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Effects of chronic antidepressant use on neurophysiological responses to tDCS post-stroke

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Abstract

Background: Transcranial direct current stimulation (tDCS) induces neuroplastic changes in the motor cortex of healthy individuals and has become a candidate intervention to promote recovery post-stroke. However, neurophysiological effects of tDCS in stroke are poorly understood. Antidepressant medications, which are commonly prescribed post-stroke, have the potential to significantly affect cortical excitability and alter responsiveness to tDCS interventions, yet these effects have not previously been examined.

Objective/Hypothesis: To examine the effects of chronic antidepressant use, tDCS, and the interaction of the two on motor cortical excitability in people with chronic stroke. Based on previous literature in nondisabled adults, we hypothesized that post-stroke, antidepressant-takers would show decreased baseline motor cortical excitability but enhanced responsiveness to anodal tDCS.

Methods: Twenty-six participants with chronic stroke (17 control, 9 antidepressant) received real and sham anodal tDCS during separate sessions at least a week apart. Motor cortical excitability was measured before and after tDCS was applied to the lesioned hemisphere primary motor cortex. We compared baseline cortical excitability and neurophysiological responses to tDCS between groups and sessions.

Results: Baseline motor cortical excitability was not different between control and antidepressant groups. Following anodal tDCS over the ipsilesional primary motor cortex, cortical excitability in the non-lesioned hemisphere decreased in controls, but, surprisingly, increased in antidepressant-takers.

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Conclusions: Chronic antidepressant use may not affect motor cortical excitability post-stroke, however it appears to reverse some of the expected effects of tDCS. Therefore future utilization of tDCS in post-stroke neurorehabilitation research should take antidepressant medication status into account.

Keywords

Stroke; rehabilitation; transcranial magnetic stimulation; neuroplasticity; motor; depression

Introduction

Despite receiving standard rehabilitation treatments, the majority of stroke survivors have persistent motor function deficits in the upper extremity [1,2], which lead to poorer quality of life [3,4]. One underlying mechanism that contributes to these deficits is altered motor cortical excitability within the primary motor cortex (M1), which can be measured with transcranial magnetic stimulation (TMS). After unilateral stroke affecting the corticospinal tract, motor evoked potential (MEP) amplitudes from the lesioned hemisphere are decreased compared to the non-lesioned hemisphere [5,6], and compared to healthy controls [6]. This decrease is associated with poor motor function recovery [7,8]. Furthermore, persistent abnormal increases of MEP amplitudes in the non-lesioned hemisphere are associated with decreases of MEP amplitudes in the lesioned hemisphere [6], suggesting an imbalance of interhemispheric excitability, which may also be associated with poor motor recovery [9]. Indeed, interventions that increase excitability within the lesioned M1, and those that decrease excitability within the non-lesioned M1 can both improve motor performance of the paretic arm [10].

Transcranial direct current stimulation (tDCS) is an intervention that can change motor cortical excitability [11-13]. Specifically, anodal stimulation of M1 increases MEP amplitudes in the stimulated hemisphere [13-15], and cathodal stimulation of M1 decreases MEP amplitudes [13,15,16]. TDCS can also affect the excitability of transcallosal pathways [12,17], thereby affecting the unstimulated hemisphere, with anodal stimulation producing decreased MEP amplitudes in the unstimulated hemisphere [18]. Thus, the use of tDCS to enhance motor recovery post-stroke is an area of great interest, with the goal of increasing cortical excitability within the lesioned hemisphere by either applying anodal tDCS ipsilesionally, or cathodal tDCS contralesionally, or both [19-25]. In fact, in people with stroke, anodal tDCS applied over the lesioned hemisphere M1 during a motor task has been shown to improve motor performance of the paretic hand [10,20], and the performance improvement is positively correlated with increases of motor cortical excitability in the lesioned hemisphere M1 [20]. However, responses to tDCS in stroke are highly variable, and not all studies show positive effects [24-26]. The reason why tDCS outcomes post-stroke are so variable is currently not known.

The heterogeneity among stroke survivors is one possible explanation for these inconsistencies [23-25], with neuropharmacological effects representing one significant source of heterogeneity. The use of antidepressant medications is of particular interest because these drugs are prescribed in up to 30% of stroke survivors [27-30]. Recent

investigations in healthy adults indicate that selective serotonin reuptake inhibitors (SSRIs), the most common class of antidepressant [31], affect motor cortical excitability and responsiveness to tDCS [32-36]. Therefore, understanding how these medications affect motor cortical excitability, and how they may interact with tDCS, are likely important considerations for using tDCS in post-stroke neurorehabilitation. Yet to date, antidepressant use has been widely ignored in post-stroke rehabilitation studies involving tDCS [10,21,26,37-40].

