Combination of transcranial direct current stimulation and methylphenidate in subacute stroke

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A B S T R A C T

Noninvasive transcranial direct current stimulation (tDCS) and methylphenidate (MP) are associated with motor recovery after stroke. Based on the potentially complementary mechanisms of these interventions, we examined whether there is an interactive effect between MP and tDCS. In this preliminary study, we randomized subacute stroke subjects to receive tDCS alone, MP alone or combination of tDCS and MP. A blinded rater measured safety, hand function, and cortical excitability before and after treatment. None of the treatments caused any major or severe adverse effects or induced significant differences in cortical excitability. Analysis of variance of gain score, as measured by Purdue pegboard test, showed a significant between-group difference (F(2,6) = 12.167, p = 0.008). Post hoc analysis showed that the combination treatment effected greater Purdue pegboard gain scores than tDCS alone (p = 0.017) or MP alone (p = 0.01). Our preliminary data with nine subjects shows an interesting dissociation between motor function improvement and lack of motor corticospinal plasticity changes as indexed by transcranial magnetic stimulation in subacute stroke subjects.

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1. Introduction

Stroke is the leading cause of long-term disability in the adult population and represents an enormous, growing burden to patients, families, and society [31,34]. However, few treatments improve motor function in subacute and chronic stroke patients, and their effects are often limited. Recent clinical trials have demonstrated that noninvasive transcranial direct current stimulation (tDCS) [25] enhances motor function in stroke patients [3,13,16,26,27]. The effects of tDCS in stroke are associated with changes in brain excitability, resulting in secondary changes in synaptic strengthening as shown by pharmacological studies, which have been conducted in healthy humans [19,24]. The mechanism of action is thought to be associated with changes in the resting membrane potential of neurons led by the constant gradient of voltage that induces ionic currents. Thus, it leads to hyperpolarization or depolarization of a cell. The direction of the current that is applied by tDCS affects the outcome. Cathodal tDCS decreases cortical excitability, whereas anodal tDCS increases it [25]. Stimulation of the unaffected hemisphere with cathodal tDCS and the affected hemisphere with anodal tDCS [8,14] has beneficial effects. In addition, tDCS, combined with physical and occupational therapy after stroke, significantly improves motor function compared with therapy alone [7,20].

Neurostimulators also increase cortical excitability. Methylphenidate (MP) is an indirect dopamine and norepinephrine agonist that enhances motor recovery after partial cortex ablation in rodents [17]. Further, MP modulates poststroke cerebral reorganization and improves motor function in stroke patients [12,18].

The effect of MP on brain excitability was examined in a randomized, parallel, double-blind study in which healthy subjects were treated with 20 mg MP or placebo [12,18,23]. MP induced...
hyperactivation of the ipsilesional primary sensorimotor cortex and hypoactivation of the ipsilesional anterior cingulum, as measured by functional magnetic resonance imaging. The hyperactivation correlated with improved motor performance, based on the finger tapping test. MP also modulated the dynamics of motor system excitability. Treatment with MP is associated with faster reaction times and fewer impulsivity errors in the response inhibition task [18], and the combination of MP and physiotherapy is significantly better than placebo plus physiotherapy [21] in promoting motor recovery after stroke.

MP and tDCS appear to enhance motor recovery by increasing excitability in the lesioned motor cortical area. Thus, we hypothesized that combining these therapies would synergize their individual effects on motor recovery. We conducted a double-blinded, randomized, placebo-controlled pilot study to examine the initial preliminary data about this combination treatment in subacute stroke patients. In addition, we compared the initial effect sizes between a nonfocal treatment (MP – pharmacological treatment) and a more focal intervention (tDCS – brain stimulation treatment).

2. Method

2.1. Subjects

This study was approved by the IRB of Spaulding Rehabilitation Hospital. All patients gave written informed consent. Inclusion criteria include first-time ischemic or hemorrhagic stroke and stroke onset within 1 month prior to study enrollment. Exclusion criteria include coexistence of advanced or terminal disease and use of certain neuropsychotropic drugs, i.e. monoamine oxidase inhibitors (such as citalpram, sertraline, moclobemid or selegilin). Inclusion and exclusion criteria are shown in details in Supplementary Methods.

2.2. Study design

Safety was assessed, based on the tDCS adverse event questionnaire [4] and cognitive status, as measured by Mini Mental State Examination (MMSE), digit span, and stroop test. We also administered open-ended questions regarding whether other adverse effects were observed during the study period (such as: “Did you experience any other adverse effects? Please name.”).

