of the pre-SMA shown to enhance motor
328 response inhibition[56] and decreased dorsal cingulate activity associated with drug cue
329 reactivity[108]. Therefore, the H7-coil has the capacity to both enhance the response
330 inhibition associated with the stopping network in disorders of addiction, and decrease
331 drug cue reactivity associated with the dorsal cingulate and ventral striatum. However, it is
332 unclear whether decreasing dorsal cingulate activity across all conditions would be the
333 optimal approach, as resting state functional connectivity between cingulate and ventral
334 striatal regions are commonly decreased in disorders of addiction. Further studies
335 investigating a state-specific effect of rTMS may be relevant with pairing H-coil stimulation
336 with drug cues with or without concurrent response inhibition. It also remains to be
337 established whether our findings are specific to wide-field deep rTMS or whether focal deep
338 rTMS (which is be more difficult to tolerate) would show similar rsFC pattern changes
339 within cingulate regions.

340 This study is not without limitations. While we did not have a sham control, we note that
341 our findings revealed both increases and decreases in connectivity – suggesting that an
342 order effect is unlikely to account for these observations. It is also technically impossible to
343 achieve a realistic sham with the H-coil, since the real stimulation evokes a specific,

unconfoundable small contraction of the anterior belly of the occipitofrontal muscle. The localization of the peak stimulus effect is also more difficult with the H-coil, since the coils' positions inside the helmet are flexible and the precise technical characteristics of the coils are proprietary to the company. We do present, however, an X-ray of the coil structure and the geometrical approximation of the coil used in the modeling of the magnetic field penetration depth (Supplemental Figure 1). Subsequent studies testing higher frequencies and/or intensities are indicated, as well as repeated stimulation sessions (over minimum 4 weeks) in preparation for clinical trials.

We highlight that non-invasive wide and deep inhibitory brain stimulation appears to decrease the underlying functional connectivity of regions immediately within the stimulation zone while enhancing functional connectivity of deeper structures such as mid-cingulate to ventral striatum. This unexpected finding might be related to the decreased influence from superficial cortical regions via decreased cortico-cortical connectivity. A deep wide-field coil allows both greater tolerability and the capacity to influence multiple relevant neural regions and cognitive functions. These dissociable findings may be relevant particularly to disorders of addiction and OCD, and have implications for designing interventional deep rTMS studies.

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Figure Legends

Figure 1. Stimulation paradigm. (A) Schematic representation of the movement of the projection of the geometric center of the H7 coil 5 cm in front of the empirically found hot-spot for the left *Tibialis anterior* muscle [41; 42]. The points represent an ideal (not neuronavigated) center of the interior of the H7 helmet. (B) Estimation of the induced electrical field intensity with distance from the coil for stimulation at 110% of the active motor threshold (AMT) – our intensity of choice, and 120% AMT and 110% resting motor threshold – higher intensities distribution modeled for comparison. The dotted line represents the theoretical intensity of the induced electrical field for AMT. (C) Sagittal section showing the area in the dorso-mesial prefrontal cortex found at an equivalent depth to the *Tibialis anterior* motor representation.

Figure 2. Intrinsic resting state connectivity maps for mesial prefrontal cortex (PFC) and mid cingulate cortex seeds to whole brain in healthy controls. Positive (yellow-red) and negative (green-blue) functional connectivity are displayed. The rectangular insets at y=8 highlighting differences in direction of connectivity of the striatum are shown for the mesial PFC (bottom row, left) and mid cingulate (bottom row, right). Coronal images (y-values shown above image) are thresholded at whole brain family wise error corrected $p<0.05$ on a standard MNI template.

Figure 3. Effects of repetitive transcranial magnetic stimulation (rTMS) on intrinsic functional connectivity in healthy controls. Functional connectivity is schematically illustrated at baseline (i.e. pre-rTMS; top left) and post-rTMS (bottom left); pre- and post-rTMS effects on seed-to-seed functional connectivity are shown in the bar graphs. After rTMS, functional connectivity between mesial prefrontal cortex (mPFC) and ventral

862 striatum (VS), and between mPFC and mid cingulate cortex (MCC) was reduced, while
863 functional connectivity between MCC and VS was increased (the thickness of the arrows
864 correspond to strength, and color to direction: red – positive connectivity, blue – negative
865 connectivity). Error bars are shown as standard error of the mean. *p<0.05, **p=0.001
866
867 **Figure 4.** Functional connectivity at rest between different regions of interest explored with
868 independent component analysis pre- and post-rTMS. Three components included
869 prominent mesial-frontal cortex (IC00, IC11 and IC38). The insert shows IC11, which
870 included supplementary motor area (SMA), pre-SMA, dorsomedial prefrontal cortex/dorsal
871 cingulate, and ventral caudate/striatum, and bilateral inferior frontal cortices was
872 significantly decreased post-rTMS. *p<0.05