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Time-dependent functional role of the contralesional motor cortex after stroke

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ABSTRACT

After stroke, movements of the paretic hand rely on altered motor network dynamics typically including additional activation of the contralesional primary motor cortex (M1). The functional implications of contralesional M1 recruitment to date remain a matter of debate.

We here assessed the role of contralesional M1 in 12 patients recovering from a first-ever stroke using *online* transcranial magnetic stimulation (TMS): Short bursts of TMS were administered over contralesional M1 or a control site (occipital vertex) while patients performed different motor tasks with their stroke-affected hand.

In the early subacute phase (1–2 weeks post-stroke), we observed significant improvements in maximum finger tapping frequency when interfering with contralesional M1, while maximum grip strength and speeded movement initiation remained unaffected. After > 3 months of motor recovery, disruption of contralesional M1 activity did not interfere with performance in any of the three tasks, similar to what we observed in healthy controls.

In patients with mild to moderate motor deficits, contralesional M1 has a task- and time-specific negative influence on motor performance of the stroke-affected hand. Our results help to explain previous contradicting findings on the role of contralesional M1 in recovery of function.

1. Introduction

Impaired motor function after stroke is typically accompanied by altered motor network activation and interaction patterns (Grefkes and Fink, 2014). During movement of the paretic hand, changes in neural activity are not limited to the affected hemisphere, but also occur in the contralesional, i.e., "healthy" hemisphere (Chollet et al., 1991; Ward et al., 2003; Weiller et al., 1992). Yet to date, the functional implications of altered contralesional neural activation remain controversial: on the one hand, data from both animal models and humans suggest a supportive role of the contralesional hemisphere on motor function (Biernaskie et al., 2005; Johansen-Berg et al., 2002; Lotze et al., 2006; Rehme et al., 2011). By contrast, this view is challenged by results from multiple studies emphasizing a potentially maladaptive influence of the contralesional hemisphere, and specifically the contralesional M1 which may exert a functionally relevant inhibition upon the ipsilesional M1 and thereby deteriorate motor function of the paretic hand (Grefkes et al., 2010; Murase et al., 2004; Takeuchi et al., 2012). These contradictory results have been attributed to different levels of motor impairment and varying time points post-stroke, which may affect the neural activation levels in contralesional M1 and their functional implications (please see Grefkes and Ward, 2014 for detailed discussion). For example, the functional role of contralesional M1 may critically depend on the extent of damage to ipsilesional M1 and its descending pathways (Di Pino et al., 2014).

Taken together, these findings highlight the question whether the functional role of the contralesional hemisphere may primarily depend on (i) the stage of cortical reorganization, i.e., time point following stroke, and (ii) which motor task has to be executed by the affected hand.

One way to assess the causal role of a cortical region in a given task lies in applying transcranial magnetic stimulation (TMS) to this region during task performance (i.e., creating a *virtual lesion* by *online TMS)* (Gerloff et al., 1998a, 1998b; Lotze et al., 2006; Pascual-Leone et al.,

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1991). Alternatively, repetitive TMS (rTMS) can be applied *offline* i.e., prior to task performance, making use of aftereffects induced by rTMS. However, these aftereffects have been shown to be inconsistent and sometimes even opposite between subjects (Hamada et al., 2013). Conversely, online TMS directly depolarizes neural tissue, thereby transiently deteriorating the task-induced fine-tuned neural activation, which in turn results in altered task performance during the time of stimulation (Walsh and Cowey, 2000) and represents a well-established and safe experimental approach (e.g., Gerloff et al., 1998a, 1998b; Lotze et al., 2006; Rossi et al., 2009; Schluter et al., 1998). As behavioral and neural effects are time-locked to the stimulation period without relevant carry-over effects, online TMS allows testing several tasks and areas within the same experimental session, yielding a better balancing of verum and control stimulation, which is hardly possible when using offline rTMS designs with repeated application of protocols on the same day (for further details see Rossi et al., 2009). Such a setup is especially useful in time-sensitive and dynamic conditions which may change over days, e.g., (sub-) acute stroke.

Therefore, in order to further our insights into the task- and time-dependent functional role of the contralesional M1 after stroke, we here applied online TMS to the contralesional M1 of recovering stroke patients during the execution of three motor tasks of varying motor demands. In a cross-over, sham-stimulation controlled, longitudinal design, 12 first-ever stroke patients were tested for (i) maximum grip strength, (ii) maximum index finger tapping frequency, and (iii) speeded movement initiation in a simple reaction time task. In order to probe time-dependent effects, patients were tested twice, i.e., in the early subacute phase (1–2 weeks post-stroke) and in the early chronic phase (3–6 months post-stroke). In addition, a group of 14 healthy age-matched controls served as physiological reference for motor performance and TMS intervention effects. Since simple motor tasks typically rely on activation within M1 contralateral to the moving hand, we hypothesized that interfering with M1 activity ipsilateral to the moving hand would not affect motor performance in healthy participants. In contrast, we expected that interfering with the contralesional "healthy" M1 modulates task performance in stroke patients, especially in the early subacute phase when contralesional activity is typically upregulated (Rehme et al., 2011; Ward et al., 2003). Moreover, we hypothesized that TMS interference with contralesional M1 may have task-dependent effects, since the level of bilateral neural activity (extending to contralesional M1), has been shown to strongly depend on the utilized motor task (Rehme et al., 2012).

