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## **Transcranial direct current stimulation in Parkinson's disease dementia: a randomised crossover trial**

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## **Abstract**

*Background:* Attentional difficulties are common in Parkinson's disease with dementia (PDD); current pharmacological treatments have limited efficacy and have associated side effects.

*Objective:* The objective of this pilot study was to assess the effects of anodal transcranial direct current stimulation (tDCS) upon attentional function in PDD.

*Methods:* The study was a randomised, double-blind, placebo-controlled crossover trial involving 44 PDD participants ( $M_{\text{age}} = 66.82$  years;  $SD_{\text{age}} = 8.05$  years), conducted at a single site, between April 2015 and June 2016. Participants completed computerised attentional tasks (simple reaction time (SRT), choice reaction time (CRT), digit vigilance (DV) and the Attentional Network Task (ANT)) after one 20-minute session of active ( $0.08\text{mA}/\text{cm}^2$ ) or placebo tDCS. The anodal electrode was applied to the left dorsolateral prefrontal cortex (DLPFC) and the cathodal electrode was applied to the right deltoid. The main outcome measures were the percentage of correct responses, mean reaction time to correct answers and coefficient of variation (SRT, CRT and DV) and the mean reaction time to correct trials by cue, and by network type (ANT task).

*Results:* Complete study data were obtained from 38 participants. Compared to placebo, no post-stimulation improvements were observed in SRT, CRT, DV and ANT attentional outcome measures (all  $p$ -values  $> 0.0025$ ).

*Conclusions:* A single 20-minute session of anodal tDCS applied to the left DLPFC was well-tolerated, but does not benefit attentional function in PDD. Further studies using different stimulation parameters (e.g. repeated stimulation) should be conducted to determine if tDCS can improve attention.

*Trial registration:* Clinical Trials Registry India (CTRI; REF/2015/03/008611)

*Keywords:* Lewy body dementia, Parkinson's disease with dementia, tDCS, transcranial direct current stimulation, attention.

*Highlights:*

- Attentional difficulties are very common in Parkinson's disease dementia (PDD).
- Current pharmacological treatments have limited efficacy and associated side effects.
- There is a paucity of well-controlled tDCS clinical trials in PDD.
- tDCS is tolerable and feasible in a PDD population.
- A single session of tDCS does not benefit attentional function in PDD.

## **Introduction**

Up to 80% of individuals with Parkinson's disease (PD) eventually develop dementia(1, 2). Parkinson's disease dementia (PDD) is characterised by a range of cognitive symptoms including executive, visuospatial and memory impairments(3, 4). Attentional dysfunction is a common and prominent feature of PDD and compared to individuals with Alzheimer's disease (AD), those with PDD tend to display greater attentional impairments, with a relative preservation of memory(5, 6). Attentional dysfunction can negatively affect quality of life in PDD(7) and may also contribute to other frequently-observed symptoms, including visual hallucinations(4, 8).

Currently, there are few effective treatments for attentional dysfunction in PDD and treatment is typically limited to the use of pharmacological agents including cholinesterase inhibitors and memantine(9, 10). However, these agents can be associated with side effects(11) and do not work in all patients. One potential non-pharmacological intervention is that of transcranial direct current stimulation (tDCS), which is a simple, inexpensive and non-invasive method of brain stimulation. This technique delivers a weak electrical current to the brain through two saline or conductive gel-soaked scalp electrodes. Modelling and empirical data suggest that tDCS modulates cortical excitability in a polarity-dependent manner, where anodal stimulation increases the underlying membrane potential by several millivolts and conversely, cathodal stimulation reduces the membrane potential(12-14).

Previous imaging and neuropathological evidence has shown that frontal atrophy is a common feature of PDD(15, 16) and that Lewy body pathology are frequently observed in anterior frontal and temporal regions(17, 18). In PDD, impairments in fronto-striatal networks, which arise from the depletion of dopamine in the striatum(19, 20) have been suggested to contribute to the executive and attention deficits.

