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Low- and High-Frequency Repetitive Transcranial Magnetic Stimulation Effects on Resting-State Functional Connectivity Between the Postcentral Gyrus and the Insula

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Abstract

The insular cortex supports the conscious awareness of physical and emotional sensations, and the ability to modulate the insula could have important clinical applications in psychiatry. Repetitive transcranial magnetic stimulation (rTMS) uses transient magnetic fields to induce electrical currents in the superficial cortex. Given its deep location in the brain, the insula may not be directly stimulated by rTMS; however, rTMS may modulate the insula via its functional connections with superficial cortical regions. Furthermore, low- versus high-frequency rTMS is thought to have opposing effects on cortical excitability, and the present study investigated these effects on brain activity and functional connectivity with the insula. Separate groups of healthy participants ($n = 14$ per group) received low (1 Hz)- or high (10 Hz)-frequency rTMS in five daily sessions to the right postcentral gyrus, a superficial region known to be functionally connected to the insula. Resting-state functional connectivity (RSFC) was measured pre- and post-rTMS. Both 1 and 10 Hz rTMS increased RSFC between the right postcentral gyrus and the left insula. These results suggest that low- and high-frequency rTMS has similar long-term effects on brain activity and RSFC. However, given the lack of difference, we cannot exclude the possibility that these effects are simply due to a nonspecific effect. Given this limitation, these unexpected results underscore the need for acoustic- and stimulation-matched sham control conditions in rTMS research.

Keywords: insula; repetitive transcranial magnetic stimulation (rTMS); resting-state functional connectivity

Introduction

The insular cortex supports the conscious awareness and emotional processing of bodily sensations, and it influences motivational decision-making (Craig, 2009). Insula function is highly relevant to drug cravings and addiction (Garavan, 2010; Naqvi and Bechara, 2009), as well as other psychiatric disorders, including post-traumatic stress disorder, social anxiety, and phobias (Etkin and Wager, 2007). Interoceptive awareness of physical sensations is represented in the posterior insula, whereas the subjective ratings and emotional valence of these sensations are represented in the middle to anterior insula, suggesting a posterior to anterior pattern of interoceptive processing (Craig, 2009). The anterior insula is functionally connected to the anterior cingulate cortex and the salience network, and may play a role in the influence of emotion on cognition (Seeley et al., 2007). Thus, the ability to modulate insula activity and its functional connections could have important clinical applications.

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive technique that uses transient magnetic fields to induce electrical currents in the cortex (Hallett, 2007). rTMS can modulate cortical excitability and induce lasting changes in synaptic plasticity (Hoogendam et al., 2010). However, the direct effect of rTMS drops quickly with distance, primarily stimulating superficial cortex (Rudiak and Marg, 1994) and cannot directly reach the insula, which is folded deeply into the lateral sulcus. Fortunately, rTMS is thought to work both through local effects at the target site and through transynaptic effects that propagate to areas functionally connected to the target site (Hoogendam et al., 2010). As such, it is possible to target superficial brain areas that are functionally connected to deeper regions, to

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induce neuroplastic and behavioral changes associated with deeper subcortical brain structures (Fox et al., 2012; Wang et al., 2014). For example, the hippocampus is located deep inside the temporal lobe and is not directly accessible by rTMS, but the hippocampus is functionally connected to the superficial lateral parietal cortex; applying rTMS to a parietal cortical target strengthened resting-state functional connectivity (RSFC) with the hippocampus and improved memory performance (Wang and Voss, 2015; Wang et al., 2014). Under this same logic, the insula may be accessible via its functional connections to the outer cortical surface. However, indirect modulation of an *a priori*-defined insula target has not yet been tested.

RSFC is the temporal dependency of spontaneous blood oxygen level-dependent (BOLD) activity fluctuations across brain regions while individuals are at rest (i.e., without any explicit stimulus or behavior), and is thought to represent the functional communication among brain regions (van den Heuvel and Pol, 2010). The co-use of RSFC and rTMS is recommended to study the effects of rTMS on brain connectivity, as well as to identify and guide rTMS target selections based on brain connectivity networks (Fox et al., 2012). However, it is important to show specificity of RSFC to rTMS frequency, stimulation site, and functional network to control for nonspecific effects (e.g., local effects of rTMS) (Fox et al., 2012). This raises an important question regarding whether rTMS can selectively strengthen or weaken ''downstream'' RSFC depending on the pulse frequency. At the stimulation site, rTMS is thought to have different effects on cortical excitability based on the pulse frequency. Low-frequency stimulation (e.g., 1 Hz) generally lowers cortical excitability, while high-frequency stimulation (e.g., 5–20 Hz) facilitates cortical excitability (Fitzgerald et al., 2006).