In healthy adults, a single dose of an SSRI increases MEP amplitudes [32], however, chronic ingestion of SSRIs produces reversed effects [36]. In individuals with *acute* stroke, one month of SSRI ingestion increases motor thresholds in the non-lesioned hemisphere compared to placebo medication, but does not appear to affect MEP amplitudes [41]. These studies suggest that SSRIs may have significant effects on motor cortical excitability in *chronic* stroke survivors, but this has not been tested. Moreover, SSRIs can interact with tDCS. Both acute and chronic application of SSRIs in healthy individuals facilitates the effects of anodal tDCS and reverses the inhibitory effects of cathodal tDCS, resulting in facilitation [34,35]. However, despite the widespread interest in investigating the use of tDCS post-stroke, to our knowledge, no one has yet examined effects of antidepressant medication status on responsiveness to tDCS in stroke survivors [19-25].

The purpose of this study was to examine the effects of chronic SSRI or selective serotonin-norepinephrine reuptake inhibitor (SNRI) use on motor cortical excitability and to examine its effects on responsiveness to anodal tDCS in chronic stroke. Based on prior work in healthy chronic antidepressant-takers and people with acute stroke [36,41], we first hypothesized that baseline motor cortical excitability would be decreased in the non-lesioned hemisphere of stroke survivors taking antidepressants, compared to those not taking antidepressants (H1). Second, based on results in healthy individuals [34,35] and the potential bilateral effects of tDCS [12,17,18], we hypothesized that the effects of anodal tDCS over the lesioned hemisphere M1 on motor cortical excitability would be enhanced in stroke survivors taking antidepressants compared to those not taking antidepressants (H2). Specifically, we hypothesized that antidepressant takers would show higher increases of motor cortical excitability in the lesioned hemisphere, and greater decreases of excitability in the non-lesioned hemisphere, compared to the control group.

Material and Methods

Participants

Twenty-six (4 female, mean $\pm$ SD, 65.46 ± 8.06 years) participants with chronic (> 6 months), unilateral stroke affecting the upper extremity (Fugl-Meyer Assessment (FMA) score < 66) participated in this study. Brain MRI or CT scan reports were obtained to verify stroke type, lesion location and damage to the corticospinal tract. Participants were assigned to either the control group ($n = 17$) or the antidepressant group ($n = 9$) according to their regularly taken medications. Individuals in the antidepressant group must have been taking a single SSRI or SNRI, and must have been on the same drug and dosage for at least 3 months at the time of testing. We opted to include individuals on either an SSRI or an SNRI because of the similar mechanisms of action of these two classes of drugs on serotonin systems.

Most SNRIs are in fact relatively selective as serotonin reuptake inhibitors [42]. Exclusion criteria for both groups included multiple strokes affecting both hemispheres, any cerebellar lesion, or any other significant neurological, cardiovascular or musculoskeletal condition besides stroke. Individuals with contraindications to TMS or tDCS were also excluded, as well as participants taking or recently withdrawing from (< 12 weeks) any medications affecting the central nervous system (except SSRIs or SNRIs, for participants in the antidepressant group). Individuals taking or withdrawing from any antidepressant medications were excluded from the control group. The experimental protocol was approved by the University of Delaware Institutional Review Board and all participants gave written informed consent. Participant demographic and clinical information are provided in Tables 1 and 2, respectively.

General Paradigm

Participants completed three testing sessions. During the first session, the upper extremity FMA [43] was performed and medication information was collected to verify eligibility and group assignment. To better understand our participants' depressive symptoms, the Geriatric Depression Scale short form [44] and the Hospital Anxiety and Depression Scale [45] were used to assess depression and anxiety levels, and the Apathy Scale [46] was used to assess apathy. Participants were also familiarized with the TMS and electromyography (EMG) setup in session 1. Sessions 2 and 3 were scheduled at least a week apart. Participants received real tDCS in one session and sham tDCS in the other session. The order of real and sham tDCS sessions were counterbalanced among participants and participants were blinded to the treatment. Motor cortical excitability of the extensor carpi radialis (ECR) muscles was measured bilaterally with TMS before and immediately after real and sham tDCS.

