Improving ideomotor limb apraxia by electrical stimulation of the left posterior parietal cortex

Nadia Bolognini,1,2 Silvia Convento,1 Elisabetta Banco,2,3 Flavia Mattioli,4 Luigi Tesio3,5 and Giuseppe Vallar1,2

Limb apraxia, a deficit of planning voluntary gestures, is most frequently caused by damage to the left hemisphere, where, according to an influential neurofunctional model, gestures are planned, before being executed through the motor cortex of the hemisphere contralateral to the acting hand. We used anodal transcranial direct current stimulation delivered to the left posterior parietal cortex (PPC), the right motor cortex (M1), and a sham stimulation condition, to modulate the ability of six left-brain-damaged patients with ideomotor apraxia, and six healthy control subjects, to imitate hand gestures, and to perform skilled hand movements using the left hand. Transcranial direct current stimulation delivered to the left PPC reduced the time required to perform skilled movements, and planning, but not execution, times in imitating gestures, in both patients and controls. In patients, the amount of decrease of planning times brought about by left PPC transcranial direct current stimulation was influenced by the size of the parietal lobe damage, with a larger parietal damage being associated with a smaller improvement. Of interest from a clinical perspective, left PPC stimulation also ameliorated accuracy in imitating hand gestures in patients. Instead, transcranial direct current stimulation to the right M1 diminished execution, but not planning, times in both patients and healthy controls. In conclusion, by using a transcranial stimulation approach, we temporarily improved ideomotor apraxia in the left hand of left-brain-damaged patients, showing a role of the left PPC in planning gestures. This evidence opens up novel perspectives for the use of transcranial direct current stimulation in the rehabilitation of limb apraxia.

1 Department of Psychology and NeuroMI-Milan Centre for Neuroscience, University of Milano-Bicocca, Milan, Italy
2 Laboratory of Neuropsychology, IRCSS Italian Auxological Institute, Milan, Italy
3 Department of Neurorehabilitation Sciences, IRCCS Italian Auxological Institute, Milan, Italy
4 SSVD Neuropsychology Unit, Department of Neurological Science and Vision, Spedali Civili, Brescia, Italy
5 Department of Biomedical Sciences for Health, University of Milan, Milan, Italy

Correspondence to: Giuseppe Vallar, MD,
Department of Psychology, University of Milano-Bicocca, Piazza dell’Ateneo Nuovo 1,
20126-Milan, MI, Italy
E-mail: giuseppe.vallar@unimib.it

Keywords: apraxia; stroke rehabilitation; motor cortex; parietal lobe

Abbreviations: tDCS = transcranial direct current stimulation; JHFT = Jebsen Hand Function Test; PPC = posterior parietal cortex

Introduction

Limb apraxia is a higher-order motor disorder, whose hallmark is the inability or difficulty to perform purposeful limb movements (gestures), typically with the upper limbs (Geschwind, 1975). Limb apraxia, as many other neuropsychological disorders (e.g. unilateral spatial neglect; Vallar, 1998), is conceived as multi-componential. A ‘core’ component includes impairments in the imitation of hand postures, use of single mechanical tools, and pantomime of tool use. These impairments are not explained by elemental deficits of motor and sensory systems, or defects in...
language comprehension (Goldenberg, 2013). The neural underpinnings of limb apraxia are characterized by a hemispheric asymmetry: lesions involve more frequently the left hemisphere, particularly the left premotor-frontal and posterior-parietal regions, rather than the right hemisphere of right-handed patients (Haaland et al., 2000; Hanna-Pladdy et al., 2001; Foundas, 2013).

An early influential anatomo-functional model of limb apraxia was put forward at the beginning of the 20th century by the German physician Hugo Karl Liepmann [for a biographical profile, see Goldenberg, 2003; Liepmann, 1908, 1925; English translations in Liepmann (1977, 1988)]. On the basis of clinical observations, Liepmann drew a distinction between a ‘movement formula’, and the motor execution of the intended gesture. The generation of the formula is mainly based on neural activity in the temporo-parieto-occipital cortex of the left hemisphere of right-handed individuals. This motor plan is conveyed to the sensorimotor central cortex of the left hemisphere, which provides motor signals to the right hand. For movements of the left hand, transfer of the formula to the sensorimotor cortex in the right hemisphere, via callosal connections, is required, as the movement plan is primarily conveyed to the left sensorimotor cortex. This hemispheric asymmetry implies that left-brain-damaged patients, who frequently show right-sided motor deficits that may mask apraxia in the dominant right hand, exhibit apraxia in the left hand, which receives planning for skilled action by the left hemisphere.

Liepmann’s model has received support by neuropsychological clinical observations (Geschwind, 1965; Leiguarda and Marsden, 2000; Goldenberg, 2013). Recently, we corroborated this view with a transcranial direct current stimulation (tDCS) study in healthy right-handed participants (Convento et al., 2014). Anodal tDCS of the right primary motor (M1) and of the left posterior parietal cortices (PPC) fastens motor performance of the non-dominant left hand, as assessed by the Jebsen Hand Function Test (JHFT; Jebsen, 1969); a slowing of motor performance is induced by the cathodal tDCS of the same areas. Instead, stimulation of the right PPC and of the left M1 is ineffective. When execution and planning stages are distinguished, the anodal tDCS of the left PPC selectively facilitates action planning, while the anodal tDCS of the right M1 modulates action execution only. Broadly in line with these findings, anodal tDCS applied to the left inferior parietal lobule of healthy participants facilitates the matching of visual hand gestures, in a perceptual same/different task (Weiss et al., 2013).

