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Functional role of ipsilateral motor areas in multiple sclerosis

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ABSTRACT

Background: In patients with multiple sclerosis (MS), motor tasks are associated with increased activation of ipsilateral motor cortical areas. We examined the role of two ipsilateral motor areas during performance of a simple motor task in MS-patients in relation to their motor impairment and CNS injury.

Methods: Single pulses of transcranial magnetic stimulation (TMS) were used to interfere transiently with neuronal processing in the contralateral (M1_{CONTRA}) or ipsilateral (M1_{IPSI}) primary motor cortex or ipsilateral dorsal premotor cortex (PMd_{IPSI}) during a simple reaction time (RT) task in 26 right-handed patients with moderately severe stable MS and matched healthy controls. Subjects responded to an auditorily presented Go signal as quickly as possible by performing isometric right thumb abductions. TMS was applied 100 msec after the Go signal. Motor impairment was evaluated by hand function tests. CNS injury was assessed by magnetic resonance spectroscopy (normalized N-acetyl-aspartate spectra, NAA/Cr), by the total cerebral T2-weighted MRI hyperintense lesion load, and by corticomuscular latency (CML) to the abductor pollicis brevis muscle.

Results: TMS applied to M1_{CONTRA} slowed RT in patients and controls. In contrast, stimulation of M1_{IPSI} or PMd_{IPSI} increased RT only in MS-patients. In patients, the relative RT changes following TMS over M1_{IPSI} or PMd_{IPSI} did neither correlate with any of the motor function tests, nor with NAA/Cr or total cerebral lesion load. However, RT changes following TMS over M1_{IPSI} correlated inversely with CML.

Conclusions: Recruitment of ipsilateral motor areas may be a functionally relevant, yet limited adaptive response to chronic brain injury in MS-patients.
INTRODUCTION

Whilst much is known about functional compensation after stroke, there is little knowledge about how and to what extent central nervous system (CNS) injury is compensated in multiple sclerosis (MS). There are fundamental differences between stroke and MS concerning the time course and the localization of the CNS pathology: In contrast to stroke with typically one acute ischemic brain lesion, MS is a chronic neurological disease that is characterized by both demyelination and axonal injury occurring widespread across the CNS [1-3] and accumulating over time. As a result, both intra- and interterritorial structural cortical networks lose their topological efficiency and are disconnected progressively.[4] In view of this chronic and global challenge by MS, it is conceivable that compensatory mechanisms differ between MS and stroke, an issue of great clinical interest with regard to potentially differential rehabilitation efforts.

Previous studies have shown T2 weighted magnetic resonance imaging (MRI) pathology to only modestly correlate with MS-induced motor deficits.[5-7] Plastic changes, such as axonal sprouting,[8] collateral pathways circumnavigating lesions in descending motor tracts [8] and cortical adaption,[9, 10] may underlie this functional compensation of brain lesions.[11, 12] These adaptive changes may involve reorganisation of cortical representations on a large anatomical scale. An important piece of evidence in support of this is derived from functional MRI (fMRI) studies.[1, 9, 12-16] For example, patients with MS show expanded activation of the ipsilateral sensorimotor cortex and of the supplementary motor area [1, 9, 13] even when matched with healthy controls for motor performance.[13] However, direct investigation of a role of ipsilateral motor areas in compensation of MS-related injury may be accomplished by employing temporary deactivation techniques, such as transcranial magnetic stimulation (TMS). This approach, also known as virtual lesion...
method,[17] has been widely used to establish specific structure-function relationships.[18]

In the present study, we tested the functional relevance of ipsilateral primary motor cortex (M1) and ipsilateral dorsal premotor cortex (PMd) on performance of a simple right hand reaction time task in MS patients using a virtual lesion approach. We addressed the question of whether these motor areas might be important for the adaptive compensation of motor impairment associated with disease-related brain injury in MS patients.
METHODS

Standard Protocol Approvals and Patient Consents

The study conformed to the principles of the declaration of Helsinki. It was approved by the Ethics committee of the Medical Faculty at the University of Würzburg. All MS patients and control subjects gave their written informed consent for research.

