TMS-evoked N100 responses as a prognostic factor in acute stroke

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Summary

Rehabilitation programs, to be efficiently tailored, need clear prognostic markers. In acute stroke, neurophysiological measures, such as motor evoked potentials (MEPs), have been proposed, although with discordant results.
The aim of this study was to identify a reliable neurophysiological measure of recovery in acute post-stroke individuals by combining MEPs and the N100 component of transcranial magnetic stimulation-evoked potentials (TEPs). Nine acute post-stroke subjects were included. Clinical evaluation performed in the first week after the event included administration of the European Stroke Scale and Barthel Index and recording of MEPs and TEPs; administration of the clinical scales was repeated after one and three months.
The presence/absence of MEPs and TEPs showed correlations with motor outcome. Individuals with a poorer outcome showed absence of both MEPs and TEPs; absence of MEPs alone was related to a partial recovery.
Given the results of this exploratory study, further investigation is needed to define the accuracy of combined use of MEPs and TEPs as an approach for predicting motor recovery after acute stroke.

KEY WORDS: transcranial magnetic stimulation-evoked potentials, TMS-EEG co-registration, stroke rehabilitation, recovery after acute stroke

Introduction

Cerebrovascular accidents affect cortical areas adjacent to the insult, but they can also affect remote areas. The consequences on brain functions depend on the site of the stroke, and the damage evolves over days or even weeks after the event. Subsequent recovery, particularly of motor function, may take weeks or months. Transcranial magnetic stimulation (TMS) is a neurophysiological technique widely used to investigate the functional state of the human cerebral cortex and corticospinal tract. It has been employed in the acute phase of stroke to evaluate the capability of the primary motor cortex to reorganize itself in order to recover functionality (Di Lazzaro et al., 1999; Hendricks et al., 2002; Vang et al., 1999). TMS variables, such as the presence or absence of the motor evoked potential (MEP) and the motor threshold, may be prognostic indicators of motor and functional recovery, particularly in people presenting with initial severe paresis (Hallet, 2000; Talelli et al., 2006; Thickbroom et al., 2002, 2004).

A recently developed technique combines TMS with electroencephalography (EEG) (Ilmoniemi et al., 1997) to show how stimulation of the superficial cortex evokes EEG responses. These responses can be studied both from the temporal perspective (slow oscillations, referred to as TMS-evoked potentials [TEPs], or fast oscillations) and from the perspective of their topographical distribution over the scalp. TEPs consist of a series of highly reproducible slow EEG oscillations induced by the TMS pulse, which last up to 300 ms (Paus et al., 2001; Komssi et al., 2002, 2004; Komssi and Kähkönen, 2006; Bonato et al., 2006; Lioumis et al., 2009; Casarotto et al., 2010). The temporal evolution of TEPs over the scalp is thought to reflect the spread of activation from the stimulation site to other cortical areas through corticocortical fibers or subcortical structures. It provides information on the reactivity and connectivity of different cerebral cortex areas (Massimini et al., 2007; Paus et al., 2001; Taylor et al., 2008) and on how this reactivity might be modulated by extrinsic factors such as sleep deprivation or alcohol intake (Del Felice et al., 2011; Kähkönen and Wilenius, 2007). In the early stages of brain damage (e.g., ischemic lesions), this "perturbational approach" may be a powerful tool for exploring how affected brain areas might causally interact and how intra-cortical connections might be modu-

lated. Indeed, the observed delay in motor recovery is often attributed to neuronal reorganization. In humans, functional imaging studies have demonstrated activation of adjacent and more distant brain areas during this neural rearrangement phase (Cramer and Bastings, 2000; Gerloff et al., 2006; Ward et al., 2004); a non-invasive, purely neurophysiological method to investigate this aspect would be valuable.

The aim of this study was to assess whether TEPs, in combination with other TMS values or as a stand-alone factor, might be a prognostic marker of functional motor recovery after an acute stroke and whether it might provide further insights into cortical reactivity and connectivity in the pathological brain.

Materials and methods

Nine persons under the age of 80 years [6 males; mean age, 63.8 years, standard deviation (SD): 9.53], who had suffered a first-ever ischemic stroke in the week prior to the experiment, were enrolled. They all had motor paresis and neuroimaging (CT or MRI) showing a single mono-hemispheric/brainstem lesion. TMS safety exclusion criteria according to the international guidelines (Rossini et al., 2015) were applied (absolute contraindication: pacemaker or metal implant holders). People with neuropathy or systemic vasculopathy were also excluded as these conditions could affect MEP responses. Individuals with cognitive disorders not able to provide consent were also excluded. Acute symptomatic seizures were not an exclusion criterion.

