Cognitive, Mood, and Electroencephalographic Effects of Noninvasive Cortical Stimulation With Weak Electrical Currents

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Objectives: The use of noninvasive cortical electrical stimulation with weak currents has significantly increased in basic and clinical human studies. Initial, preliminary studies with this technique have shown encouraging results; however, the safety and tolerability of this method of brain stimulation have not been sufficiently explored yet. The purpose of our study was to assess the effects of direct current (DC) and alternating current (AC) stimulation at different intensities in order to measure their effects on cognition, mood, and electroencephalogram.

Methods: Eighty-two healthy, right-handed subjects received active and sham stimulation in a randomized order. We conducted 164 ninety-minute sessions of electrical stimulation in 4 different protocols to assess safety of (1) anodal DC of the dorsolateral prefrontal cortex (DLPFC); (2) cathodal DC of the DLPFC; (3) intermittent anodal DC of the DLPFC and; (4) AC on the zygomatic process. We used weak currents of 1 to 2 mA (for DC experiments) or 0.1 to 0.2 mA (for AC experiment).

Results: We found no significant changes in electroencephalogram, cognition, mood, and pain between groups and a low prevalence of mild adverse effects (0.11% and 0.08% in the active and sham stimulation groups, respectively), mainly, sleepiness and mild headache that were equally distributed between groups.

Conclusions: Here, we show no neurophysiological or behavioral signs that transcranial DC stimulation or AC stimulation with weak currents induce deleterious changes when comparing active and sham groups. This study provides therefore additional information for researchers and ethics committees, adding important results to the safety pool of studies assessing the effects of cortical stimulation using weak electrical currents. Further studies in patients with neuropsychiatric disorders are warranted.

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Transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) stimulation are two low-intensity current tools of noninvasive brain stimulation that have been used since the 18th century when Galvani first developed a device to use DCs in 1780.[1] However, it was not until the 1960s that several researchers began to investigate more profoundly the biological effects of weak DCs on animals and humans.[2,3] Because of mixed results and lack of controlled studies for tDCS and tACS along with development of psychopharmacological drugs, investigations of such techniques were halted. Recently, a growing interest for these 2 techniques has emerged.

Transcranial DC stimulation is a simple, noninvasive technique that has been shown to induce significant cortical excitability changes that can persist beyond the stimulation period.[4–6] In fact, a weak superficial DC of approximately 1 to 2 mA in magnitude can readily change the excitability of the neurons,[7] and this effect can be translated in positive effects for the treatment of neuropsychiatric conditions such as depression, pain, and stroke recovery according to preliminary findings.[8–12] Transcranial AC stimulation is delivered in the same fashion as tDCS but with an alternated current. The first studies using low intensity AC were performed in the 1960s when Limoge[13] used tACS during surgery to reduce the amount of narcotics required for anesthesia. At the present time, there are several commercial devices of tACS approved by the Food and Drug Administration for clinical use for treatment of depression, anxiety, and insomnia. The renewed interest for such techniques can be understood as they might induce significant brain plasticity changes, therefore being a potential adjuvant clinical tool in neuropsychiatry.[14]

In this context, an important issue regarding such techniques is the safety of these interventions, especially considering that many different protocols and stimulation intensities are continuously tested on this field of fast development. Although different studies addressed safety aspects of tDCS,[15–18] no study systematically assessed adverse effects considering simultaneously electroencephalogram (EEG), neuropsychological measurement, and testing different parameters of stimulation (such as tDCS and tACS). Finally, a recent animal model study showed that high doses of electrical current could induce brain damage.[19]

Therefore, the objectives of our study were to study, in healthy volunteers, the safety of tDCS and tACS when applied at different sites and with different and commonly used intensities of stimulations as well as to measure their effects in pain, mood, anxiety, EEG, and cognition. Although our study only assessed

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some parameters that can be useful for safety evaluation, it adds important information, especially because we compared different techniques of electrical stimulation, to the safety pool of transcranial electrical stimulation.

