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Research Report

Action-related dynamic changes in inferior frontal cortex effective connectivity: A TMS/EEG coregistration study



Marco Zanon ^{a,b,*}, Sara Borgomaneri ^{a,b} and Alessio Avenanti ^{a,b,*}

^a Centro studi e ricerche in Neuroscienze Cognitive, Dipartimento di Psicologia, "Alma Mater Studiorum" Università di Bologna, Campus di Cesena, Cesena, Italy ^b IRCCS Fondazione Santa Lucia, Roma, Italy

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ABSTRACT

Humans show exquisite abilities to perform versatile finger movements. The inferior frontal cortex (IFC) plays a pivotal role in the visual control of such movements through connections with other sensorimotor regions. Yet, the dynamics of IFC effective connectivity during action execution are still poorly understood. Using single-pulse TMS and simultaneous EEG recording (i.e., TMS-EEG coregistration), we stimulated the left posterior IFC at rest and during a visuomotor task. We recorded TMS-evoked potentials (TEPs) to assess action-related changes in IFC connectivity and localized their sources using sLOR-ETA. We found two key time windows at ~60 and ~80 msec after IFC stimulation in which TEPs were modulated by task conditions in remote electrodes. In the first time window (~60 msec), action-related changes in TEP amplitudes were observed over frontal and temporo-parietal electrodes, reflecting increased IFC connectivity with fronto-parietal motor areas and decreased IFC connectivity with visual occipito-temporal areas. In the second time window (~80 msec), action-related TEP increases were observed in frontal, temporal and parietal regions partially overlapping with the default-mode network. No similar effects were observed when TMS was administered over a non-motor control area (the left posterior superior temporal sulcus, STS). These findings highlight dynamic changes in IFC connectivity with motor, sensory and default-mode networks. They suggest sequential stages of task-related changes in IFC connectivity possibly related to controlling and sensing actions and inhibiting default-mode brain activity during motor performance. © 2018 Elsevier Ltd. All rights reserved.

E-mail addresses: marco.zanon2@unibo.it (M. Zanon), alessio.avenanti@unibo.it (A. Avenanti). https://doi.org/10.1016/j.cortex.2018.08.004

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^{*} Corresponding authors. Centro studi e ricerche in Neuroscienze Cognitive, Dipartimento di Psicologia, "Alma Mater Studiorum" Università di Bologna, Campus di Cesena, Viale Europa 980, 47521 Cesena, Italy.

1. Introduction

The ability to perform accurate and versatile hand movements is fundamental for everyday interactions with the environment. The inferior frontal cortex (IFC; including the ventral premotor cortex and posterior part of the inferior frontal gyrus) plays a pivotal role in the motor control of individual fingers during skilled hand actions (Castiello, 2005; Davare et al., 2006, 2011; Grafton, 2010). The IFC acts as part of a larger fronto-parietal action network involved in generating motor commands and predicting the sensory consequences of performed actions (Borra & Luppino, 2017; Castiello, 2005; Christensen et al., 2007; Davare et al., 2011; Gerbella, Belmalih, Borra, Rozzi, & Luppino, 2011; Fiori, Chiappini, & Avenanti, 2018). A key concept in modern network science is that neural networks reconfigure in systematic ways to accommodate task demands (Avena-Koenigsberger, Misic, & Sporns, 2017; Bortoletto, Veniero, Thut, & Miniussi, 2015; Gonzalez-Castillo & Bandettini, 2018; Morishima et al., 2009). In line with this concept, studies have shown that motor performance is associated with reorganization of functional connections within the action network (Jin, Lin, & Hallett, 2012; Volz, Eickhoff, Pool, Fink, & Grefkes, 2015). However, how the IFC dynamically exerts its causal influence within and beyond this network during motor performance remains poorly understood, and the goal of our study was to answer this outstanding question.

IFC interactions with sensory networks and the defaultmode network (DMN) are of particular interest. Functional connections from the IFC to posterior sensory networks represent an essential component in current theories of motor control. These theories suggest that efference copies of the motor commands (generated in the frontal cortex) are sent to sensory regions, providing information about the expected sensory consequences of the movement (Franklin & Wolpert, 2011; Wolpert & Kawato, 1998). Imaging studies have suggested top-down modulation exerted by the IFC and other premotor regions over posterior sensory cortices during action execution (Christensen et al., 2007; Cui et al., 2014; Kilintari, Raos, & Savaki, 2014; Voss, Ingram, Haggard, & Wolpert, 2006). However, because of their intrinsically low temporal resolution and correlational nature, these studies failed to capture dynamic causal interactions from the IFC to other sensorimotor regions at the millisecond time scale.

The IFC is also assumed to interact with the DMN during action execution. Performing motor tasks increases activity in the IFC and other components of the action network (taskpositive regions) and reduces activity in a separate set of midline and temporo-parietal regions (task-negative regions) constituting the DMN (Fox et al., 2005, 2009). Studies have commonly reported that neural activity in the DMN is anticorrelated with that of task positive-regions, raising the possibility that the action network and the DMN continuously interact and exchange information (Fox & Raichle, 2007; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009). Yet, there is currently little neurophysiological evidence of these dynamic interactions as they unfold during action execution.

To provide this evidence, in the present study, we sought to investigate the dynamics of IFC effective connectivity during action execution by simultaneously combining online transcranial magnetic stimulation (TMS) and electroencephalography (EEG), namely TMS-EEG coregistration (Ilmoniemi et al., 1997; Miniussi & Thut, 2010). In the main experiment, we administered single pulses of TMS over the left IFC and concurrently recorded EEG signals. We traced remote neurophysiological effects of IFC stimulation by assessing the spatio-temporal distribution of TMS-evoked potentials (TEPs). TEPs induced by IFC stimulation (IFC-TEPs) were recorded while participants performed a visuo-motor task requiring them to execute individual repeated finger movements in response to a visual cue (Move) or while they remained at rest (Rest). Larger (or smaller) TEP amplitudes over local and remote brain regions are thought to reflect an increase (or decrease) in influence of the stimulated area over those regions (Ferreri & Rossini, 2013; Ilmoniemi et al., 1997; Miniussi & Thut, 2010). Thus, movement-related increases/decreases in the amplitude of IFC-TEPs can be used as proxies for changes in IFC effective connectivity due to action execution.