2. Materials and methods

2.1. Subjects

Twelve patients (mean age: 69.3 years ± 11.4 years (SD); 4 female; 1 left-handed) suffering from a first-ever ischemic stroke that caused a mild to moderate unilateral hand motor deficit (NIHSS score: 4.1 ± 1.9, range: 1–7) were recruited from the Department of Neurology, University Hospital of Cologne. Eight of twelve originally included patients could be re-assessed at a chronic stage > 3 months after stroke (158.5 days ± 67.3 days post-stroke).

Inclusion criteria were: (i) age 40–90 years; (ii) ischemic stroke as verified by diffusion-weighted magnetic resonance imaging (DWI); (iii) time elapsed from symptom onset < 14 days (average: 5.0d ± 3.2d, range: 1–10 d); (iv) unilateral hand motor deficit; (v) absence of severe aphasia, apraxia, and neglect; (vi) no visual field deficit; and (vii) no other neurological disorders. Exclusion criteria were: (i) any contraindication to TMS (e.g., epilepsy); (ii) infarcts in multiple territories; (iii) hemorrhagic stroke, and (vi) inability to perform the motor tasks because of severe hand weakness. Patient details are given in Table 1.

14 healthy controls (61.8 years ± 6.6 years; 9 female; 1 left-handed) were enrolled in the study. 5 out of 11 right-handed patients suffered from paresis of the non-dominant (left) hand. Accordingly, 5 out of 13 right-handed controls were tested with their non-dominant (left) hand. Furthermore, as the left-handed patient presented with a paretic dominant (left) hand, the left-handed control also performed the tasks with the dominant (left) hand. No significant age differences were evident when comparing patients and controls tested with the right hand (patients: 68.7 ± 11.8 years; controls: 61.9 ± 6.7 years; $p = 0.195$, independent t-test) nor for subjects performing the tasks with the left hand (patients: 69.8 ± 12.1 years; controls: 61.7 ± 7.0 years; $p = 0.183$, independent t-test).

All participants provided informed written consent before inclusion. The study was approved by the local ethics committee at the University of Cologne and it was performed in accordance to the Declaration of Helsinki.

2.2. Experimental design

TMS effects on motor performance were assessed using a within-subject cross-over design, i.e., all patients performed all motor tasks during both M1 and control stimulation during the same session. Recording both stimulation conditions in the same session has the advantage that a comparable behavioral readout is obtained, in contrast to offline rTMS where control and M1-stimulation have to be performed on different days or across different subjects due to the lasting influence on cortical excitability. This seems particularly important since subacute stroke patients may show improvements in motor function at a day-to-day rate. Of note, the order of stimulation, i.e., M1 and control stimulation, was counterbalanced across subjects.

During the maximum finger tapping task and the simple reaction time task, the performing hand was fixed to the table using two Velcro straps placed at the wrist and metacarpophalangeal joints. Hence, movements were constrained to the fingers in order to reduce the variability of task execution, which seems particularly important regarding potential changes in movement patterns compensating for loss of function after stroke (Buma et al., 2013). During the assessment of maximum grip strength, the Velcro strap placed over the metacarpophalangeal joints was removed so that subjects could hold the grip force sensor in a physiological and comfortable position.

Visual cues for all motor tasks were presented using Presentation® software (Version 0.70, www.neurobs.com), which also recorded keyboard motor responses for the simple reaction time and maximum finger tapping task. Maximum grip force was recorded using LabChart version 6.0 (ADInstruments Ltd., Dunedin, New Zealand) and analyzed via in-house MATLAB software.

All participants performed three different motor tasks probing different aspects of motor abilities in a highly standardized fashion time-locked to the brief TMS pulse trains. Each motor task was tested in several blocks of trials, and blocks were randomized across and between conditions (control-/M1-stimulation) to control for learning effects and fatigue.

2.3. Maximum finger tapping frequency task

This task was used to test fastrepetitive movements. Subjects performed vertical index finger tapping movements (approximately 2 cm in height, limited by a metacarpophalangeal Velcro strap) at maximum speed on a computer keyboard button upon a visual cue (trial duration: 3 s). A total of 10 assessments were recorded in 2 blocks with 5 trials for each condition (control stimulation, M1-stimulation).

2.4. Maximum grip strength task

This task was used to test maximum grip force generation. Maximum grip strength was assessed with a digital dynamometer (ADInstruments Ltd., Dunedin, New Zealand, connected to LabChart), upon a visual cue (trial duration: 3 s). A total of 9 assessments were performed in 3 blocks with 3 trials for each condition (i.e., 9