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Effects of anodal tDCS on motor and cognitive function in a patient with multiple system atrophy

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ABSTRACT

Purpose: Multiple system atrophy (MSA) is a progressive neurodegenerative disease characterized by postural instability, autonomic failure, cerebellar ataxia, and cognitive deficits. There is currently no effective cure. Transcranial direct current stimulation (tDCS), offers promise in amendment of motor, and cognitive performance in advanced Parkinson’s disease.

Case description: We estimated the effect of anodal tDCS on motor and cognitive function in a 66-year-old woman with moderate MSA. For the evaluation of the motor function, we used the Unified MSA Rating Scale II, the Unified Parkinson’s Disease Rating Scale Part III (UPDRS III), and the Timed Up and Go test (TUG). The battery of neuropsychological tests included the Rey’s Auditory Verbal Learning Test (RAVLT) and the Digit Symbol Substitution Test-Wechsler Adult Intelligence (DSST-WAIS-III), the Trail Making Test (TMT-A). tDCS was applied in 10 sessions. Clinical evaluations were performed at baseline, day 11, day 30, and at day 90.

Results: Anodal stimulation was associated with improvement in UPDRS III and the TUG test. A positive effect was also seen in RAVLT the DSST-WAIS-III and the TMT-A.

Conclusions: Our results suggest that tDCS has a beneficial effect mainly on motor performance in MSA, which lasts beyond the duration of the treatment.

IMPLICATIONS FOR REHABILITATION

- Multiple system atrophy is a progressive neurodegenerative disease characterized by postural instability, motor, and cognitive deficits.
- Transcranial direct current stimulation offers promise in amendment of motor and cognitive performance in advanced Parkinson’s disease.
- Stimulation was associated with significant improvement in Unified Parkinson’s Disease Rating Scale Part III and the Timed Up and Go test.
- A positive effect was also seen in auditory-verbal memory and learning in working memory and in visuomotor activity and processing speed.
- Transcranial direct current stimulation has a beneficial effect mainly on motor performance, which lasts beyond the duration of the treatment.

Introduction

Multiple system atrophy (MSA) is a progressive neurodegenerative disease belongs to the wider spectrum of parkinsonian syndromes. Neuropathologically, MSA is characterized by glial cytoplasmic inclusions of abnormally aggregated α-synuclein. Neuronal cytoplasmic and nuclear inclusions of α-synuclein have also been reported [1–4]. Parkinsonism poorly responsive to levodopa, autonomic failure, cerebellar ataxia, corticospinal dysfunction, postural instability, and gait disorders is some of the clinical features of MSA [5].

Unfortunately, there is currently no effective cure. Management of the disease involves treating symptoms and avoiding potential complications. The recent controlled trials in MSA aim to develop effective symptomatic or disease-modifying treatments [6]. Although the first outcomes are rather inconclusive the increase of the ongoing clinical research for this devastating disease is encouraging.

It has been demonstrated that transcranial direct current stimulation (tDCS), a noninvasive brain stimulation method, offers promise in ameliorating bradykinesia and improving gait and postural control in advanced Parkinson’s disease [7–10]. The possible modulating effects of tDCS on cortical excitability has raised interest in the application of the technique for the promotion of cognitive and executive function as it has been shown in the studies that emerged during the last decade [11,12]. Besides, current studies have highlighted the therapeutic potential of tDCS in patients with cerebellar ataxias and the cerebellar variant of MSA (MSA-C) [13–16]. tDCS is a safe, simple, well tolerated, and cost-effective method. Therefore, we explored the effect of anodal tDCS over primary motor and pre-motor cortices on motor...
performance in a patient with moderate to severe MSA. The secondary endpoint of interest was the possible change of neuropsychological parameters after the tDCS application.

Materials and methods

Participant

We applied anodal tDCS over the primary motor and pre-motor cortices in a 66-year-old woman with moderate MSA-P according to the current clinical criteria [5] (unified Parkinson’s disease rating scale part III (UPDRS III) = 47, unified MSA rating scale II (UMSARS) = 23, Hoehn and Yahr (H&Y) scale = stage 4; disease duration = 5 years). She weighed 62 kg and her body mass index was 24.2. Her medication included levodopa, and amantadine. The doses of the medication did not change during the study. At baseline, her Mini-mental state examination (MMSE) score was 24 points. The participant had no other relevant neurologic or psychiatric disease. The ethical committee of the Evangelismos Hospital approved the study and informed consent was obtained.

