Cholinergic Functions and Modulation of the Cingulo-opercular Alertness Network in LBD

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SPECIFIC AIMS

Fluctuating cognition is a characteristic core diagnostic feature of dementia with Lewy bodies (DLB) and is also a key clinical feature of Parkinson's disease with dementia (PDD) (1, 2). Cognitive fluctuations are a major source of disability in these Alzheimer-related Lewy body dementias (LBD) (4). The **central premise** of this R21 proposal is that cholinergic system changes in specific neural network regions underlie cognitive fluctuations in patients with LBD. Several independent lines of evidence implicate the cholinergic system in LBD. *First*, *ex vivo* post-mortem and *in vivo* acetylcholinesterase brain PET imaging studies have shown prominent cholinergic losses in LBD (5). In novel preliminary data using a vesicular acetylcholine transporter (VAChT) PET ligand, we extend these findings to show regionally distinct and prominent reductions in bilateral opercula and anterior-to-mid cingulate cortices, bilateral insula, and other areas that are part of the cingulo-opercular task control (COTC) network (14) in patients with DLB. **Therefore, the specific topography of cholinergic reductions in these DLB patients suggests preferential cholinergic involvement of the COTC** network**.** The COTC neural network is believed to play a role in maintenance of alertness (15, 16) but this remains uncertain in LDB. This **critical knowledge gap** forms the basis of **our first aim.** We postulate that cholinergic losses in key COTC neural network hubs may underlie cognitive fluctuations in LBD. *Second*, there is clinical evidence that cognitive fluctuations in LBD are amenable to treatment with cholinesterase inhibitor drugs (19). However, the efficacy of current generation cholinesterase inhibitor drugs is typically limited due to poor brain penetrance (22). Novel approaches are needed to address this clinical unmet need. We propose to use transcranial direct current stimulation (tDCS) to "excite" critical cholinergic denervation components of the COTC as an adjunct to cholinergic pharmacotherapy in a target engagement study. tDCS is an emerging non-invasive neurostimulation technology that may improve a range of neurological symptoms, including cognition. There is also evidence that tDCS may modulate cholinergic activity modulation (25). Several small studies have employed tDCS in patients with LBD and revealed encouraging improvements in attention (26), though none have examined cognitive fluctuations to date. In the **exploratory aim** we will evaluate whether target engagement by tDCS excitation of cholinergic denervated COTC hubs may affect cognitive fluctuations in LBD subjects.

Specific Aim 1: To perform detailed clinical evaluation, including measures of cognitive fluctuations, ^{18}F-fluoroethoxybenzovesamicol (^{18}F-FEOBV) VAChT PET, and brain MR imaging, in patients with LBD (n=18 enrolled; Net target completion rate = 12) in order to evaluate COTC integrity and the functional ramifications of dysfunction.

Hypothesis 1: Severity of cognitive fluctuations associates with greater cholinergic deficits in COTC network regions in patients with LBD. We will evaluate subjective measures of fluctuations as well as objective measures of working memory and cognitive control that depend on the COTC and presumably underlie such fluctuations.

Exploratory aim 2: To perform a target engagement study of 10 consecutive daily sessions of individualized tDCS to excite the bilateral opercular and anterior cingulum hubs of the COTC alertness network in patients with LBD. We will use a unique approach of creating MRI-based and VAChT PET-informed participant-specific computer models of electrical current flow through the brain in order to optimize stimulation effects and more precisely target the dysfunctional networks. tDCS dosing is traditionally defined by the amount of electrical current delivered at the scalp (e.g., 2mA); however, this neglects the individual differences in brain morphology that are known to affect the delivered dose (i.e., how much electricity reaches the brain). Thus, we will prospectively apply the MRI-based models to ensure a consistent dose is delivered to the targeted brain regions, selected from the VAChT PET scans, across participants. This approach substantially advances the field of tDCS and maximizes the probability of response at the individual level.

Exploratory hypothesis: tDCS excitation of key vulnerable cholinergic hubs of the cingulo-opercular alertness network will improve cognitive fluctuations in patients with LBD.

Positive findings of this study will advance our **scientific understanding** of the role of key hubs of the COTC network in the etiology of cognitive fluctuations in LBD. Moreover, positive findings of the exploratory target engagement study may provide the impetus for clinical trials of cholinergic augmentation with adjunct tDCS therapy for cognitive fluctuations symptom relief to enhance everyday functioning in LBD patients.

RESEARCH STRATEGY

Significance: Fluctuations in attention and alertness are a major source of disability for subjects with LBD. Current clinical treatment approaches are mainly based on pharmacotherapy but have limited clinical effectiveness. The COTC neural network is believed to play a key role in maintenance of alertness. Based on preliminary data of the topography of cholinergic denervation changes in persons with LBD we hypothesize that cholinergic denervation of this alertness network plays an important role in the pathophysiology of cognitive fluctuations in LBD. Our exploratory target engagement study proposes to examine the effects of non-invasive tDCS excitation of cholinergic denervation hubs in this network. Positive findings of this study could spur future clinical trials of targeted non-invasive neurostimulation using tDCS as adjunct to cholinergic pharmacotherapy as a novel way to manage fluctuations in alertness in people with LBD.

Innovation: There is a **high level of innovation** in this proposal as we take advantage of recent neuro-imaging advances of cholinergic VAChT PET imaging and MR-based large-scale neural network identification in LBD. These include (i) the evaluation of novel regionally distinct cholinergic system changes associated with key hubs of the COTC neural network, implicated in maintenance of tonic alertness; (ii) the proposed research will develop a non-invasive neural network stimulation approach to boost and complement the limited brain penetrance of currently used cholinesterase inhibitor drugs in DLB; (iii) We will take the unique approach of creating VAChT PET-informed participant-specific computer models of electrical current flow through the brain in order to optimize tDCS effects and more precisely target the dysfunctional networks. This approach substantially advances the field of tDCS and maximizes the probability of response at the individual level.

Scientific premise

Cognitive fluctuations in LDB: Fluctuations in cognition and alertness are key manifestations of DLB (19). Fluctuating cognition is not only a core diagnostic feature but also the most characteristic feature of DLB (1, 2, 19). Fluctuating cognition is also a key clinical feature of PDD (27). Cognitive fluctuations consisting of pronounced variations in attention and alertness are a major source of disability of patients and caregivers alike (4). The exact underlying pathophysiological processes underlying cognitive fluctuations remain unclear. However, neuroimaging and neurophysiological techniques have recently provided insight into potential drivers of the phenomenon (4). Several mechanistic theories have been posited to explain the etiology of cognitive fluctuations. Most authorities hold that cognitive fluctuations are attributable to a separate pathophysiological process to that driving progressive cognitive decline, as fluctuations by nature are transient and reversible. Putative pathophysiological models include fluctuations in cognition as an attentional disorder, as a consequence of loss of cholinergic drive, as a manifestation of failure in neuronal efficiency and synchrony, or as a disorder of sleep/arousal (4). Evidence for a hypocholinergic etiology is further provided by a highly selective animal lesion model, which demonstrated a correlate of fluctuating cognition with variable response latencies on an attention task in rats subjected to cholinergic denervation of the pedunculopontine tegmental nucleus, which is functionally linked to the cholinergic forebrain (28). The argument is further buttressed by data from both mechanistic (29) and clinical studies (30, 31) identifying improvements - albeit modest - in fluctuating cognition in patients treated with cholinesterase inhibitors.