Studies in normative populations have suggested that the application of tDCS to the dorsolateral prefrontal cortex (DLPFC) can enhance working memory, visuomotor coordination, attention and executive function(21-25). In particular, the left DLPFC has been implicated in top-down cognitive control(26), and the application of anodal tDCS to the left DLPFC may therefore benefit attention in PDD. However, very few studies have examined the use of tDCS as a therapeutic tool in neurodegenerative disease populations, although small-scale pilot studies have shown pro-cognitive benefits in patients with AD and PD(27) and the effects may continue beyond the stimulation session. In PDD, a previous pilot study from our group in Lewy body dementia (comprising both PDD and DLB patients) demonstrated that a single 20-minute session of anodal tDCS applied to the left DLPFC was well-tolerated(28). Importantly, there was tentative evidence of post-stimulation improvements in attentional (choice reaction time and digit vigilance), but not visuoperceptual, computerised task performance. Therefore, a single session of tDCS may benefit attentional function in LBD. However, the main limitation of this study was in the lack of an adequate placebo condition.

The aim of the present study was to extend these findings by investigating whether anodal tDCS, applied to the left DLPFC, is beneficial to attentional function in PDD, as compared to placebo stimulation. The current study also aimed to examine the effects of anodal tDCS in PDD in more detail; specifically, whether tDCS can benefit three anatomically distinct but functionally inter-related components of attention using the attention network task (ANT)(29): alerting, orienting, and executive control(29, 30). The ANT has previously been used in PDD, where compared to control and AD participants, individuals with PDD show slower reaction times, reduced accuracy, and compared to controls, impairments in executive and conflict networks, indicated by differences in reaction times, and impairments in executive network in terms of differences in the error rate(31). It

was hypothesised that a single session of anodal stimulation, delivered to the left DLPFC, would benefit measures of attentional function in PDD participants; specifically in choice reaction time and digit vigilance measures, and the ANT executive control component.

## **Methods**

### *Trial design*

The pilot study was a randomised (1:1 active stimulation/placebo), double-blind, placebo-controlled, crossover trial in individuals with PDD. The study was conducted at a single site (Institute of Neurosciences, Kolkata, India) between April 2015 and June 2016. The trial was stopped with a reduced number of participants as the recruitment rate of patients was lower than anticipated. There were no pre-specified stopping rules.

### *Participants*

Participants who met diagnostic criteria for probable PDD(4), as verified by two independent experienced clinicians (HK & JPT), were recruited from the Movement Disorders clinical service. The diagnosis was confirmed through detailed physical, neurological and neuropsychiatric examinations. Participants were included if they were a) aged 50 years or over; b) were stable on anti-Parkinsonian medication, and/or where applicable, cholinesterase inhibitors, for one month prior to participation; c) had clear evidence for onset of parkinsonism for at least one year before the onset of cognitive symptoms. Exclusion criteria included: a) skin allergies; b) a history of excessive alcohol intake; c) concurrent major psychiatric illness; d) significant or severe physical illness or co-morbidities; e) other neurological disorders; f) current or previous visual impairment due to

glaucoma, cataracts or macular degeneration; g) metallic or electronic implants; h) significant motor fluctuations or i) moderate-to-severe vascular disease as evidenced on available imaging. All participants provided written informed consent. The trial was registered with the Clinical Trials Registry India (CTRI; REF/2015/03/008611), the study protocol was approved by the Institutional Ethical Committee of the Institute of Neurosciences Kolkata and all participants provided written informed consent.

### *Baseline measures*

At baseline, cognitive function was assessed using the Montreal Cognitive Assessment (MoCA)(32), extrapyramidal motor function was assessed using Part III of the Unified Parkinson's Disease Rating Scale (UDPRS-III)(33), cognitive fluctuations were assessed using the One Day Fluctuation Scale (ODFAS) and Clinical Assessment of Fluctuation (CAF) scale respectively(34), and the presence of depressive symptoms was assessed using the 15-item Geriatric Depression Scale (GDS-15)(35). All assessments were administered in English by investigators fluent in both English and Bengali. Information regarding the duration of cognitive and parkinsonian symptoms, and the use of cholinesterase inhibitors were obtained, as was the equivalent levodopa dose of anti-parkinsonian medication, which was expressed in milligrams using levodopa conversion formulae reported previously(36).