Scales

For the evaluation of the motor function, we used the UMSARS [17], the UPDRS III [18], and the timed up and go test (TUG) (timed in seconds) [19]. The time that the patient took to rise from an office chair with arms, walk three meters, turn around, walk back to the chair, and sit down was calculated according to standard practice. Activities of daily living were assessed with the UMSARS I and UPDRS II (item 12). Neurological evaluations also included the Schwab and England [20] and the Hoehn and Yahr [21] scales. A battery of neuropsychological tests has been also used. A brief assessment of the participant’s mental state was obtained with MMSE [22]. Auditory-verbal memory and learning were evaluated with Rey’s Auditory Verbal Learning Test (RAVLT) [23]. Visuomotor activity and processing speed were evaluated with Digit Symbol Substitution Test-Wechsler Adult Intelligence (DSST-WAIS-III) [23]. For the working memory assessment, digit span (Forward & Backward) [24] and Trail Making Test (TMT-A) [25] were used. All measurements took place on day 0 (baseline), at 11 d (end of the intervention) and finally, during at 1- and 3-months post-intervention follow-up assessment.

tDCS

Direct current was applied through a saline-soaked pair of surface sponge electrodes surface (35 cm²) and delivered by a battery-driven, constant current stimulator (Sooma tDCS™, Helsinki, Finland). During the tDCS stimulation, a constant current of 2 mA was delivered for 30 min. To stimulate motor and pre-motor cortices the electrode was placed centrally across the scalp 8 mm anterior to Cz. Cathodes were positioned over the mastoids.

Study design

tDCS was applied in 10 sessions over two weeks (Monday–Friday) with a weekend interval washout period. During both stimulation and the clinical evaluation phases, the patient was in “on” medication condition. Clinical evaluations were performed on day 0 (visit 0: baseline), day 11 (visit 2:24 h after the 10th session), day 30 (visit 3), and on day 90 (visit 4).

Results

Effect of tDCS on motor function

Parkinsonian motor disability (UPDRS III) improved by 36.2% at day 11, 17% at 1 month and 12.8% at 3 months compared to baseline (Table 1). More specifically, the beneficial effect of stimulation was more obvious in posture and leg agility at the end of the stimulation protocol (day 11). However, the patient failed to maintain such therapeutic gains as seen during follow-up. With regard to tremor, rigidity, and upper limb bradykinesia the improvement was not striking. In terms of UMSARS II scores, no improvement was shown until the first month after the stimulation protocol completion. A mild deterioration was seen in the final follow-up visit (Table 1).

The time required to complete the 3 m TUG was reduced by 33.5% compared to baseline at 11 d, 34.7% at 1 month and 30.6% at 3 months respectively (Table 1, Figure 1).

Effect of tDCS on the activities of daily living

tDCS application had a positive effect on the activities of daily life as it was reflected on UMSARS I (Table 1). The most pronounced effect was on the activity of turning in bed and adjusting bed clothes (UPDRS II, item 12), which was improved and remained so until the last follow up visit. The activities of daily living were gradually improved during the observation period. Nevertheless, the stage of the disease did not change (Table 1).

Effect of tDCS on cognitive function

MMSE score (Table 1) improved by 15.4% at 11 d, 3.8% at 1 month, and 11.5% at 3 months.
A positive effect was also seen in DSST-WAIS-III (increase by 20.8, 16.7, and 4.1 at day 11, 1 and 3 months, respectively) (Table 1). In the RAVLT, the score increased from baseline to post-intervention by 61.5% and then decreased by 42.3 and 46.2% at 1 and 3 months, respectively (Table 1).

Discussion

To our knowledge, this study was the first to investigate the effect of anodal stimulation of the motor and pre-motor cortices in a patient with MSA-P. The main finding of our study was the improvement of the motor performance with regard to walking speed and leg bradykinesia. The anodal stimulation application was associated with improvement in the motor part of UPDRS (UPDRSIII). However, the results were not similar regarding the motor component of UMSARS (UMSARS II). A possible explanation is that these rating scales include different items. The effects on upper extremity bradykinesia and rigidity were equivocal. With regard to tremor mild deterioration was seen on the final visit. Apart from the above-mentioned tDCS’ beneficial effects in the motor domain, it also led to cognitive improvements, as seen in patients’ general mental status (MMSE), speed of processing and visuomotor coordination (DSST), auditory-verbal memory, and learning (RAVLT) performance.

