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Modelling of Transcranial Magnetic Stimulation in One-Year Follow-Up Study of Patients with Minor Ischaemic Stroke

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1. Introduction

Since its commercial advent in 1985, transcranial magnetic stimulation (TMS), a technique for stimulating neurons in the cerebral cortex through the scalp, safely and with minimal discomfort, has captured the imaginations of scientists, clinicians and lay observers [Wassermann et al, 2012]. Initially a laboratory tool for neurophysiologists studying the human motor system, TMS now has a growing list of applications in clinical and basic neuroscience. At cortical level, the abnormal amplitudes of the motor evoked potentials (MEP) may be due to the damage of the motoneurons themselves; as well as to their reduced capacity for repetitive excitation; deficit of the intracortical synaptic transmission (transfer); activation of motoneuron inhibitors, etc. At subcortical level the causes may be demyelinization, remyelinization, activation of the long-latent corticofugal fibres, axonal damage, etc. [Komori et al, 1993].

The human brain possesses a remarkable ability to adapt in response to changing anatomical (e.g., aging) or environmental modifications. This form of neuroplasticity is important at all stages of life but is critical in neurological disorders such as amblyopia and stroke [Sharma, 2012]. When MEP are obtained in the acute phase of stroke, the functional recovery of the motor deficit, as a rule, is to occur [Nowak et al, 2010; Dimyan, 2010]. The initially registered normal MEP amplitudes have a predictive value in the view of the long-term functional outcome [Stinear, 2010; Dimyan et al, 2010;].

The TMS approach was also used in the investigation of patients with lacunar strokes. The central motor conduction time (CMCT) and the threshold intensities for eliciting MEPs in the relaxed muscles were significantly increased on the affected side. MEP amplitude abnormalities were related to pyramidal signs (though they could be observed also in a

patient without any motor impairment) and occurred independently of a specific clinical picture or a radiologically confirmed lacunar lesion [Abbruzzese et al, 1991; Hufnagel et al, 1990]. Earlier studies have shown that during the acute phase of the minor ischaemic stroke (MIS), MEP amplitudes can be registered in all investigated patients [Hadjipetrova et al, 1993]. To note, the increases in the latency of the M-response and CMCT have prognostic significance for early assessment of the outcome of ischaemic stroke [Stulin et al, 2003]. Earlier studies by Ferbert and collaborators [1992] have indicated that the MEP amplitudes are a more sensitive marker for the sublclinical damage of the pyramidal tract than CMCT. A significant correlation has also been reported among the recovery of muscle strength and the amplitude of MEP [Palliyath, 2000].

The aim of this study was to perform a *post-hoc* analysis of one-year follow-up data from 40 patients with MIS and to: (i) investigate the central motor conduction time (CMCT) and the amplitude of the motor evoked potential (MEP) during the acute phase of MIS; (ii) provide evidence for a subclinical damage of the pyramidal tract; and (iii) model and predict the outcome measures at month 12 after MIS as based on earlier changes in the acute phase.

2. Methods

2.1. Patient selection, diagnosis, data collection, and main characteristics

The Plovdiv project included hospital-based incident cases of patients with minor ischaemic stroke (MIS) that were followed for 12 months to determine the estimates of central motor conduction time (CMCT) and amplitudes of motor evoked potential (MEP) and their changes and correlations over time.