MATERIALS AND METHODS

Subjects

Eighty-two healthy volunteers (44 men and 38 women), ages ranging between 18 and 64 years, participated in the study. Written informed consent was obtained from all participants at the beginning of the study, which was approved by the local Committee of Clinical. Eligibility criteria were (1) absence of acute major depression with a baseline score of more than 7 on the 17-item Hamilton Depression Rating Scale,[20] (2) absence of contraindication to tDCS such as skull defect or implanted metallic devices; (3) absence of advanced liver, cardiac, or pulmonary disease or any terminal diagnosis; (4) absence of coexistent major neurological or psychiatric diseases such as alcohol or drug dependence, epilepsy, seizures, prior neurosurgical procedures, or currently using psychopharmacologic drugs; (5) left-handedness (assessed by the Edinburgh questionnaire).

Assessments

Mood, Pain, and Anxiety

We used the Visual Analog Scale (VAS) to assess mood, pain, and anxiety at baseline and after each session of stimulation for all 4 experiments. The VAS is a self-evaluation scale ranging from 0 (no pain, no anxiety, worst mood ever) to 10 (maximum pain, maximum anxiety, best mood ever) that is useful in measuring subjective perceptions that cannot be directly measured.[21] To avoid potential confounders, subjects also completed the Beck Depression Inventory (BDI)[22] at baseline.

Cognitive Evaluation

We performed a brief battery of cognitive testing assessing attention and working memory to evaluate whether the cortical electrical stimulation (using different parameters) can affect cognitive function. We used the (1) Mini–Mental State Examination (MMSE)[23] as a global measure of cognitive functioning; (2) The Stroop Test[24] as a frontal executive functioning test; (3) and the Wechsler Adult Intelligence Scale-III (WAIS-III) digit span (forward and backward) test[25] as a measure of working memory. These tests were assessed at baseline and at the end of each experiment by a blinded rater. We used the standard forms for all neurocognitive measures, and we did not use normative adjusted scores.

Electroencephalogram

Forty-channel EEG was recorded in resting state with eyes closed for 15 minutes before (baseline EEG) and after each train of stimulation. Electroencephalographic data was acquired using an Eldith amplifier (Ilmenau, Germany), in which the raw EEG data was amplified, band pass filtered between 0.32 and 150 Hz, digitalized, and recorded. A clinical neurophysiologist monitored EEG traces and ensured that subjects did not fall asleep. Brain wave activities were observed through a qualitative analysis of EEG as to assess any paroxysmal figure and any seizure discharge before, during, and after stimulation.

Evaluation of Adverse Effects

We used an adverse effect questionnaire similar to one used by Poreisz et al,[26] which contained a binary system (yes/no) to codify for each adverse effect: headache, neck pain, scalp pain, scalp burns, tingling, skin redness, sleepiness, difficulties in concentrating, acute mood changes, visual perception changes, and fatigue, as well as an open-ended question to address for unreported adverse effects that asked whether the subject had felt or experimented any other adverse effects apart from the ones we had asked.

Intervention

We used an Eldith tDCS device in all experiments. Subjects were reclined in a chair, in resting state with their eyes closed. For each experiment, different sites and stimulation intensities were applied (explained later). Electrodes were held in place with the EEG cap and all electrodes sized 35 cm^2 (except for experiment 4 [tACS] in which we used 4 $\times$ 2-cm electrodes). For tDCS conditions, they were placed on the F3 dorsolateral prefrontal cortex (DLPFC) or on the contralateral supraorbital areas (10/20 International System of Jasper). For the AC stimulation condition, electrodes were placed in the zygomatic process bilaterally. For sham stimulation, electrodes were placed in the same sites as in the active stimulation but the current was delivered for only 30 seconds. The device was then turned off. This ensured that the subjects felt the same sensation as an active stimulation (mild tingling over the electrode) and, thus, to assure blinding—a method commonly used in tDCS trials.[27,28]

Design

The study design is shown in Figure 1. First, enrolled subjects were randomly assigned to receive either active intervention first/sham second or sham first/active second. Then at baseline, an evaluation assessing mood, pain, anxiety, and a neurocognitive battery was performed. At baseline, 15-minute EEG was then recorded. Subjects then underwent 3 trains of stimulation with different intensities according to their allocation group with EEG recording sessions between each of them. At the end, we reassessed the baseline tests and also measured adverse effects.

