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ORIGINAL ARTICLES

Lack of clinically detectable acute changes on autonomic or thermoregulatory functions in healthy subjects after transcranial direct current stimulation (tDCS)

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Background
Neuromodulatory techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have been increasingly studied as possible treatments for many neurological and psychiatric disorders. tDCS is capable of inducing changes in regional cerebral blood flow in both cortical and subcortical structures, as shown by positron emission tomography studies, and might conceivably affect hypothalamic and autonomic nervous system functions. However, it remains unknown whether acute changes in autonomic or hypothalamic functions may be triggered by conventional tDCS protocols.

Objective/Hypothesis
To verify whether tDCS, when performed with a bipolar cephalic montage, is capable of inducing acute changes in autonomic or hypothalamic functions in healthy subjects.

Methods
Fifty healthy volunteers were studied. tDCS was performed with the anode over the C3 position and the cathode over the right supraorbital region. Subjects received either real or sham tDCS. Parameters assessed before and after a 20-minute session included blood pressure, tympanic thermometry, hand skin temperature, heart rate and ventilatory rate. Plasma concentrations of cortisol were also measured in a sub-set of 10 participants.

Results
A repeated-measures, mixed-design ANOVA showed significant changes in hand skin temperature ($P = .005$) and cortisol levels ($P < .001$) after both real and sham stimulation. There were no statistically significant changes in any of the other measurements.

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Conclusions
The changes in hand temperature and cortisol levels, having occurred in both the sham and experimental groups, probably reflect a non-specific stress response to a new procedure. There were no significant changes in autonomic functions, ventilation rate or core body temperature that can be attributed to conventional tDCS applied to healthy volunteers.

Keywords transcranial direct current stimulation; tDCS; safety; autonomic nervous system; thermoregulation; cortisol

Recently, several reports have highlighted the therapeutic potential of transcranial magnetic stimulation (TMS) as a means of modulating cortical excitability in both neurologic and psychiatric patients.[1-3] This has led to a renewed interest in transcranial direct current stimulation (tDCS), which is a simpler and cheaper means of inducing cortical neuromodulatory changes than TMS.[4-9]

The use of direct transcranial currents to attempt to modify mood and other psychologic characteristics is not novel, and classical studies date from the 1960s.[10,11]

The mechanism of action of tDCS is still not completely understood, but it appears to involve both synaptic and nonsynaptic changes[12] as well as cortical and subcortical structures.[13] The putative effects of tDCS on subcortical autonomic nervous system structures have been postulated as a potential tool for the treatment of hypertension.[14]

However, tDCS safety studies conducted so far have concentrated mainly on potential local harm to the scalp and underlying cerebral tissue. Vandermeeren et al.[15] have conducted the only study in which possible cardiorespiratory and autonomic side effects were carefully studied, but these authors used a noncephalic reference instead of the usual "cephalic-cephalic" montage, and they did not measure serum cortisol or other hormones. Likewise, possible effects on body core temperature regulation were not assessed.

We have therefore tried to discover any clinically significant autonomic or thermoregulatory side effects of the most commonly used tDCS electrode montage.

Methods

Fifty healthy subjects, 18 men and 32 women, with a mean age of 30.5 years (range 19-63 years) participated in the study, which was approved by the local ethics committee. Subjects were free from the use of any drugs, including eye drops or other topical medicines.

Subjects were randomly assigned to receive either real (n = 25) or sham (n = 25) tDCS, and all underwent a single 20-minute session. All were naïve to tDCS. During the experimental sessions, subjects were comfortably seated and were asked to remain still and to refrain from talking.

In each subject, electrodes (35 cm^2 saline-soaked sponges covering conductive rubber pads) were firmly attached to the skull with the aid of Velcro straps. The skin was not abraded, and no other conductive media besides saline solution were used. The anode was placed over the C3 position of the 10-20 international system and the cathode ("reference") over the right supraorbital region. Room temperature was kept constant at 24-25°C.

A commercially available continuous current stimulator (Endophasys-D, KLD Instruments, São Paulo, Brazil) was used to apply a 1 mA of current for 20 minutes. This equipment has been approved by the national medical devices regulatory agency (ANVISA, Brasília, Brazil) for delivering therapeutic direct currents and, for the purpose of tDCS, was considered of no significant risk by the local ethics committee. In the sham condition, the current was initially turned on for 10 seconds and then gradually turned off over the course of 10 seconds, so that the tingling sensation usually felt at the beginning of real stimulation would be perceived by the participant.

Blood pressure, tympanic and hand skin temperatures, and heart rate were measured 5 minutes before and 5 minutes after the experimental sessions in all subjects. Ventilatory rate was recorded at 5-minute intervals throughout the whole session and 5 minutes after it. In 10 subjects (five from the sham group), blood samples were taken before and after experimental sessions for assessment of plasma cortisol concentrations.