This is a *post-hoc* analysis and modelling study. The patient population has been described in more detail earlier [Atanasova, 1998; Atanasova & Vukov, 1998; Atanasova, Voukov & Tchalakova, 2002; Atanassova, Chalakova & Dimitrov, 2008a]. In particular, patients with cerebrovascular disease had been hospitalized in the Clinic of Cerebrovascular Diseases (Plovdiv Healthcare Region) and 56 consecutive patients with MIS were subjected to screening. All screened, eligible patients with MIS as an initial index event who provided a written, informed consent in accordance with the Declaration of Helsinki guidelines at discharge were immediately enrolled. During the lag interval from the index event until discharge (i.e., during the hospital stay), no vascular events were observed among the 56 screened eligible patients. Of these eligible patients, 54 patients (96.4%) provided written, informed consent and were included in the current follow-up study. The other 2 eligible patients did not provide informed consent at discharge and were not enrolled (**Figure 1**). Further, till month 12, a total of 14 patients were excluded or lost to follow-up and could not provide data on the outcome, therefore, 40 patients were subjected to statistical analyses and modelling in this study. The inclusion criteria were: patients with first MIS, age > 40 years and residence in Plovdiv for at least three months before identification and enrolment [Atanassova, Chalakova & Dimitrov, 2008a]. All evaluations were performed at Medical University Hospital of Plovdiv, Bulgaria. The University Ethical Committee approved the study protocol.
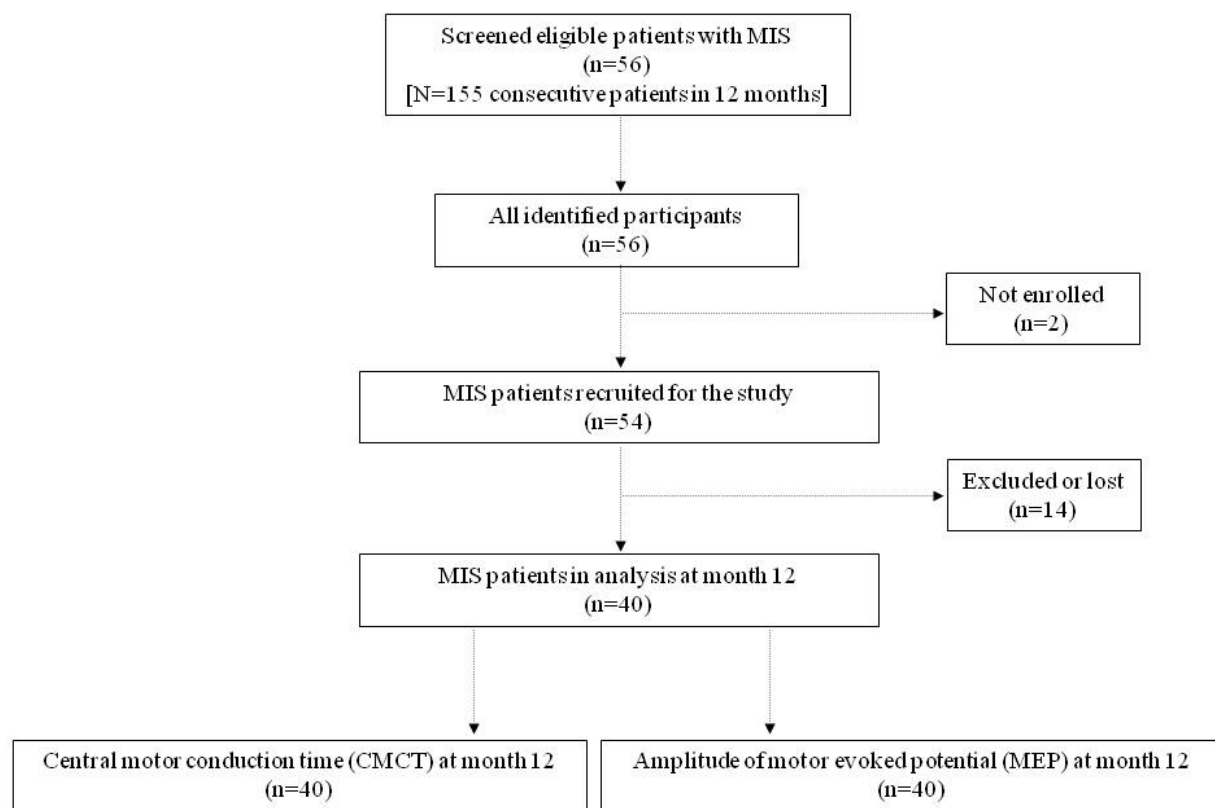
Figure 1. CONSORT flow-chart of study screening, enrolment and analysis.

Data were collected by instructed physicians and clinical (physical and neurological) examinations were conducted by study neurologists [Atanassova, Chalakova & Dimitrov, 2008a]. The assessments covered: hypertension, diabetes, dyslipidaemia, peripheral vascular disease, cardiac conditions, cigarette smoking, educational background, etc.

Initial stroke severity was assessed using the modified Rankin Scale [Bamford et al, 1990]. MIS diagnostic evaluations included CT or MRI of the brain and ultrasound evaluation and/or trans-thoracic or trans-oesophageal echocardiogram, as appropriate. A panel of stroke neurologists assessed every CV events subtype using standard diagnostic criteria and all available information for each patient. For this study, *MIS* was defined as a minor stroke if the score on the modified Rankin Scale was 1 at the first evaluation, or if the score was 0 or 1 at one-month follow-up (i.e., no symptoms, or minor symptoms that did not interfere with normal lifestyle) [Atanassova, 1998; Atanasova & Vukov, 1998; Atanassova, Voukov & Tchalakova, 2002]. In particular, acute onset was observed in 11 patients (20.4%). Extra-cranial ultrasound findings were recorded in 11 patients (20.4%). The main characteristics of the initial study cohort were as follows: 37 men (68.5%) and 17 women (31.5%), with male predominance in CV events (n=8 men) but with similar ages of 61.1±12.6 years in patients with CVE versus 62.2±9.2 years in patients without CVE (p>0.05). The mean follow-up time was 11.1±2.4 months with mean time to CV events of 5.8±2.7 months. For the purpose of this study, all MIS patients with subsequent stroke (n=8) as defined above, were excluded from the analysis.

2.1.1. Assessment of outcomes

The main outcome was defined as estimates of central motor conduction time (CMCT) and amplitudes of motor evoked potential (MEP) at month 12. We performed transcranial magnetic stimulation by MAGSTIM 200 after MIS (day 7 in month 1, month 3, and month 12) on the motor cerebral cortex bilaterally and on C7 with consecutive conduction of MEPs by surface electrodes from isometrically slightly contracted muscle *abductor policis brevis*. All measurements were taken as related to the symptomatic and asymptomatic hemispheres and differences between them were also analysed (Table 1). Normal values from 30 healthy subjects were also obtained for reference purposes.