How these frequency-dependent changes in excitability affect RSFC has been investigated by a small number of studies. Studies have reported that low-frequency rTMS increased RSFC (Eldaief et al., 2011; Vercammen et al., 2010; Watanabe et al., 2014) or had no effect (Eldaief et al., 2011); and high-frequency rTMS increased (Wang et al., 2014), decreased (Eldaief et al., 2011; Li et al., 2017; Watanabe et al., 2014), or had no effect on RSFC (Eldaief et al., 2011). A study that administered a different type of rTMS, either 5 msec interstimulus interval (ISI; i.e., excitatory) or 50 msec ISI (i.e., inhibitory) quadripulse rTMS (i.e., four monophasic pulses as a single stimulation train), reported that 5 msec ISI rTMS decreased and 50 msec ISI rTMS increased RSFC between the target site and the contralateral cortex (Watanabe et al., 2014). This is consistent with electroencephalography (EEG) studies that showed low-frequency rTMS increases and high-frequency rTMS decreases alpha-band coherence (Oliviero et al., 2003; Strens et al., 2002). Some methodological differences may underlie these inconsistencies across studies. In particular, three studies measured the immediate effects (<30 min post-rTMS) of a single rTMS session (Eldaief et al., 2011; Li et al., 2017; Watanabe et al., 2014) and two studies measured the long-term effects (>1 h post-rTMS) of multiple daily sessions (Vercammen et al., 2010; Wang et al., 2014). Nevertheless, altogether these studies have provided contradictory results, leaving a need to further test connectivity changes induced by rTMS.

The goal of this study was to modulate RSFC with the insula using low- and high-frequency rTMS. A previous investigation revealed stronger RSFC between the posterior insula and the postcentral gyrus (near the outer cortical surface) among smokers who remained abstinent during a quit attempt, compared with those who relapsed (Addicott et al., 2015). The posterior insula is strongly connected, both functionally and anatomically, to the ventral sensorimotor cortex (Addicott et al., 2015; Jakab et al., 2012). The ability to modulate this circuit could have implications for tobacco addiction. As a proof of principle using healthy subjects, rTMS was applied to a similar location on the postcentral gyrus reported in Addicott et al. (2015), and RSFC with the insula was measured before and after a course of four to five daily sessions of rTMS. A secondary analysis measured the effects of rTMS on an insula-based network. We hypothesized that 10 Hz would increase and 1 Hz would decrease RSFC (i.e., a group [10 Hz vs. 1 Hz] × time [pre- vs. post-rTMS] interaction effect) between the right postcentral gyrus rTMS target site and the bilateral insula, and produce complementary changes within the insula-based resting-state network.

Materials and Methods

Participants

Right-handed, healthy participants ($n = 28$, 8 men), ages 18–55 (mean ± standard deviation [SD] = 29 ± 11.6), were included if they had no history of significant health problems or neurological problems such as a history of head trauma or seizures, had no current diagnosis of Axis I psychiatric disorders, did not use medications known to lower the seizure threshold, had no conditions that would make magnetic resonance imaging (MRI) unsafe, had a negative urine drug screen for psychoactive drugs or medications, a negative breath alcohol screen, and among persons of child-bearing capacity—a negative urine pregnancy screen. Participants were assigned to a 10 Hz group ($n = 14$) or a 1 Hz group ($n = 14$). Subjects were assigned pseudorandomly, balancing for age and gender, and the resulting groups did not differ in age or sex distribution.

Procedure

Participants underwent an MRI scan (pre-rTMS MRI), followed by 5 consecutive days of rTMS, then a second MRI scan (post-rTMS MRI). The post-rTMS MRI was conducted at least 1 h and up to 24 h after the last rTMS session, with the majority (75%) of these scans conducted on the same day as the final rTMS session. Due to scheduling limitations, three participants in the 10 Hz group and seven participants in the 1 Hz group received four TMS sessions. The average delay (±SD) between the last rTMS session and the post-rTMS MRI scan was 6.7 ± 9 h. There was no significant difference between the 10 Hz and the 1 Hz groups in the number of TMS sessions completed or the time between last rTMS session and the post-rTMS MRI scan. These procedures were part of a larger study protocol on distress tolerance.