The action network reconfigures and increases the strength of task-relevant functional connections during motor performance (Jin et al., 2012; Volz et al., 2015), and the IFC, in particular, is thought to exert task-related, time-varying inhibitory and excitatory influences over interconnected areas (Davare et al., 2008, 2011; Fiori et al., 2016, 2017). In light of this, we expected that IFC-TEPs over motor and remote regions would differ between the Move and Rest conditions, reflecting movement-related changes in IFC effective connectivity (Bortoletto et al., 2015; Morishima et al., 2009). Specifically, we expected an action-related increase in IFC-TEPs over fronto-parietal motor regions, reflecting the generation of motor commands within the action network. Moreover, based on theories of motor control, we expected to find actionrelated suppression over posterior sensory regions, possibly reflecting prediction of the sensory consequences of performed actions. We expected these TEP modulations underlying sensorimotor processing to occur in a relatively early time window after stimulation and to show some degree of site-specificity (i.e., they were expected to be greater following stimulation of the IFC than following stimulation of a control area that is not directly involved in action execution).

Lastly, based on previous TEP studies showing that TMS over motor regions can reveal long-latency signal propagation in temporo-parietal areas overlapping with the DMN (Litvak et al., 2007), and neuroimaging evidence of anticorrelated neural activity in the action and default-mode networks (Fox & Raichle, 2007; Uddin et al., 2009), we expected to find action-related changes in IFC-TEPs over task-negative brain areas at later time windows, possibly reflecting a neurophysiological mechanism for silencing the DMN during action performance.

To test the specificity of IFC causal interactions, in a control experiment, we stimulated the superior temporal sulcus (STS), a (multi)sensory region interconnected with the IFC and the action network via temporo-parietal pathways (Keysers & Perrett, 2004). Although studies have reported action-related activity in the STS, this region is mainly involved in sensing actions, and it lacks motor neurons (Avenanti, Annella, Candidi, Urgesi, & Aglioti, 2013; Keysers & Perrett, 2004; Kilintari et al., 2014). Thus, although one might expect some

action-related changes in TEPs following stimulation of STS, we predicted that action-related modulations would be greater and more extended following stimulation of a key node of the action network (i.e., the IFC) compared to stimulation of the STS. Comparing IFC-TEPs with STS-TEPs allows us to highlight the extent to which action-related changes in IFC connectivity reflect neural interactions that are specific to the target site.

2. Methods

2.1. Participants

Twenty-four healthy volunteers took part in the study. Twelve participants (7 females; age: M = 25 years, SD = 3.4, range = 21-33) were tested in the main experiment assessing TEPs induced by IFC stimulation (IFC-TEPs) and constituted the (experimental) IFC group. The remaining twelve participants (6 females; age: M = 23 years, SD = 2.1, range = 20–28) were tested in the control experiment assessing TEPs induced by STS stimulation (STS-TEPs) and constituted the (control) STS group. All participants were right-handed according to the Oldfield Handedness Inventory (Oldfield, 1971) (mean score ± SD: 81.8 ± 17.4) and none reported any neurological, psychiatric, or other medical problems, nor any other contraindication to TMS or EEG (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of TMS Consensus Group, 2009). Participants had normal or corrected-to-normal visual acuity. The experiment was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained after careful description of the experimental procedure and the two techniques. Permission from the local ethics committee was obtained. All participants completed the experiment and none reported any discomfort or adverse effects during or after the experimental session.

2.2. Experimental procedure

The experiment was carried out in a quiet room. Participants sat in a chair 65 cm in front of a 15" PC screen where visual stimuli were displayed. Both IFC-TEPs and STS-TEPs were recorded in two experimental conditions, i.e., during action execution (Move) and at rest (Rest). Move and Rest conditions were performed in different blocks, and were accompanied by two types of brain stimulation, i.e., active TMS and sham TMS (Fig. 1). In the Move trials, participants were required to perform four abduction-adduction movements with the right thumb, index, or little finger. A short word presented at the center of the screen for 2 sec informed participants about which finger to move. Specifically, 'Pol', 'Ind' or 'Mign' (abbreviations for the Italian words 'Pollice', 'Indice' and 'Mignolo') signaled them to move the thumb, index finger or little finger, respectively. Then the presentation of a scrambled image (lasting 4 sec) worked as a Go signal: participants were instructed to start the repeated movement as quickly as possible when the scrambled image appeared on the screen. Movement execution was self-paced. Participants were instructed to keep the speed of the movement at ~1 Hz in a preliminary phase of the experiment: they were presented with a reference movie of a hand performing the requested repeated movements at 1 Hz. The reference movie was also shown in the inter-block intervals to maintain comparable



Fig. 1 – Schematic representation of the experimental design. A) Schematic representation of trial organization in blocks and mini-blocks. B) Brain areas targeted in the main (IFC) and control (STS) experiments (white dots). C) Beginning sequence (1 complete trial) of a Rest mini-block. D) Beginning sequence (1 complete trial) of a Move mini-block.

speed across the experiment. In the Rest trials, participants were presented with a fixation cross for 2 sec and then with the same scrambled image (lasting 4 sec) as in the Move trials, but were requested to keep their right hand relaxed. In both Move and Rest trials, participants were requested to fixate the screen in front of them. Both hands were placed on a desk and occluded from sight. In both Move and Rest trials, active or sham TMS pulses were delivered at a variable random delay between 1.5 and 2.5 sec after the onset of the scrambled image, that is, during action execution in Move trials. Jittered pulse delays were used to minimize any possible priming effects that could interfere with movement performance. A blank screen was presented in the inter-trial interval, which lasted for a random interval between 1 and 1.5 sec.

Trials were organized in short blocks (mini-blocks) of 6 trials of the same condition, in order to balance task and rest trials throughout the entire experiment, and, on the other hand, avoid inaccuracy due to excessive switches between conditions. The word 'Riposa' or 'Muovi' (corresponding to the English words 'rest' and 'move', respectively) was displayed for 2 sec at the beginning of each mini-block (see Fig. 1C and D) to inform the participant of the subsequent condition. Miniblocks were in turn organized in blocks of 3 Move and 3 Rest mini-blocks (i.e., each block included 18 Move and 18 Rest trials; see Fig. 1A). A short break was allowed between blocks. During the break, participants were exposed to the reference movies and postural adjustments were allowed.

To ensure the same level of attention throughout the experiment, a small black dot could appear 1 sec before the end of image presentation; participants were required to report the presence of the dot by pressing the space bar on a keyboard with their left hand. These vigilance trials were excluded from subsequent analysis.

The type of stimulation (active or sham) was changed every 3 blocks and block order was counterbalanced across participants. Six blocks of trials were presented for each type of stimulation. A total of 108 trials was presented for each condition (Rest and Move) and type of stimulation (active or sham), 18 with the dot and 90 without.

