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BRIEF COMMUNICATION

Cognitive effects of bilateral high frequency repetitive transcranial magnetic stimulation in early phase psychosis: a pilot study

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Abstract

Cognitive dysfunction is a core facet of schizophrenia that is present early in the course of the illness and contributes to diminished functioning and outcomes. Repetitive transcranial magnetic stimulation (rTMS) is a relatively new neuropsychiatric intervention. Initially used in treatment resistant depression, investigators are now studying rTMS for other psychiatric diseases such as schizophrenia. In this study we examined the effect of high frequency rTMS on cognitive function in a group of individuals with early phase psychosis. Twenty subjects were randomized (1:1) in double-blind fashion to rTMS or sham condition. Over two weeks subjects underwent ten sessions of high frequency, bilateral, sequential rTMS targeting the dorsolateral prefrontal cortex (DLPFC). Prior to beginning and following completion of study treatment, subjects completed a cognitive assessment and magnetic resonance imaging. Subjects receiving rTMS, compared to sham treatment, displayed improvement on a standardized cognitive battery both immediately following the course of study treatment and at follow-up two weeks later. Imaging results revealed that left frontal cortical thickness at baseline was correlated with treatment response. The study treatment was found to be safe and well tolerated. These results suggest that rTMS may hold promise for the treatment of cognitive dysfunction in the early phase of psychosis, and that MRI may provide biomarkers predicting response to the treatment.

Keywords rTMS · Early phase psychosis · Schizophrenia · MRI · Cognition

Background

Cognitive dysfunction is a core facet of schizophrenia (Galderisi et al. 2009) that is present early in the course of the illness and contributes to profound social and vocational impairments and overall poor outcomes (Harvey et al. 2001; Sponheim et al. 2010). Currently available interventions for schizophrenia have not shown consistent efficacy in ameliorating cognitive deficits associated with the illness (Green et al. 2004). Clearly there is a significant need for therapeutic agents that are efficacious for cognitive impairment in schizophrenia, an effect which could result in significantly improved long-term functioning and outcomes (Harvey et al. 2001).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive intervention that applies a repetitively pulsed magnetic field over the scalp to induce an electric field within a discrete area of the brain. This electric field modulates ion flow across the neuronal cellular membrane with resultant changes in neuronal polarization. The end result is altered neuronal activity in the area where the rTMS is applied (Baker and Freeston 1985). Additionally, it has been proposed that effects of rTMS maintained after the treatment period may result from treatment-induced changes in synaptic plasticity, with long-term potentiation or depression of synaptic strength being related to factors such as treatment duration or

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frequency (Hallett 2000; Hoogendam et al. 2010). rTMS has received FDA clearance for the treatment of pharmacoresistant major depression and has also been investigated for the treatment of a number of other neuropsychiatric conditions such as schizophrenia, bipolar disorder, anxiety, Tourette's syndrome, substance dependence, and Alzheimer's disease (Slotema et al. 2010).

Studies investigating the therapeutic potential of rTMS in schizophrenia have demonstrated improvements in both treatment refractory auditory hallucinations (Slotema et al. 2012, 2014) and negative symptoms (Aleman et al. 2018; Shi et al. 2014). However, few studies have examined the effect of rTMS on cognitive dysfunction. In those that have, cognition has not generally been the primary outcome of interest (d'Alfonso et al. 2002; Hoffman et al. 2005; Hoffman et al. 2003; McIntosh et al. 2004; Mogg et al. 2007). One exception is a study which demonstrated that rTMS directed bilaterally over the dorsolateral prefrontal cortex (DLPFC) significantly improved working memory performance (Barr et al. 2013). The DLPFC is an attractive target for rTMS studies in schizophrenia, as previous studies have observed that hypofrontality in this region is related to cognitive deficits associated with this illness (Barch and Ceaser 2012; Minzenberg et al. 2009). Though the result by Barr et al. (2013) was promising, numerous questions persist regarding the efficacy of rTMS for cognitive impairment in schizophrenia. In particular, it is important to note that studies of rTMS in schizophrenia have examined chronic populations where confounds associated with prolonged duration of illness may be present. Individuals with early phase psychosis (EPP) are a desirable population to study because these patients tend to have fewer psychiatric and physical comorbidities and less antipsychotic drug exposure, all of which are factors that may confound investigations of new treatment interventions. Additionally, this is an important population for study because, if effective, rTMS may represent a preventative treatment to mitigate the development of social and vocational impairment that is associated with cognitive dysfunction. Lastly, predictors of rTMS response and a better understanding of the brain mechanisms that mediate efficacy are needed.