### *Interventions*

Participants received both active and placebo tDCS, and the order of stimulation was delivered in a counterbalanced manner by a technician blinded to the stimulation condition. In order to avoid any stimulation carry-over effects, there was a minimum washout period of

24 hours between both stimulation sessions. Participants were assessed at baseline and completed the MoCA, UPDRS-III, CAF and ODFAS. Participants then received one 20 minute session of active or placebo tDCS, before immediately completing computerised tests of attentional and executive function. All computerised tasks were displayed on a standard laptop PC and responses were recorded using custom-built response button boxes, which the participant held either in their dominant hand, or in both hands, depending on the task requirements.

Each session of stimulation (2.8mA) was delivered using an Eldith DC Stimulator (Magstim, Whitland, UK), using two 35cm<sup>2</sup> electrodes soaked in conductive gel (equivalent current density: 0.08mA/cm<sup>2</sup>). The anodal electrode was placed over the left DLPFC (positioned 50% between F<sub>3</sub> and FP<sub>1</sub> on the basis of the International 10-20 system(37)) and the cathodal electrode was placed on the right deltoid muscle. During active stimulation, the current was initially ramped up to a current density of 0.08mA/cm<sup>2</sup> during a 10 second fade-in period, which was followed by a 10-second fade-out period at the end of stimulation. During placebo stimulation, the current increased during a 10-second period before delivering direct current at an equivalent current density (0.08mA/cm<sup>2</sup>) for 30 seconds, in order to ensure that participants experienced skin sensations equivalent to those experienced during active stimulation. The current then decreased during a subsequent 10-second fade-out period. When this method of placebo control has been previously used, participants have been unable to distinguish between active and placebo stimulation(38) and participants were asked whether they thought they were receiving active or placebo stimulation at the end of stimulation. During the remainder of stimulation, a very weak brief current pulse (110µA over 15ms) occurred every 550ms in order to allow the stimulator to verify that the electrodes were still attached to the patient.

### *Study procedures and outcome measures*

Participants completed four attentional tasks (simple reaction time (SRT); choice reaction time (CRT); digit vigilance (DV)) and the Attention Network Task (ANT)). Participants first completed the SRT, and the order of the DVT, CRT and ANT attentional tasks were counterbalanced between participants using an online computerised random generator. Following the administration of tDCS, participants completed one brief practice trial (consisting of 5 trials per task) before completing a full run of each task. In the SRT task, a target (letter X) was displayed for a maximum of 3000ms per trial, with a varying inter-stimulus interval, and participants were required to respond to the target as quickly as possible. In the CRT task, a target arrow which pointed left or right was displayed for a maximum of 3000ms and participants were required to respond using the corresponding button. During the DV task, a target (number 9) was continuously displayed on the right of the computer screen, and a series of digits which were cycling at 500ms were randomly displayed in the centre of the screen. Participants were required to press a button whenever the centre digit and the target digit matched. The SRT, CRT and DV tasks are displayed in Figure 1.

*[Figure 1]*

A modified version of the ANT(29) was used in the current study, which has been reported in detail elsewhere(31). Briefly, the ANT involves the display of four arrowheads, where participants are required to respond by indicating the direction of the majority of the arrowheads (Figure 2). In the congruent condition, all four arrowheads were oriented in the same direction; in the incongruent condition, one of the arrows pointed in the opposite

direction. The incongruent condition comprised an easy and hard difficulty level, where in the easy difficulty, the incongruent arrow appeared at the end and therefore showed three congruent arrows in a row; in the hard difficulty, the incongruent arrow was displayed as one of the middle two arrows, meaning only two congruent arrows were displayed in a row. This allowed for a graded difficulty attention-executive task which can be performed by the majority of dementia patients(31).

