10/02/2021

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Reviews on Recent Clinical Trials, 2018, *13*, 1-8

CLINICAL TRIAL STUDY

Efficacy of Transcranial Direct Current Stimulation Combined with Cognitive Training in the Treatment of Apathy in Patients with Alzheimer's Disease: Study Protocol for a Randomized Trial

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Abstract: ***Background:*** Apathy, commonly defined as the loss of motivation, is a symptom frequently encountered in Alzheimer's disease (AD). The treatment of apathy remains challenging in the absence of any truly effective medications. Transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) can improve cognitive disorders, but do not appear to improve apathy. Isolated cognitive training also appears to have no effect on apathy.

We propose to test the efficacy of a new procedure for the treatment of apathy in AD patients consisting of a combination of tDCS and cognitive training, based on the latest guidelines for the design of therapeutic trials in this field.

Methods/Design: This article primarily describes the design of a monocentre, randomized, double-blind trial to be conducted in France to evaluate the effect of the combination of tDCS and cognitive training on apathy compared to a group treated exclusively by cognitive training (sham tDCS). Twenty-four patients under the age of 90 years with mild-to-moderate Alzheimer's disease (Mini Mental State Examination score between 15 and 26/30) (MMSE)) presenting clinically significant apathy evaluated by the Apathy Inventory (AI) and the NeuroPsychiatric Inventory (NPI) apathy subscore will be enrolled. Severe depression will be excluded by using the NPI depression subscore. Treatment will comprise 10 sessions (D0-D11) including tDCS (bilateral prefrontal, temporal and parietal targets) and cognitive training (Cog) (6 simple tasks involving working memory, language and visuospatial function). After randomization (ratio 2:1), 16 patients will receive the complete treatment comprising tDCS and Cog (group 1) and 8 patients will be treated exclusively by Cog (sham tDCS) (group 2). The primary endpoint will be a significant improvement of the AI score by comparing baseline measures (D-15) to those recorded one month after stopping treatment (D44). Secondary endpoints will be an improvement of this score immediately after treatment (D14), 2 weeks (D29) and 2 months (D74) after stopping treatment and improvement of the MMSE score, NPI apathy subscore, ADAS Cog (Alzheimer Disease Assessment cognitive Scale subsection), ADCS-ADL (Alzheimer Disease Cooperative Study-Activities of Daily Living), FAB (Frontal Assessment Battery) and the latency of P300 evoked potentials at the same timepoints.

Conclusion: The purpose of our study is to check the assumption of tDCS and cognitive training efficacy in the treatment of apathy encountered in AD patients and we will discuss its effect over time.

ARTICLE HISTORY

Received: March 08, 2018
Revised: April 09, 2018
Accepted: April 09, 2018

DOI:
10.2174/1574887113666180416153316

Keywords: Alzheimer's disease, apathy, randomized trial, tDCS, treatment.

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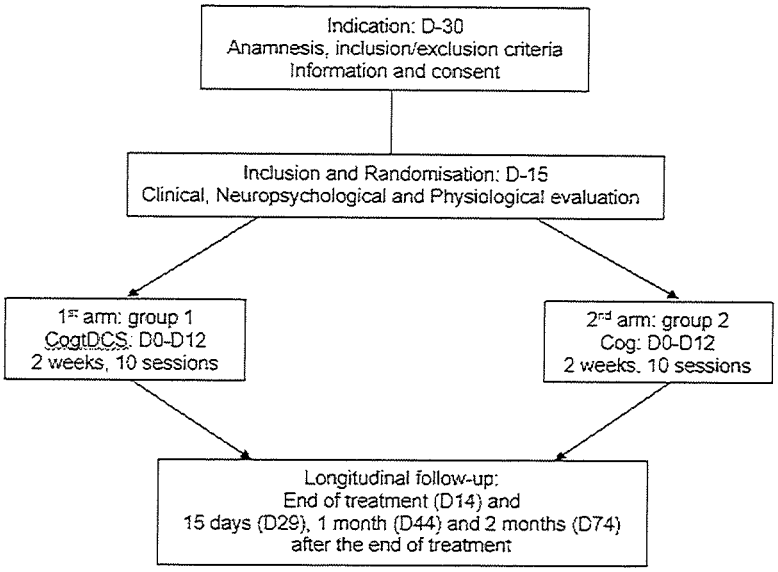

Fig. (1). Study plan. The study will last 3 months and 14 days (D-30 to D74) with a 30-day inclusion period, a 10-day treatment period and a 2-month follow-up period (D14, D29, D44, D74). Each patient will be treated (Cognitive training (Cog) combined with tDCS (transcranial Direct Current Stimulation) or Cog with sham tDCS) 10 times with one 20-minute session per day for 10 days (5 days per week and 2 consecutive weeks: D0-D12). Patients will be randomized to 2 arms. Patients and investigators will be blinded (double-blind) in the sham arm (identical cognitive training and sham tDCS). The primary endpoint will be a significant reduction of apathy evaluated by the Apathy Inventory 1 month (D44) after stopping treatment, compare to the baseline score (D-15).

left DLPFC (20 patients) did not induce any improvement compared to the sham tDCS group (20 patients). This result supported the need to bilaterally stimulate several targets in addition to the left DLPFC, in combination with cognitive training.