Repetitive transcranial magnetic stimulation

rTMS was administered using a Magstim Rapid^2 device (Magstim Company Ltd., Morrisville, NC) and an air-cooled

figure-8 coil. Participants' resting motor threshold (MT) was determined at the beginning of the first rTMS session by attaching electrodes over the participants' left hand first dorsal interosseous muscle and measuring motor-evoked potentials (MEPs) with electromyography. With the coil positioned at the optimal site over the right motor cortex, the output of the magnetic pulse was adjusted using the Adaptive Parameter Estimation by Sequential Testing (PEST) procedure (Borckardt et al., 2006).

The rTMS target site was predetermined for each participant by transforming the location of the postcentral gyrus cluster functionally connected to the posterior insula (Addicott et al., 2015) into individual anatomical space (using the pre-rTMS anatomical MRI scan), then drawing a 8×8 mm square region of interest (ROI) over the cluster location (approximate MNI coordinates: 64, −5, 28). The rTMS coil placement was guided with a neuronavigational system using infrared technology (Brainsight; Rogue Instruments, Montreal, Canada) to coregister head and coil locations with the participants' rTMS target site. Participants received either 10 Hz rTMS (100% motor threshold, 5-sec trains, 20-sec intertrain interval, 2000 pulses total) or 1 Hz rTMS (100% motor threshold, 960 pulses total). The 10 and 1 Hz conditions were matched for duration; both conditions lasted 16 min. Four participants in the 10 Hz group and three participants in the 1 Hz group received ~80% MT during the rTMS sessions due to poor tolerability of 100% MT. The average (±SD) % MT was 95% ± 8. There were no group differences in the % MT received during rTMS. During the rTMS session, participants performed a math task for 10 min and then rested for the remainder of the session.

Magnetic resonance imaging

During the MRI scans, participants completed a resting-state scan followed by a high-resolution anatomical scan. Images were acquired on a 3T General Electric MR750 scanner (Milwaukee, WI) equipped with 50 mT/m gradients. A high-resolution anatomical image was collected using a three-dimensional fast spoiled gradient-recalled echo sequence (repetition time [TR] = 8.156 msec, echo time [TE] = 3.18 msec, field of view = 25.6 cm^2, acquisition matrix = 256×256, flip angle = 12°, 166 slices, and slice thickness = 1 mm).

BOLD signal was measured using a sensitivity encoding gradient-recalled inward spiral pulse imaging sequence (SENSE spiral; TR = 2000 msec, inversion time [TI] = 0, TE = 32 msec, flip angle = 77°, acquisition matrix = 64×128, field of view = 25.6 cm^2, number of slices = 34, and slice thickness = 4 mm resulting in $4 \times 4 \times 4$ mm voxels, 150 volumes for a duration of 5 min per run). The first four image volumes were removed for stabilization and an infrared camera was used to monitor alertness. Participants were asked to keep their eyes open.

MRI data preprocessing and analysis

Resting-state functional images were preprocessed using SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12). Functional images were slice-time corrected and temporally realigned. Individual anatomical images were coregistered to the functional images. Anatomical images were then segmented into gray matter, white matter, and cerebral spinal fluid and normalized to the ICBM template, and these deformations were applied to the functional images. Images were resliced to $2 \times 2 \times 2$ mm voxels and spatially smoothed using a 5-mm full-width at half-maximum Gaussian kernel.

Subject-level RSFC was analyzed using the Conn toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). Movement and scan data outliers were detected using Artifact Detection Tools (www.nitrc.org/projects/artifact_detect) and included in the RSFC analyses as covariates of no interest. Group-level analyses were conducted in SPM12. Mixed between (group: 10 vs. 1 Hz)- and within (time: Pre- vs. Post-rTMS)-group factorial analysis of covariances investigated the main effects of group, time, and group × time interaction on RSFC. The time interval between the last rTMS session and the post-rTMS MRI scan was included as a covariate of no interest. In the primary analysis, RSFC results were confined to a bilateral insula ROI mask defined from the automated anatomical labeling (AAL) atlas with a significance threshold of $p < 0.001$ uncorrected, cluster extent >10 voxels. Exploratory whole-brain analyses were conducted with a significance threshold of $p < 0.001$ uncorrected, cluster extent >50 voxels. The secondary insula-based network analysis used the bilateral insula from the AAL atlas as a seed ROI. Images created with MRIcron (Rorden and Brett, 2000).

Results

Resting-state functional connectivity

rTMS target site connectivity. RSFC with the rTMS target site (i.e., the right postcentral gyrus) as the seed ROI was analyzed to illustrate the resting-state network of this region. Across all conditions, the rTMS target site showed positive RSFC with the bilateral pre/postcentral gyrus (extending into the posterior insula), hippocampal and parahippocampal gyri, cerebellum, and left temporal lobe. The rTMS target site showed negative RSFC with the bilateral inferior parietal lobe, right precuneus, right mid-cingulate cortex, right middle and inferior frontal gyrus, right caudate nucleus, and left cerebellum (Table 1 and Fig. 1a).