Clinically available instruments were used for blood pressure (G-Tech digital sphygmomanometer, Smart Sense Technology, Chicago, IL), tympanic temperature (Thermo-Scan Plus IRT 3520, Braun Instruments, Melsungen, Germany), and hand temperature (Electro-therm Digital Thermometer, Elizabeth, CO) measurements.

Blood pressure and digital readings of heart rate were always taken from the right arm. For tympanic membrane temperature records, an average of three left ear measurements was taken as an index of body core temperature both before and after the experimental sessions. Hand skin temperature was taken with a sensor firmly attached to the subject's right palm. Ventilatory rate was clinically assessed by a researcher who was blind to the subject's stimulation status (real or sham).

Likewise, blood samples for cortisol measurements were drawn and processed blindly.

Results

Subjects in both the experimental and control groups did not report any subjective ill effects either during or after

Table 1 Comparison of all measurements between the real tDCS and sham groups

	Group			95 IC for dif			
	Sham	Real tDCS	Mean dif	Lower bound	Upper bound	*t*	*P*
Age	31.2 (12.4)	29.8 (10)	1.44	−5.0	7.8	0.453	.653
Systolic BP							
Baseline	122.6 (16.1)	124.8 (12.2)	−2.2	−10.3	5.9	−0.545	.588
Final	119.7 (13.3)	120.8 (13.6)	−1.1	−0.87	6.6	−0.284	.788
Diastolic BP							
Baseline	80.4 (13.4)	80.5 (8.2)	−0.1	−6.4	6.2	−0.025	.980
Final	79.4 (11.8)	79.1 (8.8)	0.3	−5.7	6.2	0.095	.925
Temperature							
Baseline	23.1 (2)	22.8 (2.6)	0.4	−1.0	1.7	0.571	.571
Final	24 (2.9)	23.8 (3.3)	0.2	−1.6	1.9	0.225	.823
Tympanic temp							
Baseline	35.8 (0.6)	35.8 (0.7)	0.0	−0.4	0.4	0.067	.947
Final	35 (2.9)	35.5 (2)	−0.5	−1.9	1.0	−0.651	.518
Heart rate							
Baseline	74.4 (8.1)	72.2 (10)	2.2	−3.0	7.4	0.853	.398
Final	74.7 (7.1)	73.7 (13.1)	1.0	−5.0	7.0	0.335	.739
Ventilation rate							
Baseline	15.1 (2.4)	15.1 (1.9)	0.0	−1.2	1.2	0.000	>.99
5′	15.1 (2)	15.4 (1.6)	−0.3	−1.3	0.8	−0.540	.592
10′	15 (2.1)	15.3 (1.9)	−0.3	−1.4	0.8	−0.500	.620
15′	14.6 (2.4)	15 (1.8)	−0.4	−1.6	0.8	−0.666	.509
20′	14.7 (2.2)	15.3 (1.9)	−0.6	−1.8	0.6	−1.048	.300
25′	14.4 (2)	15.2 (1.9)	−0.8	−1.9	0.3	−1.440	.156
Cortisol*							
Baseline	21.8 (5)	14.7 (5.9)	7.1	−0.9	15.1	2.050	.074
Final	16.3 (5.7)	11.3 (5.4)	5.0	−3.1	13.1	1.421	.193

Dif = difference; BP = blood pressure; Temp = temperature. There were no significant differences between groups either at baseline or after tDCS. Significance level was set at $P < 0.05$.

* Samples collected from five subjects in each group (n = 10).

the procedure. When comparing all measured parameters, there were no significant differences between sham and experimental group either before or after tDCS (Table 1).

Body core temperatures, assessed by tympanic thermometry, did not change significantly with the procedure. A repeated measures, mixed-design analysis of variance (ANOVA) showed, however, that there were significant changes in hand skin temperature ($P = .005$) and cortisol levels ($P < .001$) before and after the procedure; skin temperature was higher after the procedure and cortisol plasma levels were lower. There was, however, no effect of group; the changes occurred both after real and sham stimulation (Table 2, Figure 1).