Large-scale neural networks and cognitive fluctuations: Graph theory analysis of functional connectivity resting state MRI has identified two distinct top-down task-control networks involved in attention (14, 32). The dorsolateral prefrontal cortex and intraparietal sulcus are hubs within the frontoparietal task control (FPTC) network. The FPTC network is important for start-cue and error-related activity and may initiate and adapt control on a *more rapid* and trial-by-trial basis. The COTC network encompasses medial superior frontal cortex, dorsal anterior cingulate, frontal operculum, anterior insula and thalamic regions (14). Effectively, the COTC graph may include parts of both the large-scale distributed network of the cingulo-opercular and salience networks (14, 32, 33). The COTC network has been implicated in important cognitive functions, including sustaining alertness, task set maintenance and salience detection of stimuli (14, 16, 34). Hence, the COTC network controls goal-directed behavior more on a set maintenance mode *using a longer duration time scale*, such as needed for maintenance of alertness (15). Clinically, this may be reflected in a lack of maintenance of a functional operative state and difficulties staying on task in DLB persons in their daily life functions resulting in cognitive fluctuations. Morphometric studies have shown atrophy in the right anterior cingulate cortex and bilateral insular regions in

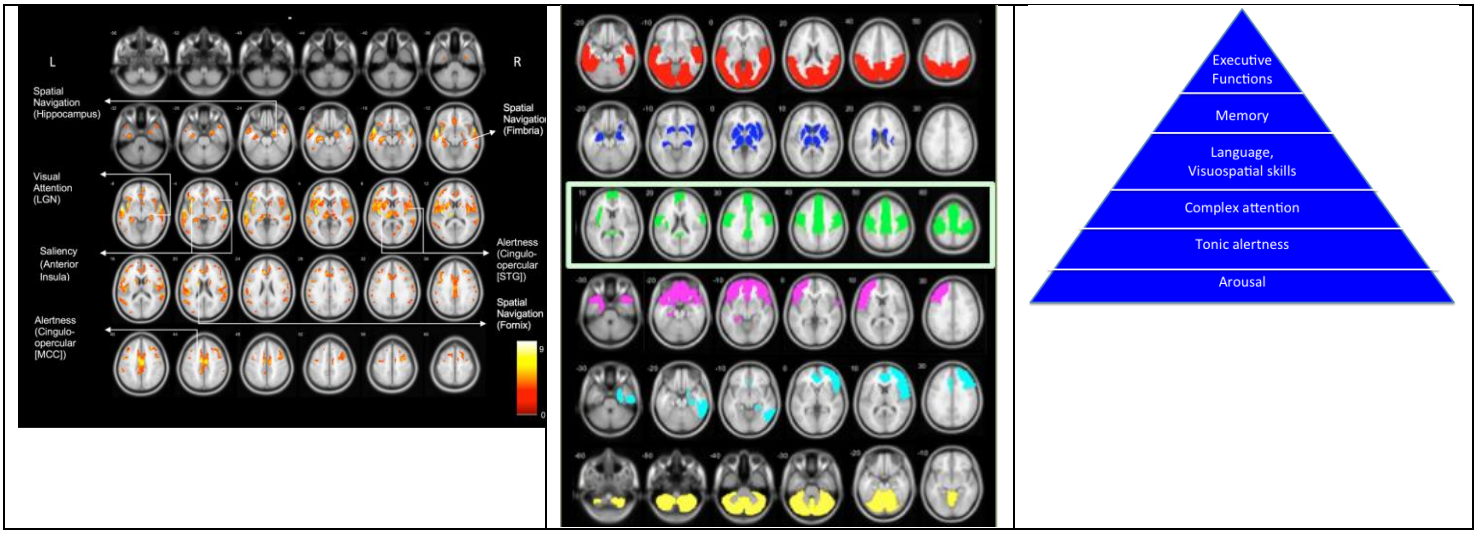
patients with prodromal DLB, 93% of who exhibited fluctuating cognition (35, 36). A prior resting state fMRI network study found evidence that cognitive fluctuations in patients with DLB correlated with widespread brain regions, including opercular/insular and anterior cingulum regions (37). These regions are implicated in the integrity of attentional circuits, and therefore provide supportive evidence for attentional impairments in cognitive fluctuations (38).

tDCS in LBD is in a nascent stage. Briefly, tDCS modulates neuronal excitability (i.e., the probability of neuronal firing) by passing a low intensity electric current between electrodes that are typically placed on the scalp according to the international 10-20 (or 10-10) system. This same measurement system is used with EEG and provides a standardized, accepted, and clinically friendly placement method. tDCS electrodes are either characterized as an anode that "introduces" the electrical current or a cathode that "collects" the current. Evidence suggests that neuronal soma under the anode(s) consistently become depolarized ("excited") (39, 40). Single session effects can last 60-90 minutes (41) and can be extended by consecutive daily sessions (see (42). Only a single tDCS study in those with DLB focused on arousal/attention. That study reported improved attention following a single session of tDCS (2.8mA) when the anode was placed over the left dorsolateral prefrontal cortex and the cathode over the right deltoid (26). Evidence from related alpha-synucleinopathies (α-Syns), particularly Parkinson disease (PD), have been favorable as reflected by enhanced working memory after 2mA over the prefrontal cortex (43, 44) as well as by enhanced phonemic fluency and functional connectivity of brain regions mediating such cognitive abilities (45).

Impact: This project builds on novel FEOBV findings, ongoing work with tDCS, and a unique patient cohort at the University of Michigan MADRC and the Ann Arbor VAMC. Promising findings in the study may augur novel neurostimulation targets to enhance cholinergic network maintenance of arousal and alertness in LBD.

Preliminary data: Topography of cholinergic vulnerability in patients with DLB using VAChT PET: Five DLB subjects and 21 normal control elderly underwent clinical assessment and ^{18}F-FEOBV PET imaging. Compared to the control group, reduced VAChT binding in DLB patients demonstrated non-diffuse but regionally distinct and prominent reductions in bilateral opercula and anterior-to-mid cingulate cortices, bilateral insula, right more than left lateral geniculate nuclei, pulvinar, right proximal optic radiation, bilateral anterior and superior thalami, and posterior hippocampal fimbria and fornices (Fig. 1). With respect to the extent of these topographic changes major hubs of the COTC network predominate the observed cholinergic denervation changes in the DLB patients.

Figure 1: Reduced cholinergic binding in key areas associated with alertness (cingulo-opercular) networks, saliency (insula), visual attention (visual thalamus), spatial navigation (fimbria/fornix). Spatial extent of changes is most prominent for the COTC network hubs.	**Figure 2:** Data-driven cholinergic sub-networks in PD. The sub-network shown in green color has striking topographic overlap with the COTC.	**Figure 3**: Pyramid of cognitive functions (modified after Scott, 2011).



Data-driven cholinergic sub-networks defined by VAChT PET in PD. We performed a principal component analysis of whole brain VOIs from FEOBV PET scans in 86 patients with PD. Different factors are shown in different colors (Fig. 2). The green colored factor (third row) has striking topographic overlap with the COTC alertness network. Importantly, analysis of cognitive test performance showed significant cognitive correlates of the cholinergic binding in the COTC hubs across all cognitive domains (attention, language, visuospatial, memory and execution). Notably, the VAChT binding topography of significant voxel based correlations with the different cognitive domains showed overlapping areas that included key hubs of the COTC alertness network including the anterior cingulum and bilateral opercular regions. We hypothesize that the shared topography of cholinergic correlates of various cognitive domains correlates with findings of functional neuroimaging studies showing a core co-activation pattern as a result of cognitive task engagement *independent* of the specific task (34, 46). The term '*task-positive'* has been reserved for this type of co-activation of different brain regions during cognitive tasks (47). Hence, the general task activation pattern suggests an involvement of foundational capacities such attentional control *common* to cognitive performance in general (15), see also a simplified model of *shared 'sub-serving'* cognitive functions in Figure 3 (48).