The other 2 main outcomes were: (i) cortical excitability, as assessed by TMS; and (ii) hand motor function, as measured by Purdue pegboard test. All methods have been used extensively in previous tDCS studies [6] and thus provide sufficient parameter values for comparability between studies.

At the first visit, patients were screened for eligibility by review of the inclusion and exclusion criteria. Subjects were randomly assigned to 1 of 3 groups: real tDCS plus placebo (tDCS group), sham tDCS plus MP (MP group), or real tDCS plus MP (tDCS + MP group). Patients completed baseline hand function and cognitive assessments 1–2 day prior to treatment. During the second visit, baseline cortical excitability was evaluated using TMS. Subjects then received a 1-time oral dose of 20 mg MP or placebo (peak serological level of MP: 1–2 h after intake [29]). Placebo, which was fruit juice flavored to match the liquid form of commercial available MP, was prepared by Spaulding hospital pharmacy. One hour after administration of the drug, patients received tDCS at 1 mA for 20 min over the primary motor cortex (M1) or sham tDCS for 10 s. Cortical excitability was measured immediately and 30 min after stimulation with real or sham tDCS. Hand function and cognitive assessment were measured right after TMS measurement. A tDCS adverse reaction questionnaire was completed on the same day. Course and time of assessments were equal for all subjects. The treatment scheme was illustrated in Supplementary Figure 1.

2.3. Assessment of cortical excitability – TMS

Measurements were performed using a Bistim2stimulator and a figure-of-eight coil (Magstim Company LTD, UK). For recordings silver/silver chloride electrodes (ADinstruments, USA) were placed over the first dorsal interosseus muscle (FDI). Measurements were done with Powerlab4/30 (ADinstruments, USA) with a band pass of 20–2000 kHz.

Cortical excitability were investigated using the techniques of TMS to measure intrahemispheric and interhemispheric changes [33]. Both the affected and unaffected M1 were studied. First, resting motor threshold (MT) was determined and re-evaluated after the treatment. Furthermore, motor evoked potentials (MEP) were assessed at an intensity of 130% of the individual MT (“MEP-intensity”). We recorded 10 MEPs for each time point (immediately before/after the treatment) and averaged their peak-to-peak amplitude and area-under-the-curve. For paired-pulse measures, initially subthreshold conditioning stimulus (70% of MT) was applied, followed at a variable interstimulus interval (ISI, 2, 3, 4, 6, 9, 10, 12 and 15 ms), by a second test (suprathreshold) stimulus (set at individual MEP-intensity). We used 3 ms ISI as intracortical inhibition and 12 ms ISI as intracortical facilitation. To measure changes in transcallosal inhibition (TCl), a subthreshold stimulus (70% of MT) was applied to the M1 of one hemisphere, and 10 ms later a suprathreshold stimulus at MEP-intensity was applied to the contralateral M1. Both hemispheres were tested.

2.3.1. Assessment of hand function

The Purdue pegboard test measures the gross movement of arm, hands, fingers, and fingertip dexterity. The pegboard contains two parallel columns of 20 holes with a shallow dish containing pegs. Subjects were instructed to place as many pegs as possible in the holes with their plegic hand in a 30 s interval. Subjects were allowed to practice for 4 trials prior to the test to reach the plateau of learning. The number of pegs placed in 30 s were recorded.

2.4. tDCS

The excitability-enhancing anode electrode (size: 35 cm²) was placed over the affected M1 (C3 or C4 according to the 10/20 EEG system). The excitability-reducing cathode electrode was placed over the contralateral healthy M1 (C3/C4 depending on the lesion side). This montage allowed simultaneously an inhibition of the activity in the unaffected M1 and stimulation of the affected M1. tDCS was applied with an intensity of 1 mA for a period of 20 min, as this has been shown to be effective and safe [30]. Current intensity was gradually increased (at the beginning of the session) and decreased (at the end of the session) to diminish its perception.

2.5. Sham tDCS

For sham stimulation, the same parameters including site and parameters of stimulation as tDCS was applied. However, the current was applied for only 10 s. This method of sham stimulation has been shown to be reliable [10]. After 10 s of stimulation, the switch was turned off, but the apparatus was still connected for 20 min. The stimulator was located behind the subject; therefore the subject did not have visual perception of on–off stimulation.