In the light of this evidence, we investigated whether tDCS applied over the left PPC, ipsilateral to the side of the lesion (ipsilesional), and over the right M1, contralateral to the side of the lesion (contralesional), can improve ideomotor apraxia in stroke patients. Ideomotor apraxia is characterized by errors in the ‘proper tempo-spatial organization of the sequence of movements that must implement the representation of the action’ (Barbieri and De Renzi, 1988), when patients are required to imitate intransitive (not involving objects or tools), symbolic (such as the sign for ‘crazy’), and non-symbolic gestures (Buxbaum, 2001; Buxbaum et al., 2008; Foundas, 2013; Goldenberg, 2013). Damage to the left inferior parietal lobule is a correlate of ideomotor apraxia (Goldenberg, 2009; Buxbaum et al., 2014); this region is activated by tasks requiring the imitation of gestures (Mühlau et al., 2005; Molenberghs et al., 2012).

Based on our study in healthy participants (Convento et al., 2014), we attempted to verify the hypothesis that anodal tDCS of the left PPC ameliorates ideomotor apraxia, improving the imitation of intransitive gestures, assessed with a standard clinical test (De Renzi et al., 1980). Then, apraxic patients were presented with the JHFT to verify whether tDCS could improve their performance in motor tasks mimicking activities of daily living.

Materials and methods

Participants

Participants were recruited in the Department of Neurorehabilitation Sciences of the IRCCS Istituto Auxologico Italiano (Milan, Italy), and in the Hospital ‘Spedali Civili’ (Brescia, Italy); they were fully right-handed, as assessed through the Edinburgh Handedness Inventory (Oldfield, 1971), and had no contraindication to tDCS (Poreisz et al., 2007; Rossi et al., 2009). Accepted recommendations for the safe use of non-invasive brain stimulation were applied (Rossi et al., 2009). The protocol was read and explained to patients and their caregivers. Participants gave their informed consent to the protocol, which had been approved by the Ethical Committee of each research centre, and was carried out in accordance with the ethical standards of the Declaration of Helsinki. Three patients (Patients P1, P2 and P4; Table 1) signed the written informed consent; for the other three patients (Patients P3, P5 and P6), the caregiver signed it, because of the patients’ inability to produce a signature, even using the unaffected left hand.

Two groups of participants entered the study: (i) six neurologically healthy controls (one male, mean age = 66.7 years, standard deviation = 6.68, range = 57–76; mean years of schooling = 11.5 ± 3.73, range 8–14), with no history or evidence of neurological disease; and (ii) six left-hemisphere-damaged patients (four males, mean age = 72.16 ± 7.2 years; mean years of schooling = 11.16 ± 9.2; duration of disease = 12.50 ± 21.53 months).

Patients had no history or evidence of previous neurological or psychiatric disorders, or dementia. The patients’ demographic and clinical data are summarized in Table 1. The two groups of participants did not differ with respect to their age [unpaired t-test, t(10) = −1.36, P = 0.2], and years of schooling [t(10) = −0.13, P = 0.9].

Baseline evaluation

The baseline assessment, performed 1 week before the first experimental session, included: (i) a standard neurological...
Table 1 Demographic and neurological data and baseline neuropsychological assessment of six left-brain-damaged patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age/sex</th>
<th>Education (years of schooling)</th>
<th>Duration of disease (months)</th>
<th>Cerebrovascular attack</th>
<th>Neurological deficit</th>
<th>Token Test Verbal fluency Immediate memories</th>
<th>Apraxia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M</td>
<td>V</td>
</tr>
<tr>
<td>P1</td>
<td>77/F</td>
<td>18</td>
<td>1</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P2</td>
<td>79/F</td>
<td>10</td>
<td>2</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P3</td>
<td>70/M</td>
<td>18</td>
<td>1</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P4</td>
<td>59/M</td>
<td>8</td>
<td>15</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P5</td>
<td>76/M</td>
<td>5</td>
<td>55</td>
<td>H</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>P6</td>
<td>72/M</td>
<td>8</td>
<td>4</td>
<td>I</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Ph/Se = phonemic/semantic verbal fluency; H = haemorrhagic; I = ischaemic; IMA = ideomotor apraxia; IA = ideational apraxia; OA = oral apraxia; CA = constructional apraxia; Right M/V/SS = motor/visual field/somatosensory deficit.

*Drawing Copy; *Rey Complex Figure; *Defective score according to available norms.

The patients’ individual scores are shown in Table 1.

Lesion data

Figure 1 shows the lesion mapping of the six left-brain-damaged patients (Rorden and Brett, 2000). CT scans had been taken between 2 and 10 weeks before the assessment in five of six patients, 24 weeks with respect to the testing in one patient (Patient P5). Regions of interest, defining the location and size of the lesion for each patient, were reconstructed by a template technique, manually drawing the lesion on the standard template from the Montreal Neurological Institute (MNI; Rorden and Brett, 2000).