Four Experiments Were Conducted

Experiment 1

Twenty-two subjects (14 men and 8 women) participated in this experiment in which the electrodes were placed as following: anode electrode on left DLPFC and cathode on the contralateral supraorbital area. Transcranial direct current stimulation was delivered in 3 trains of 10 minutes with a 15-minute interval between each train when EEG was recorded. The intensity of stimulation was 1 mA (trains 1 and 3) and 2 mA (train 2).

Experiment 2

Twenty subjects (12 men and 8 women) participated in this experiment in which a cathode electrode was placed over the left DLPFC and an anode electrode was placed over the contralateral supraorbital area. The other parameters were the same as in experiment 1.

Experiment 3

Twenty subjects (12 men and 8 women) participated in this experiment in which an intermittent (instead of continuous) anodal DC stimulation was used, with a frequency of 1 Hz (current was On for 0.5 seconds and Off for 0.5 seconds). The other parameters (including intensity of stimulation) were the same as in experiment 1.

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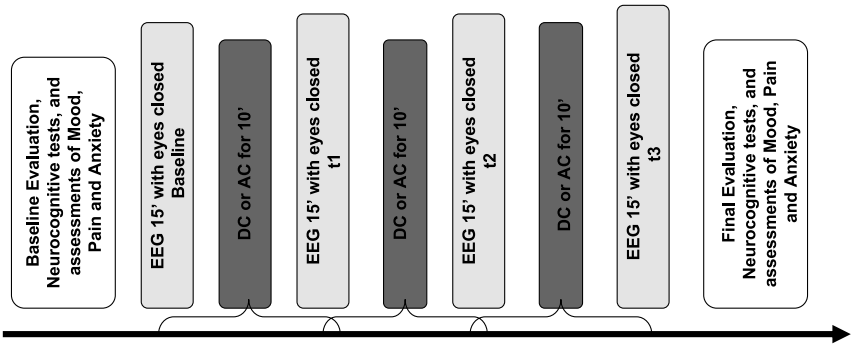

Experiment 1 – anodal tDCS over left DLPFC (F3) at 1, 2 and 1 mA (sessions 1, 2 and 3, respectively).

Experiment 2 – cathodal tDCS over left DLPFC (F3) at 1, 2 and 1 mA (sessions 1, 2 and 3, respectively).

Experiment 3 – intermittent tDCS over left DLPFC (F3) at 1, 2 and 1 mA (sessions 1, 2 and 3, respectively).

Experiment 4 – tACS over bilateral zygomatic process at 0.1, 0.2 and 0.1 mA (sessions 1, 2 and 3, respectively).

FIGURE 1. Study design. Initially, enrolled subjects were randomly assigned to receive either active intervention first/sham second or sham first/active second. Then, a baseline evaluation assessing mood, pain, anxiety, and a neurocognitive battery was performed. At baseline, 15-minute EEG was then recorded. Subjects then underwent 3 trains of stimulation with different intensities according to their allocation group with EEG recording sessions between each of them. At the end, we reassessed the baseline tests and also measured adverse effects.

Experiment 4

Twenty subjects (10 men and 10 women) participated in this experiment. Here, we performed active and sham peripheral cranial nerve AC stimulation over the bilateral zygomatic process with 4 × 2-cm electrodes. The AC stimulation was given in 3 trains of 10 minutes each with an interval of 15 minutes between each train for EEG recording. The intensity of stimulation was 0.1 mA (trains 1 and 3) or 0.2 mA (train 2) with a frequency of 50 Hz.