Outcome parameters in MIS patients (n=40 patients)	Symptomatic hemisphere (n=40 cases*)	Asymptomatic hemisphere (n=40 cases*)	p-value
Central motor conduction time (CMCT) [ms]			
at Month 1 (day 7)	9.147 ± 1.862	7.550 ± 1.465	<0.05
at Month 3	8.038 ± 1.392	7.135 ± 1.052	<0.05
at Month 12	10.720 ± 1.831	8.550 ± 1.497	<0.05
Amplitude of motor evoked potential (MEP) [mV]			
at Month 1 (day 7)	6.083 ± 1.882	8.963 ± 1.925	<0.05
at Month 3	7.293 ± 1.876	10.350 ± 2.160	<0.05
at Month 12	7.290 ± 1.757	9.880 ± 1.986	<0.05

Notes: *Number of cases (measurements) in the MIS patients with TMS values; Data are mean ± standard deviation; °Difference at p<0.05 is considered statistically significant. Abbreviations: MIS, minor ischaemic stroke.

Table 1. Main outcomes of TMS in 40 MIS patients, followed prospectively for 12 months, as measured according to the existing symptomatics (symptomatic or asymptomatic hemisphere)

As secondary outcomes, the changes from month 1 onwards, as well as the correlations between the estimates, were also analysed. The role of the symptomatics (i.e., measures for symptomatic or asymptomatic hemisphere) as a predictor of the main outcome estimates at month 12, was also investigated. The presence/absence of non-fatal or fatal CV event after MIS was considered for the diagnosis of the MIS patients with a subsequent stroke, who were to be excluded from the analyses. Thus, two2 sub-categories for each secondary outcome were established as events classification: (i) non-fatal CVE; (ii) fatal CVE. Strict evaluations were conducted in 4 visits (at baseline, at month 1, month 3 and month 12), with telephone interview every other month, till month 12. Every evaluation was carried-out by contact with the patient, family member, or caregiver. Information was collected by somatic examination, inter-current symptoms, illness or hospitalization. The in-person visits were conducted at our clinic and included measuring vital signs, physical and neurological examination. A registry reporting system was used to identify study participants who experienced nonfatal or fatal vascular events, related hospitalization or death (vascular or

nonvascular death). All records were reviewed for all outcome events, including death, and have been maintained. All outcome events were reviewed by a neurology specialist. Non-fatal strokes were validated by a study neurologist, and all deaths were to be validated, as well. Deaths were to be classified using death certificates and medical records.

Death as an eventual fatal outcome was defined as to be considered as due to stroke if there was clear documentation of a stroke from the death certificate or hospital records; deaths that would have occurred more than 30 days after the initial accident (i.e., secondary CV event) had to be considered related to the event on the grounds of a clinical judgment that relied on a clearly documented relationship to the stroke or its complications to the point of death in the medical records. Following the ascertainment procedures, all above mentioned death notifications, certificates, and autopsy protocols for all cases of death had to be collected and reviewed individually, especially for patients who died outside the hospital. In cases in which it was difficult to determine whether death was due to stroke, consensus was reached after discussion using the best available information.

2.2. Sample size, data elaboration and statistical analyses

2.2.1. Sample size estimation

The sample size of the initial follow-up cohort of 56 patients to be screened was calculated on the basis of the expected number of CV events, as described previously in more detail [Atanassova, Chalakova & Dimitrov, 2008a]. Having assumed a theoretical distribution from 0 to 50% for the non-events and based on the 3-year cumulative incidence of 24.5% for cerebrovascular events in MIS patients [Atanassova, Chalakova & Dimitrov, 2008b], 8.16% of CV events were to be expected in 12 months. Thus, it had been estimated that to give the study >95% power to detect such minimum event rate as statistically significant at p<0.05, 51 patients had to be included and analysed. A preliminary estimate of the prevalence of MIS patients that would satisfy the inclusion/exclusion criteria from all those referred to the Clinic of Cerebrovascular Diseases yearly had indicated that 56 patients with MIS had to be identified throughout a screening period of about 12 months (estimated maximum 10% drop-out). Given the pilot nature of the probabilistic modelling of the estimates and derivation of predictions at month 12 for both studied parameters (CMCT and MEP), no further sample size calculations were performed.

2.2.2. Data elaboration and statistical analyses

The main endpoint for both the central motor conduction time and amplitudes of motor evoked potentials was considered as an estimated mean (± standard deviation, S.D.) at month 12 (**Table 1**). Two other interim measures of the outcomes were also taken (at month 1 and month 3). A test for normality of distributions (Shapiro-Wilk test) was applied. The differences were analysed by two-tailed paired parametric (t-test, etc.) or non-parametric (Wilcoxon signed-rank) tests at p<0.05, as appropriate, as well as repeated-measures

ANOVA (general linear models) in the view of the symptomatic and asymptomatic hemispheres (**Figure 2 & Figure 3**). As appropriate, parametric and non-parametric correlations between CMCT and MEP at various times were also performed.