Experimental tasks

Ideomotor Apraxia Test

The test comprised 24 intransitive gestures, divided in 12 ‘symbolic’ (e.g. the sign of ‘OK’), and 12 ‘non-symbolic’ (e.g. ‘hand under the chin’) gestures. The examiner demonstrated each gesture, one at a time, with the right hand. Participants had received instructions to reproduce the demonstrated gesture with their left hand. If an item was not correctly reproduced at the first demonstration, a second one was given, up to three demonstrations. Accuracy scores at each gesture ranged from 0 to 3 (3 = correct reproduction at the first demonstration; 2 = correct reproduction at the second demonstration; 1 = correct reproduction at third demonstration; 0 = incorrect reproduction at the third demonstration). The total score ranged from 0 to 72 points. A score <53 was defective, and taken as an indication of the presence of ideomotor apraxia (De Renzi et al., 1980). During baseline evaluation, all 24 gestures were shown. In the experimental sessions, to ensure that participants performed the gestures within the temporal window of the after-effects of tDCS, 12 of 24 gestures were given, which showed a static posture or a motor sequence: thumb and index finger making a circle (sign of ‘OK’); index and medium finger abducted (sign of ‘V’, victory); index finger and little finger extended, with the others flexed (‘sign of the horns’); index finger lifted up, with the other fingers flexed; mimicking a man walking, with the index and medium fingers alternately moving forward on the table; opening and closing the index on the medium finger (sign of ‘scissors’); prone hand on the table, middle finger arched over the index finger, with the other fingers flexed; thumb constricted between the index and middle fingers; snapping fingers (the thumb and another finger) for three times; give a slap, extending the middle finger from the distal phalanx of the thumb for three times; tapping the four lateral fingers on the table three times, always starting from the index finger; supine hand on the table, flexing the index and then the middle finger on the thumb, while the other finger was kept extended. The demonstration of each gesture by the experimenter began and finished at the same position on the table. The experimenter had been trained to demonstrate each gesture as much as possible in the same way, keeping the same velocity. Participants were required to look at each demonstration, and to reproduce the shown gesture, starting immediately after the demonstration was over, as soon as the examiner’s hand had touched the table, which represented the ‘go’ signal for the patient’s reproduction of the gesture. Participants had received instruction to lay their left hand back on the table, after the completion of each trial. The participants’ performance was video-recorded for off-line analysis; the registration started when the examiner’s hand was lifted up from the table.

Jebsen Hand Function Test

This standardized 7-item test was designed as a broad measure of daily, skilled hand function, to provide a
quantitative evaluation of unilateral hand performance, by assessing speed of execution, rather than movement quality. The JHFT has been used for evaluating hand motor function in stroke patients, and for measuring the effects of neuromodulation on hand motor performance in both healthy participants, and stroke brain-damaged patients (Hummel et al., 2005; Boggio et al., 2006, 2007; Convento et al., 2014). Six of the seven tasks of the JHFT were used: turning cards, picking up small objects and placing them in a can, lifting small objects with a spoon, stacking checkers, lifting light and heavy cans. The handwriting task was excluded, as in previous tDCS studies (Hummel et al., 2005; Boggio et al., 2006, 2007), including the one on which this study was based (Convento et al., 2014).
Participants performed the tasks with their non-dominant left hand, unaffected by motor deficits in left-brain-damaged patients. They had received instructions, both verbally and through demonstration by the examiner, to perform each task as accurately, and as rapidly as possible (Jebesen et al., 1969). Total time of execution, calculated as the sum of the execution times of the six JHFT tasks, was the primary outcome for analyses. During the task, the participants’ performance was video-recorded for off-line analysis; the registration started at the beginning of the patient’s hand movement.

**Lexical search and production**

Participants received instructions to produce as many words as possible, in a limited time interval. In the baseline assessment, verbal fluency was assessed on three semantic and three phonemic cues. In the experimental session only phonemic cues were used, namely the letters ‘F’, ‘P’ and ‘L’. A time limit of 60 s was given for each letter, with a score ≤16 being defective (Novelli et al., 1986).

**Transcranial direct current stimulation**

tDCS was delivered by a battery-driven, constant current stimulator (BrainStim, EMS, http://brainstim.it), through a pair of saline-sponge electrodes (25 cm², 5 x 5 cm). In every experimental session, tDCS was applied for a total 10 min (fade-in/fade-out phases = 10 s), with an intensity of 2 mA, in accordance with current safety data (Poreisz et al., 2007).

For stimulation of the right M1, the anode was placed over C4, according to the 10:20 EEG system. When the left PPC was targeted, the anodal electrode was placed over P3. In both cases, the cathodal reference electrode was placed over the contralateral supraorbital area (Rosenkranz et al., 2000; Fregni et al., 2005; Hummel et al., 2005; Boggio et al., 2006, 2007; Nitsche et al., 2008; Bolognini et al., 2011). For sham tDCS, the same electrode montage was used, placing the anode over one of the target areas, which was randomized across participants. The same parameters of the active stimulation were used, but the stimulator was turned off after 30 s; this ensured that participants felt the initial itching sensation at the beginning of tDCS, but preventing any effective modulation of cortical excitability by tDCS (Gandiga et al., 2006). Current intensity was gradually increased (at the beginning of the session) and decreased (at the end), to diminish its perception (i.e. fade-in/fade-out phases). The sham and real modes of tDCS were activated through codes set by the BrainStim software, which controlled the tDCS device. By such codes, the device was activated by the experimenter, and it always showed on the display ‘on’, and the parameters of stimulation during the procedure, but independently of the type of stimulation (‘real’ versus ‘sham’). This method has been shown to be reliable for keeping both the experimenter and the participant blind to sham and real tDCS (Gandiga et al., 2006), and it is commonly used in tDCS investigations, both in neurological patients (Fregni et al., 2003; Bolognini et al., 2013b; Brunoni et al., 2014), and in healthy participants (Ladeira et al., 2011; Convento et al., 2012; Bolognini et al., 2013a).