Besides the motor disability, cognitive impairment is a well-known manifestation of PD and MSA-P [26]. Particularly, in MSA-P and PD [27], whereas striatal neurons impairment may lead to secondary frontal symptoms due to dorsolateral prefrontal cortex (DLPFC)-striatal loop disruption [28].

Direct cortical stimulation of M1 constitutes the classical theory which explains the beneficial effect of tDCS on intended movements. A number of reports demonstrate involvement of primary sensorimotor cortices, premotor cortices, and supplementary motor areas in MSA patients. Thus, motor cortices’ degeneration in combination with nigrostriatal pathway pathology constitutes an altered motor circuit that may be responsible for the impaired functionality observed [29,30].

Recent research on repetitive transcranial magnetic stimulation (rTMS) interventions in MSA-P patients showed that increased cerebellar activation may occur post-treatment [31,32]. Wang et al. [32] found motor improvement in MSA-P patients after rTMS over left M1, with the latter inducing increased cerebellar activation; thus, causal influence from M1 to the cerebellar dentate nucleus (DN) was attenuated in MSA-P, implying that the cerebellum exerts its influence on inhibitory cortical activity [33]. The latter has been proposed as a putative underlying pathophysiological hypothesis to account for motor impairment.

Connectivity changes mainly related to cerebellar and limbic networks from the default mode network (DMN) have been reported following rTMS over M1[27]. DMN include the medial temporal lobe/parahippocampal gyrus, medial prefrontal cortex, lateral parietal cortex/angular gyrus, and posterior cingulate cortex (PCC)/precuneus [34]. In a prototypical study, conducted by Franciotti et al. [35], it has been seen that MSA-P patients showed a significantly enhanced causal connectivity from DN to posterior cingulated cortex (PCC) as compared to PD patients and healthy controls. This seems to imply that DN influence on PCC may operate as a sort of compensatory process for DMN functions since the beginning of the disease’s course. Additionally, post-rTMS auditory-verbal memory and learning (RVMT) improvement may be possibly attributed to the known rTMS effect in modulating functional links connecting the DMN, cerebellar and limbic networks [31]. Finally, we believe that amelioration in the MMSE post-rTMS performance may be seen in the light of the above mentioned neuropsychological improvements.

Decreased connectivity between cerebellar DN and DLPFC may account for aberrant cognitive and emotional processing [36,37], and may possibly explain dysfunction of motor and cognitive cortical domains in both PD and MSA-P.

Resting-state functional magnetic resonance imaging (rs-fMRI) evidence points to cerebello-cortical networks dysfunction as putative explanatory hypothesis for motor and cognitive deficits in MSA-P and PD [38]. Moreover, lesions to the cerebellum likely induce motor and cognitive impairment by affecting cortical activity via cerebellum-thalamo-cortical circuitries [39]. Disconnection of these latter circuitries may lie on the base of motor and non-motor deficits in MSA-P and PD. Nicoletti et al. [40,41] reported morphological and microstructural alterations in the cerebellum of MSA-P patients. During the past decades, cerebellum was thought to be exclusively devoted to motor coordination. By contrary, we now know that it also supports higher-order cognitive and emotional processing [36,42].

Although patients with MSA-P have a poor response to the L-dopa, our pilot data support a response to tDCS intervention which exceeds the duration of the intervention. Although the exact mechanism underlying the therapeutic effect of tDCS remains elusive, the discrepancy between said effect and that of L-dopa alludes to the possibility that the two interventions work through different biological pathways. tDCS could complement conventional therapy in MSA-P patients. Of course, our encouraging results do not mandatory imply that they could be generalized due to the small sample of the study. The gap in the literature is remarkable as the existing studies have investigated the role of tDCS in disparate patient populations. Additionally, the optimal stimulation parameters (intensity, duration, repetition of treatment) have not been identified.

Our data suggest that tDCS has a beneficial effect mainly on motor performance, and less so on cognitive function, in MSA-P, which lasts beyond the duration of the treatment and extends to up to three months. Larger randomized controlled clinical studies are needed to confirm these encouraging results.

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Disclosure statement

No potential conflict of interest was reported by the authors.

References


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