The rationale of these 3 sessions was to expose subjects to more than 1 trial of tDCS (therefore 3 sessions of tDCS) and use different dosages. Because our aim was not to assess whether 1 or 2 sessions were associated with adverse effects but instead whether several sessions using different dosages were associated with adverse effects and cognitive worsening, we only measured effects of tDCS at the end of these 3 sessions.

Statistical Analysis

Statistical analysis was performed using STATA (StataCorp, College Station, Tex). We used paired *t* tests to compare the mean difference effect of the sham group versus the active group for each continuous variable, under the general formula for the null hypothesis: $0 = [\times(1,a) - \times(2,a)] - [\times(1,s) - (2,s)]$, in which the first index refers to time (1 = first, 2 = second) and the second index refers to group (a = active, s = sham). Thus, the null hypothesis is that the 2 scores differences do not statistically differ. Using this formula, this corresponds to the interaction term (time vs group) but in a more simplified manner.

For categorical variables, we used the Fisher exact test to compare adverse effects after active (anodal or cathodal) and sham stimulation in each experiment. Statistical significance refers to a two-tailed $P < 0.05$, we did not correct for multiple comparisons as this is an exploratory study, designed to identify potential tDCS adverse effects for further confirmation in larger clinical trials.

RESULTS

Adverse Effects

There were no significant differences regarding adverse effects between each group of stimulation (active and sham) and across each experiment (1, 2, 3, and 4). We observed a low prevalence of adverse effects: 27 in the active group (0.11%) and 20 in the sham group (0.08%) for all experiments. The main adverse effects were headache (6 patients), sleepiness (14 patients), and skin redness (11 patients [Tables 1 and 2]). Two subjects reported a sensation of shock during the train of stimulation; nevertheless, they requested to continue the intervention. This feeling was associated with current ramping up.

Assessment of Mood, Pain, and Anxiety

We performed 36 paired *t* tests, 9 for each experiment (Table 2). In experiments 1 (anodal on the left DLPFC) and 4 (cranial electrotherapy stimulation), we did not observe any significant differences between groups. In experiment 2 (cathodal on the left DLPFC), we observed a difference for VAS pain: participants in the sham group showed a slight increase in VAS whereas participants in the active group showed a slight decrease in VAS (−0.3 vs 0.22, $t = -2.58$, $P = 0.02$), although the clinical significance of this finding is probably low. In experiment 3 (tACS on the left DLPFC), we observed a difference for the Stroop Color test: subjects in the sham group performed slightly worse in the second test whereas those in the active group performed slightly better (−0.3 vs 0.32, $t = -2.08$, $P = 0.05$), again, a finding with probably low clinical significance. In addition, we performed 36 tests here without correction for multiple tests (as this was an exploratory study), we would expect 1 or 2 false-positive results.

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TABLE 1. Baseline Data of Study Participants

	Experiment 1	Experiment 2	Experiment 3	Experiment 4
Age (SD), yr	21.3 (4.9)	21.5 (4.3)	22.6 (6.7)	29.15 (9.3)
Gender (M/F)	14/8	12/8	12/8	10/10
Baseline BDI (SD)	1.22 (1.6)	1.5 (2.5)	1.4 (2.9)	1.7 (1.9)
Baseline MMSE (SD)	28.8 (1.1)	29.2 (0.8)	29.5 (0.4)	29.6 (0.7)
Adverse Effects (A/S)	18/14	6/6	3/0	0/0
Headache	3/2	0/1	0/0	0/0
Neck pain	2/2	0/0	0/0	0/0
Scalp pain	0/0	0/1	0/0	0/0
Scalp burns	0/0	0/0	0/0	0/0
Tingling	0/1	2/0	0/0	0/0
Skin redness	3/3	1/2	2/0	0/0
Sleepiness	6/4	2/1	1/0	0/0
Difficulties in concentrating	1/1	0/1	0/0	0/0
Mood changes	3/1	1/0	0/0	0/0

A/S refers to the number of adverse effects in the active (A) and sham (S) groups and M/F refers to the number of males (M) and females (F) in each group.