2.3. TMS

Single monophasic magnetic pulses were administered using a 70-mm figure-of-eight coil connected to a Bistim² TMS stimulator (Magstim Company Ltd., UK). Pulse intensity was set at 105% of the individual resting motor threshold (rMT). Although subthreshold TMS intensities can be effective in eliciting TEPs (Kahkonen, Komssi, Wilenius, & Ilmoniemi, 2005), we selected a stimulation intensity just above the rMT to ensure brain responses in local and distal areas (Nahas et al., 2001) while preventing large artifacts due to excessive temporal muscle activation. The rMT was identified in a preliminary phase of the experiment by stimulating the first dorsal interosseous (FDI) cortical representation in the left primary motor cortex and recording motor-evoked potentials (MEPs) in the resting right FDI. The rMT was defined as the lowest stimulator output able to elicit motor-evoked potentials (MEPs) with an amplitude of at least 50 μ V in the FDI in 5 out of 10 consecutive pulses (Rossini et al., 2015). In the IFC group, mean stimulation intensities \pm SD were 42.5% \pm 8.6

(range 28–56%), expressed as a percentage of the maximum stimulator output. In the STS group, mean stimulation intensities were $49.3\% \pm 7.2$ (range 39-60%).

TMS was performed in the active mode by placing the coil tangentially to the target scalp position (either IFC or STS, see next paragraph) with the handle pointing backward. In both groups, sham TMS was also performed to control for auditoryevoked potentials (AEPs) due to the TMS click discharge (Nikouline, Ruohonen, & Ilmoniemi, 1999). Sham stimulation was administered by placing the coil over the same scalp position used for active stimulation, but separated 5 cm from the scalp by means of a Plexiglas cube. Both in active and sham TMS, a thin layer of foam (50 mm) was placed between the coil and the EEG cap to attenuate the bone conduction of sound and to minimize the occurrence of trigeminal stimulation due to vibration of the coil (Zanon, Battaglini, Jarmolowska, Pizzolato, & Busan, 2013). Participants wore earplugs and an adapted masking noise was continuously played though earphones to further attenuate the confounding AEPs (Ter Braack, de Vos, & van Putten, 2015).

2.4. Neuronavigation

The correct position of the coil over the IFC and STS was identified with the SofTaxic Neuronavigation System (EMS, Italy) and marked on the EEG cap to ensure correct coil placement throughout the experiment. Before starting the experiment, the participant's brain was reconstructed in Talairach space based on an MRI template, 4 craniometric landmarks (left and right preauricular points, nasion and inion) and about 80 scalp points digitized with the Polaris Vicra Optical Tracking System (NDI, Canada). This procedure has been proven to ensure a global localization accuracy of roughly 5 mm (Carducci & Brusco, 2012).

In the main experiment, the IFC was targeted in the pars opercularis of the inferior frontal gyrus at the border with the anterior ventral aspect of the precentral gyrus (ventral premotor cortex; Talairach coordinates: x = -52, y = 13, z = 24, corresponding to Brodmann's area 6/44) as this region is involved in the control of fine hand movements and handrelated sensorimotor processing (Avenanti et al., 2012, 2013; Davare et al., 2006; Jacquet & Avenanti, 2015; Johnen et al., 2015; Tidoni, Borgomaneri, di Pellegrino, & Avenanti, 2013; Fiori et al., 2018). Small adjustments were performed to place the intersection of the coil adherent to the scalp, and not directly over the electrodes, to ensure the same distance between the coil and the scalp in all the participants. This resulted in a minimal shift of the coil forward (within the IFC area) that we measured through neuronavigation. The mean \pm SD projection of the coil position in millimeters was $x = -53.1 \pm 2.1$, $y = 15.3 \pm 7.2$, $z = 22.9 \pm 2.5$, estimated in Talairach coordinates on the cortical surface (Fig. 1B).

In the control experiment, the STS was targeted in its posterior aspect (Talairach coordinates: x = -52, y = -53, z = 9, corresponding to BA 21; see Fig. 1B) (Avenanti et al., 2013, 2018; Caspers, Zilles, Laird, & Eickhoff, 2010; Van Overwalle & Baetens, 2009). Although this region is interconnected with the action network, it does not contain motor neurons and it is thought to be involved in sensing performed actions rather than controlling them. As with IFC stimulation, small

adjustments were performed to ensure the same distance between the coil and the scalp in all the participants. The mean \pm SD projection of the coil position in mm was $x = -55.0 \pm 2.5$, $y = -52.7 \pm 1.4$, $z = 9.6 \pm 1.3$, estimated in Talairach coordinates on the cortical surface (Fig. 1B).

2.5. EMG recording and data analysis

Electromyographic (EMG) activity was recorded from the right FDI, abductor pollicis brevis (APB) and abductor digiti minimi (ADM), which were involved in the movements requested in the visuo-motor task (i.e., abduction-adduction of the index finger, thumb and little finger, respectively). Pairs of silver-chloride surface electrodes were placed in a belly-tendon montage over the three muscles with ground electrodes on the wrist. EMG signals were recorded using a Biopac MP-35 (Biopac, USA), band-pass filtered (30–500 Hz), sampled at 5 kHz and stored on a computer for off-line analyses. EMG recordings were visually inspected to discard trials in which the task was not executed correctly (<1% in both experiments). To keep consistency between EMG and TEP analyses, only trials also considered for measuring TEPs (see paragraph "EEG preprocessing and TEP analysis" below) were further analyzed.

For each trial, the EMG signal was root mean square (RMS)transformed, averaged in the 1500-msec time window following the Go signal (i.e., before any TMS) and baselinecorrected using the mean RMS signal in the 1000 msec preceding the Go signal. The baseline-corrected EMG signal was computed for each muscle and condition and submitted to parametric analyses. For each group and muscle, we checked that EMG activity was higher in the Move than in the Rest condition using paired t-tests. Then, to check motor task performance and any potential influence of TMS, EMG activity in the Move condition was analyzed using an analysis of variance (ANOVA) with Group (IFC and STS) as a betweensubjects factor, and Stimulation (active and sham), Movement (Thumb, Index, and Little finger), and Muscle (APB, FDI, and ADM) as within-subjects factors. Post-hoc analysis was carried out using Duncan tests.

2.6. EEG recordings

EEG signals were acquired with a TMS-compatible EEG amplifier (BrainAmp DC, BrainProducts GmbH, Germany) and 60 sintered TMS-compatible electrodes (EasyCap GmbH, Germany) mounted on an elastic cap according the standard 10/5 coordinate system. Three additional electrodes were used to monitor eye movements. Specifically, two electrodes were placed on the outer canthi of both eyes to record horizontal movements (hEOGl and hEORr), whereas an electrode placed beneath the left eye (vEOGl) was used to monitor vertical movements and blinks. Reference and ground electrodes were placed on the right mastoid and AFz, respectively. The impedance was kept below 5 k Ω at all electrodes, and the electrode lead wires were arranged properly in order to reduce the TMS-induced electrical artifact (Sekiguchi, Takeuchi, Kadota, Kohno, & Nakajima, 2011). The recorded signal was low-pass filtered at 1000 Hz (DC-recording), digitized at a sampling rate of 5 kHz and stored on a computer for subsequent off-line analyses.

