

Effects of transcranial direct current stimulation upon attention and visuoperceptual function in Lewy body dementia: a preliminary study

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ABSTRACT

Background: Individuals with Lewy body dementia (LBD) typically exhibit impairments in attentional and executive function. Current pharmacological treatments have limited efficacy, with associated side effects. Transcranial direct current stimulation (tDCS) may represent an alternative treatment, as cognitive improvements have been demonstrated in healthy individuals. However, no studies to date have assessed the feasibility of tDCS in an LBD population. The aim of this preliminary study, therefore, was to assess the tolerability of tDCS, as well as its effects upon attentional and visuoperceptual performance, in LBD patients.

Methods: Thirteen participants completed attentional (simple reaction time, choice reaction time, and digit vigilance) and forced-choice visuoperceptual (angle and motion perception) tasks before and after one 20-min session of active tDCS (0.08 mA/cm²). The anodal electrode was applied to the left dorsolateral prefrontal cortex and the cathodal electrode was applied to the right deltoid. Attentional (task accuracy and reaction time to correct answers) and visuoperceptual (task accuracy and difficulty) outcome measures were compared using paired t-tests.

Results: All participants tolerated stimulation and did not report any side effects during or immediately after stimulation. Post-stimulation improvements were observed in the choice reaction time (increased percentage of correct answers; $p = 0.01$) and digit vigilance (reduced mean reaction time to correct answers; $p = 0.02$) attention tasks. Visuoperceptual task performance did not improve (all p -values > 0.05).

Conclusions: Attentional, but not visuoperceptual, improvements were observed following stimulation in LBD patients. Larger-scale, placebo-controlled trials are needed to confirm whether tDCS is a useful treatment option for attentional deficits in LBD.

Key words: Lewy body dementia, dementia with Lewy bodies, Parkinson's disease with dementia, tDCS, transcranial direct current stimulation, attention

Introduction

Lewy body dementias (LBDs) include dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD). Individuals with DLB and PDD share a common underlying alpha-synuclein neuropathology and display similar neuropsychological impairments, including attentional and visuoperceptual deficits (McKeith *et al.*, 2005; Emre *et al.*, 2007; Lippa *et al.*, 2007).

The treatment of attentional and cognitive impairments in LBD is typically limited to the use of cholinesterase inhibitors (McKeith *et al.*, 2000; Emre *et al.*, 2004); however, due to the limited efficacy of these agents and their associated side effects, alternative treatments are urgently needed. One potentially promising non-pharmacological intervention is transcranial direct current stimulation (tDCS), a simple, non-invasive, and inexpensive technique in which a weak electrical current is delivered to the brain through two electrodes soaked in saline or conductive gel. This approach has a modulatory effect upon cortical excitability, where these effects are polarity-dependent: anodal stimulation typically increases

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and cathodal stimulation typically decreases the underlying neural membrane potential (Stagg and Nitsche, 2011).

The application of tDCS to the dorsolateral prefrontal cortex (DLPFC) has been shown to enhance cognitive functions including working memory, visuomotor co-ordination and decision-making in healthy individuals (Antal *et al.*, 2004; Fregni *et al.*, 2005; Fecteau *et al.*, 2007; Zaehle *et al.*, 2011). Importantly, beneficial cognitive effects following DLPFC stimulation have also been demonstrated in relevant clinical populations, including patients with Alzheimer's disease and Parkinson's disease (Elder and Taylor, 2014). Additionally, these positive effects may persist beyond the immediate period of stimulation. For example, Doruk and colleagues (2014) recently demonstrated that in patients with Parkinson's disease, ten consecutive sessions of anodal tDCS delivered to the left or right DLPFC led to short-term and longer-term (measured one month post-stimulation) improvements in executive functioning, compared with placebo stimulation.

