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Microstructure of the superior longitudinal fasciculus predicts stimulation-induced interference with on-line motor control

Borja Rodríguez-Herreros [a,c,h,1], Julià L. Amengual [b,c,1], Ane Gurtubay-Antolín [a,b], Lars Richter [d], Philipp Jauer [d], Christian Erdmann [c,e], Achim Schweikard [d], Joan López-Moliner [a,f], Antoni Rodríguez-Fornells [a,b,f,2], Thomas F. Münte [c,g,*,2]

[a] Department of Basic Psychology, Universitat de Barcelona, 08035 Barcelona, Spain
[b] Cognition and Brain Plasticity Unit, Bellvitge Research Biomedical Institute (IDIBELL), Hospitalet de Llobregat, 08907 Barcelona, Spain
[c] Department of Neurology, University of Lübeck, 23538 Lübeck, Germany
[d] Institute for Robotics and Cognitive Systems, University of Lübeck, 23538 Lübeck, Germany
[e] Department of Neuroradiology, University of Lübeck, 23538 Lübeck, Germany
[f] Institució Catalana de Recerca i Estudis Avançats (ICREA), 08010 Barcelona, Spain
[g] Institute of Psychology II, University of Lübeck, 23538 Lübeck, Germany
[h] LREN & Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, Université de Lausanne, 1011 Lausanne, Switzerland

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ABSTRACT

A cortical visuomotor network, comprising the medial intraparietal sulcus (mIPS) and the dorsal premotor area (PMd), encodes the sensorimotor transformations required for the on-line control of reaching movements. How information is transmitted between these two regions and which pathways are involved, are less clear. Here, we use a multimodal approach combining repetitive transcranial magnetic stimulation (rTMS) and diffusion tensor imaging (DTI) to investigate whether structural connectivity in the 'reaching' circuit is associated to variations in the ability to control and update a movement. We induced a transient disruption of the neural processes underlying on-line motor adjustments by applying 1 Hz rTMS over the mIPS. After the stimulation protocol, participants globally showed a reduction of the number of corrective trajectories during a reaching task that included unexpected visual perturbations. A voxel-based analysis revealed that participants exhibiting higher fractional anisotropy (FA) in the second branch of the superior longitudinal fasciculus (SLF II) suffered less rTMS-induced behavioral impact. These results indicate that the microstructural features of the white matter bundles within the parieto-frontal 'reaching' circuit play a prominent role when action reprogramming is interfered. Moreover, our study suggests that the structural alignment and cohesion of the white matter tracts might be used as a predictor to characterize the extent of motor impairments.

Introduction

One of the main functions of the brain is the on-line monitoring and control of movements. The apparent ease with which we perform even complex movements belies the abundant neural operations that are involved in this process, including several hierarchical levels of the visual and the motor system. Numerous studies have implicated the posterior parietal cortex (PPC) in the on-line control of a movement after its initiation (see Andersen et al., 1997 for review). The role of the intraparietal sulcus (IPS), a specific subregion of the PPC, in monitoring visually-guided grasping (Tunik et al., 2007) and reaching movements (Clower et al., 1996) has been widely supported by neurophysiological (Sakata et al., 1995) and brain imaging evidence (Culham et al., 2003; Frey et al., 2005). Seminal studies in monkeys suggest that parieto-frontal circuits that link the medial intraparietal sulcus (MIP in monkeys) and the dorsal premotor cortex (PMd) are thought to sustain the visuomotor transformations for the on-line control of reaching (Caminiti et al., 1996; Johnson and Ferraina, 1996; Johnson et al., 1993). In human neuroimaging studies, extensive activation of a putative homologue of MIP area, called medial intraparietal sulcus (mIPS), and the PMd have been reported during reaching and pointing movements (Colebatch et al., 1991; Desmurget et al., 2001; Kertzman et al., 1997). Many mIPS neurons discharge with changes in the location of the target relative to the hand, i.e., they scale with the extent of the 'motor error' (Andersen and Buneo, 2002). They respond not only before movement onset but also during its execution, which allows the mIPS to integrate sensory input with efference copies of

* Corresponding author at: Department of Neurology, University of Lübeck, 23538 Lübeck, Germany.
E-mail address: thomas.muente@neuro.uni-luebeck.de (T.F. Münte).
[1] These authors contributed equally to this work.
[2] These authors share senior authorship.

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outgoing motor commands. This arrangement suggests that the mIPS is a key region that provides PMd with a constant flow of neural signals associated with a continuously updated estimate of the motor error. Nonetheless, how mIPS transfers to PMd the sensorimotor information required for an appropriate supervision of reaching and which structures are used remain to be elucidated.

Just as the size and capacity of roadways can regulate the flow of traffic between different cities, the architecture of white matter (WM) tracts between different brain regions determines the amount and quality of information transmitted between these regions (Behrens and Johansen-Berg, 2005). Previous neuroanatomical studies revealed activity in the ventral aspect of the mIPS as well as the rostral part of PMd when updating a pre-specified motor instruction, suggesting a cortico-cortical parieto-frontal pathway between these areas (Johnson and Ferraina, 1996; Wise et al., 1997). In this sense, the superior longitudinal fasciculus (SLF) is the major cortical association fiber pathway linking parietal and frontal cortices in both humans and monkeys. It is subdivided into three different components (Petrides and Pandya, 1984): In humans, SLF I is medially situated in the white matter of the superior parietal lobule (Brodmann area (BA) 5) and the superior frontal gyrus (BA 8, 9, 32) (Makris et al., 2005). The second branch of the superior longitudinal fasciculus (SLF II) originates from the intraparietal sulcus and inferior parietal lobule and terminates in the superior sector of BA 6 (PMd) and the posterior regions of the inferior frontal gyrus (Schmahmann et al., 2007; Thiebaut de Schotten et al., 2012). Finally, the SLF III is further lateral and ventral and is located in the white matter of the parietal and frontal operculum (Schmahmann and Pandya, 2006). The SLF II has thus been postulated as an important neural tract within the premotor-parietal network that connects the IPS and the PMd (Boorman et al., 2007; Thiebaut de Schotten et al., 2012). In this regard, virtual *in vivo* dissections using diffusion imaging tractography have associated the anatomical asymmetry of the SLF II, unlike the SLF I and III, to the behavioral performance on visuospatial attention tasks (Thiebaut de Schotten et al., 2011).