2.7. EEG preprocessing and TEP analysis

EEG recordings were processed off-line using EEGlab v12.0.2.6b (Delorme & Makeig, 2004) and custom scripts developed in Matlab (R2010a, The Mathworks Inc., USA). First, the fast-rising, fast-falling magnetic artifact and the early TMS-evoked muscle activity were removed by cutting and interpolating (cubic interpolation) the EEG signal in the interval from 1 msec before to 15 msec after TMS administration (Rogasch et al., 2014). A high-pass filter (Hamming windowed sinc FIR filter, cutoff frequency = .01 Hz) was then applied and signals were down-sampled to 1000 Hz. Continuous signals were segmented around the TMS pulse (-100-600 msec) and baseline-corrected to a time period of 90 msec (-100 to -10 msec) preceding TMS administration. Epochs contaminated by non-stereotyped or paroxysmal noise, such as lateral eye-movement or muscle artifacts, were excluded from further analysis by visual inspection. Furthermore, epochs extracted from trials in which the black dot appeared on the screen (vigilance trials) or when participants did not execute correctly the visuo-motor task were also discarded (<1%; see paragraph "EEG preprocessing and TEP analysis" above). In the main and control experiments, these procedures left a mean \pm SD of 80 \pm 6 and 76 \pm 6 epochs per cell, respectively (IFC-TEPs: 77 \pm 11 for RestActive, 80 \pm 6 for MoveActive, 81 \pm 8 for RestSham and 82 \pm 6 for MoveSham; for STS-TEPs: 75 \pm 8 for RestActive, 78 \pm 5 for MoveActive, 75 \pm 9 for RestSham and 76 \pm 8 for MoveSham).

Residual artifacts in the EEG recordings were corrected by performing an independent component analysis with an extended infomax algorithm (Bell & Sejnowski, 1995). Independent components (ICs) were selected and removed when they accounted for residual muscle activity, blinks or decay artifacts, on the basis of their scalp topography and timecourse (Rogasch et al., 2014). ICs with an amplitude peak occurring 15-25 msec from TMS onset and localized over fronto-temporal electrodes in the proximity of the temporalis muscle (i.e., electrodes F7, FT7) were considered as accounting for the residual tail-end of the muscle artifact (Korhonen et al., 2011; Rogasch et al., 2014). TMS-related blinks were corrected by removing components with an amplitude peak occurring at about 100 msec over frontal electrodes (Rogasch et al., 2014). Finally, ICs showing a fast-rising and slow-falling time-course after the TMS pulse were removed to correct for decay artifacts (Rogasch et al., 2014).

For each participant, epochs were low-pass filtered (Hamming windowed sinc FIR filter, cutoff frequency = 100 Hz) and TEPs were computed separately as a function of stimulation (active, sham) and condition (Move, Rest). Since we were primarily interested in the early spread of activity from the IFC, we focused our statistical analysis on EEG data recorded in the interval between 20 and 90 msec after TMS. In this way, we also minimized the confounding influence of muscular, somatosensory and auditory artifacts evoked by the stimulation. Indeed, previous studies have shown that TMS-evoked muscular activity affects EEG recordings up to ~20 msec after the magnetic pulse (Ilmoniemi & Kicic, 2010; Korhonen et al., 2011), that the somatosensory-evoked potentials from trigeminal stimulation are weak and mainly localized in the contralateral hemisphere (Ilmoniemi & Kicic, 2010; Nikouline et al., 1999) and that the AEP peaks at the central electrodes at about 100 msec, with the rising phase starting not before 80 msec (Nikouline et al., 1999). In addition, the combined use of a layer of foam, earplugs and adapted noise was shown to suppress early AEP components and markedly reduce the N100 component (Ter Braack et al., 2015). Even so, it should be noted that Rest and Move trials differed only in the execution of the movements; therefore, auditory, muscular and tactile contaminations associated with active TMS were the same in both conditions.

A two-step procedure was used to identify TEP components in each experiment (IFC and STS group) and assess their modulations due to the different conditions (Flaisch & Schupp, 2013; Schupp, Schmalzle, Flaisch, Weike, & Hamm, 2012). In the first step, each time point (70 time points in the 20-90 msec range) and sensor (60 electrodes) was individually tested using a Stimulation (active, sham) x Condition (rest, move) ANOVA on EEG signals recorded in the main or the control experiment. Significant effects were thresholded at p < .05 for at least 5 continuous time points and two neighboring electrodes to provide a conservative guarding against chance findings (Flaisch & Schupp, 2013; Sabbagh & Taylor, 2000). The minimum duration of 5 msec was chosen considering the rapidly changing dynamics described for TEP components, especially in early stages (Bonato, Miniussi, & Rossini, 2006; Ilmoniemi & Kicic, 2010; Rogasch et al., 2014). The average (across all electrodes) waveform of the F-values for the Stimulation × Condition interaction was considered to set the time boundaries for each significant interval. Specifically, the full width at half maximum (FWHM) was computed for each selected peak in the waveform. In this way, for each experiment, we identified time intervals and sets of neighboring electrodes showing TEP modulations that differed between conditions. To further explore these modulations, in the second step, for each time interval we averaged TEP amplitudes across neighboring electrodes (hereafter Regions) and analyzed mean amplitudes using a repeated-measures ANOVA with Stimulation, Region, and Condition as withinsubjects factors. Post-hoc analysis was carried out using Duncan's test. Direct comparisons between IFC-TEPs and STS-TEPs are reported in the supplemental material online.

2.8. Source analysis

To provide details on the cortical activations evoked by IFC stimulation that possibly underlie action-related differences observed at the sensor-level, current source densities were estimated by projecting scalp potentials to source space by using standardized low resolution brain electromagnetic to-mography (sLORETA) (Nunez et al., 1994; Pascual-Marqui, 2002), as implemented in the LORETA-key software (v20150415, freely available at http://www.uzh.ch/keyinst/loreta). A region of interest (ROI) approach was applied to assess task-related cortical differences in both groups. ROIs were initially selected on the basis of an exploratory whole-brain analysis on source estimates of sham-corrected IFC-TEPs at the critical time windows detected at the sensor-level. Specifically, to remove effects not evoked by brain stimulation, sham-corrected TEPs (active-TEPs minus sham-TEPs)

were computed and differences between Move and Rest conditions at selected latencies were assessed by voxel-by-voxel paired-sample t-tests on the subject-wise normalized sLOR-ETA images. ROIs were identified as clusters of at least 10 contiguous (distance < 20 mm) and significant (p < .05, uncorrected) voxels. For each condition and group, mean cortical activation values across all voxels in each ROI were extracted. It should be noted that the current density estimated by sLORETA has the form of an F statistic, therefore, values are expressed in arbitrary units (Pascual-Marqui, 2002). Differences between conditions were assessed with paired-sample t-tests, separately in the two groups.