Participants were initially required to fixate on a crosshair displayed in the centre of three grey boxes. Participants completed 36 trials per run, where during each run a cue (no cue, a neutral cue or directional cue) was displayed. Targets remained on the screen until either participants responded, or 3000ms had elapsed. The time between the disappearance of the cue and target onset was exponentially distributed (700 – 3200ms) and the time between the target onset and onset of the following cue ranged from 4300ms – 8300ms, where each duration appeared three times in a pseudo-random order per run; in line with the original ANT task (29). Each of the cues appeared 12 times and 18 congruent and 18 incongruent trials per run, and easy and hard trials were equally distributed.

*[Figure 2]*

#### *Sample size calculation*

In a previous tDCS feasibility and tolerability study in LBD patients, significant post-stimulation improvements were observed in measures of attentional function (the percentage of correct responses obtained in choice reaction time task, and the mean reaction time to correct answers in the digit vigilance task), where on the basis of Cohen's  $d_z$ , large effect sizes were observed ( $d_z = 0.83$  and  $d_z = 0.80$  respectively)(28). For the current study, a more

conservative medium effect size was expected ( $d_z = 0.50$ ) for these measures of attentional function. Power analyses, using a two-tailed paired  $t$ -test, were conducted using G\*Power 3.1(39) and it was estimated that 34 participants were required at 80% power and 54 participants were required at 95% power ( $\alpha = 0.05$ ). In the previous feasibility and tolerability study, 18.75% (3 of 16) of the participants were excluded on the basis of having a poor understanding of attentional task instructions (28). Allowing for a conservative 20% participant exclusion or drop-out rate during the study (6.8 participants at 80% power and 10.8 participants at 95% power), a total of 41 participants were required at 80% power and 65 participants at 95% power.

#### *Randomisation sequence and blinding*

Participants were randomised to experience active or placebo stimulation during their first session on the basis of pre-generated random codes, where a total of 65 codes were generated in one block using an online computerised random generator ([www.randomization.com](http://www.randomization.com)). These codes were independently generated and were stored separately from the study site. Active or placebo stimulation was then administered, where a technician blinded to the type of stimulation entered a separate numeric code into the stimulator.

#### *Statistical analysis*

SRT, CRT and DV task outcome measures included the percentage of correct answers, the mean reaction time (RT) to correct answers, and the coefficient of variation (COV), as a marker of intra-individual variability (calculated on the basis of  $(SD_{RT} / M_{RT}) \times 100$ ). Power of attention (PoA) scores were also derived from reaction time data by summing

the SRT, CRT and DV reaction times to correct answers, where lower scores represent better attentional performance (40, 41). ANT task outcome measures included the RT to correct trials, broken down by cue type (no cue, neutral cue, directional cue) and by difficulty (congruent, incongruent, easy incongruent and hard incongruent), expressed in milliseconds (ms). Three network effects were also derived: a) the alerting effect, defined as the mean reaction time of the trials with no cues – trials with cues; b) the orienting effect, defined as the mean reaction time of neutral cue trials – directional cue trials; c) the executive effect, defined as the mean reaction of all (both easy and hard) incongruent trials – congruent trials; and d) the conflict effect, defined as the mean reaction time of the hard incongruent trials – easy incongruent trials.

As previously reported, participants with outliers (defined as a mean of  $\geq 2SD$  on each attentional variable) were removed from SRT, CRT and DV tasks(28). Shapiro-Wilk tests were used to assess the normality of SRT, CRT, DV and ANT outcome measures. Attentional task performance was compared between active and placebo stimulation conditions using paired *t*-tests or Wilcoxon signed-rank tests, where appropriate. SRT, CRT, DV and ANT *p*-values were adjusted for multiple comparisons using Bonferroni corrections (adjusted *p*-value = 0.0025). A chi-square test was used to assess the integrity of blinding. Additional exploratory analyses were conducted to determine whether levodopa dose potentially influenced tDCS efficacy, where attentional measures were compared using a repeated-measures analysis of variance (ANOVA) with the inclusion of baseline levodopa-equivalent dose as a covariate. In addition, analyses examined whether tDCS efficacy was influenced by the use of cholinesterase inhibitors or memantine, using a mixed ANOVA with the use of these agents, as a between-groups factor and stimulation condition as a within-groups factor. The effect of antipsychotic agents and benzodiazepines were also examined in this manner. The association between motor severity (UPDRS-III scores) and baseline

cognition (MoCA scores), and the difference between active and placebo attentional measures was examined separately, using Spearman rank correlations adjusted for multiple comparisons.