**Experimental procedure**

Each participant underwent three sessions: (i) anodal tDCS to left PPC; (ii) anodal tDCS to right M1; and (iii) sham tDCS. The order of the three sessions, separated by at least 24 h to minimize carry-over effects (Bolognini et al., 2013a; Monte-Silva et al., 2013), was counterbalanced, and randomized across participants. Both the experimenter and each participant were blinded with respect to the experimental conditions (active versus sham tDCS).

The day before the first session, patients and control participants practiced the JHFT six times to familiarize with the tasks, and to achieve a stable performance level. A previous recent study has shown that this training enabled healthy participants to reach a stable performance level (Convento et al., 2014). To verify the effectiveness of the training in stabilizing JHFT performance, the total times of execution at each training trial and at the baseline of the first experimental session were submitted to one-way repeated-measures ANOVAs, one for each experimental group, with Repetition (1 to 6) as the within-subject factor. A significant effect of Time emerged for both patients [F(5,25) = 6.61, P < 0.001, pn² = 0.57], and healthy controls [F(5,25) = 9.10, P < 0.001, pn² = 0.64], revealing a speed-up of performance between the first three training sessions (patients: first = 48.14 ± 7.61 s, second = 45.69 ± 7.90 s, third = 39.84 ± 7.49 s; controls: first = 38.00 ± 5.87 s, second = 33.95 ± 4.27 s, third = 32.46 ± 4.97 s; Bonferroni-corrected pairwise multiple comparisons: P < 0.05). Instead, no significant differences were found in the total times of execution of the JHFT between the last three training sessions, in both patients (fourth = mean 39.84 ± 9.49 s, fifth = 39.55 ± 10.23 s, sixth = 39.32 ± 9.97 s), and control participants (fourth = 32.71 ± 4.84 s, fifth = 32.89 ± 5.49 s, sixth = 31.83 ± 5.24 s). Performance speed did not change between the last training session and the first experimental session (i.e. baseline) in both patients [sixth training session = 39.32 ± 9.97 s, first experimental session = 39.32 ± 8.63 s; paired t-test, t(5) = −1.17, P = 0.20], and controls [sixth training session = 31.83 ± 5.24 s, first experimental session = 30.29 ± 4.73 s; t(5) = −0.45, P = 0.60].

During each tDCS session, participants performed the three tasks (ideomotor apraxia, JHFT, and phonemic fluency), given in a fixed order, immediately before (pre-tDCS) and after (post-tDCS) having received tDCS. This multiple-baseline design was used for controlling carry-over effects across tDCS sessions (Monte-Silva et al., 2010, 2013; Bolognini et al., 2013a). To obtain a reliable measure of motor performance, the JHFT was repeated three times
before (baseline: JHFT 1–3), and three times after stimulation (post-tDCS: JHFT 4–6).

Each experimental session for ideomotor apraxia, including training, was video recorded with a digital camera (Panasonic Lumix DMC-TZ4). Two independent operators made the subsequent off-line evaluation of performance speed based on video recordings, in order to minimize any error. Such evaluation was carried out through the use of a digital chronometer with millisecond precision, and displayed during the video playing. The total time for each gesture was calculated by starting the chronometer at the same moment of the beginning of the experimenter’s gesture production (lifting up the arm from the table), and stopping it when participants had completed their performance, and laid their hand back on the table. Execution time was calculated starting the chronometer when participants initiated the reproduction of the gesture, and stopping it at the same end point of the total time (the patient’s hand laid back on the table). In this way, by subtracting the execution time from the total time, a measure of the time required for gesture planning (the planning time) was computed (Convento et al., 2014).

For the JHFT, following the procedure of Convento et al.’s (2014) Experiment 1, the total times of performance for each of the six tasks were measured, starting the chronometer when the participant initiated the movement (following the starting signal by the experimenter), and stopping it when each activity was completed; the total times of each of the six tasks were then summed, and averaged for the three JHFT assessments. Before the analyses, the normal distribution of the data was evaluated by the Kolmogorov–Smirnov Test, and their homogeneity by Levene’s Test. Given the positive skewness of response times at the ideomotor apraxia and JHFT tests, these data were log-transformed to minimize the impact of outliers, and normalize distributions (Sokal and Rohlf, 1995). The accuracy scores at the phonemic fluency and at the ideomotor apraxia tests met the assumptions of the within-subject factors. For patients, a repeated-measures ANOVA with Session and Time as within-subject main factors was performed on the ideomotor apraxia accuracy scores, since healthy participants made no errors in this test in any session. The partial Eta squared (\(\eta^2\)), which measures the proportion of total variance that is attributable to a main factor or to an interaction (Cohen, 1973), was also calculated for each repeated-measures ANOVA. Significant main effects and interactions were analysed by Bonferroni-corrected pairwise comparisons.