Beck Depression Inventory

Beck Depression Inventory scores were not significantly different between the active and sham groups in any of the experiments (Table 1).

Qualitative EEG

There were no visual changes in the EEG of any of the subjects; neither paroxysmal figures nor seizures were recorded.

DISCUSSION

In the present study, we conducted a total of 164 sessions of electrical stimulation using weak currents on 82 healthy subjects (44 men). Our main result is that we observed a low prevalence of adverse effects with no differences between the sham and active groups and across experiments in EEG, and in almost all cognition, mood, anxiety, and pain scales when applying either tDCS or tACS.

Adverse Effects

No serious adverse events such as seizures or severe headaches were observed, and none of the subjects requested to interrupt the sessions or needed medical care after intervention. We observed only a few, mild adverse events that were distributed equally between the active and sham groups. In addition, our results showed the most common adverse effects to be mild headache, tingling, itching, and burning sensation and skin redness under the area of electrodes. This is in line with the literature.[29] Moreover, we observed that the subjects in experiments 3 and 4 presented a lower but nonsignificant frequency of adverse effects. This could have been possibly due to 2 conditions that did not use DC currents or that AC stimulation used a smaller current. On the other hand, adverse events using 1 and 2 mA were similar. In addition, subjects noticed no differences between these 2 doses, and there were no differences between the sham and active groups.

Two subjects reported a shock sensation during stimulation. Such adverse effect might be reported sporadically[29] because some individual characteristics such as type of skin sensitivity, hair, and possibly small skin lesions can create channels of low resistance thereby inducing the feeling of shock when current is concentrated in these areas. Finally, 14 subjects reported sleepiness, which could be partially explained as subjects were asked to remain in a seated, reclined state for a total of 90 minutes with their eyes closed.

The safety of the application of DC in humans has been addressed and tested by multiple studies[15–18] using different safety parameters such as type of electrodes (water-soaked sponge electrodes), size of electrodes, intensity of stimulation, and duration of stimulation. These studies concluded that the application of DC over the scalp does not induce negative effects. In addition, there is no evidence of measurable structural changes in brain tissue due to the application of DC.[30] Here, we extend these findings to intermittent and AC stimulation.

Neuropsychological Evaluation

We found no statistically significant changes in Digit Span forward and backward. This task measures the short-term memory through the repetition of a series of numbers; indicating that DC and AC currents delivered with 1 or 2m A does not worsen short-term memory. Similarly, for Stroop test, we found no significant difference between the sham versus active stimulations. In fact, in one Stroop test in experiment 3, we observed a slightly better performance in the active group. Along these lines, several studies showed not only a lack of worsening in cognitive performance but a performance enhancement, such as an improvement after active stimulation as compared with sham in the decision-making processes,[31] working memory,[28,32] visual recognition memory,[12] and verbal fluency.[16] Perhaps, the battery of tests was brief and not sensitive enough to detect improvements. We decided to have a brief battery of tests as the experiment was already too long (on average 2 hours), and if we prolonged it, cognitive changes due to fatigue would probably emerge.

Mood, Pain, and Anxiety

We observed no significant changes in the mood of healthy subjects when comparing groups of stimulation (active vs sham), a finding that is in line with previous studies.[16,33] In fact, it was not observed as a worsening in mood—as it has been previously described with the other technique of noninvasive brain stimulation (transcranial magnetic stimulation[34] nor an elated or hypomanic-like mood). In addition, no changes were observed in anxiety.