2.6. Statistical analysis

Although our sample was relatively small, this study was a pretest–posttest-design that increased the statistical efficiency due to the within-subject comparisons. For our sample of 9 subjects, we noted differences with effects sizes of 0.9 or greater (power of 80%, and alpha of 5%). Considering the exploratory nature of this study,
Table 1
Clinical and demographic characteristics.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Localization of stroke</th>
<th>Classification of stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>tDCS</td>
<td>Female</td>
<td>30</td>
<td>B/L cerebellar, right thalamic, right parietal occipital</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>50</td>
<td>Right pontine</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>50</td>
<td>Left middle cerebral artery</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>MP</td>
<td>Male</td>
<td>50</td>
<td>Right middle cerebral artery</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>44</td>
<td>Right inferior cerebellar</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>61</td>
<td>Right posterior limb of internal capsule, right occipital lobe</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>tDCS + MP</td>
<td>Male</td>
<td>68</td>
<td>Right posterior basal ganglia and external capsule</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>67</td>
<td>Posterior limb of right internal capsule</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>56</td>
<td>Posterior limb of left internal capsule</td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>P-Value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kruskal–Wallis for the comparison of continuous variables. Note: All patients were enrolled in the study between 1 week to 30 days of onset.

Table 2A
Results of cortical excitability measured by TMS and Purdue Pegboard Test. MEP amplitude of lesion and normal hemispheres. MEPs were measured in normal and lesion hemispheres at baseline, immediately, or 30 min after treatment. Values are mean ± SD.

<table>
<thead>
<tr>
<th>Normal hemisphere</th>
<th>Baseline ± SD (mV)</th>
<th>Immediate ± SD (mV)</th>
<th>30 min ± SD (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tDCS</td>
<td>1.32 ± 0.18</td>
<td>1.22 ± 0.76</td>
<td>0.89 ± 0.81</td>
</tr>
<tr>
<td>MP</td>
<td>1.01 ± 0.49</td>
<td>1.39 ± 0.73</td>
<td>0.87 ± 0.40</td>
</tr>
<tr>
<td>tDCS + MP</td>
<td>0.75 ± 0.29</td>
<td>0.67 ± 0.66</td>
<td>0.75 ± 0.26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion hemisphere</th>
<th>Baseline ± SD (mV)</th>
<th>Immediate ± SD (mV)</th>
<th>30 min ± SD (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tDCS</td>
<td>0.56 ± 0.71</td>
<td>0.55 ± 0.69</td>
<td>0.32 ± 0.39</td>
</tr>
<tr>
<td>MP</td>
<td>0.75 ± 0.68</td>
<td>0.69 ± 0.72</td>
<td>0.87 ± 0.80</td>
</tr>
<tr>
<td>tDCS + MP</td>
<td>0.30 ± 0.43</td>
<td>0.32 ± 0.41</td>
<td>0.61 ± 0.76</td>
</tr>
</tbody>
</table>

Note: Two-way ANOVA with repeated measures for MEP amplitude of lesion and normal hemispheres were performed to compare the difference within-group and among the groups. No significant statistical difference were found within subjects (P > 0.05) or between groups (P > 0.05) in either normal or lesion hemisphere.

We performed an exploratory, rather than confirmatory, statistical analysis. Kruskal–Wallis was used for the comparison of continuous variables and Chi-square for the comparison of categorical variables with regard to clinical and demographic characteristics. For measurements which there were two time points only, we used the gain score as the variable (pre-treatment minus post-treatment). However, two-way ANOVA with repeated measures was used to analyze MEP because of 3-time-point-measurement. We used ANOVA of gain score for pre-treatment and post-treatment comparison. If ANOVA test was positive, Tukey’s-Honestly-Significant-Difference test was used for post hoc multiple comparisons. Baseline values of the variables were compared using one-way ANOVA.

3. Results

We enrolled 9 postacute ischemic stroke patients (mean age: 52.9 ± 11.9 years, 7 males) within 1 month of onset of acute ischemic stroke. The clinical characteristics of each patient are summarized in Table 1 and Supplementary Table 1. There were no significant differences in baseline characteristics (age, classification of stroke, motor subscore (MS) of functional independence measure (FIM), cognitive subscore (CS) of FIM, and FIM total).