Patients and healthy controls

Twenty-six patients with definite MS aged between 23 and 60 years (38.1 ± 10.5 years, mean ± SD) were recruited from a large outpatient clinic at the Department of Neurology, University of Würzburg. Seventeen of these patients had already been included in a previous study,[19] the experiments of which had been finished several months before the present study. The recruiting physician running the outpatient clinic was naive to the scientific hypothesis of this study. Inclusion of eligible patients was based on their willingness to participate in the study and on availability of the investigators. Because there were no prior assumptions as to the magnitude of any potential effect size between patients and controls, sample size calculation was done in analogy to a prior study in MS patients.[20] MS patients underwent a thorough neurological examination, including expanded disability status scale (EDSS). To be eligible for the study, MS patients had to fulfil the following inclusion criteria: i) age between 18 and 60 years, ii) stable clinical condition within the last three months (i.e. absence of relapse, progression, or changes in therapy), and iii) exclusion of pregnancy. All MS patients were right-handed, according to a modified version of the Edinburgh Inventory. Twenty-six healthy controls were matched for age, sex, and handedness. Patient details are summarized in Table 1.
Transcranial magnetic stimulation (TMS) and EMG recording

Stimulation. Focal TMS was performed using a figure-of-eight shaped magnetic coil (outer diameter of each wing 7 cm) connected to a Magstim 200 stimulator (Magstim, Whitland, Dyfed, UK). The coil was held tangentially to the skull with the handle pointing backwards and laterally at an angle of 45° to the sagittal plane. The optimal position of the magnetic coil for eliciting motor-evoked potentials (MEPs) in the abductor pollicis brevis (APB) muscle of the dominant hand, termed “motor hot-spot”, was assessed over the left motor cortex and digitally recorded with a neuronavigational device (see below). At this optimal site, the resting motor threshold (RMT) was determined. Complete relaxation of the target muscles was continuously monitored by visual and auditory feedback from the surface EMG.

Electromyographic recordings. Surface EMG activity was recorded from the right APB muscle using surface electrodes in a belly-tendon montage. Raw signals were amplified using a differential amplifier (CED 1902, Cambridge Electronic Design, Cambridge, UK) and bandpass-filtered between 1 and 2000 Hz. EMG signals were sampled at 5000 Hz, digitized using an analogue–digital converter (CED 1401 plus, Cambridge Electronic Design, Cambridge, UK) and stored in a laboratory computer.

Neuronavigation and anatomical locations

A neuronavigational device (Brainsight, Rogue Research, Montreal, Canada) was used to increase the fidelity of positioning the magnetic coil over the course of an experiment. Anatomical locations of left primary motor cortex (M1\text{CONTRA}), right primary motor cortex (M1\text{IPSI}), right dorsal premotor cortex (PMd\text{IPSI}), and a midoccipital region (MO) were marked using Brainsight software (Fig. 1 A). The hand primary motor cortex in M1 was identified in axial and sagittal views of the brain according to the landmarks described previously.[21] PMd was considered to be
represented in the posterior part of the middle frontal gyrus, which was located around 2 cm anterior and 1 cm medial to the motor hot spot.[22, 23] MO was marked 6 cm above inion in midline.

Assessment of motor impairment and CNS injury

Motor impairment was assessed in both hands by a test battery consisting of the following items: (i) Maximal tapping rate of the index finger: Two trials of 20 seconds each were performed. The average number of taps per 10 s was taken. (ii) Nine-hole peg board test: The total duration of two trials was taken. (iii) Maximal acceleration of thumb abduction: Acceleration of 20 fastest thumb abduction movements was measured using an uniaxial accelerometer (Model 25A, Endevco Corporation, San Juan Capistrano, CA, USA; voltage sensitivity 5 mV/g). (iv) Force production performance: Subjects performed brisk isometric abductions with the right thumb against a force transducer (Grass CP122A, Grass Instruments CO, West Warwick, RI). Each subject performed 50 metronome paced (0.5 Hz) isometric thumb abductions. The number of successful attempts falling within the defined force window (30% to 40% of the individual maximum force) was taken as a measure for performance (mean of two trials). Patient no. 19 dropped out before completing task iv.

Correlations of motor tests were calculated for each hand separately. Before comparing data from motor function tests between MS patients and controls, results from the dominant and non-dominant hand were transformed to Z-scores to consider superior performance of the dominant hand to that of the non-dominant hand in healthy controls.
Central nervous system (CNS) injury was evaluated using Magnetic Resonance Spectroscopy (subgroup of 14 patients), total cerebral T2-weighted MRI hyperintense lesion load (subgroup of 12 patients), and TMS.

