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Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation

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Abstract

Objective: Brain polarization in the form of transcranial direct current stimulation (tDCS), which influences motor function and learning processes, has been proposed as an adjuvant strategy to enhance training effects in Neurorehabilitation. Proper testing in Neurorehabilitation requires double-blind sham-controlled study designs. Here, we evaluated the effects of tDCS and sham stimulation (SHAM) on healthy subjects and stroke patients' self-report measures of attention, fatigue, duration of elicited sensations and discomfort.

Methods: tDCS or SHAM was in all cases applied over the motor cortex. Attention, fatigue, and discomfort were self rated by study participants using visual analog scales. Duration of perceived sensations and the ability to distinguish tDCS from Sham sessions were determined. Investigators questioning the patients were blind to the intervention type.

Results: tDCS and SHAM elicited comparably minimal discomfort and duration of sensations in the absence of differences in attention or fatigue, and could not be distinguished from SHAM by study participants nor investigators.

Conclusions: Successful blinding of subjects and investigators and ease of application simultaneously with training protocols supports the feasibility of using tDCS in double-blind, sham-controlled randomized trials in clinical Neurorehabilitation.

Significance: tDCS could evolve into a useful tool, in addition to TMS, to modulate cortical activity in Neurorehabilitation.

Keywords: DC stimulation; Stroke; Double-blinding; Sham stimulation; Neurorehabilitation

1. Introduction

Non-invasive brain polarization through transcranial direct current stimulation (tDCS) influences cognitive functions in healthy volunteers (Antal et al., 2004; Fregni et al., 2005a; Iyer et al., 2005; Nitsche et al., 2003a) and transiently enhances motor performance in patients with chronic stroke (Hummel et al., 2005a; Hummel and Cohen, 2005; Fregni et al., 2005b). tDCS can be applied continuously and safely for up to 30 min (Hummel et al., 2005a; Iyer et al., 2005; Nitsche et al., 2005), close to the typical duration of a session of rehabilitative treatment, and can be administered in synchrony with motor training protocols (Hummel et al., 2005a). However, it remains to be determined if tDCS is amenable for use in strict randomized control trial designs in clinical Neurorehabilitation. Failure of blinding could compromise objective evaluations, resulting in biased assessment of intervention effects (Day and Altman, 2000; Schulz et al., 1995). Here, we evaluated perceived sensations, discomfort, ratings of attention and fatigue, and the ability to retrospectively identify each intervention during both tDCS and SHAM in chronic stroke

Abbreviations: tDCS, transcranial direct current stimulation; rTMS, repetitive transcranial magnetic stimulation; HV, healthy volunteers; CSP, chronic stroke patients; MMSE, mini mental status examination; VAS, visual analog scales.

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patients and healthy volunteers and the ability of investigators questioning the subjects to identify the tDCS and SHAM sessions, to determine the quality and effectiveness of this technique for double-blind sham-controlled experimental designs. Data was pooled from several studies performed over the last 3 years spanning over 170 sessions in our laboratory at the NINDS.

2. Methods

2.1. Subjects

We studied healthy volunteers (HV) and chronic stroke patients (CSP) who participated in protocols examining the effects of anodal (HV: $n=8$, 4 of them women, age 60.7 ± 6.5 yo; CSP: $n=14$, 7 of them women, age 57.6 ± 3.8 yo) or cathodal tDCS (HV: $n=16$, 8 of them women, age 46.3 ± 5.6 yo; CSP: $n=9$, 4 of them women, age 62.3 ± 4.9 yo) on motor function. MMSE was >28 in all subjects, some of whom participated in both experiments for a total of 170 sessions. Some of the subjects did not take part in all different sessions of an experiment. Results of tDCS on motor function are reported separately (Hummel et al., 2005a,b). Protocols were approved by the NINDS Institutional Review Board, and all subjects gave written informed consent to each experiment.