As attentional and executive function deficits are observed within the LBDs, this is suggestive of frontal dysfunction (Johns *et al.*, 2009). This is supported by neuropsychological studies which have observed impairments in frontally dependent attentional and executive tasks in LBD (Ballard *et al.*, 2001; Calderon *et al.*, 2001; Aarsland *et al.*, 2003); pathologically, Lewy bodies are commonly found in the anterior frontal and temporal regions (Yoshimura, 1983; Kuzuhara and Yoshimura, 1993), and in addition, neuroimaging studies have shown that frontal atrophy is a feature of LBD (Burton *et al.*, 2002, 2004). Thus, there is a broad context to suggest that there may be a reduced top-down influence of the frontal cortex in LBD. Previous studies have observed beneficial effects of DLPFC stimulation upon attention and executive functioning (Fecteau *et al.*, 2007; Gladwin *et al.*, 2012), and the left DLPFC has been implicated in top-down cognitive control (MacDonald *et al.*, 2000). Given this empirical and theoretical basis, we therefore hypothesized that the application of anodal tDCS to the DLPFC might benefit attentional and executive function in individuals with LBD. However, to date, the feasibility and tolerability, or the potential benefits of tDCS upon attentional and executive function, have not been examined in an LBD patient group.

Therefore, the primary aim of this preliminary study was to assess the feasibility of using tDCS in individuals with LBD, and to investigate the effects of tDCS upon attentional function in LBD.

Methods

Participants

Sixteen participants who met diagnostic criteria for either probable DLB or PDD (McKeith *et al.*, 2005; Emre *et al.*, 2007), as assessed by two experienced clinicians (J.P.T. and H.K.), were recruited from the movement disorders service at the Institute of Neurosciences, Kolkata, India. The diagnosis was verified by detailed physical, neurological, and neuropsychiatric examinations, including hematology and biochemistry screening, thyroid function, syphilis serology, vitamin B12 and folate level tests, and chest X-rays. Structural imaging (magnetic resonance imaging or computed tomography scans) were performed on six of the 16 participants, when clinically suggested, in order to exclude other neurodegenerative etiologies.

Participants were included if they were ≥ 60 years of age; had a Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975) score of ≥ 16 ; and were stable on anti-Parkinsonian medication or cholinesterase inhibitors for a period of one month prior to participation. Exclusion criteria included skin allergies; a history of excess alcohol intake; concurrent major psychiatric illness; significant/severe physical illness or comorbidities; other neurological disorders; current/previous visual impairment due to glaucoma, cataract, or macular degeneration; metallic or electronic implants; and significant motor fluctuations. All participants provided written informed consent and the study was approved by the local ethics committee.

Measures

Participants completed several clinical measures of cognitive and motor function prior to stimulation in order to provide information regarding disease severity. These included the MMSE (Folstein *et al.*, 1975), the Montreal Cognitive Assessment (MoCA; Nasreddine *et al.*, 2005) and Part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III; Goetz *et al.*, 2008).

Medication use

Information regarding the use of cholinesterase inhibitors, anti-depressant and anti-Parkinsonian medication was also obtained. The anti-Parkinsonian medication equivalent levodopa dose was calculated, using levodopa conversion formulae reported elsewhere (Tomlinson *et al.*, 2010), and is expressed in milligrams (mg).

Procedure

Participants completed one brief practice session of the attentional and visuo-perceptual tasks, consisting