Results

Ideomotor Apraxia Test

In both patients and control participants a reduction of planning times was found after anodal tDCS of the left PPC, with sham stimulation being ineffective (Fig. 2A). Conversely, execution times diminished after anodal tDCS of right M1 (Fig. 2B), with sham stimulation again being ineffective.

Planning time

The repeated-measures ANOVA on planning times showed significant main effects of Group \([F(1,10) = 84.51, P < 0.0001, \eta^2 = 0.89]\), Session \([F(2,20) = 6.85, P = 0.005, \eta^2 = 0.40]\), and Time \([F(1,10) = 29.58, P < 0.001, \eta^2 = 0.74]\). The Time \(\times\) Session \([F(2,20) = 27.30, P < 0.0001, \eta^2 = 0.73]\), and the Group \(\times\) Time \([F(1,10) = 14.42, P < 0.001, \eta^2 = 0.59]\) interactions were significant. The Group \(\times\) Session \([F(2,20) = 0.21, P = 0.80, \eta^2 = 0.02]\), and the Group \(\times\) Session \(\times\) Time \([F(2,20) = 0.56, P = 0.50, \eta^2 = 0.05]\) interactions were not significant. For the Session \(\times\) Time interaction, Bonferroni-corrected pairwise comparisons showed a significant difference between the pre- and the post-tDCS planning times only after left PPC tDCS (pre-tDCS = 33.67 \(\pm\) 8.67 s, post-tDCS = 28.79 \(\pm\) 8.15 s, \(P < 0.0001\)), tDCS to the right M1 did not modulate performance. Planning times after stimulation of the left PPC differed \((P < 0.0001)\) from those of all the other post-tDCS sessions (Fig. 2A). No differences in planning times in the three pre-tDCS sessions were found.

To assess the effect of tDCS in the two groups, separate repeated-measures ANOVAs were performed, with Session (right M1, left PPC, sham) and Time (pre-tDCS, post-tDCS) as the within-subjects main factors. In healthy controls, the main effect of Time \([F(1,5) = 26.03, P = 0.004, \eta^2 = 0.84]\) was significant, whereas that of Session did not attain the significance level \([F(2,10) = 2.84, P = 0.09, \eta^2 = 0.37]\). The Time \(\times\) Session interaction \([F(2,10) = 13.88, P < 0.001, \eta^2 = 0.74]\) was significant: the differences between pre- and post-tDCS planning times were significant for left PPC tDCS (pre-tDCS = 26.17 \(\pm\) 1.05 s; post-tDCS = 21.73 \(\pm\) 1.97 s, \(P < 0.01\)), but not for right M1 or sham tDCS. In patients, the ANOVA showed a significant main effect of Session \([F(2,10) = 4.24, P < 0.05, \eta^2 = 0.46]\), while the main effect of Time was not significant \([F(1,5) = 3.73, P = 0.10, \eta^2 = 0.40]\). The Time \(\times\) Session interaction was significant \([F(2,10) = 13.96, P = 0.002, \eta^2 = 0.74]\): similar to healthy
controls, for left PPC tDCS the difference between planning times pre-tDCS (41.19 ± 5.40 s) and post-tDCS (35.86 ± 4.74 s, P < 0.05) was significant; instead, no differences were found after right M1 or sham tDCS.

**Execution time**

The repeated-measures ANOVA on execution times showed significant main effects of Group [F(1,5) = 12.93, P < 0.02, \(\eta^2 = 0.72\)], whereas the main effect of Session was not significant [F(2,10) = 0.54, P = 0.60, \(\eta^2 = 0.1\)]. The Session x Time interaction [F(2,10) = 14.20, P < 0.001, \(\eta^2 = 0.74\)] was significant: the difference between execution times before and after right M1 tDCS (pre-tDCS = 31.60 ± 5.57 s, post-tDCS = 27.21 ± 5.19 s, P < 0.001) was significant; no significant differences were found for PPC and sham tDCS. In patients, the main effects of Session [F(2,10) = 0.42, P = 0.60, \(\eta^2 = 0.08\)], and of Time [F(1,5) = 0.54, P = 0.50, \(\eta^2 = 0.1\)] were not significant, whereas the Session x Time interaction was significant ([F(2,10) = 7.19, P < 0.01, \(\eta^2 = 0.59\)]. The difference between execution times before and after right M1 tDCS (pre-tDCS = 57.41 ± 10.43 s, post-tDCS = 52.53 ± 11.08 s, P < 0.05) was significant; no significant differences were found for left PPC and sham tDCS.

As shown in Fig. 3, the patients’ accuracy scores in the Ideomotor Apraxia Test increased after anodal tDCS of left PPC. The repeated-measures ANOVA showed a significant main effect of Time [F(1,5) = 25.56, P < 0.004, \(\eta^2 = 0.97\)], whereas the main effect of Session was not significant [F(2,10) = 0.90, P = 0.43, \(\eta^2 = 0.16\)]. The Time x Session interaction [F(2,10) = 5.28, P < 0.03, \(\eta^2 = 0.70\)] was significant. The difference between accuracy scores before and after left PPC-tDCS was significant (24.50 versus 28.67, P < 0.05), with an increase of correct responses. No significant differences between pre- and post-tDCS for the right M1, and the sham stimulation conditions were found.