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TABLE 2. Neuropsychological Scores for Each Group and Experiment

	Mean (SD) Change (Sham)	Mean (SD) Change (True)	Paired *t* test	*df*	*P*
Experiment 1					
Digit Span Forward	0.32 (0.78)	−0.22 (1.26)	1.6	21	0.12
Digit Span Backward	−0.36 (1.09)	−0.04 (1.25)	−0.92	21	0.36
MMSE	0 (0.61)	−0.05 (0.37)	0.29	21	0.77
Stroop Color	0.09 (1.22)	0.22 (1.52)	−0.28	21	0.77
Stroop Word	0.13 (0.64)	−0.22 (1.89)	0.72	21	0.48
Stroop Interference	0.7 (3.06)	0.5 (1.82)	0.24	21	0.8
VAS pain	−0.23 (1.35)	−0.16 (0.42)	−0.25	21	0.8
VAS anxiety	−0.29 (1.98)	0.23 (1.17)	−1.35	21	0.19
VAS mood	−0.07 (0.72)	0 (0.46)	−0.39	21	0.69
Experiment 2					
Digit Span Forward	−0.3 (1.03)	−0.2 (2.09)	−0.17	19	0.86
Digit Span Backward	−0.05 (1.39)	−0.4 (1.6)	0.72	19	0.47
MMSE	0.25 (0.64)	−0.05 (0.51)	1.67	19	0.11
Stroop Color	0.22 (0.93)	0.39 (1.93)	−0.4	19	0.69
Stroop Word	0.12 (0.78)	−0.11 (0.99)	0.96	19	0.34
Stroop Interference	0.71 (1.92)	0.63 (2.06)	0.18	19	0.85
VAS pain	−0.3 (0.73)	0.22 (0.59)	−2.58	19	0.02
VAS anxiety	0.47 (0.89)	0.62 (0.85)	−0.58	19	0.56
VAS mood	−0.02 (0.77)	−0.32 (0.81)	1.25	19	0.22
Experiment 3					
Digit Span Forward	0.2 (1.23)	0.45 (0.94)	−0.89	19	0.38
Digit Span Backward	0.1 (1.02)	−0.3 (0.92)	1.36	19	0.19
MMSE	−0.1 (9.75)	0.2 (0.95)	−0.13	19	0.89
Stroop Color	−0.3 (0.92)	0.32 (1.35)	−2.08	19	0.05
Stroop Word	0.65 (1.17)	0.11 (1.24)	1.22	19	0.23
Stroop Interference	0.52 (2.1)	0.43 (1.6)	0.14	19	0.89
VAS pain	0.12 (1.20)	0.58 (1.8)	−0.87	19	0.4
VAS anxiety	0.57 (1.18)	0.37 (0.97)	0.57	19	0.57
VAS mood	−0.27 (0.86)	0.17 (0.97)	−1.55	19	0.13
Experiment 4					
Digit Span Forward	0.25 (1.02)	−0.25 (1.01)	1.81	19	0.08
Digit Span Backward	0.1 (1.25)	0.05 (1.64)	0.13	19	0.89
MMSE	0.1 (0.31)	0.05 (0.39)	0.44	19	0.66
Stroop Color	−0.14 (1.67)	0.15 (1.5)	−0.56	19	0.57
Stroop Word	0.02 (0.75)	−0.42 (0.96)	2.03	19	0.06
Stroop Interference	0.65 (2.66)	0.4 (2.45)	0.4	19	0.69
VAS pain	0.12 (0.84)	−0.6 (2.08)	1.45	19	0.16
VAS anxiety	0.52 (1.5)	0.08 (1.7)	0.8	19	0.44
VAS mood	−0.2 (0.64)	−0.18 (0.73)	0.08	19	0.96

Digit Span Forward is a test in which the subject is asked to repeat a sequence of several digits; Digit Span Backward is when the subject is asked to repeat a sequence of several digits backward. Stroop Color is a test in which tables of 4 colors are presented, and the subject is asked to read the color; Stroop Word is a test in which neutral terms are presented in 4 different colors, and the subject is asked to read the color; Stroop Interference is the test in which the name of a color is presented in a different color, and the subject is required to read the color not the word.

df, degrees of freedom.