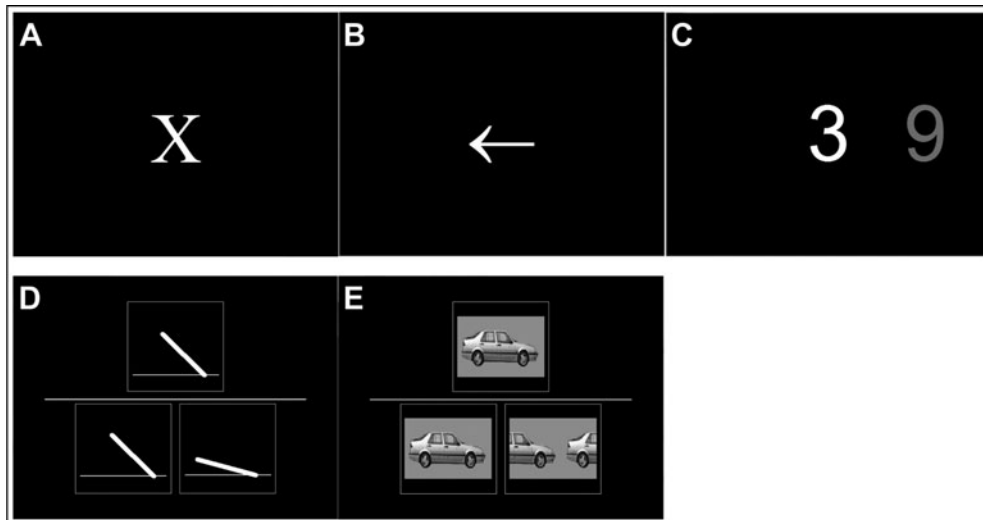


Figure 1. Attentional and visuoperceptual tasks. Task A (simple reaction time): a target (X) was displayed (maximum 3,000 ms with a varying inter-stimulus interval) and participants were required to respond as quickly as possible. Task B (choice reaction time): Participants were required to respond to an arrow, which pointed left or right (displayed for a maximum of 3,000 ms) as quickly as possible and indicating the direction in which the arrow pointed. Task C (digit vigilance): Participants were required to respond to the target digit (9; displayed on the right of the screen) when the digit displayed in the center of the screen (0–9; cycling at a rate of 500 ms) matched the target. Tasks D (angle) and E (motion perception): Participants were required to indicate whether the item displayed on the bottom left or the bottom right matched the target item (displayed in the top center of the screen) in terms of the angle (Task D) or the speed of motion (Task E). For both visuoperceptual tasks (Tasks D and E), the difficulty levels for both tasks were adjusted depending on whether the previous trial was correct, where a correct answer increased the difficulty by one step and an incorrect answer reduced the difficulty by three steps.

of five practice trials per task. Participants then completed one full run of the computer tasks (lasting for approximately 10 min) immediately prior to stimulation, and repeated the tasks 10 min post-stimulation. Participants were tested in their “on” state with regard to their Parkinsonism; this was verified by ensuring that dopaminergic medication had been administered in the previous 2 h and by assessment of motor function immediately prior to stimulation.

Three attentional (simple reaction time (SRT); choice reaction time (CRT); digit vigilance (DV)); and two forced-choice visuoperceptual (angle and motion perception) tasks were used; these tasks have previously been demonstrated to be differentially affected in LBD patients compared with controls and other dementia groups (Wesnes *et al.*, 2002; Mosimann *et al.*, 2004). These visuoperceptual tasks are not dependent upon prefrontal regions (Wood *et al.*, 2011) and performance was therefore hypothesized to be unlikely to be affected by DLPFC stimulation. Full details of the tasks are described elsewhere (Mosimann *et al.*, 2004; Wood *et al.*, 2011; 2013) and in Figure 1. Tasks were presented on a laptop PC and responses were recorded using response button boxes, which were held either in the dominant hand or in both hands, depending on the task.

Transcranial direct current stimulation

A single session of stimulation (2.8 mA) was delivered for 20 min using an Eldith DC Stimulator (Magstim, Whitland, UK), through two 35-cm² electrodes in 0.9% saline-soaked bags (equivalent current density: 0.08 mA/cm²). This level of current density has been previously used, with no reported adverse effects, in other dementia cohort studies (Huey *et al.*, 2007; Cotelli *et al.*, 2014). The anodal electrode was placed over the left DLPFC (50% between F₃ and FP₁) using the International 10–20 system (Jasper, 1958). The cathodal electrode was placed on the right deltoid muscle. All participants received active stimulation. After the stimulation session, participants were asked to provide feedback regarding their experience of the stimulation; similarly, patients and their families were contacted 24 h post-stimulation and were asked whether any residual side effects were present.

Statistical analysis

Attentional and visuoperceptual task performances were compared before and after stimulation using paired t-tests. Attentional (SRT, CRT, and DV) task outcome measures included the percentage of correct answers and the mean reaction time (RT) to correct answers. Visuoperceptual outcome

Table 1. Participant demographic and assessment data ($n = 13$)