The present study aimed to approximate the design by Barr et al. (2013) and examine high-frequency, bilateral rTMS for the treatment of cognitive dysfunction, only this time in an EPP population. Additionally, this study utilized magnetic resonance imaging (MRI) to explore the relationship between brain structure and any observed pro-cognitive effects of rTMS. Our a priori hypotheses were as follows: 1) Two weeks of bilateral high frequency rTMS would result in improved cognitive performance compared to sham stimulation and 2) structural MRI markers that are predictive of pro-cognitive effects of rTMS would be observed.

Methods

Participants

Subjects were recruited through the Indiana University (IU) Psychotic Disorders Program, within the IU School of Medicine. All study procedures were approved by the IU Institutional Review Board, protocol number 1401416429 (initially approved 20 February 2014). After receiving an explanation of study procedures, subjects gave their written informed consent prior to enrollment. Twenty subjects ages 18–35 were enrolled, of whom all were within the first five years of psychotic illness onset and diagnosed with schizophrenia ($n = 17$), schizophreniform disorder ($n = 1$), or schizoaffective disorder, bipolar type ($n = 2$) as determined by the Structured Clinical Interview for DSM-IV (SCID) (First et al. 2002). Onset of illness was defined by the first initiation of treatment, including medications or hospitalization for psychotic symptoms, as determined by patient and/or family report and medical record review. All patients were without clinically significant affective symptoms for at least one month prior to enrollment in the study. All participants were in outpatient treatment and were taking the following antipsychotic medications: paliperidone palmitate ($n = 9$), paliperidone ($n = 1$), risperidone (n = 1), olanzapine pamoate (n = 2), olanzapine (n = 2), aripiprazole (n = 2), asenapine (n = 1), and haloperidol decanoate (n = 1). Four patients were on antidepressant medications (desvenlafexine, fluoxetine, sertraline, and paroxetine). Two patients were on mood stabilizing medications (divalproex sodium and lithium carbonate). In total there were seven subjects, 4 in the rTMS group and 3 in the sham group, on multiple psychotropic medications. None were on more than one antipsychotic medication during the course of the study. Medications were stable for four weeks prior to study enrollment and adjustments were not allowed for the duration of study participation. All patients were determined to be clinically stable via Clinical Global Impression-Severity (CGI-S) (Guy 1976) score of 4 or less. To be included in the study, subjects were required to have a Brief Assessment of Cognition (BACS) (Keefe et al. 2004, 2008) t-score of 40 or less at baseline assessment. This score was chosen as it was within one standard deviation (SD) of the mean observed in studies by Keefe and colleagues and was felt to provide evidence of sufficient pre-existing cognitive dysfunction, leaving room for potential response to study treatment (Keefe et al. 2004, 2008).

At baseline, demographic information and medical history were reviewed. Subjects with any of the following were excluded from the study: Life-time history of seizures, first-degree relative with a history of idiopathic epilepsy or other seizure disorder, history of electroconvulsive therapy, any contraindication to MRI procedures, history of significant neurologic illness including loss of consciousness or post-

concussive syndrome, pregnant or breast feeding, a known IQ of less than 70 by subject report and medical history review, or a current DSM-IV-TR diagnosis of alcohol or drug dependence (excluding nicotine or caffeine). Chlorpromazine equivalent for each subject was calculated as detailed elsewhere (Gardner et al. 2010). Subjects were discontinued from the study if they missed greater than 2 consecutive or 3 total days of study treatment.

Procedures

rTMS set up and administration

After enrollment, subjects were randomly assigned (1:1) to active or sham rTMS condition. Bilateral, sequential DLPFC stimulation (i.e., right then left or left then right) ordering was randomized and counterbalanced (1:1), performed by a university research staff member who was not involved with the study. Subjects received 10 treatments of rTMS or sham over the course of two weeks.