Parametric regression modelling was used to analyse the data and develop models to predict the outcomes at month 12 (**Table 2**). The significant relationships were later explored and confirmed by probabilistic artificial neural network (ANN) modelling, irrespectively of usual statistical constraints (**Figures 4 & Figure 5**). The stopping rule of learning was assumed when a state of maximum overall correctness of prediction with minimum average learning error was reached [Sarle, 1997]. The p-values less than 0.05 were considered statistically significant. The specialised software packages for statistical (SPSS ver.18) and probabilistic modelling (EasyNN ver.6.0i) were used.

3. Results

3.1. Descriptive statistics and basic comparisons

The recruited patient cohort consisted of 54 patients (37 males and 17 females), mean age of 62 years (SD 9.6). The neurological deficit by the Rankin's scale was assess at mRs=1 (37 patients), mRs=2 (16 patients) and mRs=3 (1 patient). Most frequent minor ischaemic strokes occurred in the left carotid system (53.7%), right carotid system (31.4%), both systems (9.3%) as well as in the vertebrobasilar system (5.6%). Most frequently observed are the syndromes of the middle cerebral artery (hemiparesis and involvement of VII and XII cranial nerves), aphasias after a damage of the dominant hemisphere, upper monoparesis and motor aphasia, etc. In particular, during the mean follow-up of 11.1 ± 2.4 months, 8 secondary CV events (14.8%) were observed only in males within a mean period of 5.8 ± 2.7 months. No difference in the age of patients with CV event (61.1 ± 12.6 years) vs. those without (62.1 ± 9.6 years) was found ($p > 0.05$). The one-year risk for CVE was $\approx 15\%$ (95%CI $7.1 \div 27.7\%$). The other main demographic and clinical parameters of the initial cohort of 54 patients were reported in a more detail earlier [Atanassova, Chalakova & Dimitrov, 2008a].

The main results are summarized in Table 1. Although the distributions of CMCT at month 12 in the asymptomatic hemisphere and MEP at month 1 in the symptomatic one were slightly skewed, two tendencies could be clearly observed. While there is clearly a difference in the TMS measures according to the existing symptomatics (i.e., symptomatic or asymptomatic hemisphere), the first one is an increase of CMCT over time with higher values in the symptomatic hemisphere, while the second one is again an increase of MEP over time, but the higher values this time are observed in the asymptomatic hemisphere ($p < 0.05$).

An interesting pattern is, however, that while CMCT first decreased from month 1 to month 3 and then increased (Figure 2), the MEP amplitude, in parallel but opposite, increased in month 3 and then decreased slightly in month 12 (Figure 3). In particular, there was a significant change over time ($p < 0.001$) in CMCT and a multivariate, combined

effect of symptomatics and time (grand mean 8.523 ms, 95%CI 8.240-8.805, p=0.01). Notably, there was a statistically significant difference (adjusted for the baseline values at month 1) between the estimated marginal means of CMCT in the symptomatic (10.717 ms, 95%CI 10.191-11.244) and asymptomatic (8.023 ms, 95%CI 8.023-9.077) hemispheres (Figure 2).

There was a significant increase over time (p<0.001) in MEP amplitude, however, the multivariate, combined effect of symptomatics and time was not significant (grand mean 8.310 mV, 95%CI 7.922-8.697, p=0.309). Certainly, there was a statistically significant difference between the estimated marginal means of MEP amplitude in the symptomatic (6.888 mV, 95%CI 6.340-7.437) and asymptomatic (9.731 mV, 95%CI 9.182-10.279) hemispheres, but this was observed since month 1 and continued as such till month 12 (Figure 3).
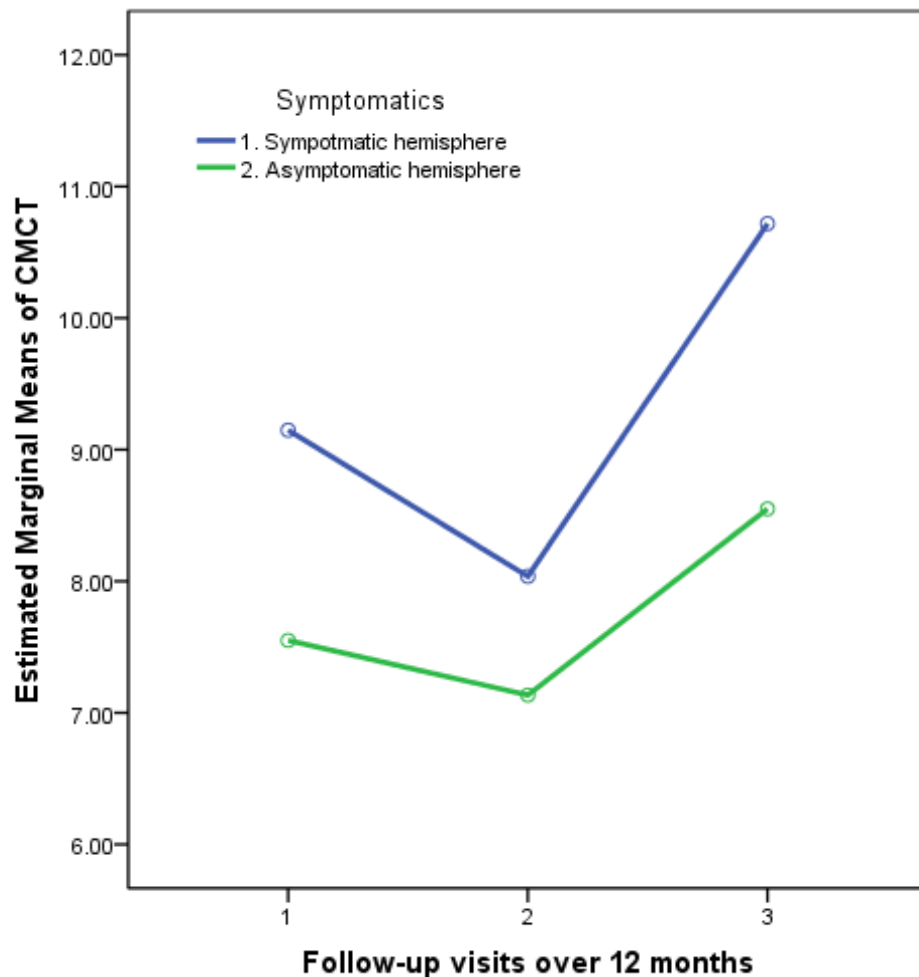

