Transcranial direct current stimulation for Alzheimer disease

ORIGINAL ARTICLE

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ABSTRACT

Background. Alzheimer disease (AD) is the most common form of senile dementia, with an incidence of 1% to 3% in the general population. Currently, there is no cure for AD, and treatments are mainly drug-based. Transcranial direct current stimulation (tDCS) is a non-invasive method to induce brain plasticity. This study aimed to investigate the effects of 10 days of tDCS over the left frontotemporal cortex on cognitive and neurophysiological functioning in AD patients.

Methods. 26 patients with AD aged 70 to 85 years were randomised to receive tDCS of the left frontotemporal cortex (n=15) or sham tDCS (n=11). Cognitive and neurophysiological functions were assessed before and after tDCS using the Milan Overall Dementia Assessment and electroencephalography (for alpha and beta bands and P300 latency and amplitude).

Results. tDCS resulted in increased cognitive functions in terms of temporal orientation, spatial orientation, reversal learning, verbal intelligence, story, production of word, and attention, as well as increased beta band and decreased P300 latency.

Conclusion. tDCS is simple, safe, inexpensive, and non-invasive method to enhance cognitive functions in patients with AD.

Key words: Alzheimer disease; Electroencephalography; Transcranial direct current stimulation

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INTRODUCTION

In Italy in 2018, 35% of the population were aged ≥ 65 years, and the life expectancy was 80.8 years for men and 85.2 years for women. Alzheimer disease (AD) is the most common form of senile dementia, affecting 10% of people older than 65 years and nearly 50% of those older than 85 years, with an incidence of 1% to 3% in the general population. It is a chronic illness with long preclinical and prodromal phases (20 years) and an average disease duration of 8 to 10 years. AD is a neurodegenerative disorder characterised by a gradual decline in numerous cognitive processes.^{1,2} On neuroimaging, AD is associated with pathological and structural changes in the brain, especially in the temporal cortex.³ On quantitative electroencephalography,

AD is characterised by increased theta power, decreased alpha and beta power, and decreased coherence in the alpha and theta band in posterior regions.⁴ These abnormalities are associated with functional disconnections of cortical areas, death of cortical neurons, axonal pathology, and cholinergic deficits, resulting in dysfunction of specific cortical areas.⁴

AD is the result of accumulation of amyloid plaques and neurofibrillary tangles. Amyloid plaques are located between neurons as dense clusters of beta-amyloid molecules, a sticky type of protein that clumps together. Amyloid plaques cause tiny filaments called microtubules to twist and disrupt the transportation of nutrients and organelles. Neurofibrillary tangles are found inside the neurons

of the brain and are caused by defective tau proteins that clump into a thick, insoluble mass.

AD behavioural effects are caused by changes in neuronal activity (changes in modulatory transmitter systems and network connectivity) secondary to the disease process; therapies that address these changes have been reported.⁵⁻¹⁰

Transcranial direct current stimulation (tDCS) is a simple, safe, inexpensive, and non-invasive method of brain stimulation. Small electrodes are placed on the scalp above the involved area. tDCS induces prolonged functional changes in the cerebral cortex through synaptic and non-synaptic mechanisms and facilitates cortical excitability and hence neuroplasticity.^{9,11-15} tDCS over the frontotemporal area improves memory in patients with AD.^{11,15} tDCS of the temporal cortex enhances name recall in healthy elderly persons¹⁶ and improves recognition memory in patients with AD.^{17,18} tDCS improves the performance of recognition tasks in patients with AD.¹² However, evidence remains insufficient to support tDCS as an intervention for AD; placebo-controlled trials are thus warranted to assess the efficacy of tDCS of the temporal cortex in patients with AD. This study aimed to investigate the effects of 10 days of tDCS over the left frontotemporal cortex on cognitive and neurophysiological functioning in AD patients.

METHODS

The study was conducted according to the Declaration of Helsinki and approved by the university research ethics committee (Reference: 2016-36). Informed consent was given by patients and their caregivers. The definition of AD was based on the National Institute of Neurological Communicative Disorders and Stroke, the Alzheimer disease and Related Disorders Association, and the Diagnostic and Statistical Manual of Mental Disorders version V. Patients with a Mini-Mental State Examination score of 12 to 25 (adjusted to the level of education) were included. Those with other neuropsychiatric diseases were excluded. 26 patients with AD aged 70 to 85 years were randomised to receive tDCS of the left frontotemporal cortex (n=15) or sham tDCS (n=11) [TABLE 1]. All patients were under treatment with cholinesterase inhibitors, and the dosage was the same during the study.