The study treatment was administered by a trained physician (MMF) using a Neuronetics Neurostar Treatment Device (Neuronetics Inc., Malvern, Pennsylvania). Double-blinded treatment was delivered via the Neurostar XPLOR™ system. NeuroStar XPLOR™ adds clinical research capability to a standard clinical NeuroStar TMS Therapy System. The NeuroStar XPLOR™ uses a three-coil system to ensure double blinding. Prior to beginning study treatment, the resting motor threshold (MT) was determined using single pulse stimulation over the left and right motor cortices, assessed as the lowest intensity producing five visible movements of the abductor pollicis brevis muscle (thumb) out of ten stimulations. A known active coil was used for MT determination. The stimulation sites were the left and right DLPFCs, defined as 5 cm anterior to the scalp positions at which the MTs were determined. This location was chosen due to its consistency with practices of prior studies demonstrating potential effects of rTMS on cognition in schizophrenia (Mogg et al. 2007; Rollnik et al. 2000; Schneider et al. 2008; Wolwer et al. 2014). The coordinate was derived by the NeuroStar system. The MT was determined separately for both the left and right hemispheres. MT location and active treatment were delivered with a modified figure-of-eight coil. Treatments were delivered within the following stimulation parameters: 110% of MT, 20 Hz, 30 trains, 1.0 s per train, 20 pulses per train, inter-train interval of 30 s (600 pulses/hemisphere, for a total of 1200 pulses/session/day). The stimulation protocol was within safety limits for rTMS (Chen et al. 1997; Rossi et al. 2009; Wassermann 1998). Bilateral stimulation was chosen to approximate the study design by Barr and colleagues which had shown an effect of rTMS on working memory in a group of subjects with chronic schizophrenia (Barr et al. 2013). The sham coil is identical in appearance to the active coil and is acoustically blinded, meaning both active and sham administration sound identical. The sham coil did not, however, produce tactile sensation. All subjects were instructed to wear earplugs during each rTMS session and were monitored by medically trained research staff throughout the entirety of each rTMS session. All efficacy outcome measures were assessed by blinded study personnel (raters) who were not permitted access to the treatment sessions.

Assessment of cognition

Subjects were administered the BACS by raters who were extensively trained. The BACS was selected because of its reliability and established validity in a schizophrenia population (Keefe et al. 2004, 2008). The BACS was administered prior to randomization, at treatment endpoint, and at a follow-up session two weeks after the completion of study treatment.

MRI acquisition and processing

Prior to randomization and at treatment endpoint, subjects underwent a magnetic resonance imaging (MRI) scan on a 3 T Skyra scanner (Siemens, Erlangen, Germany) with a 32-channel phased array head coil. Brain structure was characterized with a high-resolution T1-weighted whole-brain magnetization prepared rapid gradient echo (MPRAGE) scan with the following parameters: 160 3D sagittal slices, echo time/repeat time/inversion time = 2.91/2300/900 ms; slice resolution = 100%; Echo spacing = 7.7 ms, flip angle = 9°, field of view = 240 × 256 mm, voxel size = 1x1x1.2 mm.

Structural images were processed with the standard Freesurfer pipeline (version 6.0; http://surfer.nmr.mgh.harvard.edu) to measure cortical thickness in each subject. With this pipeline, brains are affine-registered to a standard MNI template. Next, each volume was skull-stripped and segmented into white matter and non-white matter based on intensity and neighbor constraints. Surface maps were generated for left and right hemispheres, using intensity gradients to separate gray/white matter as well as gray matter/cerebrospinal fluid. Cortical thickness at each vertex is defined as the distance between white matter and pial surfaces. The cortex was automatically parcellated into 128 distinct brain regions (Destrieux et al. 2010). Mean cortical thickness was extracted from rostral and cortical middle frontal cortex regions on each side of the brain.

Data analysis

Behavioral analysis

Summary statistics are reported for demographic, symptom, and cognitive variables at baseline. We also examined the differences in those variables between rTMS and Sham

groups by using Fisher's exact test for categorical variables and independent two-sample *t*-test for continuous variables (Table 1). First, the normality of the data was examined and found to be a valid assumption based upon the QQ plot of the residual. Then, we performed the linear mixed model (LMM) with random effects to estimate the effect sizes of rTMS in terms of improving cognitive performance as measured by the BACS composite and sub-scale scores. Since no baseline differences between active and sham conditions were detected, we only included time, treatment, and time-by-treatment interaction as covariates in the model. Based on the model, we estimated the within-group effect which was the change score from baseline to treatment end-point and two-week follow-up within each group as well as the between-group effect which was the difference in change scores between two groups. All comparisons were two-tailed. *P*-values less than 0.05 were reported as significant. We presented the mean and SD from raw data for both groups at each visit, and also illustrated the least square means, standard errors, *p*-values for within-group and between-group effects, and Cohen's d effect sizes in Table 2. As this was a pilot study we did not adjust for multiple comparisons.

MRI analysis

Cortical thickness measures were examined with repeated-measures 2 × 2 group-by-visit ANOVA tests. In addition, exploratory correlation tests within the rTMS group examined for potential relationships between cortical thickness and treatment response at endpoint and follow-up visits.