Localized magnetic resonance spectroscopy (MRS) consisted of single voxel spectroscopy measurements by a point-resolved spectroscopy SE sequence (TR / TE = 3000 / 30 ms). Based on axial, coronal and sagittal assessed T2w HASTE images (TR / TE = 2000 / 57 ms, field of view = 512 x 512 mm$^2$, slice thickness 5 mm), a spectroscopy voxel with a total volume of 80 ml was placed such that the corpus callosum was largely covered. For each measurement, two spectra with and without chemical-shift selective water suppression [24] were obtained (96 vs. 20 acquisitions) to allow for eddy-current correction [25] and water scaling. Fixed scanner calibration was confirmed by external in vitro standards. Measurements were performed on a 1.5 Tesla Magnetom Vision system (Siemens Medical, Erlangen, Germany) running on Numaris/4 (VA25A) with an eight-channel head coil. The user-independent frequency domain fitting routine by LCModel was used for spectral analysis (for details, see [26]).

The total cerebral lesion load was measured for each patient on T2 weighted MR-sequences (TR / TE = 3780 / 114 ms, 24 slices, voxel size = 1 x 1 x 5 mm$^3$, field of view = 512 x 512 mm$^2$). Volumes were spatially normalized to the Montreal Neurological Institute reference brain using the normalization parameters estimated during segmentation of the T2 scan.[27] Normalized images were written with an isotropic voxel size of 1 mm$^3$. T2 hyperintense lesions were delineated manually using MRlcron software ([28]; http://www.cabiatl.com/micro/mrlcron/).

Corticomuscular latency (CML) to the right APB was assessed by measuring the latencies of MEPs recorded from APB following TMS of the primary motor cortex.
Motor impairment data of 17 MS patients and four healthy controls, MRS data of 14 MS patients and 5 healthy controls, and CML of 17 MS patients and four healthy controls were also used in a study on rapid-onset plasticity.[19]

**Simple Reaction Time (RT) Task**

Subjects were seated in a comfortable reclining chair. An auditorily presented warning signal (duration 0.44 s) was followed at random 2.5 s to 7.5 s interval by a Go signal (duration 0.18 s). Subjects were instructed to respond to the Go signal as quick as possible by performing a brisk isometric abduction with their right thumb against a force transducer. EMG activity was recorded from the right APB muscle. RT was defined as the time between the Go signal and EMG onset (similar to [29]; Fig. 1 B). At the beginning of each experimental session subjects were familiarized with the task. Thereafter, ten test blocks were obtained. The blocks were separated by 1 minute to avoid fatigue. Each block consisted of 30 trials with 10 s intertrial interval. Single pulse TMS was delivered 100 ms after the Go signal with a stimulus intensity of 130% RMT and applied to M1\text{CONTRA}, M1\text{IPSI}, PMd\text{IPSI}, and MO (one site per block) in a pseudorandomized and counterbalanced design. Each area was stimulated twice. Two blocks were performed without TMS.

**Data analysis**

Trials with no EMG signal within 1000 ms were excluded from analysis (0.9 ± 1.8 per 30 trials in controls, 0.7 ± 1.4 in patients, p=0.310; no correlation with any of the measures of CNS injury). Median correct reaction times with and without TMS were identified for each subject. The relative change in RT from the no-TMS baseline and from the MO stimulation site, respectively, was calculated for each stimulation site. For comparison with baseline, median RTs were tested against unity using two-tailed
one-sample t-tests. The false discovery rate correction was applied to correct for multiple comparisons. Effects were considered significant if $p<0.05$. If not stated otherwise, all values are given as means $\pm$ SD.
RESULTS

Demographic and clinical features of MS patients are summarized in Table 1. EDSS scores correlated with the duration of MS (r=0.630; p=0.001).