2.2. Transcranial DC stimulation (tDCS)

Saline-soaked electrodes (5 cm×5 cm) were placed on the scalp overlying the motor cortex and on the contralateral forehead above the orbit as described previously (Hummel et al., 2005a; Nitsche and Paulus, 2000; Nitsche et al., 2005). Stimulation was applied using a constant-current regulator (Phoresor® II PM850; Iomed® Inc., Salt Lake City, Utah). In both tDCS and SHAM, the DC current was initially increased in a ramp-like fashion over several seconds (~10 s) until reaching 1 mA (current density of 0.04 μA/cm^2) (Hummel et al., 2005a,b; Iyer et al., 2005; Nitsche et al., 2003b). In tDCS, stimulation was maintained for a total of 20 min; in SHAM, it was turned off after 30 s. These parameters for sham stimulation were chosen based on previous reports that the perceived sensations on the skin, such as tingling, fade usually out in the first 30 s of tDCS (Nitsche et al., 2003b; Paulus, 2003). In both conditions, DC currents were turned off slowly over a few seconds, out of the field of view of the patients, a procedure that does not elicit perceived sensations. Session order was pseudorandomized. In all sessions both, subjects and raters, were blinded to the intervention type. The experimenter who applied the intervention (real tDCS or Sham) was different from the experimenter determining the outcome measures. Additionally, the investigator applying the intervention covered the small display of the tDCS device.

2.3. Outcome measures

In each session, subjects described the quality and approximate duration of sensations experienced during interventions, and rated their perceived discomfort through visual analog scales (VAS, from 1: 'no discomfort' to 10: 'extreme discomfort/pain'). Additionally, both before and after intervention, they rated their attention and fatigue on VAS (from 10: 'most attentive'/'least fatigued' to 1: 'least attentive'/'most fatigued'). These VAS have good internal consistency, reliability and objectivity (Chibnall and Tait, 2001; Floel et al., 2004; Folstein and Luria, 1973; Gracely, 1999; Reisine et al., 2003). After completion of each experiment (including different sessions of Sham and tDCS), subjects were asked whether they could differentiate between sessions in regard to the intervention type (tDCS from SHAM). All measurements were determined while both subject and rater were blind to the intervention. All data are expressed as mean±SEM. The main statistical analysis focused on the comparison of stroke patients

Table 1A
Summary of results: ratings of discomfort, duration of sensations, attention and fatigue

	Discomfort (VAS 1–10)		Duration (in s)		Attention (VAS 1–10)				Fatigue (VAS 1–10)			
	tDCS	Sham	TDCS		TDCS		Sham		TDCS		Sham	
					Pre-Stim	Post-Stim	Pre-Stim	Post-Stim	Pre-Stim	Post-Stim	Pre-Stim	Post-Stim
Chronic stroke patients	1.77±0.23	1.53±0.13	40.20±7.99	24.62±4.56	8.03±0.30	7.85±0.29	7.79±0.32	7.89±0.30	7.95±0.28	7.81±0.29	7.88±0.30	7.63±0.27
Elder healthy volunteers	1.53±0.23	1.32±0.11	46.00±13.62	45.00±17.75	8.67±0.26	8.92±0.31	8.86±0.29	9.03±0.25	8.71±0.26	8.86±0.31	8.50±0.31	8.75±0.26
Anodal stimulation	1.47±0.21	1.28±0.12	50.42±12.54	29.17±5.17	7.37±0.31	7.46±0.33	7.40±0.33	7.74±0.32	7.32±0.28	7.36±0.30	7.27±0.29	7.40±0.26
Cathodal stimulation	1.86±0.27	1.58±0.14	38.93±8.80	33.67±10.87	9.35±0.17	9.25±0.24	9.18±0.26	9.08±0.26	9.35±0.16	9.27±0.25	9.07±0.27	8.83±0.28
Overall	1.68±0.17	1.45±0.09	42.38±7.05	32.38±7.36	8.30±0.21	8.30±0.22	8.25±0.23	8.38±0.21	8.27±0.20	8.25±0.22	8.14±0.22	8.10±0.20

Ratings of discomfort, duration of sensation, attention and fatigue in chronic stroke patients and elder healthy volunteers. Discomfort was expressed on a VAS scale of 1–10 ('1' representing 'no discomfort' through '10' representing 'extreme discomfort/pain'). Perceived duration of sensations was expressed in seconds. Attention and fatigue were expressed on VAS scales of 1–10 ('10' representing 'most attentive/least fatigued' through '1' representing 'least attentive/most fatigued'). All ratings are expressed as mean±SEM.

