

Cortical physiology as a therapeutic target in Parkinson's disease related dementia and cognitive dysfunction: study protocol for a randomized controlled trial

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Abstract

Background: Dementia is the leading cause of nursing home placement in Parkinson's disease (PD), yet little is known about the causes of cognitive dysfunction in PD and there are no effective treatments. Our preliminary data and other published studies suggest that abnormalities in brain activity involving networks important for normal thinking and memory may contribute to cognitive dysfunction in PD and may represent a target for treatment.

Methods/Design: A randomized control trial will be conducted to assess the therapeutic potential of bifrontal repetitive transcranial magnetic stimulation (rTMS) in modulating cortical activity related to cognitive dysfunction in PD. This study will be performed at the University of Colorado Denver, Anschutz Campus, in Aurora, Colorado. Fifty-five PD patients (> 40 years of age) with mild cognitive impairment or mild dementia will be included and randomized in a 1:1 ratio to sham or real rTMS groups. Primary outcome measurement is the total score of the Mattis Dementia Rating Scale. Secondary outcome measurements are domain specific ratings of executive function, memory, language, attention, and visuospatial abilities.

Discussion: If bifrontal rTMS results in positive changes to cognitive function in PD patients with mild cognitive impairment, this may represent a new and effective treatment for PD-related cognitive dysfunction. Secondly, evaluation of any bifrontal rTMS-induced changes to cognitive function will improve the current understanding of the mechanisms behind the causes of cognitive dysfunction in PD.

Trial registration: ClinicalTrials.gov identifier: NCT02346708; registered on 9 January 2015.

Ethics: This study protocol was approved by the Colorado Multiple Institutional Review Board (COMIRB) (approval No. 13-2474) and will be performed in accordance with the *Declaration of Helsinki*.

Informed consent: Signed informed consent will be obtained from the patients or their guardians.

Key words: clinical trials; Parkinson's disease; repetitive transcranial magnetic stimulation; cognition dysfunction; cortical physiology; dementia; mild cognitive impairment; neurodegenerative diseases; movement disorders; cognitive disorders; mental disorders; randomized controlled trials

Funding: This study was supported by grants from NIH/NINDS, No. 1K02NS080885-01A1 (to BMK).

doi: 10.4103/2468-5658.191351

How to cite this article: Buard I, Martin CS, Kluger BM (2016) Cortical physiology as a therapeutic target in Parkinson's disease related dementia and cognitive dysfunction: study protocol for a randomized controlled trial. *Clin Transl Degener Dis* 1(3):91-98.

INTRODUCTION

Parkinson's disease (PD) affects 1–2% of people aged 65 and over, representing over 1 million Americans (Dorsey et al., 2007). Although traditionally characterized by motor symptoms, over the course of PD cognitive symptoms have a greater impact on patient suffering and caregiver burden (Docherty and Burn, 2010). Three-fourths of patients

surviving 20 years or longer develop dementia making it the leading cause of nursing home placement (Hely et al., 2008). Despite the high prevalence of cognitive dysfunction in PD, its pathophysiology is poorly understood and current treatments have minimal effects on symptoms or progression (Emre et al., 2004). Moreover, standard medical and surgical PD treatments have no effect on cognition and may



in fact worsen cognition (Kluger et al., 2011). Better treatment strategies for PD-related cognitive dysfunction based on an improved knowledge of neurobiological mechanisms are clearly needed.