Simple reaction time (RT) in MS patients and healthy controls

Baseline reaction time. RT without TMS was longer in MS patients (165 ± 36 ms) than in age-matched controls (133 ± 17 ms; p<0.001). The relative RT change also differed in MS patients and controls with TMS applied to MO: RT increased in healthy controls (6±6%, p<0.001), while it even slightly decreased in patients (-3±8%, p=0.050). Because MO is unlikely to be involved in processing the reaction time task, [20, 30] the increase of RT in healthy controls suggests an unspecific effect such as diverted attention. In the patient group, size of RT decrease was associated with baseline RT (r=-0.500; p=0.009) – the slower the reaction at baseline, the more it was shortened by MO stimulation. This speeding effect is explained best by facilitation effects generated by the auditory and tactile stimulation by the TMS coil.[31] This intersensory facilitation may become visible only when RTs are prolonged (MS patients), but not with normal RTs (healthy controls), suggesting a floor effect. To control for these effects, all data were normalized to MO condition as baseline.

Effects of TMS on simple reaction time (RT). RT changes normalized to MO are shown in Fig. 2. TMS changed RT differently over different brain regions in patients and controls. ANOVA with SITE (M1 CONTRA, M1 IPSI, PMd IPSI) as within-subjects factor and HEALTH (MS, Control) as between-group factor revealed a significant SITE x HEALTH interaction (F=7.14, p<0.001). Post-hoc testing showed that TMS increased RT significantly more in patients than in controls when directed to either M1 IPSI (p=0.005) or PMd IPSI (p=0.010). Stimulation of M1 IPSI and of PMd IPSI increased RT in MS patients (9±8 %, p<0.001 and 7±8 %, p<0.001), but not in controls (2±8 %,
p=0.220 and 2±7 %, p=0.220). RT was less prolonged in patients compared to controls with stimulation over M1_{CONTRA} (p=0.030).

**Correlation of RT changes with motor impairment and CNS injury**

Results of the *motor function tests* in both groups are shown in Table 2. MS patients performed worse than controls in the nine-hole peg board test (p=0.002) and in the finger tapping task (p=0.030), but not in the acceleration of thumb abduction (p=0.660) and baseline force window performance (p=0.680). On *MR spectroscopy*, NAA/Cr ratios were reduced in MS patients (1.45 ± 0.13) as compared to controls (1.74 ± 0.19; p=0.002). The median *total cerebral lesion load* in a subgroup of 12 MS patients was 5.5 [0.4 – 55.9] cm³. *Corticomuscular latency (CML)* to the abductor pollicis brevis muscle of the right hand was increased in MS patients as compared to healthy controls (22.7 ± 2.7 ms vs. 20.9 ± 1.3 ms; p=0.004). In MS patients, the relative RT changes following TMS over M1_{IPSI} or PMd_{IPSI} did not correlate with any of the motor function tests, nor with NAA/Cr on MR spectroscopy, nor with the total cerebral lesion load (after exclusion of one outlier). However, RT changes following TMS over M1_{IPSI} correlated negatively with CML in MS patients (r=-0.520, p=0.006, significant after false discovery rate correction for multiple testing of correlations based on the three stimulation sites; Fig. 3).
DISCUSSION

The present study has examined the role of ipsilateral motor areas in a simple reaction time (RT) task performed by the right hand in mild-to-moderately affected MS patients. Disruption of ipsilateral M1 or PMd by TMS increased RT in MS patients, relative to stimulation at MO, but not in healthy controls. Employing a similar TMS interference technique in patients with subacute unilateral ischemic stroke, a previous study [20] showed that TMS directed to the PMd ipsilateral to the moving hand (contralesional in the patients) slowed RT exclusively in patients, but not in matched healthy controls. This suggested that ipsilateral PMd is part of a network compensating for contralateral ischemic lesions of corticospinal projections.[20]. Our data provide direct evidence for a functional role of ipsilateral PMd in MS. In principle, the increase of RT by disrupting ipsilateral PMd could indicate that this structure is functionally recruited in the patients when it is not involved in healthy controls for processing of the same task. Alternatively, ipsilateral PMd may be part of a network processing the simple RT task even in the absence of disease. Deterioration of RT task performance by TMS interference may then arise exclusively in the patients because the disease pathology has reduced redundancy in the remaining network components [32] or has compromised the brain's capacity for rapid compensation.[33] In either case, the present findings indicate that functionally relevant motor compensation may not be limited to brain injury of sudden onset like acute ischemic stroke, but rather include chronic-relapsing neurological disorders with quite distinct pathology and a much slower temporal evolution.