Table 1B
Summary of results: statistical results chronic stroke patients vs elder healthy volunteers—attention and fatigue, perceived discomfort and duration of sensation

Factor	Attention		Fatigue		Discomfort		Duration	
	F ratio	*P* value	*F* ratio	*P* value	*F* ratio	*P* value	*F* ratio	*P* value
Intervention (tDCS vs Sham)	0.08	n.s.	0.08	n.s.	2.73	n.s.	1.57	n.s.
Time (Pre-Stim vs Post-Stim)	0.50	n.s.	0.50	n.s.	n.a.	n.a.	n.a.	n.a.
Group (CSP vs HV)	6.74	<0.05	6.74	<0.05	0.73	n.s.	1.05	n.s.
Intervention×Time	0.29	n.s.	0.29	n.s.	n.a.	n.a.	n.a.	n.a.
Intervention×Group	1.68	n.s.	1.68	n.s.	0.02	n.s.	0.73	n.s.
Time×Group	0.68	n.s.	0.68	n.s.	n.a.	n.a.	n.a.	n.a.
Intervention×Time×Group	1.01	n.s.	1.01	n.s.	n.a.	n.a.	n.a.	n.a.

RM-ANOVA with the factors Intervention (real stimulation [tDCS], Sham stimulation [Sham]), Time (before stimulation [Pre-Stim], after stimulation [Post-Stim]), Group (chronic stroke patients [CSP], healthy volunteers [HV]) was applied to analyze the present data. $P<0.05$ is defined as statistical significant, n.s., non-significant; n.a., not applicable (as there is no factor time for discomfort and duration).

and age-matched HV. Data were analyzed with separate RM-ANOVAs with the factors INTERVENTION (real stimulation [tDCS], Sham stimulation [Sham]), TIME (before stimulation [Pre-Stim], after stimulation [Post-Stim]), GROUP (Chronic Stroke Patients [CSP], Healthy Volunteers [HV]) and considered significant if $P<0.05$ (see also Tables 1A–1D). In a second analysis, differences between anodal and cathodal stimulation were evaluated with a RM-ANOVA with the factors INTERVENTION (real stimulation [tDCS], Sham stimulation [Sham]); TIME (before [Pre-Stim], after stimulation [Post-Stim]) and TYPE (anodal, cathodal). In a third RM-ANOVA analysis with the factors INTERVENTION (real stimulation [tDCS], Sham stimulation [Sham]), TIME (before stimulation [Pre-Stim], after stimulation [Post-Stim]), AGE (Young HV, Elder HV), we also examined differences in outcome measures between the elder ($\geq$55 yo, $n=15$; 63.9 ± 3.7 yo, ranging from 56 to 85 yo) and the additional group of younger ($<$55 yo, $n=9$, 26.6 ± 1.7 yo, ranging from 20 to 35 yo) HV.

3. Results

Subjects (CSP and elder HV) described no sensations (tDCS: 19.6% and SHAM: 22.2% of the group), slight tingling (tDCS: 46.4% and SHAM: 51.9%), or a transient mild burning (tDCS: 33.9% and SHAM: 25.9%) associated with the onset of stimulation. Ratings of discomfort and duration of sensations were comparable with tDCS and SHAM in both groups (Tables 1A and 1B) as were attention and fatigue across time (before [Pre-Stim] and after stimulation [Post-Stim]) and intervention (tDCS and SHAM). Elder HV reported slightly higher attention and lower fatigue scores than CSP patients (Tables 1A and 1B). Attention and fatigue appeared to be slightly higher with in subjects participating in the cathodal stimulation-Sham experiments than in those participating in the anodal stimulation-Sham experiments (Tables 1A and 1C). Levels of discomfort and duration of sensations were comparable between experiments with cathodal and anodal stimulation (Tables 1A and 1C).