4.3. Combination of Cog and TBS

In 2011, Bentwich [37] reported the results of a procedure called NeuroAD (Neuronix, Tel Aviv, Israel) combining Cog and rTMS. Cognitive training comprised 12 different cognitive tasks designed to activate memory and language circuits and circuits involved in visuospatial functions. rTMS was delivered during the performance of cognitive tasks to 6 cortical areas corresponding to these various circuits: right and left DLPFC, language areas (Broca and Wernicke) and right and left associative parietal cortex (Brodmann areas 7). This study demonstrated the rational approach. However, it was based on short follow-up, as evaluation was performed immediately after completion of 6 weeks of treatment. These results were confirmed by 2 randomized trials [38, 39] and 2 open studies [22, 40]. Suemoto [32] showed that tDCS alone, targeting the left DLPFC, did not improve apathy in AD patients. In contrast, the combination of tDCS and cognitive training can improve memory performances. In particular, Jones [41] clearly demonstrated that the combination of tDCS and cognitive training can improve memory disorders in older patients. He also showed that this protocol could induce a transfer of the learning of trained tasks to untrained tasks. In this protocol, stimulation was delivered to two cortical targets (DLPFC and parietal cortex) and cognitive training consisted of a visual and verbal task involving working memory. The results showed that patients treated with tDCS and Cog (18 patients) and patients treated exclusively by Cog (sham tDCS) (18 patients) were significantly improved. However, only patients treated with tDCS and Cog remained significantly improved 1 month after treatment, in contrast with patients treated by Cog and sham tDCS, highlighting the very transient results obtained with Cog alone. Furthermore, transfer of trained tasks to untrained tasks was only observed in patients treated with tDCS and Cog.

We propose to adopt the main principles of Jones' protocol by using cognitive tasks designed to activate frontal circuits (working memory and executive functions), parietal circuits (visuospatial functions) and temporal circuits (language) and tDCS bilaterally targeting the DLPFC, parietal and temporal cortex (CogtDCS), and to evaluate the results of this treatment on apathy. The choice of the methodology will be discussed in more detail in the Discussion.

4.4. General Study Methodology

This is a national, monocentre, controlled, randomized, in the parallel-group study (Fig. **1**).

A total of 24 patients will be included in the study. Sixteen patients will be treated with CogtDCS (group 1) and 8 patients will be treated with Cog and sham tDCS (group 2). Patients are randomized (ratio 2:1) to one of the treatment groups using a computer program. Patients will present a mild-to-moderate Alzheimer's disease with an MMSE score between 15 and 26/30 [42] and an NPI apathy subscale score corresponding to Drye's criteria [43]: Apathy can be considered to be clinically significant: 1) when it is very frequently present (score of 4 for the frequency item of the NPI), even when it is not very severe, or 2) when it is severe (score of 2 or 3 for the severity item of the NPI) and moderately fre-

2) Letter search (5 minutes). The patient is presented with a page comprising several letters and will be asked to indicate whether or not the letter "M" is on the page. This task is repeated 10 times.

3) Search for a blue vertical rectangle (5 minutes). The patient is presented with a page comprising several green or blue rectangles arranged horizontally or vertically and will be asked whether or not he/she can see a blue vertical rectangle. This task is repeated 10 times.

A total of 10 sessions will be performed: 5 sessions on the prefrontal cortex and 5 sessions on the temporoparietal cortex.

4.8. Inclusion Criteria

Adult patients under the age of 90 years with Alzheimer's disease diagnosed by a neurological and/or geriatric team specialized in the field and presenting MRI signs compatible with this diagnosis. Patients must present a so-called mild-to-moderate form of the disease (MMSE > 15 and < 26/30) [42] and a clinically significant state of apathy evaluated by the NPI apathy subscale (see General study methodology).

4.9. Exclusion Criteria

- Contraindication to tDCS, mainly seizures and presence of metallic intracranial foreign bodies (risk of heating of the metal).

- Introduction of a treatment likely to affect the course of the disease during the previous 3 weeks.

- MMSE < 15 corresponding to severe Alzheimer's disease, as, at this stage, most patients are generally unable to understand even very simple instructions, which could seriously interfere with cognitive training.

- Patients with severe language disorders (MMSE language score < 5) will be excluded for the same reasons.