Transcranial Direct Current Stimulation

tDCS was applied during quiet sitting using a battery-powered direct current stimulator (Chattanooga by DJO Global, Inc., Vista, CA) with two square saline-soaked sponge electrodes (effective area 25 cm²) (AMREX Electrotherapy, Paramount, CA). The anode was centered over the lesioned hemisphere ECR "hot spot" (identified during TMS, see details below), and the cathode was placed over the contralateral supraorbital area. For real tDCS, the current was set at 1 mA and delivered for 10 minutes. For sham tDCS, the current was set at 1 mA for 1 minute. This method creates an effective form of participant blinding [47].

Data Collection

Electromyography—EMG was collected using a 10-channel system with double differential surface electrodes with an integrated ground (Motion Lab Systems, Inc., Baton Rouge, LA). The skin over the ECR muscles was cleaned and electrodes were placed over the ECR muscle bellies bilaterally. EMG data were amplified, collected with a sampling rate of 5000 Hz and online low-pass filtered at 2000 Hz.

Transcranial Magnetic Stimulation—Participants sat in a comfortable chair with arms relaxed. A 70 mm diameter figure-of-eight coil was used in conjunction with a Magstim 200² electromagnetic stimulation unit (Magstim, Ltd., Wales, UK) for all TMS measures.

Signal 6.03 software (Cambridge Electronic Design, Ltd., Cambridge, UK) was used to control and trigger the magnetic stimulator through a 16-bit data acquisition unit (Micro 1401-3, Cambridge Electronic Design, Ltd., Cambridge, UK), and to record and store EMG data for offline analysis.

The vertex of the skull was identified and marked on the scalp. With the coil held tangential to the scalp and the handle pointing backwards at a 45° angle to the mid-sagittal line [48-50], the “hot spot” for the ECR muscle was found and carefully marked directly on the scalp. If no MEPs could be elicited from the lesioned hemisphere at 100% of the maximum stimulator output, we identified the “hot spot” as the mirror symmetrical location as that for the non-lesioned hemisphere. Resting motor threshold (RMT) was defined as the lowest stimulus intensity that produced at least 5 out of 10 MEPs in the contralateral ECR muscle with a peak-to-peak amplitude > 50 μ V [51]. Ten MEPs were collected from each ECR muscle via contralateral hemisphere stimulation at 120% RMT before and after real and sham tDCS.

Data Analysis

EMG data were analyzed with custom written software in MATLAB (MathWorks, Inc., Natick, MA). All raw EMG data were demeaned and amplification removed. EMG was notch-filtered at 60 Hz with a 2nd order Butterworth filter to remove electrical noise, and trials with baseline (10 - 60 ms before stimulus) peak-to-peak EMG exceeding 30 μ V were discarded, as this could indicate the participant was not at rest. Peak-to-peak MEP amplitudes were calculated for each trial and averaged over all trials. Post-tDCS measures were normalized to pre-tDCS (post/pre ratio) to more fairly compare participants with varying degrees of impairment.

Statistical Analysis

Statistical analyses were performed in IBM SPSS Statistics 24 (IBM Corp., Armonk, NY). Because data were not normally distributed and because of reduced data points from the lesioned hemisphere in some cases (when unable to obtain MEPs), non-parametric tests were used for all statistical comparisons. Mann-Whitney U tests were used to compare baseline motor cortical excitability between control and antidepressant groups (H1). To test whether chronic antidepressant use had any effect on responses to tDCS (H2), Mann-Whitney U tests were used to compare normalized motor cortical excitability measurements in the real tDCS session between control and antidepressant groups. Mann-Whitney U tests were also used to confirm the two groups weren't different in sham tDCS sessions. Finally, demographic and clinical characteristics between groups were compared using Fisher's exact tests or Mann-Whitney U tests.

Results

Regarding stroke participant characteristics, more participants in the antidepressant group had hemorrhagic strokes compared to the control group ($p = 0.002$). All other demographic characteristics, including age, sex, and time since stroke, were not significantly different between groups ($p > 0.49$), see Table 1. For clinical measures, participants were not different

between groups in upper extremity motor function as measured by the FMA ($p = 0.46$). However, the antidepressant group showed significantly greater depressive symptoms than the control group, based on both the GDS ($p = 0.009$) and the depression score of the HADS ($p = 0.009$), even though they were taking antidepressants. They also scored significantly higher on the apathy scale compared to the control group ($p = 0.029$). Anxiety levels were not different between groups based on the anxiety score of the HADS ($p = 0.26$). See Table 2 for details.