Results

Participants

Twenty subjects with EPP were enrolled. Tolerability was assessed by subject report before and after each treatment session. One subject in the active treatment arm discontinued participation immediately after delivery of his first post-randomization treatment train. He declined to complete subsequent procedures and therefore his data was not available for analysis. The remaining 19 subjects completed the study. The groups were well matched for age, duration of illness (DOI), gender, race, and socioeconomic status. BACS composite score and subscale scores, Positive and Negative Syndrome Scale (PANSS) scores, and CGI-S did not differ between groups at baseline (Table 1).

Cognitive performance

The rTMS group, compared to sham, demonstrated significant improvement in BACS Composite (LSE = 9.81, $p = 0.018$), Semantic and Letter Fluency (LSE = 10.33, $p = 0.014$), and Symbol Coding scores (LSE = 8.58, $p = 0.039$) compared to baseline at the two-week follow-up, but not at the treatment endpoint visit. These between-group differences were driven both by improved performance in the rTMS group and decrements in performance in the sham group. Additionally, in comparing the rTMS and sham groups, the BACS Verbal Memory scores differed when comparing baseline to both the endpoint and two-week follow-up assessment. These

Table 1 Sample characteristics at baseline (*N* = 19)

Characteristic	Sham (N = 10)	rTMS (N = 9)	*P* value
Age at Baseline (Years)	22.3 (2.0)	23.4 (3.1)	0.350
Gender			
Female	2 (20.0%)	2 (22.2%)	> 0.999
Male	8 (80.0%)	7 (77.8%)	
Race			
African American/African Heritage	8 (80.0%)	8 (88.9%)	> 0.999
White-Caucasian/European Heritage	2 (20.0%)	1 (11.1%)	
Duration of Illness (Years)	2.4 (1.1)	3.1 (1.6)	0.263
Chlorpromazine Equivalents (Grams)	423.3 (283.1)	418.4 (164.3)	0.964
Parental Socioeconomic Level	3.0 (1.6)	2.1 (1.3)	0.195
PANSS Total Negative	14.7 (5.1)	12.4 (4.1)	0.308
PANSS Total Positive	10.0 (3.7)	10.3 (3.0)	0.831
PANSS Total Score	47.4 (8.8)	45.1 (8.5)	0.573
BACS Verbal Memory	41.4 (6.7)	36.7 (10.2)	0.242
BACS Digit Sequencing	30.2 (9.0)	34.1 (12.8)	0.448
BACS Token Motor Total	25.9 (8.4)	29.0 (17.0)	0.630
BACS Semantic and Letter Fluency	40.5 (6.0)	38.7 (11.3)	0.659
BACS Symbol Coding	40.6 (6.4)	38.1 (8.9)	0.489
BACS Tower of London	42.1 (22.8)	45.3 (10.7)	0.695
BACS Composite Score	27.5 (7.9)	27.6 (11.6)	0.990
CGI-S	3.2 (0.6)	2.9 (0.8)	0.351

PANSS, the positive and negative syndrome scale; *BACS*, brief assessment of cognition in schizophrenia; *CGI – S*, clinical global impressions severity scale