In the present study, we tested whether the properties of the SLF II modulate the degree of interference on the ability to update a movement. We tested this hypothesis by using high-resolution diffusion tensor imaging (DTI) in combination with repetitive transcranial magnetic stimulation (rTMS). The rationale for the use of brain stimulation relies on the fact that purely baseline behavioral measures may encompass the integrated function of multiple brain regions. Rather, the specific impact of rTMS application in on-line motor control could be a more informative and isolated measure of a certain brain function with which to compare structural parameters (Boorman et al., 2007). A brief burst of TMS pulses over the mIPS has been shown to induce short-lived disruptions of the capacity to correct reaching movements (Della-Maggiore et al., 2004; Desmurget et al., 1999). There are an overwhelming number of studies supporting that the application of trains of rTMS can either increase or decrease the cortical excitability of the targeted region depending on the stimulation conditions, and consequently affect the behavior supported by this brain area (see Siebner et al., 2009 for review). Moreover, modulation of the neural activity is not confined to the target area but can also extent to other connected brain regions (Gerschlager et al., 2001; Siebner et al., 2000; Wassermann et al., 1998). With the advent of in vivo DTI quantitative metrics based on water diffusion, neuroimaging studies have been able to evaluate morphological changes in microstructural architecture (Darquie et al., 2001; Kimiwada et al., 2006; Le Bihan et al., 2006). By measuring fractional anisotropy (FA) — a measure which is thought to reflect the integrity and fiber density of WM fibers — we predict that an rTMS-induced breakdown of the mIPS function will affect the ability to adjust ongoing reaching movements, and that this behavioral impact might hint in the structural properties of parieto-frontal fibers linking mIPS with PMd.

Materials and methods

Participants

Twenty-four healthy right-handed volunteers (12 women; mean age 26.6 ± 4.9 years) participated in this study. All subjects were naïve with respect to the experimental procedures and the hypothesis of the study. Participants had normal or corrected-to-normal visual acuity and reported neither previous nor current neuropsychiatric disorders. Prior to their inclusion in the study, participants provided written informed consent. The study was performed according with the declaration of Helsinki and was approved by the ethics committee of the University of Lübeck. All participants were screened for MRI and TMS compatibility (Machii et al., 2006). The Edinburgh handedness inventory was required to assess right-handedness (Oldfield, 1971). All participants were paid for their participation.

Apparatus and data acquisition

An overview of the experimental setup is shown in Fig. 1. Subjects sat at a table that was 45–50 cm below the eyes. Visual stimuli were generated by an Apple MacBook 2 GHz Quad-Core and displayed on a 17 in. LCD monitor with a refresh rate of 120 Hz and a resolution of 1280 × 1024 pixels (43.3 cm of diagonal viewing size). A 3D marker with infrared LEDs was attached to the index finger tip of the hand in order to track the finger's spatial position during reaching movements. The marker was connected to and tracked by a high-speed real-time optical tracking system (Atracsys accuTrack 250, Atracsys LLC, Inc.). The spatial resolution was 0.01 mm in each spatial axis. The sampling rate of the recording was set to 200 Hz. For each movement, finger coordinates were recorded from 200 ms before the stimulus was presented on the screen (see below for a full description of the stimuli), and ended 300 ms after the end of the movement. Missing samples in recorded coordinates due to erratic orientations of the infrared marker were interpolated off-line (Tunik et al., 2005) by using spline functions (Liu and McMillan, 2006). Time series of the recorded individual position coordinates were processed with a low-pass Butterworth filter (cutoff frequency of 6 Hz) for further analysis (Mason et al., 2001; Rodriguez-Herreros and Lopez-Moliner, 2011). Velocity was derived from the smoothed time series of the marker's position by first numerical differentiation.

Stimuli and procedure

The experimental task (Adjusting Condition, AC) consisted in performing a reaching movement towards a visual target located on the screen. Prior to the initiation of the trial, participants were required to move the index finger to a red bulge situated 30 cm in front of the screen and localizable by sensory tactile feedback. After 1000 ms with the finger placed at this starting point, a small white fixation point was automatically shown as a warning signal in the center of the screen (Fig. 1A). Subjects were asked to fixate the point until a target appeared in the center of the screen (30 mm in diameter green dot), 30 cm above the surface of the table. In order to avoid participants from predicting the target onset, a variable foreperiod (300 or 800 ms) between the appearance of the fixation point and the target onset was used. Trials without (66%) and with (34%) displacement were presented in pseudorandom order. In undisplaced trials, the target remained static in the center of the screen. In contrast, displaced trials showed an unexpected lateral displacement of the target position at the time of the movement onset, 10 cm lateral to the initial position. The displacement was timed at the movement onset to assure that participants did not have relevant information about the final position of the target during the initial planning of the movement. To this aim, the movement onset was detected by a specific velocity threshold (see Behavioral analysis section) obtained from the infrared data. To discard trials