Functional MRI studies in patients with MS have demonstrated enhanced regional activation by simple voluntary movement in ipsilateral M1, in addition to ipsilateral PMd [13, 34]. Prolongation of RT after TMS to ipsilateral M1 confirmed that this region, too, is functionally active in MS. Several previous imaging studies in MS
patients have reported increased activation in ipsilateral sensorimotor cortex during simple motor tasks.[1, 9, 12, 14, 15, 35] The magnitude of ipsilateral sensorimotor cortex activation during simple finger movements was correlated with white matter lesion load of the hemisphere contralateral to the moving limb [1] or to decreases in brain NAA.[9] Similarly, in subacute stroke patients, analysis of a functional index of ipsilateral brain activation as well as of motor performance of the affected hand suggested greater TMS interference effects in more severely affected patients.[20] In view of these findings, it is perhaps surprising that we did not find statistically significant correlations between RT changes following TMS over M1_{IPSI} or PMd_{IPSI} on the one hand and any of the motor function tests, NAA/Cr ratio or cerebral lesion load on the other hand. One explanation might be that MRS parameters from brain imaging and cerebral lesion load do not reflect injury in the spinal cord, which may itself prolong RT. Of note, however, RT changes following TMS over M1_{IPSI} were inversely correlated with CML, i.e. the more affected the pyramidal tract to the dominant hand in MS patients, the less prolongation of RT occurred after TMS directed to ipsilateral M1. Likely, the inverse correlation of CML and the lack of correlation of motor function tests and NAA/Cr ratio with RT changes may indeed point to an important difference between stroke and MS: In MS, the compensating brain regions are also structurally affected by disease pathology. The capacity of ipsilateral M1 to compensate dysfunction of the contralateral corticospinal output system may decrease with higher regional injury.[36] Therefore, the interpretation of such correlations is ambiguous even in the hypothetical case of strictly regional compensation. For example, a previous study has shown that greater diffuse central brain injury was associated with higher indices of regional activation even with matched performance.[13] This may indicate that recruitment of brain regions can be more intense and more extended as a sign of more severe impairment, as if indicating
greater “demand”. Alternatively, increased activation may result from a lesser
capability of the compensating substrate due to accumulation of lesions. These two
possibilities need not be mutually exclusive – however, they lead to opposite
predictions of the results of virtual lesion studies: More recruitment by greater
“demand” would predict that a virtual lesion impairs behavioural performance in a
given task in proportion to the severity of the remote focal brain injury. The alternative
hypothesis would be that the effect of experimentally disrupting a compensating brain
region will decrease with its neuronal lesion load. In the latter case, this region might
nevertheless show increased fMRI activation, but lack full functional potency. The
inverse correlation between RT changes induced by TMS over M1_{IPSI}, and CML in
MS patients favours the latter hypothesis. However, as noted above, the decrease of
RT task performance by TMS interference may be sensitive to the functional
compensatory capacity of the entire canonical motor network participating in the
processing of the RT task of which ipsilateral M1 may only be a processing node. This
hypothesis appears unlikely, since in this case the inverse correlation would reflect
progressively increasing compensatory power of the entire motor reaction network
with increasing CNS injury. Therefore, our findings favour a model in MS in which
ipsilateral motor areas might be functionally recruited as an adaptive response to
chronic brain injury in MS patients, yet with possibly limited capacity in more
advanced disease stages. A different scenario appears to be present in chronic stroke
patients, where a TMS interference over ipsilateral M1 similar to the one used in the
present study did not lead to any prolongation of RT in the previously paretic
hand.[29] Presumably, in this case the remaining motor network has retained the full
capacity to rapidly compensate the effect of disrupting ipsilateral M1.

Interpretation of our data is limited by the fact that we only probed right hand function
in our subjects and patients. We do not have direct information about the role of the
left M1 and PMd in the same task performed with the left hand. Thus, recruitment of right PMd could be a lateralized adaptive response of the right rather than ipsilateral PMd. However, while a dominant role of the left PMd is known for action selection,[33] there appears to be no such lateralization for the RT task used here.[33] Another issue might be that TMS was applied at a fixed interval of 100 ms after the Go signal [20, 29] despite different baseline RTs in the patients as compared to the control group. However, the delay in RT is known to increase the closer the time of TMS approaches the expected time of reaction onset.[37] Given longer baseline reaction times in MS patients as compared to controls, this would predict increased TMS effects in the controls. In contrast, RT increased in the patient, but not in the control group following TMS over M1$_{IPSI}$ or PMd$_{IPSI}$. Thus, our results are unlikely to be confounded by different relative timings in patients and controls.