Table 2 Behavior outcome

Behavior Outcome	Within-Group Effect						Between-Group Effect		
	Sham (N = 10)			rTMS (N = 9)			Difference in Change Score		Effect Size
	Raw Score	Change Score Relative to Baseline		Raw Score	Change Score Relative to Baseline				
	Mean (SD)	LSE (SE)	P Value	Mean (SD)	LSE (SE)	P Value	LSE (SE)	P Value	Cohen's d, 95%
BACS Verbal Memory									
Baseline	41.40 (6.65)			36.67 (10.17)					
Endpoint	33.40 (11.91)	−8.00 (2.40)	0.002*	37.11 (12.59)	0.44 (2.53)	0.861	8.44 (3.48)	0.021*	1.17 [−0.25, 1.72]
Two-week follow-up	35.10 (12.05)	−6.30 (2.40)	0.013*	37.44 (13.26)	0.78 (2.53)	0.760	7.08 (3.48)	0.050*	0.86 [−0.14, 1.86]
BACS Digit Sequencing									
Baseline	30.20 (9.04)			34.11 (12.76)					
Endpoint	33.40 (10.73)	3.20 (2.55)	0.219	36.56 (11.30)	2.44 (2.69)	0.370	−0.76 (3.71)	0.840	−0.09 [−1.04, 0.86]
Two-week follow-up	31.60 (12.56)	1.40 (2.55)	0.587	35.22 (8.66)	1.11 (2.69)	0.682	−0.29 (3.71)	0.938	−0.03 [−0.98, 0.93]
BACS Token Motor Total									
Baseline	25.90 (8.36)			29.00 (17.04)					
Endpoint	33.50 (13.40)	7.60 (4.74)	0.059	29.78 (20.99)	0.78 (4.99)	0.877	−6.82 (6.88)	0.329	−0.33 [−1.29, 0.63]
Two-week follow-up	29.70 (12.72)	3.80 (4.74)	0.214	40.00 (16.01)	11.00 (4.99)	0.035*	7.20 (6.88)	0.303	0.42 [−0.54, 1.38]
BACS Semantic and Letter Fluency									
Baseline	40.50 (6.02)			38.67 (11.27)					
Endpoint	36.50 (11.35)	−4.00 (2.75)	0.155	40.56 (13.29)	1.89 (2.90)	0.520	5.89 (4.00)	0.150	0.52 [−0.45, 1.49]
Two-week follow-up	33.50 (10.94)	−7.00 (2.75)	0.016*	42.00 (11.88)	3.33 (2.90)	0.259	10.33 (4.00)	0.014*	0.99 [−0.02, 2.00]
BACS Symbol Coding									
Baseline	40.60 (6.40)			38.11 (8.88)					
Endpoint	37.80 (8.27)	−2.80 (2.74)	0.315	39.22 (9.96)	1.11 (2.89)	0.703	3.91 (3.99)	0.333	0.51 [−0.46, 1.47]
Two-week follow-up	36.80 (12.63)	−3.80 (2.74)	0.175	42.89 (10.25)	4.78 (2.89)	0.108	8.58 (3.99)	0.039*	1.08 [0.06, 2.10]
BACS Tower of London									
Baseline	42.10 (22.85)			45.33 (10.68)					
Endpoint	44.50 (22.71)	2.40 (4.87)	0.625	46.67 (9.79)	1.33 (5.13)	0.797	−1.07 (7.07)	0.881	−0.06 [−1.01, 0.89]
Two-week follow-up	41.20 (10.83)	−0.90 (4.87)	0.854	45.78 (6.38)	0.44 (5.13)	0.932	1.34 (7.07)	0.850	0.11 [−0.84, 1.07]
BACS Composite Score									
Baseline	27.50 (7.91)			27.56 (11.56)					
Endpoint	27.00 (12.33)	−0.50 (2.72)	0.855	29.78 (11.41)	2.22 (2.86)	0.443	2.72 (3.95)	0.495	0.31 [−0.65, 1.27]
Two-week follow-up	23.80 (11.25)	−3.70 (2.72)	0.182	33.67 (12.05)	6.11 (2.86)	0.040*	9.81 (3.95)	0.018*	1.15 [0.12, 2.18]

For within-group comparisons, scores at V13 and V14 were compared to baseline. For between-group comparisons, differences in change scores at Endpoint and Two-week follow-up were compared between two groups. Increased score is indicative of improved cognitive performance

PANSS, the positive and negative syndrome scale; *BACS*, brief assessment of cognition in schizophrenia; *SD*, standard deviation; *LSE*, least square means which was estimated based on model; *SE*, standard error. Increased score is indicative of improved task performance

differences seem to be driven primarily by declines in sham group performance rather than improvement in rTMS group performance (LSE = 8.44, $p = 0.02$ and LSE – 7.08, $p = 0.05$, respectively). Effect sizes for these results are included in Table 2.

In terms of within subject effects, the rTMS group demonstrated significant improvements on BACS Composite and BACS Token Motor scores (LSE = 6.11, $p = 0.04$ and LSE = 0.78, $p = 0.035$, respectively) at the two-week follow-up visit compared to baseline. There were no improvements in task performance at any of the endpoint visits in the rTMS group. Cognition did not improve on any measure in the sham group, but rather a statistically significant worsening of performance on BACS Verbal Memory and Semantic and Letter Fluency tasks was observed (Table 2). There were no observed effects of administration order (i.e. right then left or left then right) on cognitive or symptom measures.