Table 2 Comparison of baseline and final values of autonomic parameters, including data from both sham and real tDCS groups

	Measure			95% IC for dif			
	Baseline	Final	Mean dif	Lower bound	Upper bound	F	*P*
Systolic BP	123.7 (14.2)	120.2 (13.3)	3.5	0.0	7.1	4.003	.051
Diastolic BP	80.5 (11)	79.3 (10.3)	1.2	−0.7	3.2	1.554	.219
Temperature	22.9 (2.3)	23.9 (3.1)	−0.9	−1.6	−0.3	8.695	.005
Tympanic temp	35.8 (0.6)	35.3 (2.5)	0.5	−0.2	1.2	2.216	.143
Heart rate	73.3 (9.1)	74.2 (10.5)	−0.9	−3.7	1.8	0.452	.505
Ventilation rate*	15.1 (2.1)	14.8 (2)	0.4	−0.3	1.0	2.103	.085
Cortisol†	18.2 (6.4)	13.8 (5.8)	4.5	2.7	6.2	33.300	<.001

Dif = difference; BP = blood pressure; temp = temperature. There was a significant rise ($P = .005$) in hand skin temperature ("Temperature") as well as a significant decrease in cortisol plasma levels ($P < .001$). Significance level was set at $P < .05$.

* Final value is the 25′ measure. F an *P* are the values from the analysis of the six measures.

† Samples collected from five subjects in each group (n = 10).

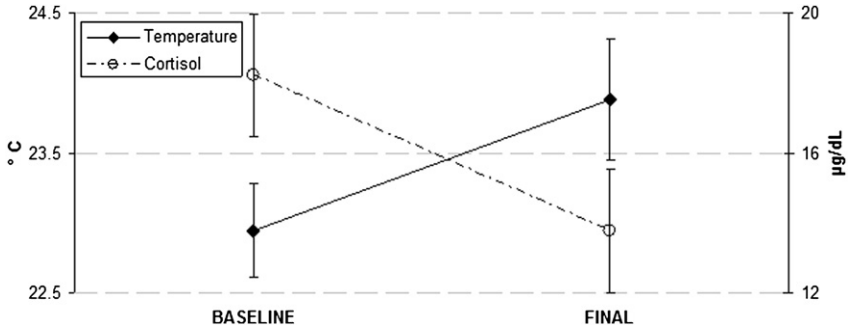

Figure 1 Skin hand temperature increased and plasma cortisol levels decreased after tDCS. Pooled data (mean ± SD) from the sham and real tDCS subgroups, n = 50.

There were no statistically significant changes in any of the other measurements.

As in Vandermeeren's experiments[15], respiratory frequency was not affected by tDCS (Figure 2).

Conclusion

Anodal tDCS over the motor cortex using the "cephalic-cephalic" montage, used in the majority of trials published so far, did not cause any clinically significant autonomic or thermoregulatory effects in the participants. The only significant changes occurred irrespective of the performance of real or sham stimulation. Such changes were probably the result of anxiety and a higher arousal level before the procedure; participants exhibited higher serum cortisol levels due to sympathetic activation and lower hand skin temperatures due to the resulting peripheral vasoconstriction.

This lack of autonomic changes is in contrast to early reports in the 1960s[10,11] of occasional side effects such as pallor, nausea, and breathing difficulties in patients undergoing bilateral scalp stimulation with a non-cephalic reference in the thigh. One might argue that autonomic side effects are more likely with a non-cephalic montage. However, in a recent study, Vandermeeren et al.[15] also used a montage with an extracephalic reference and did not find autonomic or cardio-respiratory effects of tDCS. Accornero and collaborators[16], using another "non-classical" montage (inion-neck) did not find changes in body temperature during or 20 minutes after tDCS in healthy volunteers, but they did not monitor respiratory frequency.

Anodal tDCS over the motor cortex with a cephalic reference is safe and devoid of clinically detectable autonomic or thermoregulatory effects when performed as a single session in normal volunteers. Further studies are needed to rule out possible complications in patients with preexisting dysautonomic, hypothermic or hyperthermic states, as well as those with neurological diseases or using drugs acting on the autonomic nervous system. It also remains to be determined whether several sessions over the course of weeks, as is commonly used for therapeutic trials, might result in late autonomic changes.

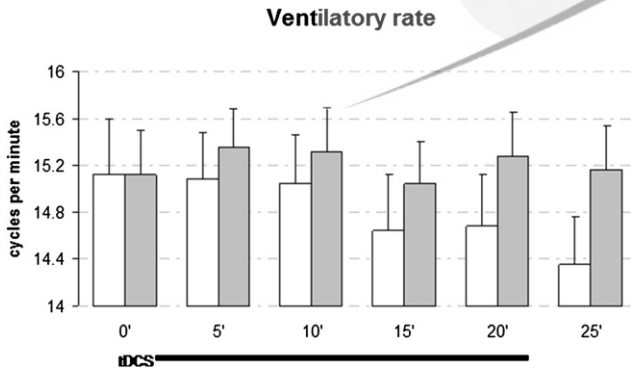

Figure 2 Mean ventilatory rates in both sham (white bars) and real tDCS (gray bars) subjects during the course of tDCS (horizontal bar at the bottom).

Supplementary data

Supplementary data related to this article can be found online at doi: 10.1016/j.brs.2011.03.009.

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