Traditional tDCS dosing methods apply a pre-specified amount of electrical current to each participant via the scalp-based electrodes with the assumption that this yields comparable current delivery to the brain. However, this fails to account for individual morphological differences in “normal” brains as well as additional disease related changes, as would be expected in our LBD cohort. Our preliminary data are from 12 cognitively intact older adults who underwent high definition (HD) tDCS over the right parietal cortex (2mA for 20 minutes). In two separate sessions (randomized to active or sham), each participant completed an fMRI task (spatial navigation) and subsequent memory test after HD-tDCS. We then created individualized MRI-based finite element models of electrical current flow for each participant.

Figure 4: Individualized models for 12 cognitively intact older adults showing the functional significance of E-fields where there were strong relationships with neurophysiologic (BOLD signal change in **2B**) and cognitive (memory test performance in **2C**) effects.

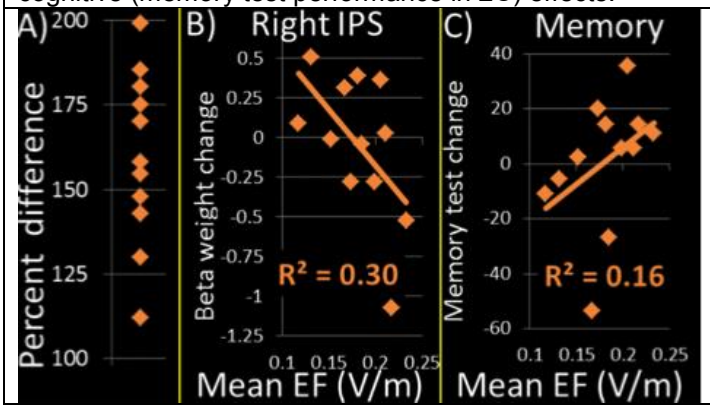


Figure 5: Individualized finite element model (left) targeting the hypo-metabolic region identified via ^{18}F-FDG PET. This resulted in increased functional connectivity and meaningful speech improvement over the course of the tDCS intervention.

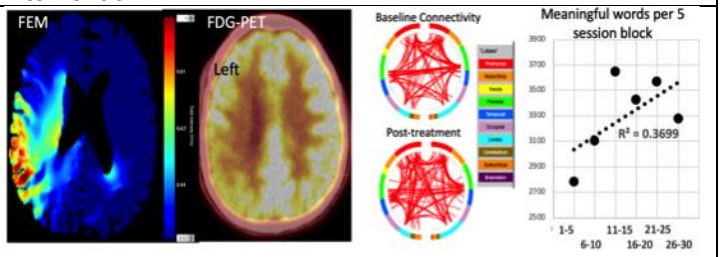
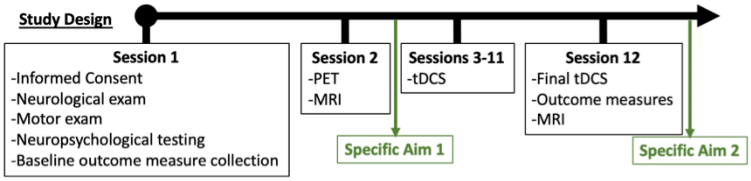


Figure 4a reveals 100% variability in the amount of electrical field (E-field) reaching a targeted brain region (intraparietal sulcus). Thus, the reference participant (represented by "100") would have required 4mA of current delivered at the scalp to achieve the same amount as the "optimal" patient received at 2mA (represented by "200"). **Figures 4B** and **2C** show the functional significance of these E-fields as there were strong relationships with neurophysiologic (BOLD signal change in **4B**) and cognitive (memory test performance in **4C**) effects. Interestingly, those receiving more electrical current showed less BOLD signal; an effect typically interpreted as evidence of increased processing efficiency. This interpretation is strengthened by the cognitive data showing a positive relationship between E-field and improved memory test performance. Together, findings indicate higher E-fields enhance both processing efficiency and memory performance. We build on these results by being the first, to our knowledge, to establish dosing using individualized finite element models; an approach that should yield far more consistent results across participants as well as more replicable procedures across future studies. As an example of this approach **(Fig. 5),** we developed an MRI-based model for a 57-year-old individual with logopenic variant primary progressive aphasia and identified a 9-electrode montage that delivered ~1V/m to the ^{18}F-FDG hypometabolic left temporoparietal junction. The participant demonstrated notable increases in functional connectivity as well as a 10-25% increase in the number of words spoken.

Overall strategy



Overview

The overarching goal of this proposal is to perform brain ^{18}F-FEOBV VAChT PET and MRI and detailed clinical and cognitive characterization in at least 12 (n=18 enrolled; Net target completion rate = 12) patients with LBD who are on stable doses of cholinesterase inhibitors, *i.e.*, at least 4 weeks. In exploratory Aim 2, we will use MRI-guided finite element models that are informed by FEOBV PET imaging to create participant-specific computer models of electrical current flow through the brain in order to optimize stimulation effects and more precisely target COTC hubs via tDCS in a target engagement study. Assessment of cognitive fluctuations will be measured by the Dementia Cognitive Fluctuation Scale (49). Details on the baseline (pre-) and post tDCS testing protocol are listed in the General Methods.

Design & subjects and consideration of **relevant biological variables**, such as gender and age: Cross-sectional neuroimaging-clinical correlation study with exploratory non-invasive neurostimulation target engagement study. Although LBD affects men more than women, we will place special emphasis on equal recruitment of women. We have no a priori rationale to expect the findings to differ as a result of sex but will directly evaluate sex differences. Effects of age will also be taken into account.

Timeline and milestones: Gross recruitment for the project will be 18 persons with probable DLB while anticipating 12-18% attrition (net recruitment target n=12). We will recruit and test 8-9 persons per year (approximately one every 2 months). Subject recruitment and testing will be completed within the first 10 months

of year 2 to allow statistical analysis and write-up of the study findings. *Milestones* of success are net completion of 6 persons for year 1 by 12 months and a total of 12 by 10 months in year 2.

Statistical analysis: The primary objective of this proposal is to establish VAChT PET COTC neural network correlates of cognitive fluctuations. We will employ generalized linear mixed models (GLMM) to accommodate correlation via fixed and random predictor effects. GLMM has the advantage that it also allows for modeling of non-normal distributions and nonlinear models. The main predictors will be bilaterally averaged opercular, insular and anterior cingulum VAChT PET binding and the summed score of the 17-item Dementia Cognitive Fluctuation Scale (49). As LBD affect men more than women, gender will be included as a key biological variable in all analyses. Other co-variates will include measures of (motor) disease severity such as modified Hoehn and Yahr stage or MDS-UPDRS part III score, global cognition (MoCA), age, and levodopa equivalent dose and use of cholinergic drugs. Analysis of exploratory Aim 2 will use GLMM to evaluate the overall tDCS effects and regression analysis of the relationship between bilaterally averaged opercular, insular and anterior cingulum VAChT PET and tDCS changes in the Dementia Cognitive Fluctuations Scale. To avoid Type II error inflation correction for multiple testing will be performed. Statistical analysis will be performed by the Department of Radiology statistician Dr. Johnson.
*Expected results***:** For aim 1, we predict that severity of cognitive fluctuations as measured by the Dementia Cognitive Fluctuation Scale (49) associate with greater cholinergic deficits in COTC network regions in patients with DLB. For our exploratory aim 2, we predict that tDCS targeting key hubs of the COTC neural network using VAChT PET-derived stimulation volumes will improve subjective and objective cognitive fluctuations in the LBD patients and as a function of the degree of cholinergic losses in the targeted regions.
Sample size considerations: Our main hypothesis will be tested using GLMM analysis. We have preliminary data obtained in persons with PD showing a correlation coefficient of R=0.59 (P<0.001) between COTC VAChT binding and attention/working memory functions yielding a power of >.95 to find a significant correlation (P<0.05). Exploratory aim 2 is a target engagement study to provide go/no go feasibility for future clinical trials.