Clinical improvement was evaluated using the European Stroke Scale (ESS) (Hantson et al., 1994), which is considered to be particularly sensitive for assessing motor deficits. Functional status was evaluated using the Barthel Index (BI) for disability (Mahoney and Barthel, 1965). Clinical examination and test scoring were performed in the first week after the stroke event and then after one and three months. Seven healthy age-matched subjects (mean age, 65.4 years, SD 5.25) served as controls. The experimenters and raters were aware of the experimental conditions; the therapists and patients were naïve to the aims and hypotheses of the study.

The study was approved by the local ethics committee and all the participants provided written informed consent.

TMS procedure

Transcranial magnetic stimulation was performed during the acute phase; it was not repeated during the follow-up visits as the physiological post-insult neural reorganization would not have allowed stimulation of the same neuronal population and its cortical connections.

During the procedure, subjects were seated comfortably with elbows flexed at 90°, hands pronated in a relaxed position. They were instructed to keep their eyes open, to avoid blinking and, in order to prevent eye movement, to stare at a stationary fixed point at the center of a screen situated one meter in front of

them. Concomitantly with the TMS stimulus, the computer triggered both the magnetic pulse and the insertion of a marker in a track of the multichannel EEG recording system. A loud click is heard when the coil discharges. The click elicits N1-P2 complex auditory evoked potentials, maximum over the central and parietotemporal regions (Nikouline et al., 1999; Tiitinen et al., 1999). The coil-generated click was masked by white noise (90 dB) played through insert earphones. All the participants confirmed that the white noise masked the coil click.

TMS was carried out with a Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The magnetic stimulus had a biphasic waveform with a pulse width of about 300 μs. In this study, stimulus intensities are expressed as a percentage of the maximum stimulator output. TMS was delivered through a figure-of-eight focal coil oriented so that the induced electric current flowed in a posterior-anterior direction over the affected M1. The coil was placed tangentially to the scalp, with the handle pointing backwards and laterally at a 45° angle away from the midline, approximately perpendicular to the line of the central sulcus, thus inducing a posterior-anterior current. This choice of orientation was based on the finding that the lowest motor threshold is achieved when the induced electrical current in the brain flows approximately perpendicular to the line of the central sulcus (Brasil-Neto et al., 1992). Motor evoked potentials were recorded from the thenar eminence (TE) on the affected side by means of Ag/AgCl surface electrodes fixed on the skin with a belly-tendon montage. We determined the optimal position for activation of the TE by moving the coil in 0.5-cm steps around the presumed hand area of the motor cortex. The site where stimuli of slightly suprathreshold intensity consistently produced the largest MEPs with the steepest negative slope in the target muscle was marked as the "hot spot".

The resting motor threshold (rMT) intensity, expressed as a percentage of maximum stimulator output, was approached from suprathreshold levels by reducing the stimulus intensity in steps of 1%. It was defined as the first stimulus intensity that failed to produce a MEP of at least 50 μV in ten out of twenty successive trials (Groppa et al., 2012). The intensity of single-pulse TMS was set at 110% of individual rMT. When the rMT could not be elicited, we stimulated at the maximum stimulator output in order to determine that the MEP was absent.

EEG data acquisition

Continuous EEG was recorded with a 32-channel TMS-compatible system (Micromed, Treviso, Italy), with an electrode anterior to Fz as the reference and an electrode posterior to Fz as the ground. Saturation of the EEG amplifiers by the TMS pulse occurs for a short time (about 15 ms) when using TMS-compatible amplifiers. Overheating of electrodes located in the proximity of the stimulating coil (Roth et al., 1992) was minimized by using TMS-compatible Ag/AgCl-coated electrodes (diameter, 8 mm; thickness, 0.5 mm) with 2-mm slits to

interrupt eddy currents. Electrode impedance was below 10 kΩ. The amplifier bandwidth was between 0.01 and 512 Hz and the signal was sampled at 1024 Hz. Activity in the right TE and in the right eye vertical electroculogram was registered from bipolar surface electrodes on two EMG channels. The amplified and bandpass-filtered (50 Hz to 5 kHz) EMG signal was fed into a SystemPlus electromyograph (Micromed, Treviso, Italy) at a sampling rate of 5000 Hz.