All participants completed the experiment with no adverse events, however, for some participants, MEPs could not be elicited from the lesioned hemisphere even with stimulation at 100% of the maximal stimulator output (MSO). In the control group lesioned hemisphere, we were able to obtain MEPs in 8 of 17 participants (47%). In the antidepressant group lesioned hemisphere, we were able to obtain MEPs in 4 of 9 participants (44%). We were able to obtain MEPs in the non-lesioned hemisphere in all participants. All data are reported in mean $\pm$ SEM unless otherwise stated.

Baseline Motor Cortical Excitability in Control vs. Antidepressant Groups (H1)

Because pre-tDCS TMS measures were comparable between sessions, baseline measures were averaged across sessions. We found no differences between groups for either RMTs or MEP amplitudes from either hemisphere (all, $p > 0.06$). Likewise, the proportion of individuals for whom we were unable to elicit MEPs in the lesioned hemisphere was also similar between groups (Fisher's exact test, $p > 0.9$). See Table 3 for details.

Effects of tDCS on Motor Cortical Excitability in Control vs. Antidepressant Groups (H2)

Figure 1 shows MEP amplitudes from the lesioned (Fig. 1a) and non-lesioned (Fig. 1b) hemispheres of control and antidepressant groups following real and sham tDCS sessions. As expected, no differences were observed between groups following sham tDCS (lesioned hemisphere: control, 1.16 ± 0.18 , 95% CI [0.81, 1.51], antidepressant, 1.39 ± 0.40 , 95% CI [0.61, 2.17], $U = 19.0$, $p = 0.68$; non-lesioned hemisphere: control, 1.27 ± 0.16 , 95% CI [0.96, 1.58], antidepressant, 1.38 ± 0.28 , 95% CI [0.83, 1.93], $U = 78.0$, $p = 0.97$). Likewise, excitability ratios remained around 1.0, indicating little deviation from the pre-tDCS time period to the post-tDCS time period.

In addition, following real anodal tDCS, there was no between-groups difference in the lesioned hemisphere (control, 1.03 ± 0.18 , 95% CI [0.68, 1.38], antidepressant, 1.08 ± 0.40 , 95% CI [0.30, 1.86], $U = 13.0$, $p = 0.68$). Like the sham condition, normalized MEPs were near 1.0 for both groups, indicating very minimal effects of anodal tDCS in this hemisphere. However, in the non-lesioned hemisphere following real tDCS, there was a highly significant difference between groups. Normalized MEPs in the antidepressant group averaged 1.96 ± 0.30 (95% CI [1.37, 2.55]), compared to 1.00 ± 0.10 (95% CI [0.80, 1.20]) in the control group ($U = 122.00$, $p = 0.001$). Note that the increase in MEPs in the non-lesioned hemisphere in antidepressant-takers post-stroke suggests a reversal of the typical effects of anodal tDCS (i.e., expected increased excitability in the lesioned hemisphere and decreased excitability in the non-lesioned hemisphere). To further illustrate this effect, Figure 2 shows the normalized MEP amplitudes from the non-lesioned hemisphere in the real tDCS session

for all individuals in control (Fig. 2a) and antidepressant (Fig. 2b) groups. Most participants in the control group, but no participants in the antidepressant group, had decreased MEPs from the non-lesioned hemisphere after real anodal tDCS was applied over the lesioned hemisphere. Instead, those in the antidepressant group uniformly showed modest to very large increases following anodal tDCS to the contralateral, lesioned hemisphere. Conversely, responses after sham tDCS were non-uniform (Fig. 2c, 2d).

Discussion

In our study of chronic stroke participants, we found that those taking an SSRI or SNRI antidepressant medication were not significantly different from non-antidepressant-takers (controls) in baseline cortical excitability levels. However, when anodal tDCS was applied to the lesioned hemisphere M1, motor cortical excitability in the unstimulated, non-lesioned hemisphere increased dramatically in participants taking antidepressants but not in controls. These results suggest that chronic SSRI or SNRI intake post-stroke significantly affects responsiveness to anodal tDCS, at least within the non-lesioned hemisphere. Specifically, anodal tDCS effects are reversed in the contralateral, non-stimulated hemisphere, such that excitability is facilitated following anodal tDCS.