## **Results**

### *Participant flow*

A total of 44 PDD participants ( $M_{\text{age}} = 66.82$  years;  $SD_{\text{age}} = 8.05$  years) were entered into the study. Two participants were excluded after enrolment. Participants were then randomised ( $n = 42$ ) and initially allocated to either active or placebo stimulation, before crossing over to placebo or active stimulation after a washout period (Figure 3). A total of four participants were excluded from analysis as only one stimulation session was completed. This resulted in a final sample of 38 participants ( $M_{\text{age}} = 66.63$  years;  $SD_{\text{age}} = 8.39$  years). Baseline demographic and clinical details are provided in Table 1.

*[Table 1]*

*[Figure 3]*

### *Outcomes*

There were no significant differences between active and placebo stimulation conditions in SRT, CRT or DVT attentional tasks, including in the levels of task accuracy, in the response time to correct answers, in the coefficient of variation or power of attention (all  $p$ -values  $> 0.0025$ ; Table 2). Comparisons of the ANT showed that there were no differences

between active and placebo in the reaction time to correct trials (no cue, neutral cue, directional cue, congruent, all incongruent, incongruent easy or incongruent hard; all  $p$ -values  $> 0.0025$ ; Table 3). In addition, analysis of additional ANT components showed there were no significant differences between active and placebo conditions in alerting, orienting, executive or conflict effects (all  $p$ -values  $> 0.0025$ ).

Additional exploratory analyses indicated that there were no significant differences between SRT, CRT and DVT attentional tasks, or in the ANT, with the inclusion of baseline levodopa equivalent dose as a covariate (all  $p$ -values  $> 0.0025$ ). The use of cholinesterase inhibitors or memantine did not influence the SRT, CRT, DVT attentional tasks or the ANT, as indicated by the lack of interaction between the use of cholinesterase inhibitors or memantine and stimulation condition; all  $p$ -values  $> 0.0025$ ). Similarly, the use of antipsychotic agents or benzodiazepines did not influence tDCS efficacy. Baseline UPDRS-III and MoCA scores were also not associated with the difference between active and placebo attentional outcome measures (all  $p$ -values  $> 0.0025$ ). No adverse or serious adverse events were reported at any point in the study and the blinding integrity was maintained ( $p > .05$ ).

*[Table 2]*

*[Table 3]*

## **Discussion**

This randomised double-blind crossover trial demonstrated that a single 20-min session of tDCS applied to the left DLPFC does not lead to post-stimulation improvements in attentional function, as compared to placebo. However, importantly, these findings provide

further evidence to indicate that tDCS, with a current density of  $0.08\text{mA}/\text{cm}^2$ , is feasible and well-tolerated in individuals with PDD and can therefore inform stimulation parameters for further tDCS studies in PDD.

Whilst a single session of tDCS did not appear to improve attentional function in PDD, the choice of stimulation parameters, including the current density, frequency and stimulation duration, can significantly impact upon the efficacy of tDCS as a dementia treatment method(27). Although a single session of tDCS can have sustained effects, and result in immediate improvements to an executive function task (42, 43), repeated stimulation sessions may be useful therapeutically in dementia: one motor skill acquisition study indicated that healthy individuals who received active tDCS over a period of five consecutive days displayed better performance relative to placebo, where the effects were additive and persisted up to a three month follow-up period (44). It is therefore possible that repeated stimulation sessions may be of therapeutic utility in PDD. However, an important consideration of using repeated stimulation sessions in dementia populations is with regards to the safety, as whilst a single session of tDCS with a relatively high current density ( $0.08\text{mA}/\text{cm}^2$ ) is tolerable in PDD patients, the tolerability of repeated stimulation sessions has not yet been assessed. Similarly, higher current densities might be needed to induce an effect; however, increasing the current intensity may increase the perceived discomfort and be uncomfortable or poorly-tolerated, and therefore caution is needed.