Functional connections between cortical regions are important for normal cognition and memory (Friederici, 2011; He et al., 2012) and alterations in functional cortical connectivity may contribute to cognitive dysfunction in PD (Bosboom et al., 2009). In the past decade, modern network theory has emerged as a powerful tool to describe the organization of functional brain networks using the mathematics of graph theory (Stam and van Straaten, 2012). Two fundamental measures are path length, defined as the average distance between any two nodes in a network and a measure of global efficiency and integration; and the clustering coefficient, defined as the average number of mutually connected nodes surrounding each node and a measure of local efficiency and modularity. An optimal balance between global and local efficiency can be achieved through clustered modules connected through integrating links, a design termed small-world architecture (Wylie et al., 2012). It is well-established that healthy brain networks demonstrate small-world architecture (Rubinov and Sporns, 2010). Importantly, loss of small world features is associated with cognitive dysfunction in multiple sclerosis and Alzheimer's disease (AD) (Sanz-Arigita et al., 2010; de Haan et al., 2012; Hardmeier et al., 2012). Known features of PD neurophysiology relevant to network connectivity include reduced cortical inhibition (Lefaucheur, 2005), which may lead to disrupted modularity, and pathological subcortical oscillations (Pogosyan et al., 2010), which may drive increased randomness. Our pilot data and other studies (Wu et al., 2009) suggest that network architecture is abnormal in PD, but its relationship to cognitive dysfunction has not been examined.

Magnetoencephalography (MEG) measures cortical activity on a millisecond time scale and can provide highly informative data for graph theory analyses (de Haan et al., 2012; Hardmeier et al., 2012). Advantages of MEG *versus* fMRI include high temporal resolution, ability to separate oscillatory spectra and direct measurement of neuronal activity (Robinson et al., 2012). MEG has been used to examine the mechanisms of cognitive therapeutic agents in PD such as acetylcholinesterase inhibitors (de Haan et al., 2008).

Repetitive transcranial magnetic stimulation (rTMS) modulates brain activity using repeated pulses from a magnetic coil over the scalp. rTMS may induce effects through changes in cortical excitability (Daskalakis et al., 2006), neuroplasticity (Chen and Udupa, 2009), gene expression (Aydin-Abidin et al., 2008), neurotrophic factors (Wang et

al., 2011), and neurotransmitters including dopamine (Cho and Strafella, 2009). Recent studies further show that rTMS can modulate focal oscillatory activity (Barr et al., 2009) and network connectivity (Fox et al., 2012; Shafi et al., 2014). Our preliminary data suggest that rTMS similarly affects network connectivity in PD. The therapeutic potential of rTMS is established in certain neuropsychiatric illnesses, including Food and Drug Administration (FDA) approval for depression (Connolly et al., 2012). rTMS can also improve cognitive function in healthy older adults (Kim et al., 2012), Alzheimer's disease (AD) (Rabey et al., 2013), and PD (Boggio et al., 2005; Srovnalova et al., 2011). Limitations of prior PD studies include not specifically enrolling subjects with cognitive impairment, not controlling for depression, not assessing the durability of benefits and not tying rTMS effects to mechanisms. In this study we address these limitations in a clinical and mechanistic trial of rTMS in PD patients with mild cognitive impairment (MCI).

Objectives

rTMS can improve cognition in PD without dementia (Srovnalova et al., 2011), PD with depression (Boggio et al., 2005), older adults (Sole-Padullés et al., 2006) and in AD (Cotelli et al., 2008) but has not been tested in PD-MCI. Given the need for improved cognitive treatments and possible differences in rTMS effects on PD-MCI pathophysiology, it is important to specifically test rTMS in this population. Prior studies as well as our own pilot data suggest that rTMS modulates cortical connectivity (Fox et al., 2012; Shafi et al., 2014); thus rTMS provides not only a potentially effective intervention but an important causal test of the theoretical link between cortical connectivity and cognitive dysfunction in PD. Our clinical objective for this experiment is to determine whether rTMS improves cognitive outcomes in PD-MCI. Our mechanistic objective is to determine whether rTMS normalizes patterns of cortical connectivity using MEG. We hypothesize that high-frequency bifrontal rTMS will partially normalize patterns of cortical connectivity linked to frontal nodes and will improve cognitive measures.