3. Results

3.1. Task performance

The inspection of EMG activity in the Move and Rest conditions ensured that participants in the main and control experiments correctly followed the instruction to move their fingers only in the Move condition. As expected, EMG activity was higher in the Move condition than in the Rest condition for all muscles (all p < .001, see Table S1 in the supplemental material online). To test accurate finger selection during the motor task, we performed a Group x Stimulation x Movement x Muscle ANOVA on EMG activity during Move trials. A significant main effect of Movement ($F_{2,44} = 25.14$, p < .001) and, most importantly, a Movement \times Muscle interaction was found ($F_{4,88} = 75.57$, p < .001) which confirmed that the participants accurately selected the target finger. Indeed, the APB, FDI, and ADM showed differential patterns of activity according to their specific engagement in each movement (see Fig. 2).



Fig. 2 – Task-dependent EMG activity. Baseline-corrected RMS of EMG activity recorded in APB, FDI, and ADM during the execution of abduction-adduction movements of the thumb, the index finger, and the little finger. Asterisks indicate significant comparisons: * = p < .05; *** = p < .001. Error bars indicate SE.

EMG activity was not influenced by the type of TMS (active or sham) or the targeted area (IFC or STS), as suggested by the lack of a significant main effect of, or any interactions with, the factors Stimulation and Group (all p > .1; Table S2).

3.2. Exploratory analysis of TEPs induced by IFC stimulation

In the main experiment, TMS over the IFC induced a spread of responses in local and distal cortical areas, which were detected by the concurrent EEG recordings. Overall, IFC-TEPs showed a negative peak at fronto-central electrodes and a posterior positive peak over parietal and occipital regions (Fig. 3B). We investigated differences between IFC-TEPs in Move and Rest conditions, considered as a proxy for changes in IFC effective connectivity related to action execution.

The initial exploratory analysis highlighted three time windows in which the Stimulation (active, sham) x Condition (Move, Rest) interaction was significant in at least two neighboring electrodes (Fig. 3A). Significant effects were initially detected at ~45 msec after TMS (range: 39-47 msec) in two central electrodes (i.e., FC6 and C6) contralateral to the stimulated IFC. More widespread effects were detected in two following time windows: a first interval was found at ~60 msec after TMS (range: 56-67 msec) over fronto-central and bilateral temporo-parietal electrodes; whereas a second significant interval was detected at ~80 msec after TMS (range: 77-86 msec) over fronto-polar and right temporal electrodes. Because of the consistent number of electrodes showing significant effects and the corresponding greater mean F-value (Fig. 3A), we decided to focus only on the 56-67 msec and 77-86 msec time intervals to statistically assess differences in TMS-evoked activity at both the sensor (TEPs) and source (sLORETA) levels.

3.3. Task-dependent modulation of IFC-TEPs in the first interval (56–67 msec)

3.3.1. Sensor-level analysis

In the first interval (56-67 msec), different TMS effects were observed across three scalp regions (frontal regions, and left and right temporo-parietal regions). Visual inspection of Fig. 4 suggests that, across regions, TEPs were generally larger when induced by active rather than sham stimulation. Moreover, the experimental group showed a movement-related increase in TEPs induced by active stimulation of the IFC in the frontal and right temporo-parietal regions, and a reduction in TEP amplitudes in the left temporo-parietal region. These modulations were supported by statistical analyses. We performed a Stimulation (active and sham) x Region (frontal, left and right temporo-parietal) x Condition (Move and Rest) ANOVA on mean values extracted from the frontal (Fp1, AF3, F1, F3, FC1, Fpz, Fz, FCz, Fp2, AF4, F2, F4, FC2, AF8 and F6), left temporo-parietal (FT7, T7, TP7 and CP5), and right tempoparietal (FT8, C6, T8 TP8, CP4, CP6, P2, P4 and P6) electrodes. The analysis showed a series of main effects and interactions, including a significant 3-way interaction ($F_{2,22} = 4.45$, p < .001), indicating different task-dependent TMS effects across regions. To further test this interaction, post-hoc pairwise comparisons were computed to compare Move and Rest conditions across stimulations and regions. TEPs induced by active stimulation of the IFC were larger (more negative) in the Move condition relative to the Rest condition over the frontal region (p < .001). Larger (more positive) TEPs were also detected in the Move condition relative to the Rest condition over right temporo-parietal electrodes (p = .007), whereas TEPs were smaller in the Move condition relative to the Rest condition over the left temporo-parietal region (p = .003). No differences between conditions were found for TEPs induced by sham stimulation (all p > .56).

3.3.2. Cortical sources

The sensor-level analysis of the first time interval showed that, during action performance, IFC-TEPs induced by active TMS were larger in frontal and right temporo-parietal electrodes and reduced in left temporo-parietal electrodes. Task-dependent modulations were specific to active stimulation of the IFC, as they were absent during sham stimulation. These findings suggest that, during action performance, the IFC reconfigures its influence over an extended network of anterior and posterior brain regions. We thus used sLORETA to highlight cortical sources underlying task-dependent (sham-corrected) TEP modulations. sLORETA estimates showed 9 ROIs (Fig. 5 and Table S3).

Four ROIs were found in the frontal cortex and included motor cingulate (ROI_{int1} 1), bilateral dorsal premotor (ROI_{int1} 2 and 3) and right insular areas (ROI_{int1} 4). ROIs_{int1} 1–4 showed larger sLORETA estimates in the Move condition relative to the Rest condition (all p < .03). A different pattern was found in two left occipital extrastriate and anterior temporal ROIs (ROI_{int1} 5 and 7, respectively) and in a right ventral prefrontal ROI (ROI_{int1} 6), which showed reduced sLORETA estimates in the Move condition relative to the Rest condition (all p < .03). Finally, two ROIs were found in the right temporo-parietal region, including the extrastriate visual areas and extending into the inferior and posterior parietal cortex (ROI_{int1} 8), and in a more superior and rostral sector of the posterior parietal cortex extending into the somatosensory cortex (ROI_{int1} 9). Both ROIs showed greater sLORETA estimates for the Move condition than for the Rest condition (all p < .03).