Pitfalls and alternative strategies: *Effects of neural networks other than the COTC*: It is possible that large-scale neural networks other than the COTC may be more robust drivers of an association between cholinergic system changes and cognitive fluctuations than the COTC hubs per se. For this purpose, we will compute VAChT binding changes in hubs of networks, such as the dorsal attention, ventral attention or central executive networks for alternative analyses. The MRI based computational model (CM) for each participant allow us to determine the extent to which any such network effects were affected by tDCS, thereby parsing direct effects of stimulation (i.e., the electrical field – EF) delivered to the associated brain regions) from those arising from between-network connectivity changes. Given the nature of the R21 mechanism, our goal is to evaluate the feasibility of the proposed methods and detect any evidence of change in the outcome measures so we will not include a sham control group at this preliminary stage. Positive findings in this study will allow a subsequent R01 application to include an appropriate control group as in Co-PI Hampstead's ongoing studies.
Target engagement study: We will perform an exploratory open-label tDCS target engagement study to provide causative evidence of cingulo-opercular alertness network involvement in the pathophysiology of cognitive fluctuations. Positive results will provide guidance for future clinical dose-finding trials. We propose 10 tDCS sessions based on Co-PI Hampstead's experience with ongoing clinical trials and evidence of cumulative and persistent improvements following multiple sessions (typically ~5+) in other populations (see (42). As an initial step, this design balances feasibility (*i.e.*, participant burden) by providing a sufficient and known (via the EF maps) dosage for each participant.
Effect of acetylcholinesterase inhibitor drugs on FEOBV binding: We have selected the ^{18}F-FEOBV PET radioligand because of its high affinity and selectivity binding to the VAChT based on stereospecificity of biological effects, pharmacologic blocking studies and *in vivo* brain autoradiography and metabolites studies (50). FEOBV PET studies appear to be not significantly affected by cholinesterase inhibitor drugs based on preliminary rodent data (Dr. Kirk A. Frey, University of Michigan).

General methods

Clinical characterization: All subjects will undergo a general clinical assessment. Severity of motor parkinsonism will be assessed using the Movement Disorder Society-revised Unified Parkinson's Disease Rating Scale (MDS-

UPDRS) (51). Neuropsychological testing measures are presented in Table 1. Neurobehavioral and sleep assessment will consist of Epworth Sleepiness Scale for daytime somnolence (52); The Mayo Sleep Questionnaire for sleep quality and disturbances (53); The Spielberger State Trait Anxiety scale for trait anxiety levels (54). The Brief Psychiatric Rating Scale will be used for the assessment of hallucinations (55). We will use the Geriatric Depression Scale for the assessment of depression (56). The Apathy Evaluation Scale (AES) clinician version will be used to assess apathy severity (57). Patient on dopaminergic medications will be testing in the medication 'on' state. The test battery will be repeated after the target engagement tDCS study.

Outcome measures:

Primary outcome measures. The *subjective* report of fluctuations will be evaluated using the 17-item Dementia Cognitive Fluctuations scale (49), which was developed to address limitations in prior scales, e.g., (58, 59) and has good test-retest and inter-rater reliability.

Secondary outcome measures include: **1)** Neuroimaging (see below). **2)** Objective measures of working memory (n-back test) and **3)** cognitive control (Stroop Color Word Interference Test) will serve as outcome variables for secondary analyses given the known deficits in those with LBD (60-63), relationship to the COTC (15), and positive benefits after tDCS (26, 64).

Table 1: Typical Neuropsychological tests (comparable measures may be used as necessary to accomplish study aims)

Overall mental status	Montreal Cognitive Assessment Scale (3) PD-Cognitive Rating Scale (6-11)
Intelligence	WAIS-III: Information(12) (OPTIONAL)
Attention & Cognitive Control	n-back test (13), Stroop Color Word Interference Test (17) WAIS-III: Digit Span, Digit Symbol-Coding (12)
Language	Boston Naming Test (30 item) (18) (OPTIONAL) D-KEFS verbal fluency test
Learning & Memory	Hopkins Verbal Learning Test—Revised (20) Brief Visuospatial Memory Test—Revised (90)
Visuospatial/Construction	Clock drawing (21) Benton Judgment of Line Orientation (23)
Executive/Working Memory	Stroop Color Word interference Test, D-KEFS Verbal Fluency Test, Trail Making Test, Sorting Test (24) (OPTIONAL) WAIS-III: Matrix Reasoning (OPTIONAL), Digit Backwards (12)
Information processing speed	D-KEFS: Trail Making Test (24) WAIS-III: Digit Symbol-Coding (12) (OPTIONAL) Reaction time (Colorado Assessment Tests)

Exploratory outcome measures include: **1)** *Attention dependent mobility functions:* Dopamine medication refractory postural instability and gait difficulties (PIGD) motor features are common in LBD. These mobility impairments are highly dependent on allocation of attentional resources (65). Expectedly, fluctuations in cognition may be a cause for falls or freezing of gait in LDB. For this reason, we may also perform a sensor-based gait and postural control test battery in the study to explore tDCS target engagement of cognitive fluctuations mediated mobility parameters. This test battery will include postural sway using tests such as the iSWAY and instrumented Timed Up and Go test (iTUG) Mobility Lab modules (APDM, Inc., Portland, OR) (66-68), dynamic balance using the Mini-BESTest (69) with sensored subtests, and electronic gait mat assessment using the Protokinetics Zeno™ Walkway (Protokinetics LLC, Havertown, PA) for spatiotemporal gait measurements. Our team has special expertise in the assessment of PIGD motor features (70). These mobility assessments will be used for a *post hoc* analysis. **2)** Additional exploratory measures include objective measures such as WAIS-III Digit Span and **3)** Digit Symbol Coding (12) to measure attention and cognitive control, **4)** PD-Cognitive Rating Scale (6-11) as an objective measure of overall mental status, **5)** Colorado Assessment Tests Reaction Time to objectively measure information processing speed, and **6)** Clock drawing (21) as an objective measure of visuospatial construction.

tDCS stimulation sessions: Our preliminary data highlight the need for individualized approaches to stimulation that assure sufficient electric field delivery to the bilaterally targeted brain region based on significant cholinergic denervation (defined as binding below the 5th percentile of age and gender matched controls) of the COTC opercular, insula and anterior cingulate hubs. Additionally, we overcome the weaknesses associated with traditional large electrodes (e.g., 35 cm^2) by integrating multi-electrode HD tDCS since this approach allows for greater flexibility in montage configuration. The protocol provides a 30-second ramp-up period in which the electrical current is gradually increased, followed by 20 minutes of stimulation at the amplitude specified by the model (this will vary by participant), and finally a 30-second ramp down period during which the electrical current is gradually removed (71). A computational model (CM) will be created for each participant using a resolution structural MR scan in order to move beyond the “one size fits all” dosing approach that is currently the “gold

standard". The CMs provide quantitative values about the electrical field (E-field) in the targeted COTC neural network brain region(s) of each participant (note that values will be available for all brain regions but our primary analyses will focus on those involved in the COTC). Full details of CMs are available in the literature (72-75) and we will employ the most common approach, which involves finite element models (FEM) using the newly available ROAST pipeline (76). Once calculated, the E-fields can be visualized and values extracted for the desired regions of interest (COTC in our study). An example of this approach is shown above in Figure 5 and these models have been validated against intracranial recordings, e.g., (77). Given our prior review of the literature (78), we will develop montages that provide a minimum of 1 V/m to the key regions of each participant's COTC. This approach overcomes known limitations in the standard administration of tDCS and increases the probability of positive results. We aim for 10 sessions split as 3-5 per week (71), with 4-5 sessions during the first week. Doses of cholinesterase inhibitor drugs will be kept the same throughout the duration of the study.