Magnetic resonance imaging results

Cortical thickness

There were no significant changes in thickness of rostral or caudal middle frontal cortices when comparing Baseline vs. Post-treatment scans in either hemisphere (group-by-visit interaction: all $F(1,17) > 1.69$; $p > .21$). At two-week follow-up, the change in BACS composite score from baseline was significantly predicted by baseline left caudal middle frontal cortex thickness at baseline ($r(9) = .74$; $p = .022$) (Fig. 1). In other words, thicker left prefrontal cortex predicted a greater improvement in overall cognitive function at the follow-up two weeks after the end of rTMS administration. BACS performance at treatment endpoint was not predicted by thickness. Mean rostral middle cortical thickness had similar relationships on the left and right but failed to reach statistical significance ($p > .27$). There was no association between

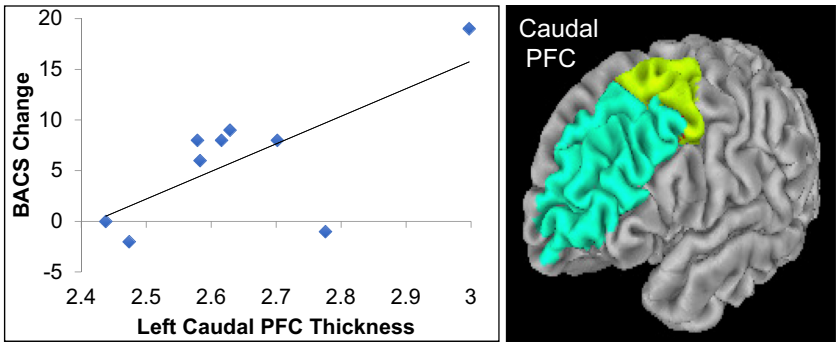

Fig. 1 Association of Baseline PFC Thickness with BACS Composite Change at Two-Week Follow-Up Visit. Left caudal middle frontal cortex thickness at baseline positively predicted treatment response at two week follow-up ($r(9) = 0.7$; $p = 0.022$)

antipsychotic medication exposure and cortical thickness in either group at baseline or endpoint scan.

Safety and tolerability

Study treatment was well tolerated by subjects, with the exception of one individual who elected to discontinue study participation immediately after receiving his first treatment train due to application site discomfort. His data was not used in the study analysis. Adverse events in the active group consisted of earache ($n = 1$), headache ($n = 2$), and application site discomfort ($n = 2$). Adverse events in the sham group included headache ($n = 3$), gum sensation ($n = 1$), and muscle twitching ($n = 1$).

Discussion

This pilot study examined the effects of high frequency rTMS on cognition in an EPP population and attempted to identify, via MRI, structural predictors of rTMS response. The results provide preliminary evidence that ten sessions of bilateral 20-Hz rTMS targeting the DLPFC, compared to sham stimulation, may be associated with improved cognitive performance, as demonstrated by a change in BACS composite score. Improvement in BACS sub-scales including Symbol Coding, Semantic and Letter Fluency, and Token Motor Task was also demonstrated, though these results were driven in part by worsening cognitive performance in the sham arm over the course of the study. Interestingly, some of the cognitive findings were not immediately apparent after ten sessions of treatment, but rather were observed at the follow-up visit two weeks after the final rTMS administration. Additionally, it is important to note that subjects in the sham arm displayed worsening cognitive function over the course of the study. This could indicate that rTMS may improve some cognitive domains as well as preserve cognitive function where it might have otherwise been lost, thus explaining our observation. These findings may have been influenced by post-stimulation mechanisms related to altered neural plasticity (Siebner and Rothwell 2003). Research has suggested that rTMS after effects, possibly mediated by long-term potentiation (LTP) like mechanisms (Ziemann et al. 2008) or metaplasticity (Hulme et al. 2013), may influence the plasticity state of neuronal networks post-treatment (Ziemann and Siebner 2008). Thus, it is possible that alterations in synaptic plasticity were occurring in the period between the end of treatment and study follow-up visit which contributed to the continued improvements in cognition in the rTMS group. This is supported by the fact that most BACS domains and the Composite Score showed progressive improvement from baseline. However, larger studies would be needed in order to investigate this idea further. While there were no changes in cortical thickness in association with rTMS, baseline left prefrontal cortical thickness did predict a greater cognitive response to rTMS at the two-week post-treatment visit. Finally, rTMS was found to be safe and generally well tolerated in this patient population.

Previous studies in healthy individuals have demonstrated that rTMS administration may result in positive cognitive effects. One group demonstrated beneficial effects of right DLPFC low frequency rTMS but detrimental effects of right DLPFC high frequency rTMS on recognition memory, while observing no changes with either left sided stimulation protocol (Turriziani et al. 2012). A meta-analysis by Hsu and colleagues revealed that rTMS was associated with improved cognition in healthy older adults as well as those with Alzheimer's disease (Hsu et al. 2015). As is the case with many realms of rTMS investigation, differences in study design and population complicate overarching interpretation of results. With regard to investigations of rTMS for the treatment of cognitive dysfunction in an EPP population, to our knowledge the present study is the first to examine this question.