METHODS/DESIGN

Study design

A randomized controlled clinical trial with two parallel arms will be designed. Fifty-five PD-MCI subjects will be randomized to a 10-day course of real or sham bifrontal high frequency rTMS. Subjects will be recorded at rest during the MEG scan. We will measure cognitive and MEG outcomes pre-treatment and on the day of the last treatment and repeat cognitive measures 28 days post rTMS to assess

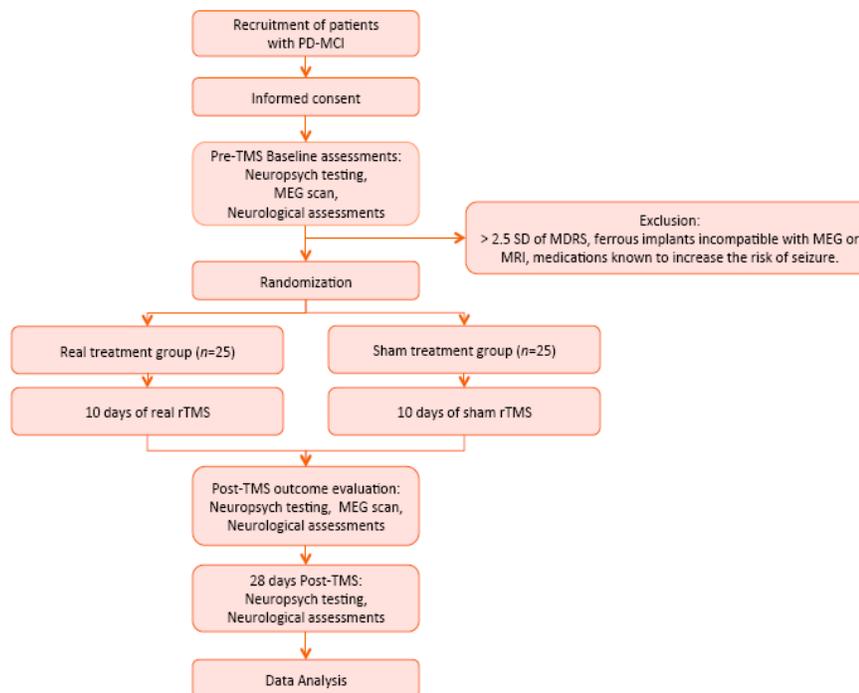


Figure 1: Flow chart of the trial.

PD: Parkinson's disease; MCI: mild cognitive impairment; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation; MDRS: Mattis Dementia Rating Scale; MEG: magnetoencephalography; MRI: magnetic resonance imaging.

the durability of cognitive changes. The flow chart of this trial protocol is shown in **Figure 1**.

Study participants

We will recruit 55 participants over the age of 40 from the Movement Disorders Center at University of Colorado Denver. PD subjects diagnosed with probable PD using UK Brain Bank Criteria (Hughes et al., 1992) and with MCI using the Movement Disorder Task Force 2012 criteria (Litvan et al., 2012) as well as a Clinical Dementia Rating scale score (CDR) less than 2 (Morris, 1993) will be enrolled in the study. All study visits will be performed in subjects' best dopaminergic "On" state. PD MCI and mild dementia subjects will be tested on anticholinesterase therapy, if already taking these medications given the potential difficulty of finding drug naïve subjects; long half-life of these medications; and desire to find measures robust to medication effects as seen in prior MEG studies (de Haan et al., 2008).

Inclusion criteria

- Diagnosis of probable PD according to the UK Brain Bank Criteria
- Age > 40 years
- MCI or mild dementia according to the Movement Dis-

order Task Force 2012 Criteria and a CDR less than 2

Exclusion criteria

- Features suggestive of other neurological disorders
- Deep brain stimulation
- Evidence for active depression or Hospital Anxiety Depression Scale (Zigmond and Snaith, 1983) score > 11
- Motor symptoms expected to interfere with scanning
- Contraindications to TMS:
 - History of seizures or status epilepticus
 - Unstable coronary artery disease
 - Hydrocephalus
 - Implantable electrodes, cerebral spinal fluid shunts, skull plates or other intracranial metal
 - Medical devices including pacemakers or other implantable stimulators or pumps
 - Subjects taking medications known to lower seizure threshold
 - Pregnancy

Withdrawal criteria

- Subjects are allowed to withdraw at any time, for any reason, and will not lose the any benefit or right as a result of withdrawal.