Masked bilateral insula analysis. Pre- to post-rTMS changes in RSFC (time effect) between the rTMS target site and the insula were analyzed by applying an ROI mask of the bilateral insula. RSFC increased with the left insula. There was also a trend toward increased RSFC with the right insula (trend level: $p < 0.005$, cluster extent >10 voxels). There were no clusters where RSFC decreased from pre- to post-rTMS, nor were there any effects of group or group × time interactions (Table 1 and Fig. 1b).

Exploratory whole-brain analysis. Pre- to post-rTMS changes in RSFC (time effect) between the rTMS target site were explored with every other voxel in the brain. RSFC increased with the bilateral precuneus and the left insula. RSFC decreased from pre- to post-rTMS with the bilateral inferior occipital cortex, cerebellum, precuneus, left middle temporal lobe, and right superior temporal gyrus. There was an interaction effect (10 Hz Pre >10 Hz Post and 1 Hz Post >1 Hz Pre) in the right superior temporal gyrus. There were no effects of group (Table 1).

Insula-based network analysis. The secondary analysis measured pre- to post-rTMS changes in RSFC (time effect)

Table 1. Results of the Group (10 vs. 1 Hz) by Time (Pre vs. Post) Analysis of Covariance (Using Time Interval Between Last Repetitive Transcranial Magnetic Stimulation Session and Second Magnetic Resonance Imaging as a Covariate of No Interest) of the Repeated Transcranial Magnetic Stimulation to the Right Postcentral Gyrus Target Site for Resting-State Functional Connectivity

	Left/right	*MNI coordinates*	*Maximum* t-*value*	*No. of voxels*
rTMS target site connectivity				
Positive connectivity across all conditions				
Pre/postcentral gyrus Posterior insula Superior temporal lobes Paracentral lobule Supplementary motor area	Bilateral	64, −8, 24	17.39	12302
Cerebellum	Left	−14, −60, −22	5.12	82
Cerebellum	Right	18, −62, −24	4.71	56
Hippocampus/parahippocampus	Right	24, −14, −24	4.75	215
Hippocampus/parahippocampus	Left	−24, −18, −18	4.10	118
Inferior temporal lobe	Left	−48, 8, −34	4.49	61
Negative connectivity across all conditions				
Supramarginal gyrus Inferior parietal lobe	Right	54, −42, 40	6.18	614
Inferior parietal lobe	Left	−54, −50, 50	5.44	151
Inferior parietal lobe	Left	−32, −46, 46	5.49	112
Precuneus	Right	2, −46, 52	4.56	154
Midcingulate cortex	Right	8, −30, 38	4.72	68
Cerebellum	Left	−32, −70, −30	4.45	61
Caudate nucleus	Right	12, 0, 18	4.28	88
Middle frontal gyrus	Right	38, 42, 20	4.19	113
Inferior frontal gyrus	Right	44, 40, −4	4.16	97
Masked bilateral insula analysis				
Time effect: post > pre rTMS				
Insula	Left	−42, 4, 2	4.56	49
Insula*	Right	44, 14, −8	3.18	14
Insula*	Right	48, 6, 2	2.89	12
Exploratory whole-brain analysis				
Time effect: post > pre rTMS				
Insula	Left	−42, 4, 2	4.56	52
Precuneus	Left	−8, −54, 52	4.48	58
Precuneus	Right	8, −56, 54	4.25	116
Time effect: pre > post rTMS				
Inferior occipital cortex	Left	−30, −80, 0	5.78	170
Inferior occipital cortex	Right	26, −88, −6	4.96	138
Middle temporal lobe	Left	−70, −26, −10	5.44	85
Superior temporal gyrus	Right	68, −8, −8	5.08	77
Cerebellum	Left	−40, −80, −28	5.25	117
Cerebellum	Right	24, −82, −28	4.74	107
Precuneus	Bilateral	−2, −54, 34	4.58	66
Medial superior frontal gyrus	Bilateral	0, 54, 30	4.06	50
Interaction effect: 10 Hz (pre > post) and 1 Hz (post > pre)				
Superior temporal gyrus	Right	60, −16, 6	4.43	60
Insula-based network analysis				
Time effect: pre > post rTMS				
Middle occipital gyrus Inferior occipital gyrus	Right	34, −70, 10	5.20	207
Inferior occipital gyrus	Left	−44, −76, −4	4.62	89
Superior parietal gyrus	Right	14, −54, 70	4.49	100
Cerebellum	Right	32, −58, −24	6.00	81
Group effect: 10 Hz >1 Hz				
Anterior cingulate cortex	Bilateral	0, 50, 12	5.46	168
Interaction effect: 10 Hz (pre > post) and 1 Hz (post > pre)				
Middle temporal gyrus	Right	48, −52, 8	4.47	82