Scientific rigor: All tests and neuroimaging procedures used in this proposal have been validated and protocols have been published. Both PET and MR neuroimaging assessments will follow established and published acquisition protocols. Neuroimaging analysis will include well-validated and widely used software packages and processing pipelines such as SPM12, FreeSurfer, FSL, and AFNI. All equipment for mobility testing is commercially available and vendor-provided (validated) outcome parameters will be used. The neuropsychological test battery includes tailored components for use in LBD patients (63). We will rigorously guard against Type I and Type II errors and correct all our statistical inferences with family-wise error and false discovery rate corrections where appropriate. This reproducible and rigorous methodological and analysis approach will ensure results and conclusions that can be replicated by other investigations.

Magnetic resonance imaging (MRI) will be performed on a 3 Tesla Philips Achieva system (Philips, Best, The Netherlands) or comparable MRI system (e.g., GE 3T system). Some MRI scans/parameters may change to accomplish study goals; though typical parameters are included below. A 3D inversion recovery-prepared turbo-field-echo was performed in the sagittal plane using TR/TE/TI=9.8/4.6/1041ms; turbo factor=200; single average; FOV=240x200x160mm; acquired Matrix = 240x200x160 slices and reconstructed to 1mm isotropic resolution. Resting-state fMRI scans will serve as a secondary outcome measure and be acquired using a 32-channel head coil and multi-band sequence (79), with nominal parameters: (TR/TE/FA = 720/34/52, 2mm isotropic resolution, 72 slices). Data are collected with eyes fixated on a cross for 10 minutes (80), though we may ultimately implement a continuous stimulus presentation framework (e.g., children's movie) since this is replacing the typical resting-state paradigm in the literature. Pre-processing follows our standard pipeline that includes physiologic noise reduction and thorough motion correction (81, 82). Graph theory analysis or comparable methods will be used to identify the most highly connected nodes following published methods. Briefly, ROIs will be represented as nodes and pairwise correlations, based upon the mean time series for each ROI, will serve as weights over corresponding edges, thresholded by FDR correction, $p<0.05$ or appropriate correction methods (81, 82). Change from baseline will serve as the primary measure of interest.

PET imaging will be performed in 3D imaging mode on a Biograph 6 TruPoint PET/CT scanner (Siemens Molecular Imaging, Inc., Knoxville, TN), which acquire 63 transaxial slices (slice thickness: 2.4 mm) over a 15.2 cm axial field-of-view. Images were corrected for scatter and motion. Subjects will be scanned in the dopaminergic medication 'on' state. **^{18}**F-FEOBV will be prepared as described previously (83, 84). ^{18}F-FEOBV delayed dynamic imaging will be performed over 30 minutes (in six 5-minute frames) starting 3 hours after an intravenous bolus dose injection of 8 mCi [^{18}F]-FEOBV (85). A white matter reference tissue approach will be used to determine VAChT binding as previously reported (86). The PET imaging frames will be spatially coregistered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session (87). Statistical parametric mapping (SPM) software (SPM12; Wellcome Trust Centre for Neuroimaging, University College, London, England [https://www.fil.ion.ucl.ac.uk/spm/software/spm12/] will be used for PET-MRI registration using the cropped T1-weighted MR volumetric scan. Freesurfer software (http://surfer.nmr.mgh.harvard.edu) will be used to define cortical and subcortical volumes-of-interest (VOI).

Functional Near Infrared Spectroscopy (fNIRS): enables the evaluation of brain functioning via scalp optodes that use LED or lasers to emit/detect changes in cerebral blood oxygenation. In contrast to information derived from the fMRI BOLD signal that can identify portions of the hemodynamic response, the fNIRS signal offers

added information regarding the coupling between tissue metabolic activity and its blood supply. Supporting direct measures of both oxy- and deoxyhemoglobin, with deep tissue penetration, the NIRS signal supports real-time evaluation of related biometrics that are known to influence brain function. While fNIRS has lower spatial resolution than fMRI, it has superior temporal resolution and is highly user friendly since it can be performed in an office setting. Using this technology will grant us another valuable tool through which to measure changes induced by the tDCS.

PI Hampstead has purchased two NIRSport2 units (NIRx.com), which will enable up to 64 channels and whole head coverage. fNIRS is safe and accepted as a measure of neurophysiology. Data can be acquired during "rest" (e.g., eyes open staring at fixation cross) or task (e.g., during a memory task). The NIRSport2 units can also be worn as a "backpack" which enables measurement of brain functioning during ecologically-relevant tasks (e.g., making a pot of coffee, moving through one's environment). This lightweight, wearable brain imaging system will allow us to study cerebral blood oxygenation during activities. A typical fNIRS "session" is anticipated to be 60-120 minutes. The typical session will include 1) placing the cap/headgear that contain fNIRS optodes on the participant's scalp, 2) ensuring optimal contact with the scalp (e.g., moving hair to ensure the sensors are not blocked from the scalp), 3) performing the task and/or "resting-state", 4) removing the fNIRS optodes. The user-friendly nature of fNIRS enables multiple measurement sessions, which will be determined based on participant/study needs.
When participants have an MRI in this study, there are structural and functional sequences. For participants who require sedatives or for other reasons are unable to tolerate the fMRI, we will continue to obtain the structural portion of the MRI at the first imaging visit (visit 2). This is necessary to determine dosing. We will do fNRIS in place of the functional portion of the fMRI prior to the start of tDCS. At the second imaging session (visit 12), the participants who had fNIRS at visit 2 will have fNIRS repeated in place of the MRI

Protection of Human Subjects

i) Human Subjects

Description of subject populations: LBD patients (n=18; M/F; 50-90 years) who have cognitive fluctuations and who are on stable doses of cholinesterase inhibitors (i.e., at least 4 weeks) will be recruited to participate in this study. DLB patients will meet the Fourth consensus report of the DLB Consortium inclusion criteria for probable DLB (2). Subjects will be identified according to the following recognized DLB features: spontaneous parkinsonian motor signs, fluctuating attention and concentration, recurrent well-formed visual hallucinations, presence of REM behavioral sleep disturbance, anosmia/hyposmia, or autonomic dysfunction (2). PDD patients will meet the criteria by Emre *et al.* (88).

Exclusion criteria:
1. *Exclusion criteria include*: (a) Subjects with contra-indications to MR imaging and/or tDCS, including pacemakers or claustrophobia, brain aneurysms; (b) Evidence of large vessel stroke or mass lesion on MRI; (c) Use of anti-cholinergic or neuroleptic drugs, (d) Evidence of atypical parkinsonism on neurological exam, (e) Major untreated psychiatric illness, such as bipolar disorder, (f) pregnancy (determined at the first study visit, (g) other neurological conditions such as epilepsy, stroke, multiple sclerosis, or moderate to severe brain injury deemed to be the primary cause of impairment (h) Sensory impairments that significantly limit one's ability to see or hear, (i) significant history of recent alcohol or drug dependence, (j) Previous major radiation exposure.

Recruitment: Participants will be recruited from the NIA P30-funded MADRC where Dr. Hampstead is the Clinical Core leader. The Carl Rinne Lewy Body Dementia Initiative within the MADRC provides longitudinal monitoring and multiple supportive activities for those with DLB. Most participants have expressed an interest in intervention related studies and, given Dr. Hampstead's ties to the MADRC, all participants will be available for screening and potential enrollment. Other potential recruitment avenues include UM DataDirect, the UM Health Research Recruitment Registry (umhealthresearch.org), and community outreach activities. Potential participants may also be recruited from UM Lewy Body Dementia Biomarkers study (HUM00120024).

ii) Sources of Materials:

Information gathered specifically for this research project includes test results from clinical test scales, psychometric cognitive measures, neurobehavioral rating scales, clinical motor data, questionnaires, and data derived from the PET that reflect the amount of vesicular cholinergic transporters and from brain MRI and/or fNIRS.

iii) Potential Risks:

Confidentiality of Research Information: The research data to be collected from subjects will consist of confidential information relating to clinical, motor, cognitive, neurobehavioral and neuro-imaging functions. These research data are not intended for entry into the subjects' clinical medical records. However, the data remain potentially discoverable. This may lead to violation of privacy and embarrassment of the subject.