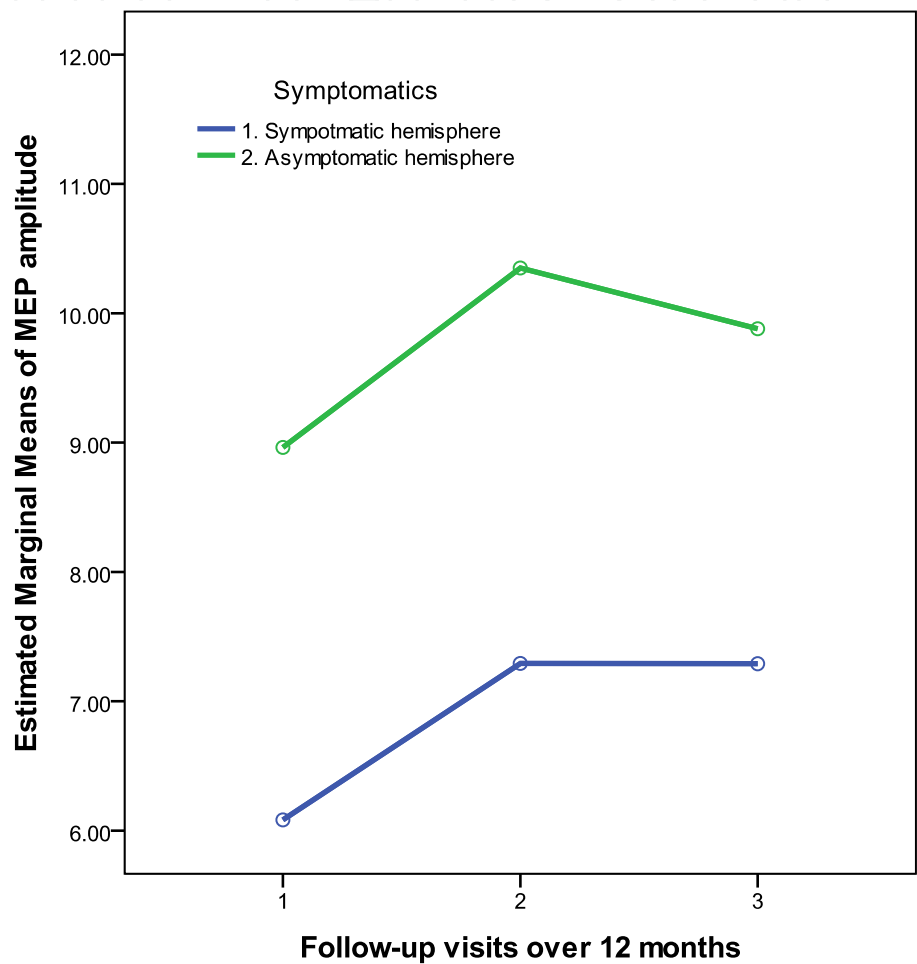**Figure 2.** General linear modelling (repeated ANOVA) of CMCT changes from month 1 till month 12

Figure 3. General linear modelling (repeated ANOVA) of MEP amplitude changes from month 1 till month 12

Since these changes appeared to be parallel, we tested also the correlations between the measurements of TMS parameters at different months. In particular, there was a weak inverse, but significant correlations between CMCT and MEP (Spearman's Rho=-0.45-0.46, p<0.05). Notably, the highest positive correlations were observed between CMCT at month 1 and the following months (0.60-0.81, p<0.05) as well as between MEP at month 1 and the following months (0.78-0.87, p<0.05). The latter relationships provided the opportunity to model and predict the outcome at month 12 in the two TMS parameters.