Previous studies have examined the potential role of rTMS in treating schizophrenia, with varying effects. Most investigations have examined rTMS for treatment refractory auditory hallucinations or negative symptoms. Less is known about the impact of rTMS on cognitive dysfunction in schizophrenia, as relatively few studies have examined cognition as a primary focus (Hasan et al. 2016b).

Our results are in-line with some previous studies that have demonstrated an effect of high frequency rTMS on cognitive dysfunction in schizophrenia. A four-week study of individuals with chronic schizophrenia that bilaterally targeted the DLPFC with 20 Hz rTMS at 90% of resting MT demonstrated improved 3-back accuracy for targets in the treatment group when compared to a sham group (Barr et al. 2013). Similarly, another group administered 10 Hz, 110% MT rTMS over the left DLPFC in a group of 32 individuals with chronic schizophrenia. Following ten stimulation sessions over two weeks, the authors observed improved performance on the Wisconsin Card Sorting Test in subjects on active treatment when compared to a sham condition (Mittrach et al. 2010).

Other studies, however, have not shown rTMS-mediated improvement in cognition. Prikryl and colleagues employed three weeks of treatment with 10 Hz rTMS versus sham over the left DLPFC, at 110% of MT, yet failed to show statistically significant improvement in working memory (Prikryl et al. 2012). Likewise, Hasan and colleagues examined three weeks of unilateral (DLPFC) 10 Hz rTMS in 156 subjects with predominant negative symptoms and failed to show a significant difference in cognitive function (Hasan et al. 2016a, b). Discrepant findings of the effectiveness of rTMS to improve cognitive deficits in schizophrenia may be the result of inconsistencies in treatment parameters, including coil design, frequency, intensity, and study population. Thus, direct comparison to the present study is difficult.

With regard to rTMS treatment parameters, in this study a stimulation frequency of 20 Hz was selected because evidence to date suggests it may promote improved cognition in schizophrenia populations (Barr et al. 2013; Levkovitz et al. 2011). In addition to trials that examined cognition directly, there is a subset of studies using 20 Hz stimulation that looked at cognition as a secondary outcome and have shown promising results. A small, open-label study utilized 20 Hz stimulation with targeting guided by electroencephalography and demonstrated an improvement on the visual memory reproduction subtest of the Weschsler memory scale (Cohen et al. 1999). Rollnik and colleagues utilized a double-blind, cross-over design focusing on the effect of 20 Hz rTMS on general symptomatology, but also demonstrated a statistically non-significant improvement on a measure of frontal lobe-related cognitive functioning (Rollnik et al. 2000). However, it should be noted that another study using 20 Hz rTMS showed no differences in cognitive function after treatment (Novak et al. 2006). As noted previously, other methodologic differences make comparisons between studies difficult. Potential superiority of 20 Hz rTMS may be due to the differential effects of stimulation frequency on synaptic plasticity. It is thought that higher frequencies may promote greater synaptic long-term potentiation, or synaptic strength, versus lower frequency stimulations (Hallett 2000; Hoogendam et al. 2010). Future studies should endeavor to explore these differences in order to better understand the treatment potential for rTMS and to better define the mechanisms by which rTMS exerts said theraputic effects. Magnetic resonance imaging may be one such way to better understand the biologic mechanism of rTMS.

Few studies to date have examined the effects of rTMS via magnetic resonance imaging. Vercammen and colleagues observed a preliminary relationship between response to rTMS and resting state functional connectivity (Vercammen et al. 2010). Similarly, another study observed increased activation during an in-scanner word generation task in a small group of patients and controls in response to rTMS treatment of auditory hallucinations (Fitzgerald et al. 2007). A recent study used deformation based morphometry to identify bio-markers of negative symptom response to high frequency rTMS, demonstrating that improvements in negative symptoms were associated with volume gains in hippocampal, parahippocampal, and precuneal regions after three weeks of treatment (Hasan et al. 2017). To our knowledge, however, no studies have utilized structural MRI to identify bio-markers of cognitive response to rTMS in schizophrenia. The current results revealed no significant changes in thickness of rostral or caudal middle frontal cortices when comparing baseline vs. post-treatment scans in either hemisphere (all visit x group $p > .21$), though left caudal middle frontal cortex thickness at baseline did positively predict treatment response. The rostral middle cortical thickness had similar relationships on the left and right but failed to reach statistical significance. These findings indicate that structural properties at baseline could be useful in identifying candidates best suited to rTMS treatment.