Clinical Testing: Risks in regard to the clinical assessment are limited to fatigue, frustration and momentary embarrassment that may occur when one experiences difficulty performing a task or learning a new skill.

MRI scan: There is a substantial risk to persons who have metallic objects inside their bodies, as the magnet in the MR scanner can cause these to move. Consequently, participants with pacemakers or metallic objects located in the eye, ear, brain or blood vessel walls will be excluded. There is a potential risk of heart rhythm disturbances in patients who have previous heart rhythm abnormalities or in patients who have certain types of heart pacemakers. If an X-ray study is required to rule out the presence of metallic fragments, the maximum radiation dose to the involved body area will be 0.3 rems (a unit of radiation dosage), with minimum exposure of the other areas of the body. Participants who developed claustrophobic anxiety during scanning found that this fear dissipated within 15 min while remaining in the scanner, or as necessary, after exiting the scanner. There also is the potential that imaging could reveal a previously unrecognized but pre-existing abnormality. Many such abnormalities are not clinically significant, but they may cause anxiety or require further investigation by a personal physician. If one of the investigators identifies such an abnormality, they will contact the personal physician, who will arrange for appropriate care.

PET scans & venipuncture: Insertion of a catheter for intravenous injection of the PET radiopharmaceutical may be commonly associated with slight pain or bruising at the puncture site and rare chance of infection. Participation in this research study will involve exposure to radiation associated with the PET transmission scans and the administration of the radioactive drugs. The exposure for a single ^{18}F-FEOBV PET and the CT scan is 6.9 mSv. The total study exposure for the DLB subjects will be 13.8% of the annually allowed exposure limit for radiation workers. These exposure levels are considered low with acceptable risk by the University of Michigan RDRC. Participants will be instructed to void two hours post injection to minimize bladder exposure. This radiation dose is not expected to produce any harmful effects, although there is no known minimum level of radiation exposure for non-radiation workers considered to be totally free of the risk of causing genetic defects or cancer. The risk associated with the amount of radiation exposure participants receive in this study is considered low and comparable to everyday risks. No PET studies will be performed on pregnant or potentially pregnant women, as confirmed by pregnancy testing. The use of ^{18}F-FEOBV is considered to be generally safe and effective as approved by the University of Michigan Radioactive Drug Research Committee in accordance with Food and Drug Administration regulations (21 CFR 361.1). Adverse reactions to FEOBV used in this study have not been reported. However, the possibility exists for a rare reaction to any of the drugs or procedures to which the participant will be exposed. Certified staff will be in attendance at all times during the study and an emergency cart will be in close proximity. Other physical risks involve possible muscle aches from lying still.

Risks Associated with fNIRS: As the name implies, fNIRS uses near infrared light to measure cerebral oxygenation using LED and/or lasers. The only known risks are associated with damage to the eye or skin following prolonged exposure to bright lights. NIRx, the manufacturer of NIRSport2, has obtained safety test certifications for all their products. We have obtained the Optical Safety R3 document, which covers eye/retinal and skin exposure and revealed that the LED are within safety limits when at least four time steps are employed. The NIRSport2 units provide an eye safe intensity of 25mW$_{max}$ per wavelength, with a time-switched; selectable

between 70 and 160Hz rate. The Aurora software that controls the NIRSport2 unit has imposed limits on the maximum allowable intensity in order to mitigate risk. Thus, there is little possibility of injury when following these safety guidelines. Participants will be informed of such potential risk and the unit will be turned off should participants report discomfort or significant feeling of heating/burning.

Risks Associated with tDCS: The general consensus is that tDCS is safe. In a meta-analysis of over 200 tDCS studies conducted from 1998 to 2010, 56% of studies mentioned some type of adverse effect (see Table 1, which was taken directly from Brunoni et al., 2011). The effects were generally minor, including itching, tingling, headache, burning sensation and discomfort limited to the scalp site where the tDCS electrodes were applied. To date, there have been no reports of seizures or other severe events induced by tDCS (Brunoni et al., 2011; Nitsche & Paulus, 2011; Bikson et al., 2016). Importantly this is the case in both healthy volunteers and in different populations of patients, including patients with disorders where there might be an increased risk of seizures (e.g., dementia, recent stroke, epilepsy). In one study applying tDCS transcranially to the frontal cortex in rats, Liebetanz et al found that cathodal tDCS increased the threshold for localized seizure activity (i.e., lowered the risk of seizure occurrence), while anodal tDCS had no effect on the seizure threshold.

Table 2. Frequency of adverse effects in 117 (active group) and 82 (sham group) experiments. Side effects were reported per study and counted as positive if even 1 patient within the study reported experiencing the symptom. Data taken directly from Brunoni et al., 2011.

Itching	46 (39.3%)	27 (32.9%)
Tingling	26 (22.2%)	15 (18.3%)
Headache	17 (14.8%)	13 (16.2%)
Burning	10 (8.7%)	8 (10%)
Discomfort	12 (10.4%)	11 (13.4%)
Total	117 studies	82 studies

We recently published a manuscript (Reckow et al., 2018, *Brain Stimulation, 11,* 991-997) describing the safety, tolerability, and blinding of HD-tDCS using data from 101 older adults who took part in our prior and ongoing studies. All participants received HD-tDCS for 20-30 minutes at 2 mA (n=66, 31 active) or 3 mA (n=35, 20 active). Participants completed the standardized side effect questionnaire (included below) and were asked whether they received active or sham stimulation at the end of each session. **Results** revealed that there were no serious adverse effects/events, supporting the safety of HD-tDCS. No participants withdrew. Tolerability was comparable between active and sham HD-tDCS regardless of intensity (2 mA and 3 mA) in first session (see Tables 2 & 3 below – taken from the manuscript). There were no significant group differences between individuals correctly stating their stimulation condition indicating adequate blinding. These findings persisted when multiple session data (i.e., 190 additional sessions) were considered. Our **conclusions** were that HD-tDCS appears well tolerated and safe with effective sham-control in older adults. Our ongoing studies consistently administer at least 3-4 mA per electrode with comparable results.

Table 2
Frequency of endorsement (%) of side effects during stimulation naïve first sessions of active (Sessions = 51) and sham (Sessions = 50) HD-tDCS from 101 participants.

	None		Mild		Moderate		Severe		$\chi 2$	df	*p*
	Active	Sham	Active	Sham	Active	Sham	Active	Sham			
Headache	98	94	2	6	0	0	0	0	1.083	1	.362
Neck Pain	98	98	2	0	0	2	0	0	2.000	2	.999
Scalp Pain	82	94	10	4	6	2	2	0	3.557	3	.271
Tingling	41	44	45	42	12	10	2	4	0.529	3	.954
Itching	76	80	16	20	8	0	0	0	4.225	2	.154
Burning	49	50	33	34	18	12	0	4	2.590	3	.531
Skin Redness	100	94	0	6	0	0	0	0	3.154	1	.118
Sleepiness	86	88	8	12	6	0	0	0	3.390	2	.249
Concentration Changes	88	90	8	8	4	2	0	0	0.323	2	.999
Mood Changes	98	96	2	2	0	2	0	0	1.031	2	.745
Other Symptom	84	83	12	17	4	0	0	0	2.288	2	.457

Table 3
Frequency of endorsement (%) of side effects during stimulation naïve first sessions of HD-tDCS from 101 participants, broken down by 2 mA (Active = 31, Sham = 35) vs. 3 mA (Active = 20, Sham = 15) Sessions.