## 3.2. Statistical and probabilistic modelling of the outcome at 12 months

The parametric regression modelling indicated that the CMCT outcome at month 12 can be predicted by the initial values at month 1 and whether or not these have been observed in the symptomatic or asymptomatic hemisphere (Fmodel=33.323, p<0.001, Table 2). The same is valid for the MEP amplitude outcome at month 12 (Fmodel=55.0.09, p<0.001, Table 2), although the role of the symptomatic as a predictor is with a marginal statistical significance (p=0.051).

Outcome parameters in 40 MIS patients	Independent variables	Standardized coefficient β*	p-value
Central motor conduction time at month 12	CMCT at month 1	0.448	<0.001
	Symptomatics	-0.354	<0.001
Amplitude of motor evoked potential at month 12	Amplitude of MEP at month 1	0.642	<0.001
	Symptomatics	0.183	0.051

Notes: *The predictor "symptomatics" is a categorical variable referring to the particular hemisphere, with two categories: symptomatic and asymptomatic. The constants, unstandardized coefficients β and their standards errors are available from the authors upon request. Abbreviations: TMS, transcranial magnetic stimulation; CMCT, central motor conduction time; MEP, motor evoked potential.

Table 2. Parametric regression modelling to predict the TMS outcomes in 40 patients at month 12

The above relationships were further investigated by a probabilistic modelling, employing artificial neural network (ANN) methodology, which has not the usual constrains of a parametric regression analyses (Figure 4 & Figure 5). The ANN for modelling and predicting CMCT at month 12 contained 9 nodes with 2 hidden layers, with two potential predictors: CMCT at month 1 and symptomatics (symptomatic or asymptomatic hemisphere) (Fig. 4). The structure for predicting the resulting outcome node was obtained when the average error decreased below the target value of 0.049.
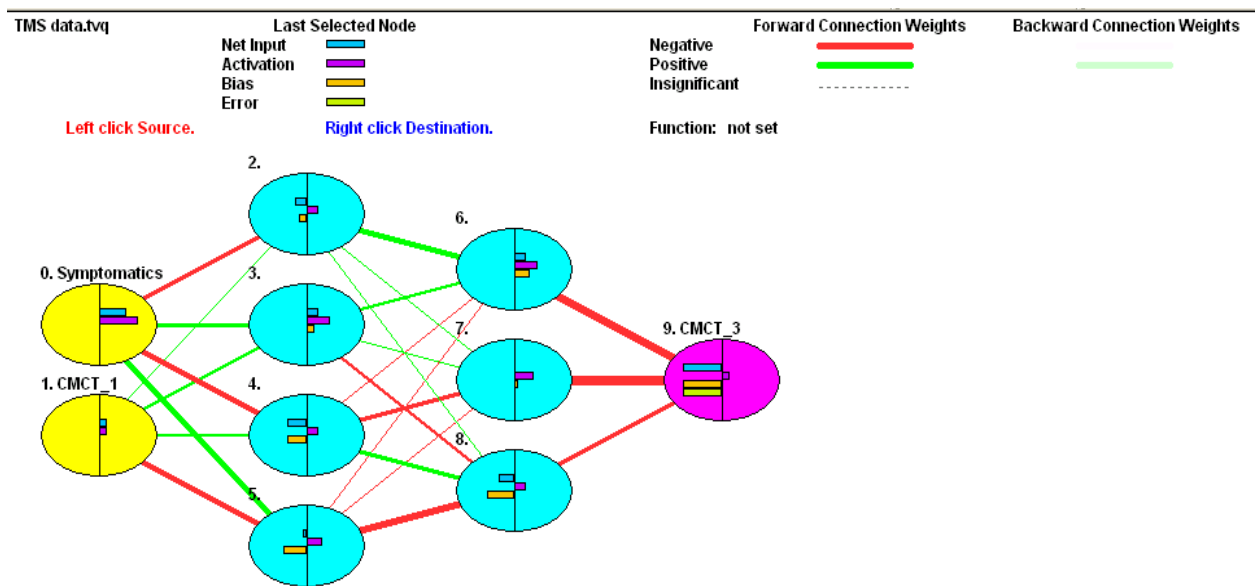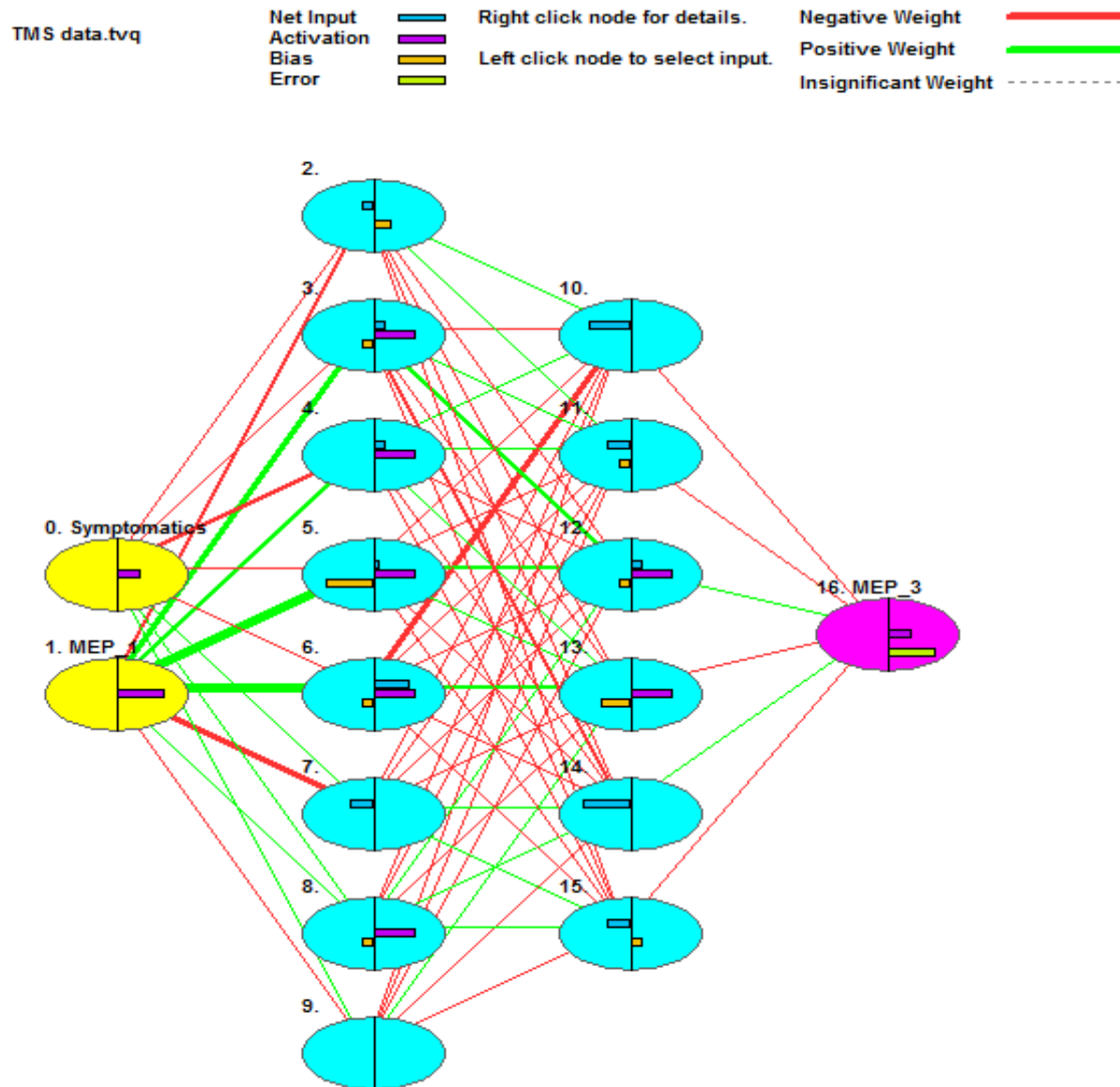
Legend: Yellow circles (No.0–1) on the left indicate 2 input variables. The magenta circle (No.9) on the right is the output variable (outcome). The nodes of two hidden layers are grouped vertically and coloured in cyan: hidden layer 1 (nodes No.2–5); hidden layer 2 (nodes No.6–8). ANN nodes description: Each node contains small bar charts indicating the basic functional parameters – net input (cyan bar), activation (magenta bar), bias (orange bar) and error (yellow bar). The hidden nodes are connected by lines, showing the type and strength of weights: the red and green lines indicate negative and positive weights, respectively. The thicker the line is, the heavier the weight.