**Table 1: Schedule of events**

	Baseline*	← 2 weeks →		28 days post rTMS
		rTMS sessions 1–9	rTMS session 10	
Informed consent	X			
MRI	X			
Real/sham rTMS		X	X	
Neuropsychological assessments:	X		X	X
- Primary outcome: Mattis Dementia Rating Scale				
- Secondary outcomes: Trail B, Verbal Fluency, Stroop, California Verbal Learning Test, Boston Naming Test, Brief Test of Attention, Judgement of Line Orientation				
Magnetoencephalography (MEG):	X			
Resting state for MEG outcomes				

*Baseline procedures to be completed within 1 week or rTMS session 1.

- Subjects may be withdrawn if the study doctor thinks that being in the study may cause the subject harm or for any other reasons.

Recruitment

Subjects will be recruited from the University of Colorado Hospital (UCH) Movement Disorders and Neurobehavior clinics and Denver Health Medical Center Movement Disorder Clinics which see over 3,000 patients annually, 40% of whom have PD and 10% of whom have PD-MCI (approximately 300 patients per year).

Randomization

After enrollment and screening assessment, PD-MCI subjects will undergo neuropsychological testing, magnetoencephalography (MEG) recordings, and MRI. PD-MCI subjects will then be randomized in a 1:1 ratio into real or sham TMS groups using MAPLE 9.0 software (Waterloo, Canada). Subjects will also be counterbalanced by side of initial stimulation (left vs. right hemisphere).

Interventions

TMS will be administered using a 70-mm diameter air-cooled figure-of-8 Stimulator to the right and left dorsolateral prefrontal cortex (DLPFC; Brodman area 46). TMS will consist of 10 sessions (over two weeks) of 20 Hz repetitive TMS given at 90% resting motor threshold (RMT) for 25 trains of 30 pulses per train, inter-train interval of 30 seconds for a total of 750 pulses per hemisphere, which is well within the most recent international TMS safety guidelines (Rossi et al., 2009).

This dose and duration of rTMS is based on physiological studies of healthy adults (Barr et al., 2009) and treatment studies of cognition in PD (Srovnalova et al., 2011) and AD (Cotelli et al., 2008). RMT will be determining as the

lowest TMS intensity needed to produce a motor-evoked potential of at least 50 μ V in 50% of the trials delivered.

Sham stimulation will be delivered using a sham coil fitted with electrodes to mimic both the auditory and somatic sensation of real TMS (Triggs et al., 2010).

Outcome measures

Outcome measures will be assessed at baseline and post-intervention. Cognitive outcomes will also be assessed 28 days post-intervention (**Table 1**).

Primary outcome measure

Total score of the Mattis Dementia Rating Scale (MDRS) (Mattis, 2002), which measures multiple cognitive domains and is validated in PD (Llebaria et al., 2008).

Secondary outcome measures

- Executive function (Trail B, Verbal Fluency, Stroop) (Delis et al., 2001)
- Memory (California Verbal Learning Test – version II) (Delis, 2000)
- Language (Boston Naming Test) (Kaplan et al., 1983)
- Attention (Brief Test of Attention) (Schretlen, 1997)
- Visuospatial (Judgement of Line Orientation) (Benton et al., 1978)
- Unified Parkinson's Disease Rating motor section (Fahn et al., 1987) used as a covariate in models for disease severity

Other outcome measures

An important secondary question is whether connectivity in specific networks is associated with domain specific deficits. Our primary MEG outcome measure will be network small-worldness, calculated as the ratio of the mean clustering coefficient to the mean path length normalized



to a randomly connected network (Humphries and Gurney, 2008). Secondary MEG outcome measures will include global efficiency (a measure of global integration related to path length), nodal efficiency (a measure of modularity) (Wylie et al., 2012), and degree distribution (a measure of network resilience) (Barabasi and Albert, 1999).