Significance threshold for insula ROI analysis: $p < 0.001$ uncorrected, cluster extent >10 voxels (*trend for significance: $p < 0.005$, cluster extent >10 voxels). Significance threshold for whole-brain analyses: $p < 0.001$ uncorrected, cluster extent >50 voxels. Voxel size = 2 mm^3.
ROI, region of interest; rTMS, repetitive transcranial magnetic stimulation.

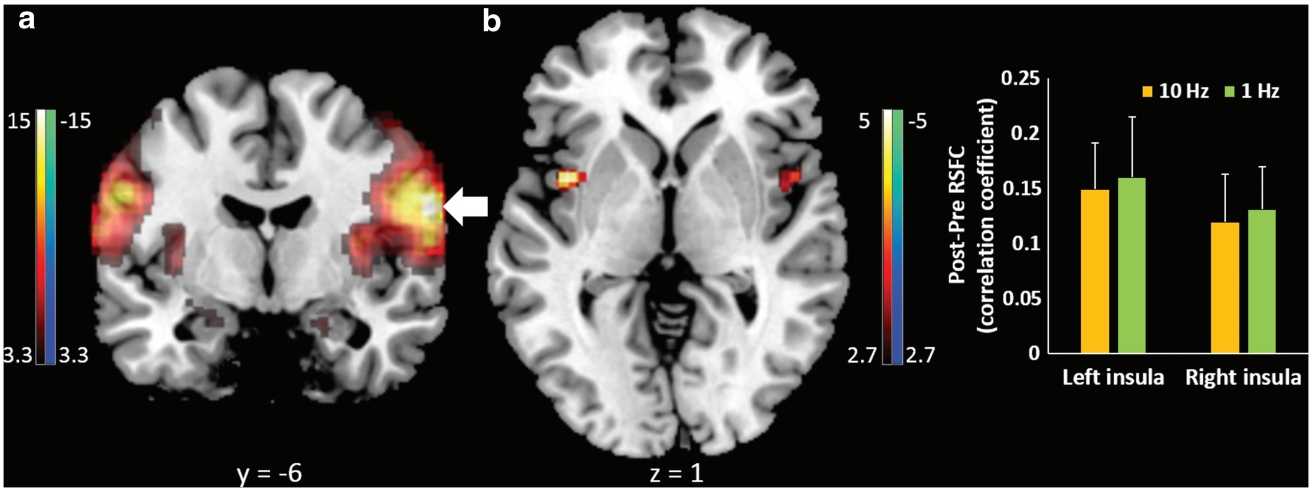

FIG. 1. **(a)** Positive RSFC from the rTMS target site (average location indicated by arrow) to all other voxels in the brain. Results are averaged across time and group conditions. Color bar is *t*-scores from 3.3 to 15. **(b)** Ten and one hertz rTMS to the target site in the right postcentral gyrus increased RSFC to the left insula, with a trend toward increased RSFC in the right insula (neurological convention). Color bar is *t*-scores from 2.7 to 5. Graph represents average RSFC difference values (correlation coefficients) extracted from clusters shown above. Error bars are standard error of the mean. RSFC, resting-state functional connectivity; rTMS, repetitive transcranial magnetic stimulation. Color images are available online.

between the bilateral insula and every other voxel in the brain. RSFC decreased from pre- to post-rTMS with the bilateral inferior occipital gyrus, right parietal gyrus, and right cerebellum. There was a group effect (10 Hz >1 Hz) in the bilateral anterior cingulate, and an interaction effect (10 Hz Pre >10 Hz Post and 1 Hz Post >1 Hz Pre) in the right middle temporal gyrus (Table 1).

Discussion

In summary, four to five daily sessions of 1 or 10 Hz rTMS were administered to the right postcentral gyrus. We found increased pre- to post-rTMS RSFC between the postcentral gyrus and the bilateral insula, as well as increased RSFC with the bilateral precuneus and decreased RSFC with several regions, including the occipital cortex, precuneus, and cerebellum. These results contradicted the hypothesis that low- and high-frequency rTMS would have opposite effects on RSFC. Rather, they produced similar long-term (>1 h post-rTMS) effects on RSFC within the postcentral gyrus network.