**Jebsen Hand Function Test**

Figure 4 shows that in both patients, who were overall slower, and control participants total times decreased after tDCS of both right M1 and left PPC, as compared to pre-tDCS, while sham stimulation was ineffective. The repeated-measures ANOVA showed significant main effects of Time [F(1,10) = 31.75, P < 0.0001, \(\eta^2 = 0.76\)], and of Group [F(1,10) = 8.38, P < 0.02, \(\eta^2 = 0.45\)], while the main effect of Session [F(2,20) = 1.90, P = 0.17, \(\eta^2 = 0.16\)] was not significant. The Time x Session interaction was significant [F(2,20) = 24.73, P < 0.0001, \(\eta^2 = 0.71\)]. The Group x Time [F(1,10) = 0.12, P = 0.70, \(\eta^2 = 0.01\)], Group x Session [F(2,20) = 0.96, P = 0.40, \(\eta^2 = 0.08\)], and Group x Time x Session [F(2,20) = 1.30, P = 0.30, \(\eta^2 = 0.11\)] interactions did not attain the significance level. For the Time x Session interaction, the differences between total times at the baseline and after anodal tDCS of both right M1 (pre-tDCS = 35.05 ± 8.66 s, post-tDCS = 32.61 ± 7.85 s, P < 0.001), and left PPC...
(pre-tDCS = 33.88 ± 7.03 s, post-tDCS = 31.62 ± 6.05 s, P < 0.0001) were significant, showing a speed up of performance (Fig. 4).

In healthy controls the repeated-measures ANOVA showed a significant main effect of Time [F(1,5) = 11.73, P < 0.02, \( \eta^2 = 0.68 \)], whereas the main effect of Session [F(2,10) = 0.22, P = 0.81, \( \eta^2 = 0.04 \)] did not attain the significance level. The Session × Time interaction [F(2,10) = 12.08, P < 0.002, \( \eta^2 = 0.71 \)] was significant. Total times before and after right M1 tDCS (pre-tDCS = 29.86 ± 5.08 s, post-tDCS = 27.72 ± 4.81 s, P < 0.001), and left PPC tDCS (pre-tDCS = 29.37 ± 4.24 s, post-tDCS = 27.73 ± 3.80 s, P < 0.01) were significantly different; no differences were found for sham tDCS. For patients, the repeated-measures ANOVA showed a significant main effect of Time [F(1,5) = 29.58, P < 0.003, \( \eta^2 = 0.86 \)], whereas the main effect of Session [F(2,10) = 3.07, P = 0.09, \( \eta^2 = 0.38 \)] did not reach significance. The Session × Time interaction [F(2,10) = 13.55, P < 0.001, \( \eta^2 = 0.73 \)] was significant. Total times before and after right M1 tDCS (pre-tDCS = 40.26 ± 8.64 s, post-tDCS = 37.52 ± 7.41 s, P < 0.05), and left PPC tDCS (pre-tDCS = 38.39 ± 6.48 s, post-tDCS = 35.51 ± 8.45 s, P < 0.01) were significantly different; no differences were found for sham tDCS.

Phonemic fluency

Control participants scored higher (38 ± 12.9) than left-brain-damaged patients (3.5 ± 3.4). As shown in Fig. 5, no significant modulation of verbal performance was induced by tDCS. The ANOVA showed a significant main effect of Group [F(1,10) = 37.04, P < 0.0001, \( \eta^2 = 1 \)], while the main effects of Session [F(2,20) = 0.75, P = 0.50, \( \eta^2 = 0.15 \)], and Time [F(1,10) = 1.47, P = 0.20, \( \eta^2 = 0.19 \)], as well as the Group × Session [F(2,20) = 0.39, P = 0.60, \( \eta^2 = 0.10 \)], Group × Time [F(1,10) = 1.72, P = 0.20, \( \eta^2 = 0.22 \)], Session × Time [F(2,20) = 0.08, P = 0.90, \( \eta^2 = 0.06 \)], and Group × Session × Time [F(2,20) = 0.44, P = 0.60, \( \eta^2 = 0.11 \)] interactions were not significant.

Effects of time since stroke and of lesion size and location

To control for time since stroke, lesion volume, and size of the parietal and frontal damage, which could have influenced the effects of tDCS in apraxic patients, one-way repeated-measures ANCOVAs were performed. Time (pre-and post-tDCS) was the within-subject factor; the linear and interactive covariates were length of illness (time since stroke in months, Table 1), total lesion volume (mean lesion volume = 63.13 cm³ ± 55.42 range = 5.8–156 cm³), and the sizes of the parietal and frontal damages,
measured in each patient by estimating the number of voxels of damage of these regions (Rorden and Brett, 2000; Bolognini et al., 2012). The dependent variables were the scores in the sessions where a significant tDCS effect had been detected by the previous ANOVAs, namely: planning times and accuracy scores at the Ideomotor Apraxia Test, and total times at the JHFT, before and after left PPC tDCS; execution times at the Ideomotor Apraxia Test and total times at the JHFT, before and after right M1 tDCS. Table 2 shows that in the majority of the repeated-measures ANCOVAs, the main effect of Time was significant, confirming the reliability of the effects by PPC and M1 tDCS. Importantly, the interaction between Time and the covariates was significant only for the parietal lesion covariate, in the analysis of the parietal tDCS effect on the planning times at the Ideomotor Apraxia Test ($P < 0.03$).