Discomforts or risks

There are minimal risks involved in the proposed research. There are no known risks from MEG recordings. In appropriately screened subjects, the primary risk of MRI is claustrophobia and anxiety which is remediable by removal from the scanner. Cognitive testing as proposed in this study may induce boredom or restlessness. Any new neuropsychiatric diagnoses detected during screening (*e.g.*, depression) will be referred for appropriate treatment, including emergent treatment if indicated. TMS as proposed in this study has a minimal risk (less than 1 in 1,000) of inducing seizures in appropriately screened subjects or other adverse events (Rossi et al., 2009). Notably, there have been no cases of epilepsy (recurrent seizures) or status epilepticus (prolonged seizure considered a medical emergency) with TMS. The risks of TMS in PD are similar to that of the general population (Vonloh et al., 2013). Transient motor worsening has been reported with supplementary motor area TMS in PD, but not with the frontal targets we have proposed. There have been reports of hearing loss with repeated TMS pulses and thus all subjects will be required to wear ear plugs, similar to MRI. There is a slight risk of headache and neck pain, which is typically self-resolving and/or treatable with over the counter analgesics.

All subjects will be required to wear hearing protection and will be supervised by study personnel during all aspects of this study. A neurologist will be available either in person or on-call within the building in the event of a seizure or other adverse study events. Study personnel involved in human subject interactions will be trained not only in human subjects protection but will be also basic life support (BLS) certified and trained in seizure safety and what to do in the event of other medical emergencies. All adverse events will be reported to the IRB within 5 days and seizures or other significant adverse events associated with TMS will additionally be reported to the FDA.

Data collection and processing

MRI data collection

Individual anatomical MRI's will be obtained to localize DLPFC using Brainsight software (Brainsight, Rogue Research Inc., Montreal, Canada) for frameless stereotactic navigation (Paus, 1999). MRI scans will be acquired using a G.E. 3.0 T Signa, whole body magnet with an Excite upgrade and 8-channel head coil using a 3-D, extended dynamic

range, inversion recovery SPGR ASSET parallel imaging sequence with excellent gray/white contrast. The T1-weighted series will consist of 1 mm thick coronal images to be aligned with MEG using SPM8 software (Rojas et al., 2008).

MEG data collection

Magnetic field data will be recorded using a whole head neuromagnetometer (4D Neuroimaging) with an array of 248 sensors at rest with eyes open for 2 minutes and closed for 2 minutes at a 678 Hz sampling rate. Data will be processed offline using a 0.1–100 Hz band pass filter. Data will be manually examined and five 6-second artifact free epochs for both eye-open and closed conditions will be selected for further analyses. Artifact correction if needed will be performed using independent components analysis (Jung et al., 2000). Sensors will be realigned to a common sensor array to allow group level analysis in a shared brain space (Ross et al., 2011)

MEG data processing

Individual anatomical MRI images will be acquired and co-registered with MEG source results for location accuracy using BESA MRI software (BESA MRI 2.0; MEGIS Software GmbH, Germany). Following data acquisition, there are four major steps for graph theory analysis (de Haan et al., 2012). First, data will be transformed into the frequency domain using Morlet wavelets and parceled into six standard frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), low beta (12–20 Hz), high beta (20–30 Hz) and gamma (30–60 Hz) (Teale et al., 2008). Further analyses will be performed separately for each band. Second, the strength of functional connectivity must be calculated among all sensors. Granger causality will be used for this step, providing a directional weighted measure of connectivity suitable for graph theory (Pollonini et al., 2010; Ding et al., 2011). Third, functional connections between nodes will be used to create a network graph. This is matrix representing the directed weighted connection strengths between all sensors for each frequency band. Advantages of creating a weighted network graph include ensuring full connectedness and avoiding potentially arbitrary thresholds required for binary networks (Rubinov and Sporns, 2010). Finally, graph analyses can be performed on the network graph using the Matlab-based Brain Connectivity Toolbox (Rubinov and Sporns, 2010) and custom Matlab code.