Subjects did not experience any severe adverse events throughout the study. Three subjects report mild tingling with tDCS stimulation. Cognitive function was measured to monitor adverse reactions with tDCS. There were no significant changes in cognitive function between the 3 treatment groups, as measured by MMSE, stroop test, and digit span (Supplementary Table 2). There were no significant changes in blood pressure and heart rate (Supplementary Table 3). There was no significant difference in the baseline values of the above variables (Supplementary Table 4).

3.1. Cortical excitability

MEP was measured in the normal and lesioned hemispheres at baseline, immediately after treatment; and 30 min after treatment. The means and standard deviations (SD) are presented in Table 2A. Two-way ANOVA with repeated measures showed that there was no significant effect of time after treatment on MEP in the unaffected hemisphere ($F_{(2,8)} = 1.832, P > 0.05$) or in the lesioned hemisphere ($F_{(2,8)} = 0.053, P > 0.05$). There was no significant between-group difference in the unaffected hemisphere ($F_{(2,4)} = 0.408, P > 0.05$) or in the lesioned hemisphere ($F_{(2,4)} = 0.338, P > 0.05$).

Table 2B
Intracortical inhibition and intracortical facilitation. Intracortical inhibition and intracortical facilitation were measured using pair-pulse at baseline and immediately after treatment.

<table>
<thead>
<tr>
<th>Intracortical inhibition</th>
<th>Normal hemisphere</th>
<th>Lesion hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔInhibition ± SD</td>
<td>F (df)</td>
<td>P</td>
</tr>
<tr>
<td>tDCS</td>
<td>1.26 ± 1.27 mV</td>
<td>1.202 (2, 6)</td>
</tr>
<tr>
<td>MP</td>
<td>0.51 ± 0.96 mV</td>
<td>0.41 ± 1.35 mV</td>
</tr>
<tr>
<td>tDCS + MP</td>
<td>0.11 ± 0.23 mV</td>
<td>1.202 (2, 6)</td>
</tr>
<tr>
<td>ΔFacilitation ± SD</td>
<td>F (df)</td>
<td>P</td>
</tr>
<tr>
<td>Normal hemisphere</td>
<td>0.11 ± 0.23 mV</td>
<td>0.41 ± 1.35 mV</td>
</tr>
<tr>
<td>Lesion hemisphere</td>
<td>0.81 ± 0.64 mV</td>
<td>0.53 ± 1.73 mV</td>
</tr>
</tbody>
</table>

ΔInhibition: Intracortical inhibition after treatment-Intracortical inhibition at baseline. ΔFacilitation: Intracortical facilitation after treatment-Intracortical facilitation at baseline. ANOVA for gain score was used to compare the difference in ΔInhibition or ΔFacilitation among the groups.
Table 2C
Transcallosal inhibition (TCI). MEP amplitudes was also measured during TCI exerted from the lesion to the normal hemisphere or from the normal to the lesion hemisphere. TCI was conducted at baseline or immediately after completion of treatment.

<table>
<thead>
<tr>
<th>From Lesion to Normal Hemisphere</th>
<th>ΔTCI ± SD</th>
<th>F(df)</th>
<th>P</th>
<th>From Normal to Lesion Hemisphere</th>
<th>ΔTCI ± SD</th>
<th>F(df)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>tDCS</td>
<td>−0.06 ± 0.15 mV</td>
<td>0.488 (2, 6)</td>
<td>0.64</td>
<td>tDCS</td>
<td>0.09 ± 1.36 mV</td>
<td>0.076 (2, 6)</td>
<td>0.93</td>
</tr>
<tr>
<td>MP</td>
<td>0.04 ± 0.51 mV</td>
<td></td>
<td></td>
<td>MP</td>
<td>0.10 ± 0.33 mV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tDVS + MP</td>
<td>−1.11 ± 2.54 mV</td>
<td></td>
<td></td>
<td>tDVS + MP</td>
<td>−0.19 ± 0.36 mV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ΔTCI: transcallosal inhibition after treatment-transcallosal inhibition at baseline. Values are Δ score ± SD. ANOVA for gain score was performed to compare the difference among the groups.

Table 2D
Purdue Pegboard Test: The number of pins that the subject inserted into the peg-hole within 60 min was recorded as scores.

<table>
<thead>
<tr>
<th>Δscore ± SD</th>
<th>F(df)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>tDCS</td>
<td>0.9 ± 0.19</td>
<td>12.167 (2, 6)</td>
</tr>
<tr>
<td>MP</td>
<td>0.8 ± 0.38</td>
<td></td>
</tr>
<tr>
<td>tDVS + MP</td>
<td>1.8 ± 0.19</td>
<td></td>
</tr>
</tbody>
</table>

Δscore: after treatment score-baseline score. ANOVA for gain score was utilized to analyze the difference among the groups.