This result indicates that the slowing down of planning times by left PPC tDCS was influenced by the extent of the damage affecting the stimulated area (i.e., left PPC). The three patients (Patients P1, P5 and P6) with parietal damage (number of voxels = 1730, 4761, 1373, respectively) showed an average smaller reduction of planning times ($-4.44$) at the Ideomotor Apraxia Test (Patient P1 = −4.83 s, Patient P5 = −5.38 s, Patient P6 = −3.11 s), whereas the three patients with a spared parietal cortex

### Table 2: One-way ANCOVAs ($F$, $P$ and $\eta^2$ values) with the within-subjects factor Time, and Lesion volume, Length of illness, Parietal lesion and Frontal lesion as linear and interactive covariates

<table>
<thead>
<tr>
<th>Test</th>
<th>Covariate</th>
<th>Time</th>
<th>Time by covariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideomotor apraxia test</td>
<td>Planning time — left PPC</td>
<td>$F = 26.8$, $P &lt; 0.01$, $\eta^2 = 0.87$</td>
<td>$F = 4.6$, $P = 0.1$, $\eta^2 = 0.53$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 7.6$, $P &lt; 0.05$, $\eta^2 = 0.65$</td>
<td>$F = 1.3$, $P = 0.3$, $\eta^2 = 0.24$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 18.9$, $P &lt; 0.01$, $\eta^2 = 0.82$</td>
<td>$F = 0.4$, $P = 0.6$, $\eta^2 = 0.85$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 33.8$, $P &lt; 0.01$, $\eta^2 = 0.89$</td>
<td>$F = 11.6$, $P &lt; 0.03$, $\eta^2 = 0.74$</td>
</tr>
<tr>
<td>Execution time — right M1</td>
<td></td>
<td>$F = 15.2$, $P &lt; 0.01$, $\eta^2 = 0.79$</td>
<td>$F = 6.2$, $P = 0.07$, $\eta^2 = 0.60$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 3.4$, $P = 0.1$, $\eta^2 = 0.45$</td>
<td>$F = 2.4$, $P = 0.2$, $\eta^2 = 0.37$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 21.9$, $P &lt; 0.01$, $\eta^2 = 0.84$</td>
<td>$F = 2.4$, $P = 0.2$, $\eta^2 = 0.37$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 7.7$, $P &lt; 0.05$, $\eta^2 = 0.66$</td>
<td>$F = 0.9$, $P = 0.4$, $\eta^2 = 0.17$</td>
</tr>
<tr>
<td>Accuracy — left PPC</td>
<td></td>
<td>$F = 9.4$, $P &lt; 0.04$, $\eta^2 = 0.70$</td>
<td>$F = 0.2$, $P = 0.7$, $\eta^2 = 0.45$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 5.4$, $P = 0.08$, $\eta^2 = 0.57$</td>
<td>$F = 0.1$, $P = 0.8$, $\eta^2 = 0.02$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 7.8$, $P &lt; 0.05$, $\eta^2 = 0.66$</td>
<td>$F = 0.2$, $P = 0.7$, $\eta^2 = 0.04$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 18.3$, $P &lt; 0.01$, $\eta^2 = 0.82$</td>
<td>$F = 2.5$, $P = 0.2$, $\eta^2 = 0.38$</td>
</tr>
<tr>
<td>JHFT</td>
<td>Total time — left PPC</td>
<td>$F = 37.9$, $P &lt; 0.01$, $\eta^2 = 0.90$</td>
<td>$F = 0.2$, $P = 0.67$, $\eta^2 = 0.05$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 40.1$, $P &lt; 0.01$, $\eta^2 = 0.90$</td>
<td>$F = 2.1$, $P = 0.2$, $\eta^2 = 0.33$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 35.2$, $P &lt; 0.01$, $\eta^2 = 0.89$</td>
<td>$F = 0.6$, $P = 0.5$, $\eta^2 = 0.12$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 33.1$, $P &lt; 0.01$, $\eta^2 = 0.89$</td>
<td>$F = 0.2$, $P = 0.7$, $\eta^2 = 0.04$</td>
</tr>
<tr>
<td></td>
<td>Total time — right M1</td>
<td>$F = 10.7$, $P &lt; 0.03$, $\eta^2 = 0.72$</td>
<td>$F = 0.7$, $P = 0.4$, $\eta^2 = 0.14$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 9.1$, $P &lt; 0.04$, $\eta^2 = 0.69$</td>
<td>$F = 1.1$, $P = 0.3$, $\eta^2 = 0.22$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 8.5$, $P &lt; 0.04$, $\eta^2 = 0.68$</td>
<td>$F = 0.5$, $P = 0.5$, $\eta^2 = 0.11$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$F = 13.76$, $P &lt; 0.02$, $\eta^2 = 0.77$</td>
<td>$F = 1.7$, $P = 0.3$, $\eta^2 = 0.29$</td>
</tr>
</tbody>
</table>

Significant effects in bold.