		None		Mild		Moderate		Severe		$\chi 2$	df	*p*
		Active	Sham	Active	Sham	Active	Sham	Active	Sham			
Headache	2 mA	97	97	3	3	0	0	0	0	0.008	1	.999
	3 mA	100	87	0	13	0	0	0	0	2.828	1	.176
Neck Pain	2 mA	97	97	3	3	0	0	0	0	2.015	2	.723
	3 mA	100	100	0	0	0	0	0	0	N/A	N/A	N/A
Scalp Pain	2 mA	84	91	10	6	6	3	0	0	0.915	2	.618
	3 mA	80	100	10	0	5	0	5	0	3.387	3	.496
Tingling	2 mA	48	49	36	40	13	8	3	3	0.387	3	.939
	3 mA	30	33	60	47	10	13	0	7	1.728	3	.781
Itching	2 mA	68	77	19	23	13	0	0	0	4.811	2	.099
	3 mA	90	87	10	13	0	0	0	0	0.094	1	.999
Burning	2 mA	42	54	29	31	29	8	0	6	6.105	3	.092
	3 mA	60	40	40	40	0	20	0	0	4.667	2	.101
Skin Redness	2 mA	100	97	0	3	0	0	0	0	0.899	1	.999
	3 mA	100	87	0	13	0	0	0	0	2.828	1	.176
Sleepiness	2 mA	84	89	10	11	6	0	0	0	2.348	2	.391
	3 mA	90	87	5	13	5	0	0	0	1.455	2	.755
Concentration Changes	2 mA	90	86	3	11	7	3	0	0	1.967	2	.444
	3 mA	85	100	15	0	0	0	0	0	2.461	1	.244
Mood Changes	2 mA	100	94	0	3	0	3	0	0	1.827	2	.999
	3 mA	95	100	5	0	0	0	0	0	0.772	1	.999
Other Symptom	2 mA	83	82	10	18	7	0	0	0	2.931	2	.223
	3 mA	85	87	15	13	0	0	0	0	0.019	1	.999

Table 4
Frequency of group estimation (%) during stimulation naïve first sessions ($n = 95$; Active Sessions = 46, Sham Sessions = 49), collapsed across all intensities and durations.

	Said Sham ($n = 28$)	Said Active ($n = 41$)	Said DK ($n = 26$)	$\chi 2$	df	*p*
Sham ($n = 49$)	26.5	42.9	30.6	0.689	2	.679
Active ($n = 46$)	32.6	43.5	23.9			

Note. DK = "Don't Know".

Additionally, several important safety/tolerability points should be made: **1)** prior research with pad-based tDCS has revealed the possibility of skin lesions or burns. While this typically has occurred when best practices were violated (e.g., using water instead of saline), the data above demonstrate that skin redness (i.e., a precursor for burns that reflects increased skin temperature) was virtually non-existent in our HD-tDCS data. In fact, the only redness occurred in those randomized to the sham group. We believe this reflects the difference in electrode preparation as HD-tDCS uses a known quantity of gel (~10ml) that is housed within tailor made holders – this results in reliable and standard preparation across participants. In contrast, pad-based tDCS is prone to saline drip due to over saturation or pressure from the head-strap as well as heating due to inadequate sponge saturation. **2)** the absence of differences between active and sham HD-tDCS at either 2 or 3 mA supports the proposed study methods. **3)** We implemented a 10-minute "saturation" phase that significantly reduces impedance levels (baseline mean = 1.16 (SD=.97); 10-minute mean = 0.82 (SD=.80), $t(232)=18.25$, $p<.001$) and presumably increases comfort. We are in the process of completing a manuscript describing these data. **4)** We follow best practices in monitoring safety data with tDCS and will specifically use the questionnaire provided by Brunoni and colleagues (2011), which is included below.

Animal work has revealed that a standard dose, including those used in the current study, are substantially below that necessary to cause brain lesions in animal models ((89); see figure to right – taken directly from Liebetanz's study). In fact, consultant Bikson recently completed a comprehensive review of over 32,000 tDCS sessions and found no unexpected adverse events or severe adverse events (PI Hampstead is a co-author on this study, which was published in 2016 in *Brain Stimulation*). In this same review, a variety of data and simulation approaches determined that a constant current of 67mA to 173mA would be needed to cause a parenchymal lesion. Thus, our intended dose is far below the estimated lesion threshold.

Figure 6: From Liebetanz et al., 2009

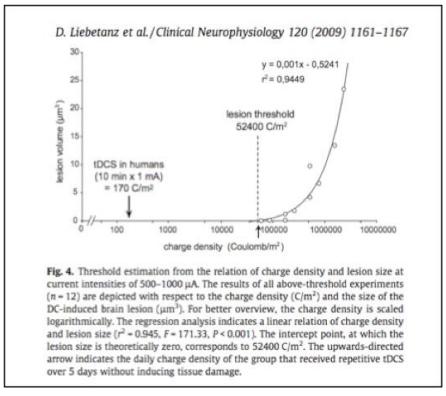


Fig. 4. Threshold estimation from the relation of charge density and lesion size at current intensities of 500–1000 µA. The results of all above-threshold experiments ($n = 12$) are depicted with respect to the charge density (C/m²) and the size of the DC-induced brain lesion (µm³). For better overview, the charge density is scaled logarithmically. The regression analysis indicates a linear relation of charge density and lesion size ($r^2 = 0.945$, $F = 171.33$, $P < 0.001$). The intercept point, at which the lesion size is theoretically zero, corresponds to 52400 C/m². The upwards-directed arrow indicates the daily charge density of the group that received repetitive tDCS over 5 days without inducing tissue damage.

Consistent with these data, a multiple consensus statements on the state-of-the-art of tDCS concluded that tDCS is safe, with minimal adverse effects and risks, even in patient populations, if appropriate

guidelines are followed (39, 42). We intend to follow safety guidelines in regards to dosing and will use a current strength of 4mA (or less) per channel and duration of 20 minutes per session.

We will use a Soterix Medical Inc. multichannel clinical trial HD-tDCS stimulation unit with double blinding capability, which is considered an investigational device by the FDA. Based on the safety information provided above, review of the scientific literature, and consultation with colleagues, we believe this device is of non-significant risk (NSR). The University of Michigan IRBMED has accepted this designation in our ongoing work. This stimulator has a number of built-in safety features that limit the maximum possible current. It operates off of 9v batteries, which limits the available power and prevents possible surges. This system gradually adds and subtracts current in order to avoid a sudden discharge that may be aversive (but not "damaging") to the participant. There are automatic shut offs built in the event of excessive resistance or other factors that could affect stimulation.

Risks associated with clinical, neuropsychological and behavioral testing: This study involves cognitive tests and questionnaires. The cognitive tests are not harmful but some people find them frustrating and concerning. Risks in regard to the neuropsychological and behavioral assessment are limited to fatigue, frustration and momentary embarrassment that may occur when one experiences difficulty performing a task or learning a new skill. Some people may be uncomfortable/embarrassed disclosing personal information or become a little nervous about memory testing, and may experience discomfort or become tired. Trained research assistants, however, are all under the direct supervision of the study MPI who is a Board Certified Clinical Neuropsychologist. Study team members are very well experienced in the assessment of older individuals and persons with dementia, understanding the need for breaks, gentle reassurance, or reinforcement. All assessments will be stopped if requested by the participant.

iv) Adequacy of protection against risks:

Recruitment and Informed Consent:

Subjects will be recruited from the MADRC. Individuals willing to participate will be scheduled for the research procedures at which time the nature and risks of the procedures will again be reviewed with the subjects and an informed consent form will be obtained by one of the study investigators or their designee. Electronic informed consent may be utilized via HIPAA and FDA approved SignNow at a date prior to the initial study visit. One copy of the signed consent form will be given to the subject, one will be placed in the patient's medical record and a third will be kept in the patient's study binder. Study visits will take place at the UM Functional Neuroimaging, Cognitive & Mobility Laboratory where Dr. Bohnen has his office and the MADRC where Dr. Hampstead has his office. Imaging procedures will be performed at the University of Michigan Medical Center.