	DLB ($n = 5$)	PDD ($n = 8$)
Age (years): mean (SD)	65.00 (7.71)	64.63 (8.16)
Gender: (male/female)	3/2	7/1
Duration of motor symptoms (years since onset): mean (SD)	3.80 (2.39)	11.75 (3.73)
Duration of cognitive symptoms (years since onset): mean (SD)	4.00 (2.91)	2.63 (1.51)
Presence of visual hallucinations: n (%)	2 (40)	7 (87.5)
Presence of delusions: n (%)	3 (60)	7 (87.5)
Presence of apathy: n (%)	4 (80)	8 (100)
Presence of excessive daytime sleepiness: n (%)	2 (40)	4 (50)
Presence of depression or anxiety: n (%)	3 (60)	6 (75)
Presence of cognitive fluctuations: n (%)	3 (60)	6 (75)
MMSE: mean (SD)	20.60 (3.05)	22.00 (2.56)
MoCA: mean (SD)	17.60 (3.65)	19.38 (2.45)
UPDRS-III: mean (SD) ^a	12.75 (5.56)	28.50 (9.44)
On cholinesterase inhibitors: n (%)	1 (20)	0 (0)
On anti-Parkinsonian medication, n (%)	5 (100)	8 (100)
On anti-depressant medication, n (%)	0 (0)	3 (37.5)
Levodopa equivalent dose (mg): mean (SD)	320.00 (168.08)	935.50 (599.38)

Notes: DLB: Dementia with Lewy bodies; PDD: Parkinson's disease with dementia; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; UPDRS-III: Unified Parkinson's Disease Rating Scale Motor Subscale.

^aUPDRS-III data missing for one participant.

measures included the percentage of correct answers and the task difficulty, expressed either as degree values (angle task, where a lower degree value indicates better performance) or relative speed values (cars task, where a lower relative speed indicates a better performance). Outliers (≥ 2 SD) were removed from each RT task. As the aim of the current preliminary study was to assess the feasibility and tolerability of tDCS in LBD participants, analyses were not adjusted for multiple comparisons. Effect sizes are reported as Cohen's d_z .

Results

Three participants were excluded from the study prior to stimulation, due to a poor understanding of task instructions. This resulted in a final sample of 13 participants (8 PDD; 5 DLB; Mean, $M_{\text{age}} = 64.77$ years, $SD_{\text{age}} = 7.66$ years). Demographic details are included in Table 1. All participants tolerated stimulation and did not report any side effects, other than a brief tingling sensation underneath the electrodes, during or immediately after stimulation. No adverse events were reported.

The percentage of CRT correct answers significantly increased following stimulation ($t(12) = -2.98$, $p = 0.01$, $d_z = 0.83$). DV improvements were also shown, where the mean RT to correct answers ($t(11) = 2.77$, $p = 0.02$, $d_z = 0.80$) was significantly reduced following stimulation. Eleven participants (84.6%) showed a positive CRT task response, displaying an increased percentage of

correct answers following stimulation, and nine participants (69.2%) showed a positive DV task response, with a reduced mean RT to correct answers following stimulation. No other significant post-stimulation differences were shown in the remaining attentional or visuoperceptual tasks (all p -values > 0.05). The results are summarized in Table 2.

Discussion

This preliminary study indicates that the use of tDCS, with a current density of 0.08 mA/cm^2 , is both feasible and well-tolerated in a group of individuals with LBD, as no residual post-stimulation side effects were reported by participants or their families. This study also demonstrated that a single 20-min session of tDCS, applied to the left DLPFC, led to post-stimulation improvements to some aspects of attentional, but not visuoperceptual, function in LBD patients. In particular, there were improvements in CRT accuracy and in DV reaction times, although there was also a broader tendency for post-stimulation improvements in all other CRT and DV attentional measures. This differential benefit is likely to be due to the placement of electrode over the DLPFC rather than parietal or visual areas, since previous studies have shown that stimulation delivered to the DLPFC enhances working memory and decision-making (Fregni *et al.*, 2005; Fecteau *et al.*, 2007), and in the case of left DLPFC stimulation, can enhance attentional function (Gladwin *et al.*,

Table 2. Attention and visuo-perceptual task performance pre- and post-tDCS stimulation ($n = 13$)

ATTENTION TASKS	PRE-STIMULATION		POST-STIMULATION		
	MEAN	SD	MEAN	SD	EFFECT SIZE (d_z)
SRT: correct answers (%)	94.87	7.77	94.36	8.86	0.13
SRT: mean RT (ms; correct answers) ^a	454.65	130.63	453.65	139.41	0.01
CRT: correct answers (%)	71.79*	28.34	87.69*	20.92	0.83
CRT: mean RT (ms; correct answers) ^a	620.44	202.90	608.78	157.18	0.12
DV: correct answers (%)	75.64	15.60	81.41	26.53	0.30
DV: mean RT (ms; correct answers) ^a	632.85*	100.16	582.93*	58.42	0.80
<i>Visuo-perceptual tasks</i>					
Angle: correct answers (%)	85.11	7.36	84.88	7.15	0.02
Angle: difficulty (degrees) ^b	24.01	16.56	23.63	18.99	0.02
Motion: correct answers (%)	70.36	13.18	75.90	11.49	0.44
Motion: difficulty (relative speed) ^c	2.61	0.97	2.56	1.00	0.07

Notes: SRT: simple reaction time; CRT: choice reaction time; DVT: digit vigilance; ms: milliseconds; RT: reaction time.