3.4. Task-dependent changes in IFC-TEPs in the second interval (77–86 msec)

3.4.1. Sensor-level analysis

In the second time interval (77–86 msec), different TMS effects were observed in two scalp regions (frontal and right temporoparietal regions; Fig. 6). We performed a Stimulation x Region x Condition ANOVA on mean values extracted from the frontal (AF3, F3, Fpz, Fp2, AF4, AF8, F4, and F6) and the right temporo-parietal (T8 and CP6) electrodes. The analysis showed a series of main effects and interactions including a Condition x Stimulation \times Region interaction ($F_{1,11} = 10.70$, p = .001).

Post-hoc pairwise comparisons showed that TEPs induced by active stimulation of the IFC were larger (more negative) in the Move condition relative to the Rest condition over the frontal region (p = .005). Larger (more positive) TEPs were also detected in the Move condition relative to the Rest condition over right temporo-parietal electrodes (p = .01). No differences



Fig. 3 – EEG responses evoked by TMS over the left IFC (main experiment). A) 2-D plot indicating the time points and electrodes showing significant effects (Stimulation \times Condition interaction) in the first exploratory step of statistical analysis (x-axis: time from TMS pulse in msec; y-axis: electrodes) and mean F-values of the Stimulation \times Condition interaction at each time point across electrodes. In both plots, vertical dashed lines represent the boundaries of the significant intervals. B) Grand average TEPs recorded during rest (Rest) and action execution (Move). TEPs induced by sham stimulation were point-by-point subtracted from TEPs induced by active IFC stimulation. The two significant time intervals (56–67 and 77–86 msec) are highlighted in different colors (blue and purple). The red cross indicates the approximate position of the stimulation site with respect to the EEG sensors. The gray bar indicates the 16-msec interval that was removed and interpolated to exclude the magnetic artifact.



Fig. 4 – Task-dependent changes in IFC-TEPs in the first interval (56–67 msec) after stimulation (main experiment). A) Scalp map for the Stimulation \times Condition interaction (contrast: [MoveActive–MoveSham]–[RestActive–RestSham]). The three electrode sets considered for the analyses are highlighted in different colors. B) Changes in IFC-TEP amplitudes over time for each region (Frontal, L temporo-parietal, and R-temporo-parietal), stimulation (Active and Sham) and condition (Rest and Move). The significant interval is highlighted in blue (56–67 msec), whereas the gray bar indicates the 16-msec interval that was removed and interpolated to exclude the magnetic artifact. Histograms on the right represent mean IFC-TEP amplitudes by region, stimulation, and condition. Asterisks indicate significant comparisons: * = p < .05; ** = p < .01; *** = p < .001. In addition to the Move *vs* Rest comparisons reported in the main text, further post-hoc comparisons are shown. Error bars represent SE.

between conditions were found for TEPs induced by sham stimulation (all p > .23).

3.4.2. Cortical sources

Analysis of sham-corrected sLORETA estimates of cortical sources showed 3 ROIs possibly underlying task-related changes in IFC connectivity (Fig. 7 and Table S4). The three ROIs showed larger sLORETA estimates in the Move condition relative to the Rest condition (all p < .02) and included a ventral site in the mesial prefrontal cortex (ROI_{int2} 1) and two posterior clusters, including bilateral occipito-parietal areas (cuneus/precuneus; ROI_{int2} 2) and right temporo-parietal cortices (ROI_{int2} 3).

In sum, based on the sLORETA estimates of shamcorrected TEPs, the movement-related changes observed after IFC stimulation in the frontal and the right temporoparietal electrodes were likely due to differential activations of prefrontal and parietal sites partially overlapping with, or near to, key nodes of the DMN.

3.5. Task-dependent changes in TEPs induced by STS stimulation

In the control experiment, we recorded TEPs induced by active and sham stimulation of the left STS, which acted as a control site. At ~60 msec following stimulation, STS-TEPs showed a positive peak over left frontal electrodes and a negative peak over right parietal and temporal electrodes (Fig. 8B). We tested differences between STS-TEPs in Move and Rest conditions as a proxy for changes in the effective connectivity of the control region during action execution.

The initial exploratory analysis highlighted a main time interval between 58 and 72 msec when the Stimulation × Condition interaction was significant (Fig. 8A). In particular, a set of fronto-central electrodes (F3, FC3, C3, and CP3) and a set of right temporo-parietal electrodes (C2, C4, C6, FT8, T8, TP8, CP2, CP4, and CP6) were detected. The Stimulation x Region x Condition ANOVA showed a significant three-way interaction ($F_{1,11} = 19.28$, p = .001; Fig. 8C). Post-hoc



Fig. 5 – Task-related changes in current source density in the first interval (56–67 msec) after IFC stimulation (main experiment). Mean sham-corrected activities for Rest and Move conditions were extracted from selected ROIs, at 56–67 msec. The ROIs are shown in different colors and overlaid on a three-dimensional model of a standard brain. Bar plots depict mean values for each ROI in the two experimental conditions. Asterisks indicate significant comparisons: * = p < .05; ** = p < .01. Error bars represent SE.



Fig. 6 – Task-dependent changes in IFC-TEPs in the second interval (77–86 msec) after stimulation (main experiment). A) Scalp map for the Stimulation × Condition interaction (contrast: [MoveActive – MoveSham] – [RestActive – RestSham]). The two electrode sets considered for the analyses are highlighted in different colors. B) Changes in IFC-TEP amplitudes over time for each region (Frontal, and R-temporo-parietal), stimulation (Active and Sham) and condition (Rest and Move). The significant interval is highlighted in purple (77–86 msec), whereas the gray bar indicates the 16-msec interval that was removed and interpolated to exclude the magnetic artifact. Histograms on the right represent mean IFC-TEP amplitudes by region, stimulation, and condition. Asterisks indicate significant comparisons: * = p < .05; ** = p < .01; *** = p < .001. In addition to the Move vs Rest comparisons reported in the main text, further post-hoc comparisons are shown. Error bars represent SE.



Fig. 7 – Task-related changes in current source density in the second interval (77–86 msec) after IFC stimulation (main experiment). Mean sham-corrected activities for Rest and Move conditions were extracted from selected ROIs, at 77–86 msec. The ROIs are shown in different colors and overlaid on a three-dimensional model of a standard brain. Bar plots depict mean values for each ROI in the two experimental conditions. Asterisks indicate significant comparisons: * = p < .05; ** = p < .01. Error bars represent SE.

comparisons further showed that TEPs induced by active stimulation of the STS were larger (more positive) in the Move condition than in the Rest condition in the right temporoparietal electrodes (p = .008). In the fronto-central electrodes, TEPs induced by active stimulation were non-significantly larger (more negative) in the Move condition than in the Rest condition (p = .09). No significant differences between conditions were found for TEPs induced by sham stimulation (all p > .09).