Complementary results were found using the rTMS target site and the bilateral insula as seed ROIs in whole-brain analyses. rTMS decreased connectivity between the seed regions and the right and left lateral inferior occipital cortices, as well as the right cerebellum. There were also similar group by time interaction effects in connectivity with the right temporal gyrus. This suggests that the changes in RSFC between the postcentral gyrus and other brain regions could have been due to the modulation of the insula-based network. Modulation of insula connectivity could have therapeutic implications, by affecting the interoceptive sensations represented in the posterior insula and/or the emotional processing of these sensations in the anterior insula. While several other rTMS studies have attempted to stimulate the insula directly (de Andrade et al., 2012; Dinur-Klein et al., 2014), or have reported indirect effects in the insula (Li et al., 2017; Vercammen et al., 2010), this is the first study to show changes in RSFC in an *a priori*-defined insula region. This study has a number of strengths, including a five-session rTMS protocol that may be more relevant to the long-term, therapeutic effects of rTMS compared with one-session protocols (although the inconsistent number of sessions across participants is a weakness), and the selection of an *a priori* ROI known to have structural and functional connections to the rTMS target site. In support of the hypothesis, rTMS to the postcentral gyrus does appear to affect RSFC with the insula; however, it was hypothesized that low-frequency (1 Hz) and high-frequency (10 Hz) rTMS would have opposing effects on RSFC, but there were no group x time interaction effects in RSFC with the insula.

To our knowledge, this is the first multisession investigation of low- and high-frequency rTMS on long-term (≥1 h) RSFC effects. It is possible that both frequencies produce similar long-term modulations on RSFC, since little is known regarding these indirect connectivity effects. However, given the lack of difference, we cannot exclude the possibility that these effects are simply due to scalp stimulation, the effect of time, or another nonspecific effect. The insula is activated by a variety of bodily sensations (Craig, 2009) and the increased RSFC may be related to muscle contractions in the scalp caused by the electromagnetic pulse. The fact that RSFC increased significantly with the contralateral insula supports this interpretation.

The immediate, acute effects of rTMS on cortical excitability are thought to last from 20 min (Valero-Cabre et al., 2007) up to 1 h (Siebner et al., 2003). Since the MRI scan was administered at least 1 h after the last rTMS session, our results are unlikely to represent the acute effects of rTMS on the scalp or in the cortex. However, without an acoustic- and stimulation-matched sham control, the strength of conclusion from these findings is limited.

This preliminary study was designed to determine whether low- or high-frequency rTMS increased RSFC to the insula, which was the desired effect, before conducting a larger study comparing active to sham rTMS among smokers. However, these results are important in their own right because there

have been at least four published studies that have administered low- and high-frequency rTMS with an expectation of changing RSFC rTMS without a sham control (Cocchi et al., 2015; Davis et al., 2017; Eldaief et al., 2011; Watanabe et al., 2014), and only one study mentions this as a potential limitation (Davis et al., 2017). Our results showing no rTMS frequency differences on RSFC also underscore some inconsistencies and gaps in knowledge regarding the relationships between MEPs, BOLD activation, and RSFC that impede the formulation of accurate hypotheses. Sham conditions should always be included in future research to avoid this limitation.

The description of low and high rTMS frequencies as down- or upregulating cortical excitability, respectively, comes from MEP data (Fitzgerald et al., 2006; Pascual-Leone et al., 1994). MEPs are an electromyographic measure of the contralateral muscle contraction induced by single TMS pulses to the primary motor cortex. Long trains (e.g., 10 min) of low rTMS frequency (1 Hz) tend to produce small reductions in MEP size, but there is no consistent evidence of affecting cortical inhibition. The cumulative effect of short trains (e.g., 5 sec) of high rTMS frequency (5–20 Hz) applied over periods of 10 min or more tends to increase MEP size (reviewed in Fitzgerald et al., 2006). Research on the relationship between MEPs and the BOLD signal has been mixed. An early study (Pascual-Leone et al., 1998) reported that 10 Hz rTMS enhanced, and 1 Hz diminished, the task-elicited BOLD response in the primary motor cortex target site. However, later studies have shown that both low-frequency rTMS and high-frequency rTMS increase regional cerebral blood flow (CBF) and BOLD activation at rest (Baudewig et al., 2001; Denslow et al., 2005; Lee et al., 2003; Rounis et al., 2005) and during motor performance (Lee et al., 2003), as well as an absence of effects during motor performance (Rounis et al., 2005). A more recent study reported no consistent effects of 1 Hz rTMS on the BOLD signal in the primary visual cortex target site (Caparelli et al., 2012). These results suggest that the BOLD response to rTMS cannot generally be predicted by MEP data. Since both MEPs and BOLD signals are indirect measures of cortical activation, neither can conclusively demonstrate that low-frequency rTMS and high-frequency rTMS are cortically inhibitory and excitatory, respectively.