^a $n = 12$.

^bLower degree value indicates better performance.

^cLower relative speed indicates better performance.

* $p < 0.05$.

2012). Speculatively, our data suggest that as the left DLPFC has a suggested role in top-down cognitive control (MacDonald *et al.*, 2000), anodal stimulation, which can modulate cortical excitability by increasing the membrane potential (Stagg and Nitsche, 2011), might help improve the degree of top-down influence of the left DLPFC in LBD.

Whilst not placebo-controlled, the results of the present study may also support the notion that visuo-perceptual performance in LBD is less dependent on fronto-executive function; posterior cortical function may be more relevant for these tasks and this would be consistent with the parieto-occipital deficits apparent in LBD (Colloby *et al.*, 2002). It is likely that task-specific electrode montages will be needed to improve visuo-perceptual function in LBD; the application of anodal stimulation to right parietal areas has been shown to result in visuo-perceptual improvements within healthy individuals (Bolognini *et al.*, 2010). Therefore, the efficacy of anodal stimulation to parietal areas should be tested within LBD.

Limitations of the current study include the absence of a sham condition and the lack of correction for multiple comparisons in our analyses. However, by its nature, this study is exploratory in terms of highlighting potential benefits, determining tolerability, and helping to inform stimulation parameters; the details of which are currently lacking in LBD and can be determined by studies with small sample sizes and studies that are open-label in design (Elder and Taylor, 2014). Although the present study assessed a small sample of patients, a current density of 0.08 mA/cm²,

delivered for a period of 20 min, was shown to be both acceptable and tolerable in LBD patients. Whilst this level of current density has previously been used in other dementia cohort studies (Huey *et al.*, 2007; Cotelli *et al.*, 2014), this has not been the case in LBD, and importantly, these stimulation parameters could be used in future placebo-controlled studies in LBD.

While post-stimulation performance improvements were not observed across all task measures, the influence of training effects cannot be excluded from the present study. For this reason, placebo-controlled trials are necessary to confirm these results. However, the present study contributes important pilot data in LBD, as it has been recommended that the results of all studies, including those which are negative, are reported in order to advance the clinical utility of tDCS and to allow the inclusion of eligible studies in future meta-analyses (Elder and Taylor, 2014).

Finally, it was not possible to examine whether stimulation differentially benefits DLB or PDD patients in the present study; certainly whilst there is significant overlap neuropathologically and clinically between both conditions (McKeith *et al.*, 2005; Emre *et al.*, 2007; Lippa *et al.*, 2007), differences between the two groups have been suggested (Park *et al.*, 2011). Nevertheless, these preliminary data suggest that tDCS may benefit both patient populations, thus supporting large-scale trials in both patient groups.

In conclusion, this study indicates that tDCS is feasible and is well tolerated in an LBD population, adding to the current lack of data in this patient group. This study also provides tentative evidence

to suggest that the delivery of tDCS to the left DLPFC might benefit attentional function in LBD. However, larger placebo-controlled trials with repeated stimulation sessions are needed, and are now justified, in an LBD population to confirm this; promising data in PD have suggested that tDCS can offer sustained benefits upon executive functioning (Doruk *et al.*, 2014) and it would be relevant to explore if these effects are carried over into LBD.

Conflict of interest

None.

Description of authors' roles

G. J. Elder conceived and designed the study, analyzed and interpreted the data, and drafted the manuscript. M. J. Firbank analyzed and interpreted the data, and revised the manuscript. H. Kumar, P. Chatterjee, T. Chakraborty, and A. Dutt conceived and designed the study, assisted with the recruitment of participants, and revised the manuscript. J-P Taylor conceived and designed the study, analyzed and interpreted the data and revised the manuscript. All authors have approved the final version of the manuscript.

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