However, we showed that in all groups (except the sham group of experiment 1), anxiety decreased in both groups. Fregni et al[35] also had this finding in a fibromyalgia trial. It is possible that anxiety increased at the beginning of the study due to unfamiliarity to the procedure[9]; on the other hand, it is possible that tDCS has anti-anxiety effects—in fact, some studies reported that food, alcohol, and smoking craving, an unpleasant felling of an unbearable, urgent need that is commonly associated with anxiety, are substantially reduced after a single tDCS intervention.[36–38] However, here, the latter hypothesis is unlikely because the sham and active groups showed similar endpoint scores.

Finally, we observed that in experiment 3, the subjects in the active versus the sham group had different changes in pain. However, the subjects started the study feeling no pain, and it was not expected that tDCS/tACS would induce pain as tDCS reduces pain[39] and emotional discomfort associated with pain [40] in healthy subjects. Thus, this finding might probably be a false-positive result.

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Parameters of Stimulation

One important finding of our study was that we studied different intensities and modalities of stimulation. Here, similarly to the study of Iyer et al,[16] we did not find differences between 1 and 2 mA in EEG findings. In addition, we also showed that intermittent DC stimulation and AC stimulation are associated with similar profile of adverse effects as compared with constant DC stimulation. This finding is relevant in the context of recent studies showing significant behavioral effects associated with intermittent DC stimulation[41,42] and recent studies showing that tACS might induce behavioral and neurophysiological effects.[1,43]

Limitations

Some limitations should be underscored: (1) because we used a preformatted adverse effects form, it is possible that other adverse effects were not noticed. However subjects were asked using an open-ended question whether they experienced other adverse effects. Another possibility is that other adverse effects were not noticed if they are associated with a low frequency of occurrence. Although this is a possibility, we studied a total of 504 stimulation sessions and thus we believe it to be a reasonable number to detect other adverse effects; therefore, other nonreported adverse effects would have a frequency lower than 0.2%. (2) We performed 36 analyses; therefore, it was expected to observe approximately 2 false-positive results because we did not correct for multiple comparisons. This would be however desirable in an exploratory study aiming to detect safety concerns with the use of noninvasive brain stimulation; and (3) the relatively low sample size of each experiment might have increased the probability of type II error (false-negative results).

Another important aspect is that safety in our study was assessed using report of adverse effects, cognitive changes, subjective changes, and EEG; therefore, we cannot rule out that stimulation was associated with no damage as a very small injury might not be detected by our tests. That is a current limitation of human in vivo studies, even considering the use of biochemical products of neuronal degeneration such as neuron specific enolase that has a low sensitivity. A current elegant animal study addressed the safety limits of tDCS in an animal model.[19]

Clinical Implications

Our results add new data to the safety pool of studies in cortical stimulation using weak electrical currents. Here, we also showed that AC and intermittent stimulation are not different from stimulation with constant current. Our findings also support the safety of 2 mA doses, supported by some authors to have a larger effect when compared to 1 mA.[16,44] In addition, we showed that both techniques have a very low incidence of adverse effects (less than 0.2%), which indicates a potential role of tDCS and tACS in clinical settings because tolerability is an important cause of treatment discontinuation.[45] Moreover, because of its own nonpharmacological approach, these techniques have no interference in the hepatic CYP450 system and thus no severe harmful pharmacological interactions.

All together, our study shows that tDCS and tACS are tolerable, and together with animal data[19] and other safety studies,[16,26,30] tDCS and tACS seem to be secure methods when applied in healthy volunteers in doses commonly applied in clinical trials. Although our study has not addressed their use in patients with neuropsychiatric disorders, our results should be taken in account when designing future trials.

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