The efficacy of tDCS in PDD may also be boosted using concurrent cognitive training, which may have a beneficial synergistic effect; as suggested by one study in healthy adults(45). However, it is not clear whether the efficacy of this approach is influenced by different levels of cognitive impairment in PDD, or whether adherence is also affected. As such, concurrent tDCS and cognitive training protocols may need to consider the stratification of patients by the level of cognitive severity.

The concurrent use of psychotropic medication is relevant, since therapeutic agents used in PDD may influence tDCS efficacy. In the present study a high proportion of participants were observed to be taking cholinesterase inhibitors; this is relevant as the administration of rivastigmine has been shown to negate the effects of anodal tDCS(46). Whilst the administration of the N-methyl-D-aspartate (NMDA) receptor antagonist dextromethorphan can suppress the effects of anodal tDCS(47), and levodopa medication may also influence stimulation efficacy(48), additional exploratory analyses suggested that those who were taking the NMDA receptor antagonist memantine to treat the symptoms of dementia, or levodopa, or those patients taking antipsychotic medication or benzodiazepines, did not show a differential treatment response compared to those who were not taking any of those agents.

Participant heterogeneity, in terms of the level of cognitive impairment, may also have contributed to the present negative findings; differential therapeutic effects of tDCS depending upon dementia severity have been observed in AD(49). Furthermore, the dual hypothesis of cognitive dysfunction suggests that the cognitive impairment observed in PDD occurs due to a combination of dopaminergic-related executive fronto-striatal dysfunction, and cholinergic-related visuospatial, posterior, cortical and temporal lobe dysfunction(50); therefore, stimulation to the DLPFC alone may not be sufficient. However, whilst the application of tDCS to the DLPFC is likely to modulate activity in frontal areas, as neither the severity of motor symptoms or baseline cognition were associated with the change in outcome measures in the current study, and the use of cholinergic medication did not influence efficacy, the dual hypothesis of PDD is unlikely to fully explain the negative findings in the current study. Future studies should also consider the use of brain imaging in order to account for individual differences in brain morphometry or atrophy, as the tDCS current flow can be influenced by structural brain changes (51).

Strengths of the current study include the large sample size compared to other dementia tDCS studies. To our knowledge, this is the largest tDCS study conducted in a PDD population despite the fact that the *a priori* recruitment target was not achieved, however, the expected drop-out rate and power calculations were extremely conservative. A further strength is in the double-blind, placebo-controlled design of the study, as tDCS studies in the dementias frequently do not include a placebo control(27) and by the crossover design employed. This study also provides additional important information regarding the tolerability of tDCS in a PDD population and can therefore help to inform stimulation parameters of future trials. A potential limitation is in the concurrent use of medications including cholinesterase inhibitors, memantine and levodopa, which may have interacted with the use of tDCS as a treatment(46-48). However, it was considered impractical and unethical to withdraw these agents from a PDD population, as this may have resulted in the clinical deterioration of patients prior to study entry, and additional analyses suggested that medication use did not influence stimulation efficacy. Furthermore, whilst we did not use validated Bengali patient assessment measures in the present study, this limitation was minimised as trained investigators fluent in both English and Bengali administered all study measures.

In conclusion, a single 20-minute session of anodal tDCS delivered to the left DLPFC does not benefit attentional function in individuals with PDD. Despite the negative results, this study contributes information regarding stimulation parameters for future trials and also provides further evidence indicating that tDCS is feasible and tolerable in a PDD population. It is possible that repeated multiple stimulation sessions and the use of concurrent cognitive training protocols may be needed to demonstrate any potential benefits of tDCS upon attentional function in PDD.

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