Paired-pulsed TMS was used to measure intracortical inhibition and facilitation in the normal and lesioned hemispheres. ANOVA for gain score was performed to analyze the differences in intracortical inhibition and facilitation. As shown in Table 2B, intracortical inhibition and facilitation did not differ significantly with any treatment.

Cortical excitability was further evaluated by transcallosal inhibition (TCI). It has been reported that TCI from the normal to lesioned hemisphere correlates positively with motor function after stroke [2]. Single-pulsed TMS was used to induce TCI. As shown in Table 2C, we did not observe any significant differences in TCI after the treatments. There was no significant difference in the baseline values of TMS measurements (Supplementary Table 4).

3.1.1. Hand motor function assessment

Purdue pegboard test was performed to measure hand function before and after treatment. One way ANOVA for gain score revealed significant differences among the groups, \( F(2,6) = 12.167, P = 0.008 \) (Table 2D). Post hoc comparisons using Tukey’s HSD showed that combination treatment induced significantly greater hand improvement than tDCS alone \( (P = 0.017) \) or MP alone treatment \( (P = 0.01) \) (Table 2E). To further analyze the effect of the individual treatment, we performed paired t test which showed that tDCS as well as combination treatment induced significant improvement in hand function \( (P = 0.015 \) and 0.004 respectively), but not MP alone treatment \( (P = 0.149) \) (Supplementary Table 5). The combination treatment effected about 36% improvement in Purdue pegboard test.

4. Discussion

tDCS has many advantages in motor rehabilitation—it is a portable and inexpensive medical device that induces significant neuroplasticity that translates into motor benefits [2,6,9,16]. Moreover, MP has been tested in subacute stroke patients to improve initiation of movements. Our preliminary data suggest that beneficial effects on motor recovery with the combination of tDCS and MP in subacute stroke patients may be significantly more extensive than those of tDCS alone or MP alone.

Reactivation of neural activity in motor areas of the lesioned hemisphere and inhibition of cortical excitability of the unaffected hemisphere correlate with good recovery of the affected hand [2]. In fact, previous studies have shown that interhemispheric imbalance is associated with poor recovery due to the excessive transcallosal inhibition from the unaffected hemisphere to the affected hemisphere [22]. In this context, anodal tDCS over the lesioned hemisphere in chronic stroke patients is used to increase cortical excitability of the affected motor cortex while the goal of cathodal tDCS is to inhibit the inhibitory outputs from the unaffected hemisphere.

Although our preliminary data do not show any differences in cortical excitability versus baseline, we believe that they do not contradict findings from previous studies. Most differences in excitability in tDCS studies have been reported in healthy subjects, and these effects cannot be translated linearly in subjects with neural changes [13,35]. Further, we examined subjects with subacute stroke; thus, the effects on cortical excitability in them might differ from those in chronic stroke subjects and healthy subjects. It is possible to speculate here that the inhibitory tonus in the affected motor cortex in subacute phases of stroke may have prevented us to see changes in corticospinal plasticity. The differences between findings might also be attributed to the number of sessions. In our paradigm, a single session was chosen to avoid carryover effects and allow us to understand the preliminary effects of the combination treatment. Such a design might have been insufficient to induce significant changes in excitability.

In this study, data suggest that hand function may improve significantly with tDCS and combination tDCS and MP, as measured by Purdue pegboard test, but not by MP alone. The combination of tDCS and MP effected the largest improvement in Purdue pegboard test score (Δscore = 1.8)—approximately 36%. This effect could be larger than previous studies that showed improvements of movement speed after MP of about 20% [11] and improvement of about 14.9% of the Jebsen-Taylor Hand Function Test. Furthermore, combined treatment may have generated significant improvement as compared to tDCS or MP alone. These data necessitate larger studies to confirm the hypothesis that we have tested in this study.