Protection Against Risk:

Confidentiality of Research Information: The possibility of unintended disclosure of medical or research data is minimal, but not entirely impossible. We will employ stringent safeguards against unintended and inappropriate discovery and dissemination of personal medical and research data in our subjects by a multi-layered approach. All data bearing potential subject identifiers will reside solely in locked files in the offices of the study investigator. Original data collection documents will be maintained in secure files under the control of the investigators. Entries regarding details of the research project and its results will not be submitted to clinical medical databases. Electronic databases in the project will employ subject codes that cannot be linked directly to participants without a "key", possessed only by the study investigators in a secure location, and maintained separately from the databases. Databases will not be housed on systems with internet access, preventing unauthorized intrusions. Personal information that would directly identify study subjects will not be used in any publications or presentations resulting from this research study, unless separate written permission is given by the subject (or proxy). Any superfluous records will be shredded.

Clinical, cognitive and behavioral Testing: Great care will be taken to minimize distress.

In addition to a lunch and afternoon rest break, subjects are given multiple short breaks during the clinical testing day when needed. Subjects will be addressed in a courteous manner that does not infringe the patient's dignity. Physicians and trained personnel with considerable experience working with older individuals and patients with PD or dementia will perform all evaluations and administer tests. These individuals are prepared to respond to patient anxiety, concern and other behavioral changes as appropriate to the situation. Offering breaks and reassuring subjects will further minimize risks when necessary. If needed for some subjects, the clinical testing protocol can be split over 2 days. The UM functional neuroimaging, cognitive and mobility laboratory has facilities to allow rest breaks when needed. The PI has several studies with 1-day clinical testing and 1-day imaging protocols in similar patient populations. Except when subjects are severely demented, our PD participants who are typical septuagenarians or octogenarians have no difficulties completing these protocols. There is a risk of falling with the gait and balance tests. During clinical examination and testing, the subject will be constantly supervised by the research staff and guard against falls when the patient is standing. During over ground walking subjects will be closely guarded, with "spotters" at gait initiation and turning.

MRI Scan: Additional safety is built into standard protocols of the Functional MRI Laboratory at the University of Michigan, where the MRI will be performed. These require the senior MRI technologist and study staff to also screen each participant prior to beginning the MRI. These individuals are independent of our study staff and have complete institutional authority to cancel scans should any potential safety issues arise.
Pads and blankets are provided to make the scan as comfortable as possible and subjects are asked to wear foam earplugs to reduce the loud noises made by the MRI scanner. Individuals scanned are able to talk to the technologist throughout the study and can indicate right away if they wish to stop the study and get out of the scanner. To prevent the risks associated during the MRI scan with implanted devices or metal imbedded in the body, the study staff and the radiology staff review the subject's medical history and medical records. Specifically, we will seek evidence of neurosurgical procedures, cardiac procedures including pacemaker placement, and orthopedic surgery. In addition, individuals are strongly urged to identify any and all surgeries they have had to assess the chance that any metal in the body. Also subjects will be asked if they have had any occupation (for example, being a metal worker) or other experience that might have left metal fragments in the body. Subjects with a history of metal work (*e.g.*, welding) or injury related to metallic foreign matter, will undergo a radiograph of the affected area to ensure the safety of proceeding with MR scanning. The potential risks related to MR scanning will be further minimized in the following manner: 1) Claustrophobia from MR imaging will be reduced by thoroughly explaining the procedure and nature of the scanner to subjects in advance of scanning. Subjects who have a significant history of claustrophobia will not be entered in the study. Furthermore, the study will be terminated at the subject's request. The UM fMRI Lab has a mock MRI scanner that we use as necessary to ensure participants are comfortable in the MRI environment (e.g., in those with possible claustrophobia).
2) Subjects with contraindications to MR scanning, including but not limited to aneurysm clip, pacemaker, intraocular metal, and cochlear implant, will be excluded from the study.

PET Scan & venipuncture: A nuclear medicine technologist will perform the PET studies under the supervision of a physician who is a specialist in nuclear medicine. A physician or nurse will be available at all times during the study, and any adverse reactions will be treated immediately. A fully equipped medical cart is located in the Nuclear Medicine suite. We will use aseptic techniques and highly trained personnel to minimize the risks associated with venipuncture. No PET studies will be performed on pregnant or potentially pregnant women, as confirmed by pregnancy testing within 48 hours prior to each PET imaging session. In order to lessen the pain and fatigue of lying still, the subject will be given a break outside of the scanner midway through the procedure.

Observational Study Monitoring Plan: (please see below).

Potential Benefits of the Proposed Research to the Subjects and Others:

In the course of this study patients will receive clinical evaluations including cognitive testing and, imaging studies. No direct immediate benefit of these studies is anticipated. Although generally the results of these examinations will not be made available to their treating physician, if a significant, unexpected abnormality is detected this will be reported to the patient and his/her physician.

Importance of the Knowledge to be Gained:

Data obtained from this research will become important for the development of improved understanding of mechanisms underlying impaired turning functions and mobility impairments in patients with PD. Such mechanisms would provide a rational basis for targeted intervention in PD patients with decreased turning functions putting them at risk of falls and freezing of gait.

Observational Study Monitoring Plan:

The independent safety monitor, Dr. Shawn McClintock, who has been approved by the NIA as a safety monitor will review the tDCS side effect/safety data twice in the first recruitment year (6 months after the first participant is enrolled and at 12 months). Biannual reviews will continue if any safety concerns emerge during this first year. Annual reviews will be conducted (at the time of the IRBMED continuing review/renewal) if no safety concerns are evident.
The co-PIs will be responsible for monitoring any break in confidentiality and for reporting any adverse events following IRB guidelines. For purposes of this study, an adverse event (AE) is defined as any unfavorable or unintended change in structure, function, signs, or symptoms temporally associated with participation in this study, whether or not a causal relationship with the study has been established. Clinically significant abnormalities may be considered an AE if deemed appropriate by the co-PIs. Unexpected worsening of a pre-existing condition is also considered an AE, as is the discovery of an abnormal finding during physical exam that was not included in the medical history. Breaches of confidentiality will be considered related to the research whenever they occur and will be reported. Withdrawals from the study and the reason for these withdrawals will also be reported.

The co-PIs are in daily contact with the Project research staff who will test the participants, score and enter the data and will monitor their procedures to ensure that confidentiality is maintained. The co-PIs will ensure that the IRB is notified of any adverse event following the IRB guidelines. Expected and unexpected serious (including fatal) adverse reactions and major unresolved disputes between the research investigator(s) and the research participant or between research investigator(s) will be expeditiously reported to the IRB. At the time of renewal, the IRB will be provided with a summary indicating the frequency of the monitoring, cumulative adverse event data, information regarding participant safety or ethics changes, confidentiality issues, benefit-to-risk changes and recommendations on continuing, changing or terminating the study.

Inclusion of Women and Minorities:

Inclusion of Women:

Women will be included in this research project. Males and females will be given equal priority in recruitment. However, because DLB affects males more than women we expect to recruit a higher percentage of males. The PI will monitor recruitment of women to this project throughout the study, and institute procedures to enhance the enrollment of women, if numbers are not adequate.

Inclusion of Minorities:

Enrollment targets are based on population estimates of the 2010 US census for the state of Michigan. Estimates are < 1-2% (or N <1) for American Indian/Alaska natives, Native Hawaiian or Other Pacific Islander, and Asian Americans for Michigan.

Inclusion of Children

Justification for Exclusion of Children:

No children will be included. LBD occurs predominantly in late-life and, indeed, the risk of developing PD increases with increasing age. In rare cases with clear familial inheritance, the onset of the disease may occur in the 30's and 40's, but there is no evidence of clinical LBD in children. Therefore, the research topic to be studied is not relevant to children.

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