Effects of Antidepressants on Baseline Motor Cortical Excitability Post-Stroke

At baseline, chronic intake of antidepressants in stroke survivors did not appear to affect either RMTs or MEP amplitudes in either hemisphere. Our results only partially agree with a previous study in people with *acute* stroke, which found that chronic administration of citalopram increased intracortical inhibition and RMTs in the non-lesioned hemisphere but found no changes in the lesioned hemisphere [41]. The differences between these two studies suggest that there may be important differences in brain chemistry and effects of antidepressant medications on motor cortical excitability that occur with the progression from acute to chronic stroke. It is also possible that the duration of antidepressant treatment may also play a role. In the previous study, the SSRI medication was prescribed for 1 month prior to testing, whereas in our sample, the medication had been taken for at least 3 months. In healthy individuals (non-depressed and non-stroke-affected), chronic paroxetine administration induced opposite effects on motor cortical excitability compared to an acute dose [36], presumably due to receptor desensitization and downregulation over time [52,53]. It is possible a similar mechanism explains our lack of differences between groups in baseline excitability. Also, it is important to acknowledge that we were only able to obtain MEPs in the lesioned hemisphere in a subset of participants ($n = 8$ control; $n = 4$ antidepressant); this reduced number limited our ability to detect changes in the lesioned hemisphere. However, this could not explain the observed lack of effects in the non-lesioned hemisphere.

Effects of Antidepressants on tDCS-Induced Motor Cortical Excitability Changes Post-Stroke

Following anodal tDCS, we found a large and significant increase in MEP amplitudes in the non-lesioned hemisphere in the antidepressant group compared to the control group, indicating that antidepressant medications may alter responsiveness to anodal tDCS.

Interestingly, previous studies in healthy adults have also shown that SSRIs can alter responsiveness to tDCS: SSRIs appear to enhance the effects of anodal tDCS and reverse the effects of cathodal tDCS, turning the inhibitory effect normally associated with cathodal stimulation into a facilitatory one [34,35]. In the current study, we showed that antidepressant medications combined with anodal tDCS, in the context of a stroke-damaged brain, also alters responsiveness to tDCS in the direction favoring enhanced facilitation, but this appears to be a reversal of the expected effect of inhibition of the contralateral, non-stimulated hemisphere.

Understanding the potential mechanism for this important effect will require multiple future studies. However, one possibility for a shift toward more facilitation rather than inhibition is that serotonin can cause a reduction in potassium conductance and thereby induce neuronal depolarization [54,55]. Serotonin is also known to block long-term depression (LTD) in slice preparations [56]. Other potential mechanisms could involve serotonin's known effects on acetylcholine [57], GABA [58] and/or dopamine activity [59], which also modulate tDCS effects [16,60,61].

We did not detect changes between groups in the lesioned (stimulated) hemisphere following real anodal tDCS and neither group appeared to show a significant change from pre-tDCS levels in the lesioned hemisphere (normalized MEPs remained near 1.0, indicating no difference from baseline). At a minimum, we expected that non-antidepressant-takers would show increased excitability in the lesioned hemisphere following anodal tDCS, as has been shown relatively consistently in healthy adults [13-15] and in studies of stroke survivors [62,63]. Our sample of stroke participants differs from previous studies in that our participants appear to have been somewhat more heterogeneous and had, on average, lower functional levels (compare with Suzuki et al. [62]). This may have increased the heterogeneity of responses to tDCS and/or reduced overall responsiveness to tDCS in our sample. And, as described above, because we were only able to obtain MEPs in the lesioned hemisphere in a subset of participants, we may not have had enough participants to detect differences. For the non-lesioned hemisphere, the average MEP change in the control group was minimal, indicated by the average normalized MEP amplitude value of near 1.0. However, after assessing each individual's performance, it is clear that most participants had decreased MEPs after anodal tDCS (Fig. 2a). The direction of this change is consistent with the theory that anodal tDCS induces increased interhemispheric inhibition from the stimulated to the non-stimulated hemisphere [12,17] and thereby induces inhibition in the non-lesioned hemisphere, and appears to have been achievable despite the lack of MEP changes in the lesioned hemisphere. However, the exact mechanism for this remains unclear.