Placebo effect of tDCS was controlled with sham stimulation. The sham stimulation had the same parameters (site and parameters of stimulation); however, current was applied for only 10 s. Skin sensations that are associated with turning stimulation on/off

Table 2E
Tukey’s HSD was used for post hoc multiple comparisons.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SE</th>
<th>P value</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>diff</td>
<td></td>
<td></td>
<td>Lower bound</td>
</tr>
<tr>
<td>tDCS+MP vs tDCS</td>
<td>0.89</td>
<td>0.22</td>
<td>0.017</td>
<td>0.21</td>
</tr>
<tr>
<td>tDCS+MP vs MP</td>
<td>1.0</td>
<td>0.22</td>
<td>0.010</td>
<td>0.32</td>
</tr>
<tr>
<td>tDCS vs MP</td>
<td>0.1</td>
<td>0.22</td>
<td>0.874</td>
<td>−0.57</td>
</tr>
</tbody>
</table>
were avoided by changing the current level slowly at the beginning and end of stimulation. Using this method, subjects were not able to distinguish the sham stimulation from real tDCS [10]. It should be underscored that 1 mA tDCS is associated with reliable blinding; differently than blinding of 2 mA tDCS that has been questioned especially in cross-over studies.

TDCS, administered per current stimulation guidelines (i.e. duration, intensity), is safe for use in healthy subjects and patients with neurological injury [2,15]. The most common side effects of tDCS are moderate fatigue; sensations of mild tingling, light itching, slight burning, and mild pain under the electrodes. Less frequently, subjects report headache, trouble concentrating, nausea, and sleep disturbances. Skin lesions in the form of burns have been reported following administration of tDCS [28]. No epileptic seizures that are caused by tDCS have been observed in humans. In this preliminary study, 2 subjects reported mild tingling, and 1 subject complained of mild fatigue. In stroke, most tDCS studies have been conducted in chronic stroke subjects, noting the following adverse effects including mild headache, local tingling, fatigue. In this study, we administrated tDCS in subacute stroke subjects within 1 month of onset of stroke. We did not observe any severe side effects.

The common side effects of methylphenidate include addiction, agitation, anxiety, insomina, decreased appetite, headache, heart palpitation. Serious side effects include seizures and blurred vision, visual hallucination. Overdose of methylphenidate may cause sudden heart attack, kidney damage and psychosis etc. In this study, MP was only administrated in a single dose. No severe side effect was observed in MP alone or combined MP with tDCS. However this study only assessed 9 patients; thus future trials need to address safety especially for the combined MP and tDCS intervention.

Based on the preliminary nature of this investigation, we were unable to determine the mechanisms of the effects in this study. We can only speculate regarding the synergistic effects of MP and tDCS. The most likely mechanisms are the potentiation and strengthening of tDCS effects by MP, particularly at the subcortical level. This proposed mechanism is in line with the report that amphetamine, a similar catecholaminergic re-uptake inhibitor as MP, enhances tDCS-induced cortical excitability in healthy subjects [23]. Furthermore, a recent study that examined the combination of tDCS and a serotonic drug (sertraline) has reported that the effects of tDCS are significantly potentiated compared with tDCS and sertraline alone in major depression [5]. It is hypothesized that tDCS could primarily modulate cortical excitability and may generate “top-down” effect [5]. On the other hand, MP mostly increases subcortical dopamine neurotransmission and may affect serotonic pathway via dopamine system in a “bottom-up” manner [32]. We hypothesize that combination treatment may induce alteration in both “top-down” and “bottom-up” systems.

The main limitations of this study are its small sample size and short duration (single session). Although a larger sample size would have given additional power to compare the combination treatment and individual regimens, our goal was to test for the first time the potential interaction between tDCS and MP as to provide preliminary data for further studies. As discussed, we believe that our single-session-only design was optimal, given the preliminary nature of this study and small sample size. Finally, given the extensive testing each subject underwent (thus reducing variability) and also the restricted inclusion criteria (especially regarding baseline motor function and time window after stroke), this small sample size study can provide preliminary data that may be of relevance to be reported as preliminary data for further studies.

Based on our findings, clinical trials should be designed using large sample sizes and longer treatment durations to determine whether combination treatments are a significant option for motor recovery rehabilitation strategies.

5. Conclusion

The combination treatment may result in greater improvements in hand function than tDCS alone or MP alone. However, the mechanisms of the interaction are not clear. In this preliminary study, we did not observe any major or severe adverse effects or induced significant differences in corticospinal excitability in any of the three treatments. Although the lack of corticospinal plasticity may be intriguing, it may also indicate differential plasticity mechanisms in acute vs. cortical stroke phases that may be useful to guide future development of interventions aiming to modulate M1 plasticity.

Conflict of interest

QM Wang is supported by NIHKO8 (HD074668). No conflicts of interest have been reported by the authors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2014.03.011.

References