Data analysis

EEG data were analyzed with the Vision Analyzer (BrainAmp 32MRplus, BrainProducts GmbH, Munich, Germany) software using event-related averaging. Epoching of the TMS-related scalp EEG responses was performed off-line. Epochs started 100 ms before and ended 300 ms after TMS onset. We then averaged the event-related waveforms (TEPs). The mean number of trials contributing to final averages ranged between 70 and 100. Trials with any kind of artifact were manually rejected.

MEPs were considered altered in the presence of amplitude asymmetry. There is no consensus on the definition of when there is an asymmetry in MEPs. We applied the criterion used for somatosensory evoked potentials: asymmetry is present when the amplitude differs by more than 50% or the central conduction time is altered (difference of more than two SD between the two sides) (Burke et al., 1999). In the patients in whom MEPs could not be elicited, we stimulated with the maximum stimulator output to confirm the absence of MEPs.

Among the TEP components, the N100 deflection, which was clearly represented in all recordings, was taken into account for further analysis. N100 was considered in a dichotomous manner: present, when a deflection with the same latency, but not necessarily the same amplitude, as the equivalent component evoked in the control group was elicited; absent when response peaks were not detectable.

Statistical analysis

Changes in neurological scores were analyzed using the Wilcoxon signed rank test for non-parametric comparisons between pre- and post-observation values. The effects of TIME and MEP/TEP presence/absence, MEP presence/absence, and TEP presence/absence were investigated using a repeated measures analysis. A value of p<0.05 was taken as statistically significant. Pearson's correlation coefficient (significance at p<0.05) was used to study possible correlations between neurophysiological parameters and motor improvements.

Results

All the subjects tolerated the stimulation procedure, and no adverse effects (i.e. seizures) were observed. Table I details the brain lesion sites and the clinical assessment scores. An overall significant improvement in motor

Table I - Participants' age, lesion site and neurophysiological findings in the acute phase and neurological/functional status in the acute phase and after one month and three months of follow-up.

	Age	Lesion site	ESS (T0)	ESS (T1)	ESS (T2)	BI (T0)	BI (T1)	BI (T2)	MEPs (T0)	TEPs (T0)
Pt1	66	*internal capsule*	93 *19*	100 *24*	100 *24*	80	100	100	*present/normal*	*present*
Pt2	58	*frontal cortical-subcortical*	95 *19*	96 *24*	100 *24*	80	80	90	*present/altered*	*absent*
Pt3	58	*thalamus-midbrain*	80 *16*	97 *20*	100 *24*	40	100	100	*present/altered*	*present*
Pt4	78	*frontal subcortical*	80 *15*	90 *20*	94 *24*	75	90	100	*present/altered*	*present*
Pt5	59	*frontoparietal cortical-subcortical*	46 *10*	70 *16*	80 *18*	15	50	60	*present/altered*	*absent*
Pt6	71	*frontal cortical-subcortical*	58 *12*	75 *18*	80 *20*	30	60	65	*present/altered*	*absent*
Pt7	75	*brainstem*	50 *8*	70 *14*	75 *16*	15	30	30	*absent*	*present*
Pt8	50	*fronto-temporo-parietal cortical-subcortical*	45 *10*	54 *12*	63 *14*	15	30	40	*absent*	*absent*
Pt9	73	*fronto-temporo-parietal cortical-subcortical*	53 *2*	54 *8*	65 *12*	15	30	35	*absent*	*absent*

Abbreviations: ESS=European Stroke Scale; BI=Barthel Index; MEPs=motor evoked potentials; TEPs: transcranial magnetic stimulation-evoked potentials; T0=acute phase; T1=one month of follow-up; T3=three months of follow-up. The upper limb ESS subscores are reported in *italics* (24 represents the best performance).

(ESS, Z=-2.7; p=0.01) and functional (BI, Z=-2.7; p=0.01) scores between recording sessions was observed. In the controls, a sequence of positive and negative deflections peaking at precise intervals after the TMS stimulus was recorded. Differences between the elicitability of MEPs and TEPs (namely the N100 component) were noted among the subjects (Table I).