Degrees of freedom = 1, 4.
 Damage to the left motor architecture, in the lesion-based neuropsychological approach proposed by Liepmann (1925). We found a double dissociation (Teuber, 1955; Vallar, 2000) between the effects of stimulation of M1 of the right hemisphere (reduction of execution time, but not of planning time), and those of stimulation of the PPC of the left hemisphere (reduction of planning time, but not of execution time). In Liepmann’s model, planning and motor execution neural systems are anatomo-functionally organized serially; this architecture, in the lesion-based neuropsychological approach, is unable to reveal a functional double dissociation (Teuber, 1955; Vallar, 2000). Damage to the left motor cortex brings about a motor deficit, masking apraxia, which is then assessed in the left hand of left-brain-damaged patients, with a posterior parietal damage. However, motor execution systems are symmetrically located in the two hemispheres: the right (for the right hand), and the right (for the left hand). The two execution systems receive signals from the posterior regions of the left hemisphere (mainly involved in movement planning, with a hemispheric asymmetry), through left intrahemispheric connections to the left sensorimotor cortex, and a callosal projection to the right sensorimotor cortex. Accordingly, in left-brain-damaged patients, the functional independence of the two systems is suggested by the presence of limb apraxia in the left hand, unaffected by motor deficits, contrasted with the frequently present motor deficits in their right hand. The occurrence of left-sided motor deficits in right-brain-damaged patients without apraxia in the right hand completes the double dissociation. In unimpaired participants, the effects of anodal tDCS to the left PPC, with a decrease of planning, but not of execution, times by the left hand, and to the right M1, with a decrease of motor execution, but not of planning, times, represents a double dissociation, not of deficits, but of the tDCS enhancing effects, coherent with the present neuropsychological data in left-brain-damaged patients with ideomotor apraxia. Importantly, in apraxic patients the effects of tDCS to the left PPC are not confined to latencies, but they also result in an increase of accuracy scores in the Ideomotor Apraxia Test, suggesting a possible clinical relevance of the present findings for rehabilitation. These findings converge in indicating that the neural network modulated by tDCS is functionally spared, at least in part. Whether this functional sparing reflects post-lesion changes involving neural plasticity in structurally spared regions taking over the damaged function, enhanced residual function of hypo-functioning regions, or both mechanisms, is unclear (Will et al., 2008; Berlucchi and Buchtel, 2009; Berlucchi, 2011). However, as the effects found in left-brain-damaged patients are qualitatively similar to those found in neurologically unimpaired participants by means of tDCS (Convento et al., 2014), one mechanism may involve a partly preserved function with similar neural underpinnings. In line with this view, the amount of the lesion affecting the left parietal cortex influences the patients’ reduction of planning times. The neural regions involved in the function of interest (the programming of action by the upper limbs) under physiological conditions, when spared by the brain damage, may still play a role in the temporary functional recovery driven by anodal tDCS. Patients with left parietal damage appear to show a minor improvement at the test for ideomotor apraxia, than patients without parietal involvement. Similar findings were obtained in right-brain-damaged patients with left neglect, namely: the greater is the estimated lesion volume, the smaller is the tDCS-induced reduction of the rightward bias in the line bisection task (Sparing et al., 2009).

Although the duration of the tDCS effects was not directly assessed, our multiple-baseline design allows the control of carry-over effects across sessions, separated by at least 24h: the absence of significant differences between the baseline performances across tDCS sessions suggests that the enhancements by tDCS vanished after 24h. Future studies will be of importance for determining whether multiple, consecutive applications of tDCS to the left parietal cortex may induce a long-lasting, and maybe larger, improvement of ideomotor apraxia.

In line with the present findings, unilateral (anodal stimulation of the left inferior frontal gyrus of the damaged
hemisphere, or cathodal stimulation of the homologous region of the right hemisphere, Marangolo et al., 2011), and bilateral tDCS (Marangolo et al., 2013) improve apraxia of speech, and other aspects of aphasia. In this study, no effects were found on phonemic fluency, in line with repeated observations that fluency is modulated by tDCS delivered to the left premotor cortex (Broca’s area) of right-handed healthy participants (Cattaneo et al., 2011). In this study, the frontal stimulation was delivered to M1 of the right hemisphere. The absence of effects on phonemic fluency, together with the positive effects on motor and apraxic functions, provide further evidence against interpretations in terms of non-specific tDCS effects.

The present evidence opens perspectives for delivering anodal tDCS to the damaged left hemisphere, as an adjuvant to behavioural treatment (Bolognini et al., 2009) in the rehabilitation of apraxia. The present effects seem robust, in the face of patients’ sample size (n = 6), differences in length of illness, lesion size and location. These variables did not influence the effects of tDCS, which have neural specificity, as indicated by the role of the spared left PPC. This evidence is encouraging for a clinical rehabilitation trial. Limb apraxia has an adverse influence on the functional abilities, and on patients’ responsiveness during physical and language therapies (West et al., 2008). To date, limb apraxia is a not adequately treated disorder (Dovern et al., 2012), with a need to develop new therapeutic strategies; the present study suggests that tDCS may be a therapeutic option for limb apraxia.

**Funding**

This work has been supported in part by F.A.R. from the University of Milano-Bicocca to G.V., and by Ricerca Corrente Grants from the Italian Ministry of Health to the IRCCS Istituto Auxologico Italiano.

**References**