Furthermore, there is a significant gap in knowledge regarding how changes in regional BOLD activity affect RSFC strength within a brain network. One study reported that task-related BOLD response in a particular brain region predicted that region's positive RSFC strength with the task-positive functional network (Mennes et al., 2010). Altogether, it may be hypothesized that if high-frequency rTMS increases MEP size and enhances the regional BOLD signal to the target site, then RSFC strength should be strengthened within that brain network. However, a direct comparison of MEP amplitude and changes in RSFC revealed no correlation between the two measures (Nettekoven et al., 2014). Importantly, an evidence-based theoretical model describing the relationships between MEP, BOLD, and RSFC, as well as how these relationships are affected by both immediate rTMS and long-term rTMS, is needed to guide future hypotheses.

Conclusion

In conclusion, our results challenge the expectation that low- and high-frequency rTMS will have opposing effects on RSFC, and a sham control is absolutely necessary to interpret such unexpected results. The lack of a sham control is a limitation that should be avoided in future research. In addition, there is little evidence among the extant literature to support the broad hypothesis that high- versus low-frequency rTMS will selectively increase or decrease the strength of RSFC with a secondary brain region. Finally, these results and others need replication and meta-analyses to systematically address Type I and II errors and allow for a stronger interpretation of this line of research.

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Author Disclosure Statement

The authors report no competing financial interests exist.

References

Addicott MA, Sweitzer MM, Froeliger B, Rose JE, McClernon FJ. 2015. Increased functional connectivity in an insula-based network is associated with improved smoking cessation outcomes. Neuropsychopharmacology 40:2648–2656.

Baudewig J, Siebner HR, Bestmann S, Tergau F, Tings T, Paulus W, Frahm J. 2001. Functional MRI of cortical activations induced by transcranial magnetic stimulation (TMS). Neuroreport 12:3543–3548.

Borckardt JJ, Nahas Z, Koola J, George MS. 2006. Estimating resting motor thresholds in transcranial magnetic stimulation research and practice: a computer simulation evaluation of best methods. J ECT 22:169–175.

Caparelli E, Backus W, Telang F, Wang G, Maloney T, Goldstein R, Henn F. 2012. Is 1 Hz rTMS always inhibitory in healthy individuals? Open Neuroimag J 6:69–74.

Cocchi L, Sale MV, Lord A, Zalesky A, Breakspear M, Mattingley JB. 2015. Dissociable effects of local inhibitory and excitatory theta-burst stimulation on large-scale brain dynamics. J Neurophysiol 113:3375–3385.

Craig AD. 2009. How do you feel—now? The anterior insula and human awareness. Nat Rev Neurosci 10:59–70.

Davis SW, Luber B, Murphy DLK, Lisanby SH, Cabeza R. 2017. Frequency-specific neuromodulation of local and distant connectivity in aging and episodic memory function. Hum Brain Mapp 38:5987–6004.

de Andrade DC, Galhardoni R, Pinto LF, Lancelotti R, Rosi J, Marcolin MA, Teixeira MJ. 2012. Into the Island: a new technique of non-invasive cortical stimulation of the insula. Neurophysiol Clin 42:363–368.

Denslow S, Lomarev M, George MS, Bohning DE. 2005. Cortical and subcortical brain effects of transcranial magnetic stimulation (TMS)-induced movement: an interleaved TMS/functional magnetic resonance imaging study. Biol Psychiatry 57:752–760.

Dinur-Klein L, Dannon P, Hadar A, Rosenberg O, Roth Y, Kotler M, Zangen A. 2014. Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: a prospective, randomized controlled trial. Biol Psychiatry 76:742–749.

Eldaief MC, Halko MA, Buckner RL, Pascual-Leone A. 2011. Transcranial magnetic stimulation modulates the brain's intrinsic activity in a frequency-dependent manner. Proc Natl Acad Sci U S A 108:21229–21234.

Etkin A, Wager TD. 2007. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry 164: 1476–1488.

Fitzgerald PB, Fountain S, Daskalakis ZJ. 2006. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol 117:2584–2596.

Fox MD, Halko MA, Eldaief MC, Pascual-Leone A. 2012. Measuring and manipulating brain connectivity with resting state functional connectivity magnetic resonance imaging (fcMRI) and transcranial magnetic stimulation (TMS). Neuroimage 62:2232–2243.