For tDCS, direct current was transferred via a saline-soaked pair of surface sponge electrodes (35 cm²) by a battery-driven, constant-current stimulator. According to the 10-20 international system for electroencephalographic electrodes placement, the dorsolateral prefrontal cortex was stimulated with the anode electrode placed over F3-F7, and the left temporal cortex was stimulated with an anode electrode placed over F7. The reference cathode electrode was placed over the right supraorbital area. The dorsolateral prefrontal cortex is associated with working memory performance, according to neuroimaging, repetitive transcranial magnetic stimulation, and tDCS studies. Patients and examiners were blind to the type of tDCS.

Cognitive function was assessed before and after tDCS using the Milan Overall Dementia Assessment (MODA).^{19,20} The test-retest reliability of MODA was 0.83.²⁰ MODA comprises one behavioural scale and two test sections. The behavioural scale measures five activities of daily living: walking, dressing, personal hygiene, control of sphincters, and eating. Answers are sought from a close relative. Scores for each aspect range from 0 (in need of total supervision) to 3 (total autonomy), with an overall score of 0 to 15.

The first test section assesses (1) temporal orientation (5 questions on the day of the week, the date of the month, the month, the year, and the time of day, with scores range from 0 to 10), (2) spatial orientation (3 questions on topographical information on the town and country, with scores range from 0 to 3), (3) personal orientation (7 questions on personal background, with scores range from 0 to 10. Standardised items are weighted differently according to face value difficulty), and (4) family orientation (12 questions on name and age of four different family members, and whether they are alive or dead, with scores range from 0 to 12). Total scores range from 0 to 35.

The second test section is based on an Italian standardised series of neuropsychological tests and assesses attention (digit cancellation, reversal learning), intelligence (logical reasoning), memory (prose memory), language (verbal comprehension, fluency), space cognition (finger agnosia, constructional apraxia), and visual perception (figure completion, street test). Only the easiest items were

TABLE 1
Demographic data of 26 patients with Alzheimer disease

Patient	Sex/ age, y	Education, y	Mini Mental State Examination score	Disease duration, y
Transcranial direct current stimulation (tDCS) group (n=15)				
1	M/72	5	22	3
2	M/70	8	18	4
3	M/83	5	18	3
4	F/76	10	23	1
5	M/81	3	22	1
6	F/71	8	20	2
7	F/79	5	20	3
8	M/77	5	19	2
9	F/72	7	22	3
10	M/69	8	21	3
11	M/68	8	20	2
12	M/71	8	19	3
13	F/73	7	21	2
14	M/75	8	20	1
15	F/73	8	17	2
Sham tDCS group (n=11)				
1	F/69	5	20	3
2	F/70	8	18	4
3	F/80	5	19	3
4	F/76	8	21	1
5	M/81	4	22	2
6	F/70	8	20	2
7	M/77	5	20	1
8	M/77	5	19	1
9	M/71	7	22	2
10	F/80	8	21	1
11	M/74	8	21	2

chosen to avoid a 'floor performance' in demented patients. Total scores range from 0 to 50.

In addition, the effects of tDCS on beta and alpha bands and on P300 latency and amplitude were evaluated using electroencephalography. P300 reflects attention, stimulus evaluation, judgment, and decision-making. P300 latency increases in patients with AD compared with those without AD,⁵ but there is no consensus on P300 amplitude.

Statistical analysis was performed using SPSS (Windows version 22; IBM Corp, Armonk [NY], US). Level of significance was set at $\alpha=0.05$. The Kolmogorov-Smirnov test was used to ascertain normal distribution of data. The tDCS and sham tDCS groups were compared in terms of MODA scores. Repeated-measures analysis of variance of between-group (group) and within-group (phase and subscale) factors were performed to detect the effects of time on dependent variables. Bonferroni corrected t tests were used for post-hoc analysis ($p<0.01$).

RESULTS

There was no adverse effect associated with tDCS. Repeated-measures analysis of variance showed that the effect of group was not significant, but the effect of the phase $\times$ group interaction was significant ($F(1,24)=12.98$, $p<0.001$), as was the effect of time $\times$ phase $\times$ subscale interaction ($F(1,24)=12.96$, $p<0.01$) [TABLE 2]. This indicated that sham tDCS resulted in a stable trend over time, whereas tDCS resulted in an increase trend in some subscales over time. Post-hoc analysis was conducted separately for the two groups.

From pre-test to post-test, tDCS significantly improved cognitive functions in terms of temporal orientation ($t(14)=1.99$, $p<0.05$), spatial orientation ($t(14)=2.01$, $p<0.05$), reversal learning ($t(14)=2.87$, $p<0.01$), verbal intelligence ($t(14)=2.19$, $p<0.04$), story test ($t(14)=2.89$, $p<0.01$), production of word ($t(14)=2.23$, $p<0.04$), and attention ($t(14)=1.99$, $p<0.05$). However, sham tDCS resulted in significantly decreased cognitive functions in terms of temporal orientation ($t(9)=2.51$, $p<0.05$), verbal intelligence ($t(10)=2.25$, $p<0.05$), and street test ($t(10)=2.89$, $p<0.05$).