Sample size calculation and statistical analysis

We will address our primary clinical research question by determining whether there is a significant group difference between the real and sham treated PD-MCI patients on the MDRS change following rTMS using repeated measures ANOVA. We will address our primary physiologic research



question by determining whether there is a significant difference between the real and sham treated PD-MCI patients on change in MEG measures of small-worldness using repeated measures ANOVA. Secondary analyses will include determining group differences in change on measures of quality of life, domain specific neuropsychological results and durability at the 28-day post-TMS. If cognition is improved we will use regression modeling to determine if these improvements were associated in changes in small-worldness or other MEG features.

With a total sample size of 50 (25 per group allowing for 5 drop-outs from original 55) we will be able to determine a between group difference of 10 points on the MDRS (assuming a standard deviation of 13 as per prior trials and an effect size 0.77) (Dujardin et al., 2006) with 80% power and 0.05 significance. This sample size is comparable to prior Parkinson's disease dementia studies. For example, a study of rivastigmine in Parkinson's disease dementia detected significant change on the MDRS with only 28 subjects (Dujardin et al., 2006).

Ethical considerations

The study protocol has been approved by the Colorado Multiple Institutional Review Board (approval No. 13-2474) and will be performed in accordance with the *Declaration of Helsinki*. PD-MCI patients may be considered a vulnerable population due to cognitive dysfunction but are necessary to answering our research questions. We are cognizant of this issue and will carefully assess potential participant's understanding of the study, particularly of study activities and risks. If there are any concerns on the part of the investigator or potential participant, we will require that their guardian participate in the consenting process and sign an informed consent. We will also require that PD-MCI subjects give consent, or at minimum assent if fully informed consent is not possible. Our protocol and consent forms will be approved by our local institutional review board (IRB) before approaching any potential subjects.

DISCUSSION

PD is the second most common neurodegenerative disease, affecting over one million Americans and dementia is the most common cause of nursing home placement in this population (Dorsey et al., 2007; Hely et al., 2008). Our understanding of the neurobiological mechanisms of cognitive dysfunction in PD is limited and we do not have efficacious treatments. This research aims to evaluate the potential for TMS to induce durable changes in PD cognitive function and connectivity. Given the burden of dementia in this population, we feel that the minimal risks involved are justified both to individual PD and PD-MCI subjects,

the larger population of PD and PD-MCI patients, and to society as a whole. Recent TMS studies using published safety guidelines suggest that the risks of TMS may be even lower than previously described. Even using conservative estimates and anticipating some discomfort from prolonged sitting and cognitive testing, we argue that this research is imperative to advance this field and ultimately to provide relief to these patients and their caregivers. This research will address this significant public health issue in three major ways: 1) Identify abnormalities in cortical connectivity associated with cognitive dysfunction in PD; 2) Develop a MEG biomarker for cognitive dysfunction in PD; and 3) Evaluate the potential for TMS to induce durable changes in PD cognitive function and connectivity.

Prior TMS trials are often questioned regarding the adequacy of patient blinding with certain sham procedures. Our sham involves both auditory and tactile stimulation, and in fact resulted in a similar improvement in depression as real TMS in our recent trial (Triggs et al., 2010). Subject retention, particularly with PD-MCI, may be difficult with 2 weeks of daily treatment. We will use similar procedures to our PD apathy rTMS trial where we maintained 100% retention. Finally, our sample size is relatively small to detect clinically significant changes. This is in part due to budgetary limitations and one goal of this trial is to serve to develop a more definitive, larger trial with longer-term follow-up. Changes in sensor location over repeated recordings may result in false attribution of brain activity changes. To address this issue, sensors will be realigned to a common sensor array to allow repeated group level analysis in a shared brain space (Ross et al., 2011).

Trial status

At the time of the submission of this manuscript, approximately 90% of the patients had been recruited.

Conflicts of interest

None declared.

Author contributions

BMK wrote the funding proposal for this study. IB and CSM coordinated the recruitment of participants and data collection during the study. IB and BMK supervised the progress of the study. IB and CSM contributed in the manuscript preparation. All authors approved the final version of the paper.

Plagiarism check

This paper was screened twice using CrossCheck to verify originality before publication.

Peer review

This paper was double-blinded and stringently reviewed by international expert reviewers.



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