Young HV described no sensations (tDCS: 10.5% and SHAM: 15.0% of the group), slight tingling (tDCS: 73.7% and SHAM: 65.0%), or a transient mild burning (tDCS: 15.8% and SHAM: 20.0%) with the onset of stimulation. Young HV showed slightly higher perception of discomfort (on the VAS 1–10; young HV: 2.62 ± 0.3, elder HV: 1.42 ± 0.3) and a non-significant trend towards lower attentional levels ($F=3.34$, $P=0.08$) especially in the post determination (on the VAS 0–10; young HV: 7.91 ± 0.5, elder HV: 8.98 ± 0.3) compared to elder HV independent of intervention type (Table 1D).

None of the subjects or investigators were able to distinguish between tDCS and SHAM sessions. Out of the

Table 1C
Summary of results: statistical results anodal vs cathodal stimulation—attention and fatigue, perceived discomfort and duration of sensation

Factor	Attention		Fatigue		Discomfort		Duration	
	F ratio	*P* value	*F* ratio	*P* value	*F* ratio	*P* value	*F* ratio	*P* value
Intervention (tDCS vs Sham)	0.23	n.s.	2.60	n.s.	2.95	n.s.	3.63	n.s.
Time (Pre-Stim vs Post-Stim)	0.32	n.s.	0.47	n.s.	n.a.	n.a.	n.a.	n.a.
Type (anodal vs cathodal)	29.99	<0.05	37.65	<0.05	2.05	n.s.	0.06	n.s.
Intervention×Time	0.42	n.s.	0.21	n.s.	n.a.	n.a.	n.a.	n.a.
Intervention×Type	0.43	n.s.	0.96	n.s.	0.02	n.s.	1.28	n.s.
Time×Type	1.72	n.s.	1.02	n.s.	n.a.	n.a.	n.a.	n.a.
Intervention×Time×Type	0.42	n.s.	0.28	n.s.	n.a.	n.a.	n.a.	n.a.

RM-ANOVA with the factors Intervention (real stimulation [tDCS], sham stimulation [Sham]), Time (before stimulation [Pre-Stim], after stimulation [Post-Stim]), Type (anodal, cathodal) was applied to analyze the present data. $P<0.05$ is defined as statistical significant, n.s., non-significant; n.a., not applicable (as there is no factor time for discomfort and duration).

Table 1D
Summary of results: statistical results young vs elder healthy volunteers—attention and fatigue, perceived discomfort and duration of sensation

Factor	Attention		Fatigue		Discomfort		Duration	
	F ratio	*P* value	*F* ratio	*P* value	*F* ratio	*P* value	*F* ratio	*P* value
Intervention (tDCS vs Sham)	0.08	n.s.	0.28	n.s.	0.93	n.s.	2.74	n.s.
Time (Pre-Stim vs Post-Stim)	0.73	n.s.	0.01	n.s.	n.a.	n.a.	n.a.	n.a.
Age (young HV vs elder HV)	3.34	n.s.	0.75	n.s.	17.10	<0.05	0.69	n.s.
Intervention×Time	0.09	n.s.	0.08	n.s.	n.a.	n.a.	n.a.	n.a.
Intervention×Age	0.17	n.s.	0.07	n.s.	0.02	n.s.	2.05	n.s.
Time×Age	5.72	<0.05	1.77	n.s.	n.a.	n.a.	n.a.	n.a.
Intervention×Time×Age	0.50	n.s.	0.08	n.s.	n.a.	n.a.	n.a.	n.a.

RM-ANOVA with the factors Intervention (real stimulation [tDCS], sham stimulation [Sham]), Time (before stimulation [Pre-Stim], after stimulation [Post-Stim]), Age (young healthy volunteers [Young HV], elder healthy volunteers [Elder HV]) and their interactions was applied to analyze the present data. $P<0.05$ is defined as statistical significant, n.s., non-significant; n.a., not applicable (as there is no factor time for discomfort and duration).

170 sessions reported here, one healthy volunteer reported headache during one session, which resolved after intake of a single oral dose of acetaminophen (325 mg).