The effect of time $\times$ phase interaction was significant in P300 latency ($F(1,24)=7.16$; $p<0.01$, TABLE 3). This indicated that only tDCS resulted in decreased P300 latency. In addition, from pre-test to post-test tDCS resulted in increased beta band ($t(14)=3.34$, $p<0.01$, TABLE 3).

DISCUSSION

tDCS resulted in increased cognitive functions in terms of temporal orientation, spatial orientation, reversal learning, verbal intelligence, story test,

TABLE 2
Milan Overall Dementia Assessment (MODA) subscale scores before and after transcranial direct current stimulation (tDCS)

MODA subscale	Pre-test		Post-test	
	tDCS group	Sham tDCS group	tDCS group	Sham tDCS group
Temporal orientation	4.20±1.373	3.60±0.699	4.87±1.187	2.70±0.675
Spatial orientation	2.27±0.799	2.00±0.471	2.80±0.862	1.90±0.316
Personal orientation	8.53±0.919	8.20±0.919	8.07±0.961	7.50±0.850
Family orientation	8.60±1.056	9.40±1.174	8.73±2.086	8.70±0.949
Autonomies	11.80±1.740	12.30±1.337	11.07±1.831	11.70±1.059
Reversal learning	3.53±0.743	3.90±0.876	4.20±0.676	3.70±0.823
Verbal intelligence	3.80±1.146	4.40±1.075	4.53±0.990	3.20±1.033
Story test	3.60±0.986	3.90±0.876	4.27±0.594	3.50±1.080
Production words	3.27±1.438	3.10±0.876	2.60±1.454	2.90±0.919
Token test	4.87±0.516	4.60±0.516	4.60±0.910	4.30±0.949
Digital agnosia	3.53±0.990	3.10±1.370	3.47±0.915	2.90±1.197
Constructive apraxia	2.73±0.799	2.10±0.994	2.73±0.594	1.80±0.789
Street test	2.60±0.632	2.00±0.943	2.60±0.632	1.80±0.789
Attentional test	8.20±1.320	8.50±0.850	8.93±0.799	8.20±0.789

TABLE 3
Alpha and beta bands and P300 latency before and after transcranial direct current stimulation (tDCS)

Test	Pre-test		Post-test	
	tDCS group	Sham tDCS group	tDCS group	Sham tDCS group
Alpha band	8.3±0.403	8.3±0.411	8.5±0.435	8.1±0.582
Beta band	13.3±1.6	13.5±1.4	15.4±1.0	13.4±1.5
P300 latency	351.4±28.9	358.6±30.6	332.6±21.7	356.9±32.6

production of word, and attention, as well as increased beta band and decreased P300 latency. Our results differed from those reported no increase in memory performance after tDCS.²¹ This may be because our patients had less severe AD and thus were more receptive to tDCS, which is less effective in advanced stages of AD with reduced neuroplasticity (long-term potentiation).²¹ Nonetheless, our results are in accordance with other studies.^{9,11,12,14,15} For example, one study reported increased visual recognition memory scores by 8.9% at 1 month after 5 consecutive days of 30-minute tDCS of the temporal cortex in patients with AD.¹¹

One limitation of the present study was the small sample size, and thus interpretation of findings

should be cautious. Large-scale randomised controlled studies are warranted. In addition, comparison of different levels of severity of AD is necessary, as AD is associated with reduced neuroplasticity (long-term potentiation), which is inversely associated with severity.²¹ In addition, there may have been test-retest discrepancy of MODA. In our study, MODA scores showed no coherence, although a study of 186 AD patients reported adequate ($r=0.83$) test-retest reliability of MODA.²² Thus, it is necessary to compare MODA with different cognitive tests to assess the level of coherence between different cognitive processes. Longitudinal follow-up studies are warranted to assess whether cognitive functions after tDCS increase with time, and to what extent severity of

AD is predictive of levels of neuroplasticity. Further studies are needed to determine the role of tDCS in treatment of AD and what professional support is needed for this increasing patient group.

CONCLUSION

tDCS is simple, safe, inexpensive, and non-invasive method to enhance cognitive functions in patients with AD.

DECLARATION

The authors had no affiliations with or involvement in any organisation or entity with any financial interest (such as honoraria, educational grants, membership, employment, consultancies, stock ownership, other equity interest, expert testimony, or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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