A number of caveats should be considered when interpreting the findings of this pilot-study. First, the study examined a relatively small sample. However, this was a pilot study and the results were not intended to provide confirmative analysis with full statistical power. Rather, the aim was to explore the potential effect sizes of rTMS on some study outcomes in order to justify the rationale for future clinical trials. In order to account for the small sample size, statistical comparisons were reported for both with-in and between-group differences. While our results suggest that we reached the threshold of significance, the large theoretical sample size used in the linear mixed model (LMM) necessitates caution in interpretation of the effects. Nonetheless, these results were only possible because of the medium to large effect size of rTMS on cognition, providing compelling data for further study. A second notable factor is the short duration of treatment. Although cognitive improvement with rTMS has been demonstrated to occur as early as after four weeks (Barr et al. 2013), the present study demonstrated improvement after two weeks of stimulation. It is possible that a longer treatment duration in the present study could have resulted in greater treatment effects. However, it has been posited that

individuals with EPP, compared to those with chronic schizophrenia, may be more responsive to standard clinical treatments (Szymanski and Woerner 1993). We believed it reasonable to anticipate that individuals with EPP may similarly respond to rTMS more quickly. Subsequent studies should explore the benefits of varying treatment durations in order to further refine our understanding of the therapeutic potential for rTMS in schizophrenia. A potential limitation was defining the DLPFC stimulation site as 5 cm anterior to the site of MT location. Though previous studies have used this approach and demonstrated an effect of rTMS on cognitive measures in schizophrenia (Mogg et al. 2007; Rollnik et al. 2000; Schneider et al. 2008; Wolwer et al. 2014), an investigation by Fitzgerald and colleagues demonstrated that this approach may result in stimulation of a site that is in actuality posterior to the DLPFC as identified by more precise neuronavigational procedures. The authors aptly point out that studies using the 5 cm rule may be inconsistently stimulating the DLPFC, which could explain the moderate success of many rTMS studies (Fitzgerald et al. 2009). It is conceivable that more robust results in the present study may have been realized had a more reliable neuronavigational approach to DLPFC identification be used, and this would be important for future investigations. Other considerations include the potential impact of antipsychotic medication exposure and of duration of illness. Though this study attempted to mitigate these confounds by including only EPP subjects, none were antipsychotic naïve and none were within their first episode of psychosis. Though there is no clear consensus on what constitutes the early phase of a psychotic illness, we believe it appropriate to consider the subjects in the current study as such. However, it is possible that prodromal or unreported illness pathology could have occurred prior to engaging in treatment, which could underestimate the duration of illness. Future research examining rTMS in first episode antipsychotic naïve populations, would serve to more clearly define the physiologic and symptomatic response of psychosis to rTMS treatment.

In summary, we demonstrated that 20 Hz, bilateral rTMS may improve cognitive dysfunction early in the course of a psychotic illness. Additionally, we observed that frontal cortical thickness may positively predict response to this treatment. Although additional, well powered studies are needed to replicate these findings, these results raise the possibility of not only altering the course of cognitive deficits early in the illness, but also of being able to add to our understanding of the biologic mechanisms by which rTMS produces these effects. In light of the paucity of treatment options for cognitive dysfunction and the significant impact that cognitive dysfunction has on overall functioning and outcomes in schizophrenia, this may represent an important treatment option in early-psychosis intervention.

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Author contributions Drs. Francis and Hummer conceived and designed the study. Dr. Francis, Dr. Hummer, Nikki Mehdiyoun, Andrew Visco, Matthew Yung, and Teresa Kulig were responsible for data acquisition. Dr. Francis, Dr. Hummer, Ziyi Yang, Dr. Vohs, Matthew Yung, Mehrdad Motamed, Dr. Zhang, and Dr. Breier analyzed and interpreted the data. Dr. Francis, Dr. Hummer, and Nikki Mehdiyoun supervised the study. Dr. Francis, Dr. Hummer, Ziyi Yang, and Dr. Zhang were responsible for drafting the manuscript. All authors contributed to and have approved the final manuscript.

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Compliance with ethical standards

All procedures performed in this study were in accordance with the ethical standards of the Indiana University School of Medicine Institutional Review Board, the Indiana University Department of Psychiatry Data Safety Monitoring Board, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all patients for being included in the study.

Conflict of interest Dr. Francis received a Neuronetics Investigator Initiated Program award which supplied research materials, but not financial support, for this study. Dr. Liffick was an employee at Indiana University at the time the research was completed. She is currently employed at Eli Lilly and Company. She is also a minor shareholder in the company. All other authors declare that they have no conflicts of interest.

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