Figure 4. Artificial neural network trained with 40 patients to predict the CMCT outcome at month 12

The modelling confirmed the finding from the parametric regression analysis (β=0.448, Table 2) for a slightly higher relative (predictive) importance of the CMCT at month 1 (0.301) than symptomatics (β=-0.354, relative importance = 0.290, not shown).

The ANN for modelling and predicting MEP at month 12 contained 16 nodes with 2 hidden layers, with two potential predictors: MEP at month 1 and symptomatics (symptomatic or asymptomatic hemisphere) (Fig. 5). The structure for predicting the resulting outcome node was obtained when the average error decrease below the target value of 0.049. The modelling confirmed the finding from the parametric regression analysis (β=0.642, Table 2) for a quite higher relative (predictive) importance of the MEP at month 1 (relative importance = 230.19) than symptomatics (β=0.183, relative importance = 62.06, not shown).

Legend: Yellow circles (No.0–1) on the left indicate 2 input variables. The magenta circle (No.16) on the right is the output variable (outcome). The nodes of two hidden layers are grouped vertically and coloured in cyan: hidden layer 1 (nodes No.2–9); hidden layer 2 (nodes No.10–15). ANN nodes description: Each node contains small bar charts indicating the basic functional parameters – net input (cyan bar), activation (magenta bar), bias (orange bar) and error (yellow bar). The hidden nodes are connected by lines, showing the type and strength of weights: the red and green lines indicate negative and positive weights, respectively. The thicker the line is, the heavier the weight.