Functional recruitment of ipsilateral motor areas might be an adaptive response to chronic brain injury in MS patients which possibly differs from that in stroke patients. Because compensation may have limited capacity in more advanced MS stages, rehabilitation therapy may have to be tailored to the stage of MS in the individual patient.
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Figure legends

Figure 1: (A) Sites of single pulse TMS in relation to brain anatomy as illustrated in a structural MRI of one subject. Brain surface reconstruction at 6 mm below the dura mater as viewed from above. Right side corresponds to the subject's right side. (B) Schematic overview of the simple reaction time (RT) experimental procedure.

Figure 2: Effect of site of TMS intervention on relative changes of simple reaction time (RT) (%) in 26 MS patients (dark grey columns) and 26 matched control subjects (light grey columns). PMd_{IPSI}: ipsilateral (right) dorsal premotor cortex; M1_{IPSI}: ipsilateral (right) primary motor cortex; M1_{CONTRA}: contralateral (left) primary motor cortex. Error bars indicate the standard error of the mean (SEM). Double asterisks indicate significant difference from baseline (two-tailed, one-sample t-test) after false discovery rate correction. Single asterisks denote significant differences between MS patients and control subjects.

Figure 3: Correlation of changes of the simple reaction time following TMS over M1_{IPSI} (%) with corticomuscular latency (CML).
Table 1: Clinical characteristics of patients and controls

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</table>

Means 38.3 10.4 Median 2.3  Means 36.5
± SD  ± 10.5 ± 6.1 [range]  [1-6.5] ± SD  ± 11.6

*Patients listed by gender and age

m = male; f = female; EDSS = expanded disability status scale; RRMS = Relapsing-Remitting MS;
SPMS = Secondary Progressive MS; DMT = disease modifying therapy with immunomodulators; GA =
glatiramer acetate; IF = interferon beta; AZA = azathioprine; MIT = mitoxantrone; NAT =
natalizumab; (FTY) = fingolimod; randomized controlled treatment trial: FTY or Placebo.
Table 2: Motor performance in MS patients and controls

<table>
<thead>
<tr>
<th>Motor test</th>
<th>Hand</th>
<th>MS patients</th>
<th>Controls</th>
<th>p value (Z-scores)</th>
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<tr>
<td>Maximal tapping rate of the index finger (taps/10 s)</td>
<td>dominant</td>
<td>46.8 ± 11.0</td>
<td>48.7 ± 6.9</td>
<td>0.020</td>
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<tr>
<td></td>
<td>non-dominant</td>
<td>39.5 ± 7.9</td>
<td>44.3 ± 6.1</td>
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<tr>
<td>Nine-hole peg board test (s)</td>
<td>dominant</td>
<td>25.2 ± 27.9</td>
<td>17.2 ± 1.8</td>
<td>0.002</td>
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<tr>
<td></td>
<td>non-dominant</td>
<td>22.0 ± 7.0</td>
<td>17.8 ± 1.5</td>
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<tr>
<td>Maximal acceleration of thumb abduction (m/s²)</td>
<td>dominant</td>
<td>25.3 ± 11.0</td>
<td>25.5 ± 14.8</td>
<td>0.660</td>
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<tr>
<td></td>
<td>non-dominant</td>
<td>24.1 ± 11.6</td>
<td>26.1 ± 12.8</td>
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<tr>
<td>Force window performance</td>
<td>dominant</td>
<td>28.3 ± 6.0</td>
<td>29.0 ± 6.2</td>
<td>0.680</td>
</tr>
</tbody>
</table>
Figure 1

A

B

Warning signal

Go signal

2.5 to 7.5 s random

10 s intertrial interval

Recording 1 s

Time [s]
Figure 2

Changes of simple reaction time (%)

PMd$_{\text{IPSI}}$  M1$_{\text{IPSI}}$  M1$_{\text{CONTRA}}$

*  **  **
Figure 3

Changes of simple reaction time following TMS over M1\textsubscript{PSI} (%)