In sum, the control experiment showed action-related TEP modulations occurring at 58–72 msec after STS stimulation. A particularly consistent modulation was observed over a right temporo-parietal region, with larger negative TEPs for the Move than for the Rest condition. This modulation was similar to one of the modulations observed in the main experiment (i.e., the modulation of right temporo-parietal IFC-TEPs during interval 1: 56–67 msec), although the set of electrodes was less extended for STS-TEPs than for IFC-TEPs. Yet, the overlapping time window of action-related modulations in IFC-TEPs and STS-TEPs raises the question of whether action-related changes in IFC-connectivity observed in interval 1 are specific to IFC stimulation.

In the supplementary material we have formally addressed the issue of site-specificity of IFC-TEP modulations. Figure S1 shows that action-related changes in IFC-TEP amplitude at ~60 msec over frontal and left temporo-parietal regions are specific to IFC stimulation (also see Figure S2 for convergent sLORETA evidence), whereas right temporo-parietal modulations are similar following IFC and STS stimulation.

4. Discussion

It is widely held that the posterior sector of the IFC plays a pivotal role in implementing motor commands for fine control of finger movements, via interactions with multiple motor areas distributed throughout the cortex (Borra & Luppino, 2017; Davare et al., 2011; Grafton, 2010). We tested the

hypothesis that, during voluntary hand actions, the left IFC exerts causal influences over the action network, as well as sensory and default-mode networks, through distinct corticocortical mechanisms. Using an inductive approach to TMS-EEG coregistration (Ferreri & Rossini, 2013; Miniussi & Thut, 2010), we provided direct evidence of dynamic changes in IFC connectivity with these three networks during action execution. Our study highlighted two time intervals -within the first 90 msec after IFC stimulation- in which the IFC-TEPs recorded during execution of the visuo-motor task (i.e., the Move condition) differed from those recorded at rest (i.e., the Rest condition), reflecting movement-related changes in IFC effective connectivity. The high temporal resolution of EEG allowed us to establish the time window in which these taskdependent changes occurred, and sLORETA was used to localize the networks affected by IFC stimulation. Earlier modulations occurred at 56-67 msec from TMS-induced IFC activation. They indexed an increase in IFC connectivity with fronto-parietal motor areas, and decreased IFC connectivity with posterior (multi)sensory areas - possibly reflecting implementation of the motor command and processing of its sensory consequences, respectively. Subsequently, taskrelated modulations of IFC connectivity with neural regions overlapping with and/or near to the DMN appeared at ~77-86 msec from TMS-induced IFC activation, and might reflect a cortico-cortical mechanism for maintaining anticorrelated activity with task-negative regions.

A control experiment showed that most of these transient interactions were specific to IFC. Indeed, stimulation of the control area STS induced an action-related increase in connectivity in a single time window (58–72 msec) partially overlapping with the earlier IFC interactions, but affecting a less extended pool of electrodes. Overall these findings indicate two temporally distinct functional stages of IFC causal interactions, which may drive the neural computations necessary for controlling and sensing actions and silencing default-mode brain activity during motor performance.



Fig. 8 – Task-dependent changes in STS-TEPs (control experiment). A) 2-D plot indicating the time points and electrodes showing significant effects (Stimulation × Condition interaction) in the first exploratory step of statistical analysis (x-axis: time from TMS pulse in ms; y-axis: electrodes) and mean F-values of the Stimulation × Condition interaction at each time point across electrodes. A single significant time interval ranged from 58 to 72 msec (vertical dashed lines represent the boundaries of the significant intervals). B) Grand average TEPs recorded during rest (Rest) and action execution (Move). TEPs induced by sham stimulation were point-by-point subtracted from TEPs induced by active STS stimulation. C) The middle part of the panel depicts the scalp map for the Stimulation × Condition interaction (contrast: [MoveActive–MoveSham]– [RestActive–RestSham]). The two electrode sets considered for the analyses are highlighted in different colors. On the left and right parts of the panel, changes in STS-TEP amplitudes over time for each region (Frontal, and R-temporo-parietal), stimulation (Active and Sham) and condition (Rest and Move) are shown. The significant interval is highlighted in light blue, whereas the gray bar indicates the 16-msec interval that was removed and interpolated to exclude the magnetic artifact. Histograms represent mean TEP values by region, stimulation, and condition. Asterisks indicate significant comparisons: * = p < .05; ** = p < .01. Error bars represent SE.

4.1. Fronto-parietal action networks for the generation of motor commands

In the first time interval (~60 msec), we found that when participants performed the visuo-motor task, IFC-TEPs became larger over frontal and right temporo-parietal electrodes, and smaller over left temporo-parietal electrodes. These opposite task-related changes in TEP amplitudes suggest that the IFC exerts its influence over a distributed set of cortical areas through different neural mechanisms, and sLORETA source estimation supported this hypothesis (see below and the next paragraph). Because larger TEPs in remote regions reflect an increase in the influence of the stimulated area over those remote regions (Ferreri & Rossini, 2013; Ilmoniemi et al., 1997; Miniussi & Thut, 2010), our data highlight movement-related increases in IFC effective connectivity with widespread frontal and parietal cortical networks. sLORETA highlighted a set of frontal motor areas (ROI_{int1} 1–4) showing increased activity during the execution of the movement. These areas included the dorsal and medial portions of the left premotor cortex (dPMc, pre-SMA/SMA proper), extending into the cingulate cortex (CMA) and a more caudal portion of the lateral premotor cortex in the right hemisphere, including the precentral gyrus and the insula (see Fig. 5). Moreover, increased activity was found over sectors of the right somatosensory and posterior parietal cortex (ROI_{int1} 8 and 9). These findings might reflect a functional stage associated with generating and implementing motor commands for performing the task. Indeed, in the Move trials, participants performed a visuo-motor task in which they were instructed by a visual cue about which finger to repeatedly abduct-adduct at ~1 Hz. Therefore, the task required them to select the appropriate effector based on learned visuo-motor mappings and organize the temporal progression of muscle synergies according to stored templates (i.e., the actions shown in the reference movies that were repeatedly observed offline throughout the experiment). The increased connectivity with dPMc, SMA/preSMA and CMA is thus in accordance with the established roles of these premotor regions in coding visuomotor associations, as well as in spatio-temporal organization of motor commands and action monitoring (Davare et al., 2006; Gallivan & Culham, 2015; Nachev, Kennard, & Husain, 2008; Shima & Tanji, 1998, 2000). Notably, the IFC and all these premotor and cingulate regions modulate finger cortical representations in the primary motor cortex and project downstream to the spinal cord, suggesting that they form an integrated frontal network subserving the integration of single motor programs into a common motor plan (i.e., the repeated execution of abduction-adduction), and the temporal coordination, implementation and monitoring of that motor plan (Amiez & Petrides, 2014; Hoshi & Tanji, 2007; Nachev et al., 2008). The increased connectivity with somatosensory and posterior parietal regions indexes IFC interactions with an extended fronto-parietal network involved in sensorimotor transformation and fine control of manual movements, encompassing both hemispheres (Gallivan & Culham, 2015).