Figure 5. Artificial neural network trained with 40 patients to predict the MEP amplitude outcome at month 12

4. Discussion

The one-year follow-up established a statistically significant dynamics in the MEP and CMCT outcomes. During the acute phase of the ischaemic stroke in the symptomatic hemisphere we found prolonged CMCT and reduced MEP amplitudes, similar to the findings by other authors [Segura et al, 1990]. When abnormal MEP amplitude is found, it is most likely the case of mainly functional disturbances of the pyramidal tract conduction, with a pathogenesis due to the acute disorder of cerebral circulation [Braune et al, 1996]. This may probably explain the prolonged latencies of MEP and reduced MEP amplitudes in the asymptomatic hemisphere. The decrease of the CMCT and the significant increase of the MEP amplitude (without reaching the normal values) at month 3, an according to Hadjipetrova et al [1993] – even at the 20-th day after the index event – could be explained with temporary functional compensation after MIS.

According to some authors, the MEP amplitudes are a more sensitive marker than CMCT in the view of assessing the damage of the corticospinal tracts as a result of the brain ischaemia. After the acute phase, there might be a facillitation at cortical level, which could allow an increase in the MEP amplitude and may eventually explain the increases in the MEP amplitude at month 3 in our patients. In particular, the MEP amplitudes in the asymptomatic hemisphere achieve the normal values at month 3 and month 12. In the same time, it is known that the minor ischaemic strokes are most likely of lacunar type (i.e., "deep", "subcortical"). The proportion of cortical clinical syndromes in our patients is relatively small and we could hypothesize that the abnormal MEP amplitudes might be present also in distant ischaemic lesion as it was shown earlier [Laloux et al, 1991].

At month 12, even in patients without neurological deficit and without recurrent cerebrovascular accidents, the CMCT is increased in both hemispheres. MEP amplitudes at month 12 are also reduced in the view of the normal values. These later changes are most likely due to the appearance of new asymptomatic structural changes of the corticospinal tracts during the progression of cerebrovascular disease.

Last but not least, following the revealed correlations, we were also able to create predictive models for the outcomes at month 12. For both the CMCT and MEP amplitude, the regression models were based on the initial measures at month 1 and symptomatics (i.e., pertaining to symptomatic or asymptomatic hemisphere). We confirmed our results further by using such probabilistic approach as artificial neural networks modelling. ANN proved to be very useful in the current analysis as it allowed us to assess the role of potential predictors of CMCT and MEP at month 12 as continuous outcomes, without the possible constraints of parametric models (e.g., normal distribution of the outcome, etc.). To note, ANN had been successfully used in other medical fields [Mecocci, 2002; Grossi, 2011; Azarkhish et al, 2012; etc.] and, in neurology, in particular [Mecocci, 2002; Shanthi et al, 2009; for a recent overview see Atanassova & Dimitrov, 2011].

5. Conclusions

This *post-hoc* analysis of one-year follow-up clinical trial data, obtained in 40 patients with minor ischaemic stroke, but without neurological deficit or recurrent cerebrovascular incidents, established a statistically significant dynamics in the MEP and CMCT outcomes after transcranial magnetic stimulation. During the acute phase of the ischaemic stroke (at day 7 in month 1) we performed an initial measurement on the motor cerebral cortex bilaterally and on C7 with consecutive conduction of MEPs by surface electrodes from isometrically slightly contracted muscle *abductor policis brevis* and found prolonged CMCT and reduced MEP amplitudes in the symptomatic hemisphere. By following consecutive measurements at the end of month 3 and month 12, we revealed that the CMCT was increased in both hemispheres and MEP amplitudes were reduced, thus both remaining with abnormal values. At the interim measurement, CMCT were shorter but still abnormal in both hemispheres while the MEP amplitudes were lower, mostly in the symptomatic hemisphere. The changes at the end of the follow-up are most likely due to the appearance of new asymptomatic structural changes of the corticospinal tracts during the progression of the cerebrovascular disease.

We observed a parallel dynamics and found correlations between CMCT and MEP at various times, preserving a significant asymmetry among the two hemisepheres. There was a statistically significant correlation between the initial values of CMCT and MEP and the outcome measurements at month 12. The parametric regression modelling indicated that CMCT outcomes at month 12 can be predicted by the initial values at month 1 and whether or not these have been observed in the symptomatic or asymptomatic hemisphere. The same is valid for the MEP amplitude outcomes at month 12, although the role of the symptomatics as a predictor is with a marginal statistical significance. The probabilistic ANN modelling confirmed the role of early CMCT (month 1) and hemisphere symptomatics in predicting the outcome at month 12. Given the dynamics of CMCT and MEP changes, we could postulate that cerebrovascular disease progression post-MIS may have most likely determined the subclinical damage of the pyramidal tract and its underlying mechanisms.

6. Future directions

Early MEP recordings in acute stroke patients provide valid prognostic information; they may become more useful for specific treatment decisions than presently available MRI surrogate parameters (Wohrle, 2004). The presence of MEP and disruption of the corticospinal tract on diffusion tensor tractography at the early stage of corona radiata infarct are indicative of a high probability of good and poor motor outcome at the chronic stage, respectively. We would suggest that further studies involving more parameters for TMS are warranted (Kwon, 2011).

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