Regardless of mechanism, the overall finding of reversed effects of anodal tDCS in the non-stimulated, non-lesioned hemisphere M1 of chronic antidepressant-takers is highly relevant. It is also important to note that the effect was quite robust: no participant in the antidepressant group showed the expected inhibition in the non-stimulated hemisphere, whereas 12 of 17 (70.6% of participants) in the control group did (between group difference, $p < 0.002$, Fisher's exact test). Given that antidepressant intake is rarely considered in clinical intervention studies of anodal tDCS for post-stroke recovery, this observation could provide one explanation for mixed and/or negative findings in studies where anodal tDCS

was expected to inhibit the non-stimulated hemisphere but instead may have caused facilitation. Of note, most clinical trials that have used tDCS for post-stroke rehabilitation have not reported MEP amplitude changes [10,19,25,37,40,64].

Limitations

The greatest limitation of this study is the reduced sample size for the lesioned hemisphere data, due to the fact that no MEPs could be elicited for a substantial proportion of participants in both groups. Although this limits interpretation of the data from the lesioned hemisphere, it does not impact the findings from the non-lesioned hemisphere. Thus the altered responsiveness to anodal tDCS observed in the non-lesioned hemisphere is an unambiguous result. What remains to be investigated in future studies with larger sample sizes is the potential for additional effects in the lesioned hemisphere. Another limitation is that, although we limited inclusion in the antidepressant group to those only taking one SSRI or SNRI, individual medications can have unique mechanisms of action [65], which may affect motor cortical excitability and/or responses to tDCS differently. Future studies should examine and compare each medication individually. We also performed only a very limited set of TMS measures and did not assess responsiveness to cathodal tDCS. Certain other measures, such as intracortical inhibition, intracortical facilitation and interhemispheric inhibition, reflect changes in other cortical pathways, and may provide mechanistic evidence for our results. Testing of cathodal tDCS would also provide valuable insight into potential mechanisms. Finally, because of significant symptoms of depression and apathy in our antidepressant group, we cannot rule out that the effects seen in our study were an effect of depression and/or apathy rather than the medication per se.

Conclusions

Our results show unexpected and complex changes of SSRI/SNRI usage on motor cortical excitability and responses to tDCS in chronic stroke survivors, which are different from those experienced by healthy individuals, and different from those experienced by stroke survivors not taking antidepressants. Thus the combination of a brain lesion due to stroke and the chronic ingestion of certain antidepressant drugs produces complex interactions in the brain that impact cortical excitability and responses to tDCS. Importantly, these interactions appear to be significant, with the potential to reverse some of the expected physiological effects of anodal tDCS contralaterally. Therefore, careful attention should be paid to antidepressant medication status in future clinical studies utilizing tDCS post-stroke. This and additional factors that can contribute to individual differences in responses to tDCS in stroke need to be thoroughly investigated.

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Highlights

- In chronic stroke, neurophysiological effects of tDCS can be atypical.
- Chronic antidepressants may reverse some responses to anodal tDCS post-stroke.
- Antidepressant use should be considered and reported in stroke studies using tDCS.

Figure 1.

Group mean normalized (ratio, post-to-pre tDCS values) MEP amplitudes from the M1 of the lesioned (a) and non-lesioned (b) hemispheres. In each, responses to real (left) and sham (right) tDCS are shown. The antidepressant group is shown in light gray bars; the control group is in dark gray bars. Error bars, ± 1 SEM. *Significantly different between control and antidepressant groups, $p < 0.05$.

Figure 2.

Individual normalized resting MEP amplitudes from the non-lesioned hemisphere M1 before and after real (top) and sham tDCS (bottom); each line represents data from one individual. In the control group, most participants had decreased resting MEPs (values < 1) after real tDCS (a). In the antidepressant group, most participants had increased MEPs (values > 1) after real tDCS (b), and no participant had decreased MEPs. On the contrary, after sham tDCS, both the control group (c) and the antidepressant group (d) had an even spread of responses around 1.

TABLE 1.

Participant demographic information.