Garavan H. 2010. Insula and drug cravings. Brain Struct Funct 214:593–601.

Hallett M. 2007. Transcranial magnetic stimulation: a primer. Neuron 55:87–199.

Hoogendam JM, Ramakers GMJ, Di Lazzaro V. 2010. Physiology of repetitive transcranial magnetic stimulation of the human brain. Brain Stimul 3:95–118.

Jakab A, Molnar PP, Bogner P, Beres M, Berenyi EL. 2012. Connectivity-based parcellation reveals interhemispheric differences in the insula. Brain Topogr 25:264–271.

Lee L, Siebner HR, Rowe JB, Rizzo V, Rothwell JC, Frackowiak RSJ, Friston KJ. 2003. Acute remapping within the motor system induced by low-frequency repetitive transcranial magnetic stimulation. J Neurosci 23:5308–5318.

Li XB, Du L, Sahlem GL, Badran BW, Henderson S, George MS. 2017. Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex reduces resting-state insula activity and modulates functional connectivity of the orbitofrontal cortex in cigarette smokers. Drug Alcohol Depend 174:98–105.

Mennes M, Kelly C, Zuo XN, Di Martino A, Biswal BB, Castellanos FX, Milham MP. 2010. Inter-individual differences in resting-state functional connectivity predict task-induced BOLD activity. Neuroimage 50:1690–1701.

Naqvi NH, Bechara A. 2009. The hidden island of addiction: the insula. Trends Neurosci 32:56–67.

Nettekoven C, Volz LJ, Kutscha M, Pool EM, Rehme AK, Eickhoff SB, et al. 2014. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. J Neurosci 34:6849–6859.

Oliviero A, Strens LH, Di Lazzaro V, Tonali PA, Brown P. 2003. Persistent effects of high frequency repetitive TMS on the coupling between motor areas in the human. Exp Brain Res 149:107–113.

Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. 1998. Study and modulation of human cortical excitability with transcranial magnetic stimulation. J Clin Neurophysiol 15:333–343.

Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M. 1994. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 117:847–858.

Rorden C, Brett M. 2000. Stereotaxic display of brain lesions. Behav Neurol 12:191–200.

Rounis E, Lee L, Siebner HR, Rowe JB, Friston KJ, Rothwell JC, Frackowiak RSJ. 2005. Frequency specific changes in regional cerebral blood flow and motor system connectivity following rTMS to the primary motor cortex. Neuroimage 26:164–176.

Rudiak D, Marg E. 1994. Finding the depth of magnetic brain-stimulation—a reevaluation. Electroencephalogr Clin Neurophysiol 93:358–371.

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27:2349–2356.

Siebner HR, Filipovic SR, Rowe JB, Cordivari C, Gerschlager W, Rothwell JC, et al. 2003. Patients with focal arm dystonia have increased sensitivity to slow-frequency repetitive TMS of the dorsal premotor cortex. Brain 126:2710–2725.

Strens LH, Oliviero A, Bloem BR, Gerschlager W, Rothwell JC, Brown P. 2002. The effects of subthreshold 1 Hz repetitive TMS on cortico-cortical and interhemispheric coherence. Clin Neurophysiol 113:1279–1285.

Valero-Cabre A, Payne BR, Pascual-Leone A. 2007. Opposite impact on (14)C-2-deoxyglucose brain metabolism following patterns of high and low frequency repetitive transcranial magnetic stimulation in the posterior parietal cortex. Exp Brain Res 176:603–615.

van den Heuvel MP, Pol HEH. 2010. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 20:519–534.

Vercammen A, Knegtering H, Liemburg EJ, den Boer JA, Aleman A. 2010. Functional connectivity of the temporo-parietal region in schizophrenia: effects of rTMS treatment of auditory hallucinations. J Psychiatr Res 44:725–731.

Wang JX, Rogers LM, Gross EZ, Ryals AJ, Dokucu ME, Brandstatt KL, et al. 2014. Targeted enhancement of cortical-hippocampal brain networks and associative memory. Science 345:1054–1057.

Wang JX, Voss JL. 2015. Long-lasting enhancements of memory and hippocampal-cortical functional connectivity following multiple-day targeted noninvasive stimulation. Hippocampus 25:877–883.

Watanabe T, Hanajima R, Shirota Y, Ohminami S, Tsutsumi R, Terao Y, et al. 2014. Bidirectional effects on interhemispheric resting-state functional connectivity induced by excitatory and inhibitory repetitive transcranial magnetic stimulation. Hum Brain Mapp 35:1896–1905.

Whitfield-Gabrieli S, Nieto-Castanon A. 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2:125–141.

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