Only one subject (no. 1) had normal MEPs over the affected side, associated with the presence of TEPs. A subgroup of five subjects (no.s 2, 3, 4, 5, 6) presented altered MEP responses: among these, two participants (no.s 3 and 4) also had elicitable TEP responses (no.s 2, 5, 6 had no recordable TEP response). In the last subgroup of subjects (no.s 7, 8, 9), no MEPs could be elicited, while TEP responses were evoked in only one (no. 7).

Motor recovery over time appeared to be significantly related to the initial presence of MEPs, with both a within-subject effect (TIME; $F_{(2)}=21.431$; p=0.0001) and a between-subjects effect (MEP presence/absence; $F_{(1)}=9.662$; p=0.017). The presence of TEPs, on the other hand, had a significant within-subject effect (TIME; $F_{(2)}=23.989$; p<0.0001) but no between-subjects effect (TEP presence/absence; $F_{(1)}=2.467$; p=0.16). On correlation analysis (Pearson's correlation, p=0.005 as significant), a clear correlation emerged between MEPs and neurological status in the acute phase (r=0.724; p=0.03) and at three months post-stroke (r=0.819; p=0.007), while no correlation could be found between TEPs and these variables (vs ESS T0: r=0.57, p=0.1; vs ESS T2: r=0.517, p=0.15).
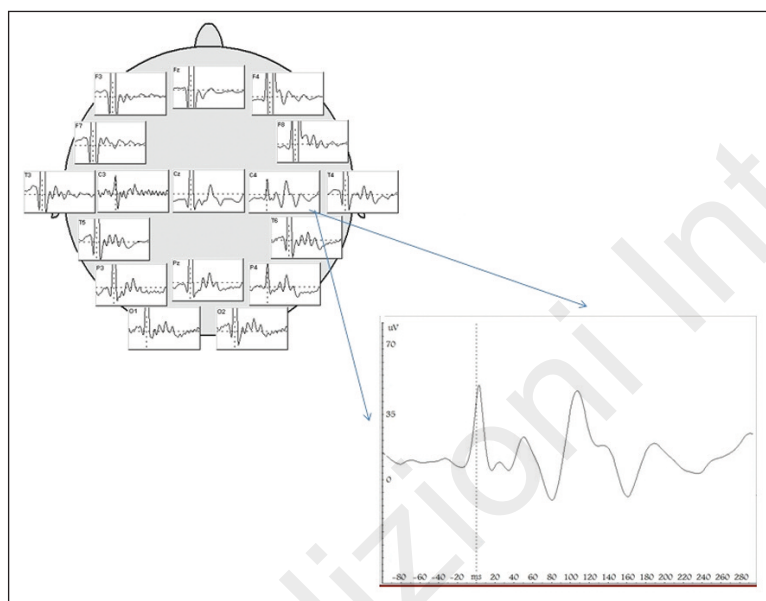

Figure 1 - TMS-evoked potentials in a participant with an initially mild motor paresis (no.1).
The figure shows TEPs over the entire scalp and a magnified image of a TEP evoked over C4 (lesional hemisphere). The morphology and latency of the N100 component of TEP were preserved over the scalp.
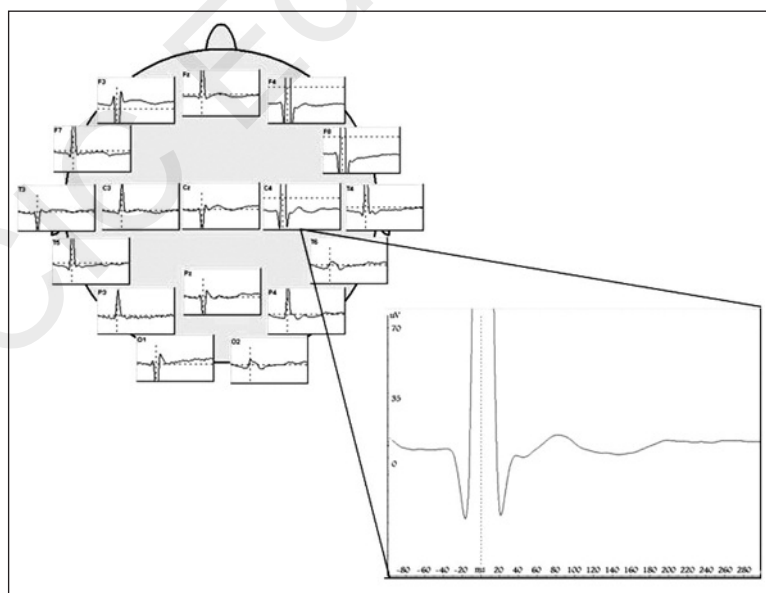

Figure 2 - TMS-evoked potentials in a participant with an initially moderate motor paresis and good motor recovery (no.3).
The figure shows TEPs over the entire scalp and a magnified image of a TEP evoked over C4 (lesional hemisphere). The morphology and latency of the N100 component of TEP, although less evident and of reduced amplitude compared to those evoked in the previous figure, were preserved over the scalp.