4. Discussion

The findings of minimal discomfort (1–2 out of 10), absence of overt effects on subjective ratings of attention or fatigue, and easiness of blinding investigators, healthy volunteers and stroke patients indicate that tDCS can be used in the setting of strict double-blind sham-controlled randomized trials in Neurorehabilitation and cognitive neuroscience.

Differences in perceptual cues as well as presence of side effects often blur double-blind, sham-controlled experimental designs (Day and Altman, 2000; Schulz et al., 1995). In the last few years, non-invasive brain stimulation emerged as a powerful tool to study and to modulate human brain function (Cohen et al., 1998; Pascual-Leone et al., 2000; Paulus, 2003; Wassermann and Lisanby, 2001). Transcranial magnetic stimulation (TMS) first, has brought solid

Table 2
tDCS and rTMS

	TDCS	rTMS
Quality of sensations (Anand and Hotson, 2002; Hummel et al., 2005a; Paulus, 2003)	No sound, mild transient tingling sensations, no twitches	Sound, tingling, muscle twitch under the coil if suprathreshold
Duration of sensations (Anand and Hotson, 2002; Hummel et al., 2005a; Paulus, 2003)	Only in the initial few seconds of application, then fades	All along application
Discomfort of sensations (Hummel et al., 2005a)	Transient and mild	Mild if subthreshold, higher if suprathreshold
Up-regulation/down-regulation of cortical excitability (Chen, 2000; Nitsche and Paulus, 2000; Nitsche et al., 2005; Pascual-Leone et al., 1998; Priori et al., 1998; Wassermann and Lisanby, 2001)	Well documented	Well documented
Focality of stimulation (Cohen et al., 1998; Jahanshahi and Rothwell, 2000; Nitsche and Paulus, 2000)	Less focal	More focal
Duration of modulatory effects (Ardolino et al., 2005; Huang and Rothwell, 2004; Hummel et al., 2005a; Nitsche and Paulus, 2001; Nitsche et al., 2003c; Siebner and Rothwell, 2003)	From seconds to hours	From seconds to hours
Time resolution (Paulus, 2003; Siebner and Rothwell, 2003)	Poor: seconds	Excellent: milliseconds
Capacity to elicit a virtual lesion (Antal et al., 2004; Jahanshahi and Rothwell, 2000; Siebner and Rothwell, 2003)	Less tested, but promising	Well documented
Ease of design sham-controlled double-blind studies (Hummel et al., 2005a; Lisanby et al., 2001)	Less difficult	More difficult
Ability to administer simultaneously with motor training	Easily done	More difficult
Safety of intervention (Hummel et al., 2005a; Nitsche et al., 2003a; Wassermann, 1998)	Safe so far but further studies needed	Well documented
Simplicity of application	Easily applied	Easily applied, but requires additional holder to keep coil in constant position
Cost	Lower	Higher

Brief comparison between tDCS and rTMS for: quality of sensations, duration of sensations, discomfort of sensations, modulation of cortical excitability, focality of stimulation, duration of modulatory effects, time resolution, capacity for virtual lesions, sham-control, administration in parallel with training, safety, simplicity of application and costs.

advances of knowledge in cognitive neuroscience and Neurorehabilitation (Hallett, 2000; Jahanshahi and Rothwell, 2000). More recently, brain polarization in the form of tDCS emerged as a promising complementary tool to rTMS with specific advantages and disadvantages (Table 2). In the present study, both tDCS and SHAM produced sensations of comparable quality, minimal discomfort and duration. Moreover, neither healthy volunteers nor post-stroke patients were able to distinguish between tDCS and SHAM sessions, underlining its effectiveness for double-blind procedures. Our findings also suggest that tDCS did not elicit overt interference with attention or motivation, required for performance of cognitive tasks in Neurorehabilitation. Our results support the view that, under presently used stimulation parameters (Hummel et al., 2005a; Iyer et al., 2005; Nitsche et al., 2003a), tDCS is safe in both healthy volunteers and patients with stroke.

In summary, results from this study showed that tDCS, a form of non-invasive brain stimulation complementary to rTMS, can be successfully used in the setting of double-blind trials in Neurorehabilitation and cognitive neuroscience in healthy volunteers and patients with stroke.

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