- Patients with an episode of severe depressive diagnosed by DSM-V criteria [44], an NPI-Depression [45] score ≥ 4, or modification of antidepressant treatment during the previous 3 months.

4.10. Study process (Table 1)

The screening visit (D-30) will include Patient Information Leaflet presentation, Consent Form completion, and inclusion/exclusion criteria checking. The medical research team will be in charge of enrollment and assignation of participants to the treatment. The study manager will generate the allocation sequence.

4.11. Randomization

During the baseline inclusion visit (D-15) participants will be randomized into two groups by a computerized random number generator with a permuted block design (ration 1:2) without stratification or minimization. The investigators will be not informed of the block size to maintain adequate blinding.

4.12. Blinding

Research nurses and medical doctors, who will perform tDCS sessions and cognitive training, will be the only persons to know the allocated sequence. Just after the randomization, they will receive an automatic e-mail on the patient's allocation on their individual professional mailbox. Patients will not be informed of the group to which they will belong.

4.13. Follow-up and Assessments

Patients will be assessed by the investigators immediately before (baseline) and at the end of the treatment (D14), and then 2 weeks (D29), 1 month (D44), and 2 months (D74) after the end of the treatment.

The following variables will be documented during the screening visit (D-30): sociodemographic data (age, gender, laterality, professional and marital status); medical history (date of diagnosis, disease duration, psychiatric and addictive comorbidities, somatic event history, treatments prescribed).

The following variables will be evaluated before and at the end of the treatment as shown in Table **1**: ADAS-Cog (Alzheimer Disease Assessment Scale-cognitive subsection) [46], MMSE (Mini-Mental State Examination) [47], NPI (Neuropsychiatric Inventory) apathy subscale [45], ADCS-ADL (Alzheimer Disease Cooperative Study - Activities of Daily Living) [48], FAB (Frontal Assessment Battery) [49], dependence [50] and Zarit Burden Interview [51, 52]. Variations in cognitive evoked potentials (P300) will be evaluated by comparing latencies recorded at D-15, D14 (at the end of the treatment) and D74. P300 [53] is an evoked potential measured in electroencephalography observed 300 milliseconds after stimulation requiring the subject to make a decision. It is an objective marker of some cognitive functions (memory and decision-making). A significant improvement of the scores corresponding to untrained tasks (word recognition (ADAS-Cog), verbal fluency [54], judgement of line orientation [55], Digit Span [56]) would reflect improvement of learning capacities [41].

5. STATISTICAL ANALYSIS

We will compare the variables documented during the screening visit (sociodemographic and medical history data) and at baseline (clinical scores) between the two groups of patients (group 1 treated with CogtDCS versus group 2 treated with Cog and sham tDCS) using the following statistical tests: a Mann-Whitney U test (or parametric t-test in case of normally distributed data, if shown by the Kolmogorov-Smirnov test) for continuous variables and a chi-squared test (or Fisher's exact test, if appropriate) for categorical variables. All evaluation scores (MMSE, ADASCog, Apathy Inventory and NPI apathy subscore) recorded before and after treatment will be analyzed by repeated measures analysis of variance to evaluate consecutive changes in each group (group 1 treated with CogtDCS and group 2 treated with Cog and sham tDCS). Univariate analyses were performed first as recommended [57]. Results will be considered significant if $p < 0.05$.

schizophrenic patients [59], but much less common in the context of AD. One of the few studies performed in this setting, conducted by Rosenberg [64], evaluated the efficacy of methylphenidate on apathy and demonstrated significant improvement of the NPI apathy subscore, but not the AES. Administration of the AES also requires special training and regular practice for at least 1 year is recommended [66], which probably explains why the inter-rater reliability of the results is described as only good [65]. In contrast, the AI, used at the diagnostic step of this study, is relatively easy to use with an excellent inter-rater reliability of the results [65], which is why we decided to use this scale to evaluate the results of this protocol. We also decided to use the NPI for evaluation of the results, because the NPI apathy subscale is relatively easy to use and is considered to be reliable [65], and this score is already used in the diagnostic step to define the severity of apathy.

Randomized studies using improvement of apathy as a primary endpoint were conducted over periods ranging from 4 to 8 weeks [43, 67, 68]. The ADMET study [43] was sufficiently long (6 weeks) to demonstrate statistically significant improvement of the NPI apathy subscale. The follow-up duration of our study (8 weeks) therefore appears to be sufficient, although long-term effects can be achieved when using additional maintenance sessions [69]. A disadvantage of a longer study duration would also be possibly severe deterioration of apathy in the sham arm [42].

We hope that this protocol, based on the most recent data of the literature and the guidelines established in this field, will be able to demonstrate the value of the tDCS-cognitive training combination in the treatment of apathy of AD patients.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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