Control Group						
PID	Sex	Age (yrs)	Time Since Stroke (m)	Side of Stroke	Stroke Type	Stroke Location
01	M	74	9	R	I	S
02	M	66	29	R	I	S
03	F	63	31	R	I	S
04	F	68	45	R	I	S+C
05	M	76	34	R	I	S
06	M	51	125	L	I	S+C
07	M	73	10	L	I	S
08	M	55	45	R	I	C
09	M	68	9	R	I	S
10	M	77	24	R	I	S
11	M	65	25	R	I	S
12	M	70	7	L	I	S
13	M	73	30	R	I	S+C
14	M	64	72	R	I	S
15	M	47	25	R	I	S
16	M	57	50	L	I	S
17	F	69	17	L	I	S
mean $\pm$ SD		65.65 $\pm$ 8.72	34.53 $\pm$ 28.91			
Antidepressant Group						
PID	Sex	Age (yrs)	Time Since Stroke (m)	Side of Stroke	Stroke Type	Stroke Location
18	M	79	64	L	I	S
19	M	63	31	R	H	S
20	M	58	22	R	I	S+C
21	F	61	29	R	I+H	S
22	M	69	66	L	H	S
23	M	69	133	R	I+H	S
24	M	55	32	R	I	S
25	M	64	11	R	I	S+C
26	M	68	10	R	H	S
mean $\pm$ SD		65.11 $\pm$ 7.13	44.22 $\pm$ 38.85			
<i>p</i>	1.000 [#]	0.634	0.491	1.000 [#]	0.002 ^{#*}	1.000 [#]

Abbreviations: PID = participant identifier; M = male; F = female; yrs = years; m = months; R = right; L = left; I = ischemic; H = hemorrhagic; S = subcortical; C = cortical.

[#]Fisher's exact test; all others Mann-Whitney U tests.

* Statistically significant between control and antidepressant groups.

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TABLE 2.

Participant clinical information.

Control Group					
PID	UE-FMA	GDS	HADS-A	HADS-D	AS
01	32	1	1	2	2
02	33	0	0	0	2
03	60	0	0	1	4
04	60	0	0	0	7
05	59	1	2	2	7
06	12	5	7	3	5
07	63	6	6	5	24
08	10	0	7	5	5
09	58	1	0	3	7
10	27	2	4	3	5
11	61	1	3	1	9
12	61	0	2	1	8
13	59	1	3	1	7
14	21	1	0	2	6
15	49	6	5	7	8
16	52	2	1	2	7
17	60	3	2	4	3
mean ± SD	45.71 ± 18.80	1.76 ± 2.05	2.53 ± 2.48	2.47 ± 1.91	6.82 ± 4.89
Antidepressant Group					
PID	UE-FMA	GDS	HADS-A	HADS-D	AS
18	8	3	0	4	5
19	9	2	3	5	12
20	15	9	5	9	13
21	59	3	3	5	19
22	47	2	1	4	11
23	14	2	1	2	7
24	60	3	6	2	4
25	60	6	9	10	28
26	64	5	7	9	18
mean ± SD	37.33 ± 25.02	3.89 ± 2.37	3.89 ± 3.06	5.56 ± 3.05	13.00 ± 7.68
p	0.458	0.009 *	0.263	0.009 *	0.029 *

Abbreviations: PID = participant identifier; UE-FMA = upper extremity Fugl-Meyer Assessment score; GDS = geriatric depression scale score; HADS-A = anxiety score of the Hospital Anxiety and Depression Scale; HADS-D = depression score of the Hospital Anxiety and Depression Scale; AS = apathy score.

* Statistically significant between control and antidepressant groups, Mann-Whitney U tests for all variables.

TABLE 3.

Baseline motor cortical excitability

Group	Resting motor threshold (%MSO)		MEP amplitude (mV)	
	Non-lesioned	Lesioned	Non-lesioned	Lesioned
Control	45.26 ± 2.66 [40.05, 50.47] (n=17)	57.78 ± 6.29 [45.45, 70.11] (n=8)	0.39 ± 0.06 [0.27, 0.51] (n=17)	0.30 ± 0.12 [0.06, 0.54] (n=8)
Antidepressant	44.11 ± 2.12 [39.95, 48.27] (n=9)	44.75 ± 4.15 [36.62, 52.88] (n=4)	0.24 ± 0.05 [0.14, 0.34] (n=9)	0.19 ± 0.07 [0.05, 0.33] (n=4)
	$U = 71.5$	$U = 12.0$	$U = 42.0$	$U = 18.0$
	$p = 0.79$	$p = 0.41$	$p = 0.07$	$p = 1.00$

Data shown represent means ± 1 SEM. 95% confidence interval shown in square brackets. 'n' indicates the number of participants available for each measure.

Abbreviation: MSO = maximum stimulator output; MEP = motor evoked potential.