Discussion

We applied a perturbational approach to assess brain reactivity in people with a recent stroke, in order to establish correlations between electrophysiological findings and functional recovery. The main finding of this study is that combining MEP and TEP responses after stimulation of the affected hemisphere seems to provide a better neurophysiological predictor than do the single parameters alone. Indeed, altered ipsilesional MEP responses were predictors of better neurological score and outcome when the N100 response from the affected hemisphere was present. Conversely, absence of TEP associated with presence of MEP was correlated with a less satisfactory recovery.

Of note, focusing on a single TEP deflection (i.e. N100) allows immediate interpretation of cortical reactivity data, which is of paramount importance for the translation of this examination paradigm into clinical practice.

Decisions about rehabilitation needs of people with stroke are often difficult and controversial. Rehabilitation programs are lengthy and expensive and often the benefits fall short of expectations. There is a need for specific and sensitive criteria to select people who are most likely to benefit from rehabilitation. Neurophysiological measures seem to offer such an indication, although a general consensus on their significance is still lacking. Our data contribute to this issue, by suggesting that a combination of two relatively easily obtainable parameters could support decisions concerning the rehabilitation process.

Some studies conducted in the acute phase of stroke showed, using MEP threshold and amplitude measures, a relationship between motor recovery and the degree of motor impairment (Pennisi et al., 1999; Pizzi et al., 2009; Rapisarda et al., 1996). The absence of MEPs, more than amplitude variations, seems to be predictive of recovery (Di Lazzaro et al., 2010), but consensus on this issue is still lacking. On the contrary, changes in motor cortex excitability in the intact hemisphere have been reported as having solid prognostic value (Manganotti et al., 2002, 2008).

The rationale for combining MEPs and TEPs lies in the fact that the two parameters explore different circuits: descending corticospinal tracts in the case of MEPs, and cortical-subcortical circuits in the case of TEPs. We observed that TEP components – when recordable – evoked during the acute phase of a stroke were comparable to those of healthy controls. TEPs provide additional insight into the integrity of cortical-subcortical pathways: subsequent deflections are generated by different, interconnected neuronal ensembles unrelated to the descending long tracts. Observing how neuronal module interactions are modified by an ischemic lesion opens a window onto cortical-subcortical network integrity that will substantially contribute to recovery (Gerloff et al., 2006; Ward et al., 2004). The combination of MEPs, investigating the descending pathways, and long-latency TEPs (i.e. N100) thus provides a more comprehensive assessment of the functional brain state.

In our study, patients presenting a favorable outcome showed reliable TEP responses spreading over the scalp, reflecting the integrity of the cortical-subcortical network, signalling a sparing of wider brain areas than in those people who do not recover well. Another interesting finding, independent of the pathology and indirectly confirming the cortical-subcortical origin of TEPs, is that the people with brainstem lesions had normal TEPs without MEP responses.

The small sample size is, however, a weakness of this exploratory study. From a technical point of view, we did not extend the analysis to short-latency TEPs due to their inconstant appearance on traces. Nonetheless, given our interest in investigating subcortical functional connections, the choice to focus on long-latency potentials, namely P100, was deemed appropriate. In addition, the decision to focus on a single TEP component was an attempt to render this protocol applicable in the clinical setting. We are quite confident that the recorded N100 was not the first deflection of the auditory evoked potential, given the effective noise masking and the lack of a clear-cut second wave (N190), as well as the fact that it was not recorded in all our patients. On the other hand, we have to acknowledge that recording TEPs requires dedicated equipment as well as trained personnel, both factors that could prevent the widespread diffusion of this neurophysiological examination.

Given these interesting, although preliminary results, a future direction of research will be to determine whether, in a larger sample and with a longer follow-up, TEP responses alone might prove to be a reliable prognostic factor to aid in the rehabilitation process.

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