Most of these action-related changes in connectivity were specific to IFC stimulation, as they were not observed following stimulation of the STS (Figure S1 and S2). However, in the control experiment, larger TEPs over right posterior electrodes in the Move compared to the Rest condition were found at ~60 msec (Fig. 8) and these action-related STS-TEP modulations were comparable to IFC-TEP modulations. While the STS does not possess motor neurons, this region is interconnected with the action network via the parietal cortex and it can be modulated by action performance, suggesting it might be involved in action-related sensory processing (Avenanti et al., 2013; Keysers & Perrett, 2004; Kilintari et al., 2014). Thus, our findings may indicate that changes in connectivity during action execution are not unique to motor nodes of the action network (Jin et al., 2012; Volz et al., 2015), but extend to (multi)sensory areas interconnected with it, thus pointing to a massive reorganization of functional connectivity in sensorimotor networks for performing and sensing actions. In light of this, it could be speculated that the transient and simultaneous influences of the IFC and the STS over posterior nodes of the network might contribute to processing sensory aspects of action performance (also see the section 4.2 below).

In sum, these findings expand previous knowledge by highlighting, for the first time, the temporal occurrence of IFC causal interactions with an extensive fronto-parietal action network involved in action execution, and indicate that these interactions occur at about 60 msec from IFC activation. Moreover, our findings show that a more posterior sector of the network simultaneously interacts with a sensory region – the STS – thus highlighting that action performance is associated with a vast and transient reorganization of neural interactions across motor and sensory areas.

4.2. Antero-to-posterior interactions for predicting sensory action consequences?

The main experiment provides further evidence of actionrelated transient reconfigurations of sensori-motor interactions. Indeed, the involvement of the action network was associated with a simultaneous task-related change in the influence of the IFC over posterior sensory areas in the left hemisphere. Specifically, left temporo-parietal IFC-TEPs were suppressed during the visuo-motor task, suggesting a reduction in the effects of IFC stimulation (i.e., a reduction in IFC effective connectivity) due to action execution. sLORETA suggested this effect mainly occurred over visual areas in the left hemisphere with peaks of deactivation over left inferotemporal (ROI_{int1} 5) and lateral extrastriate visual areas (ROI_{int1} 7), suggesting top-down suppression of an occipitotemporal network supporting visual perception (Logothetis & Sheinberg, 1996). Interestingly, task-related TMS effects also occurred in occipital areas encompassing the visual motion area (V5/MT+) and posterior sectors of the extrastriate body area (EBA), which are implicated in the visual (and multisensory) processing of motion and human body parts, respectively (Downing, Jiang, Shuman, & Kanwisher, 2001; Dumoulin et al., 2000; Orlov, Makin, & Zohary, 2010). Although these regions do not possess motor neurons, activity in several occipital and temporal areas can be modulated by action execution (Gallivan & Culham, 2015; Lingnau & Downing, 2015). Monkey studies have found deactivation of the inferotemporal cortex during action performance (Kilintari et al., 2014). Interestingly, in the temporal cortex, visual neurons responding to the sight of a movement are inhibited when the movement is caused by the monkeys' own actions (Hietanen & Perrett, 1993, 1996); moreover tactile neurons reduced their firing when monkeys were actively generating the tactile stimulus (Mistlin & Perrett, 1990). Deactivations in visual and polysensory areas of the occipito-temporal cortex have been interpreted as reflecting inhibition of the expected sensory consequences of one's own action (conveyed via efference copies of the motor command), rather than visual feedback of the executed movement or the motor command itself (Keysers & Perrett, 2004). In light of this, one might interpret our changes in IFC connectivity as reflecting action-related modulation of sensory processing in the left occipitotemporal cortex (i.e., contralateral to the moving hand), possibly due to gating of self-generated sensory information associated with a prediction of the sensory consequences of the right hand finger movements (Christensen et al., 2007; Cui et al., 2014; Voss et al., 2006). This is also in line with current theories of motor control (Franklin & Wolpert, 2011; Wolpert & Kawato, 1998), which rely on the existence of backward connections projecting from the frontal motor areas towards posterior areas that carry a copy of the motor program (i.e., the efference copy) in order to anticipate the change in sensory inputs resulting from the voluntary movement (Crapse & Sommer, 2008; Franklin & Wolpert, 2011).

In sum, the results observed in the first time interval (at about 60 msec) provide evidence of two parallel streams of IFC connections modulated during action execution. Firstly, IFC interacts bilaterally with a fronto-parietal action network involved in generating motor commands and monitoring performed actions. Secondly, it interacts –through feedback connections– with occipito-temporal networks involved in action-related sensory processing.

4.3. Task-related IFC connectivity extends beyond the action network

As expected, we found that IFC stimulation recruited areas beyond the action network at a second time interval (77-86 msec). These later task-related IFC-TEP modulations were characterized by larger amplitudes over bilateral frontal and right temporo-parietal electrodes during action execution. The analysis of cortical sources with sLORETA suggested that task-related IFC-TEP modulations were due to recruitment of ventro-medial prefrontal areas (ROI_{int2} 1), including the orbito-frontal cortex, the pars orbitalis of the inferior frontal gyrus and subgenual cingulate cortex; the right inferior parietal cortex, extending into the right temporo-parietal junction (ROI_{int2} 2); and a bilateral occipital network extending into the precuneus (ROI_{int2} 3). Parts of these regions are considered to comprise the DMN or are proximal to its main nodes. Neural activity in the DMN is decreased during active tasks and anticorrelated with neural activity in the IFC and other fronto-parietal regions (Fox & Raichle, 2007; Fox et al., 2005). Thus, our findings suggest increased IFC causal interactions with brain areas overlapping with the DMN, and might reflect a cortico-cortical mechanism for tuning down this network during motor performance.

4.4. Technical issues and limitations

We used stimulation and EEG preprocessing procedures to minimize confounding TMS-evoked artifacts. However, because IFC and STS scalp positions were in proximity to cranial muscles, TMS induced muscle activity in the initial EEG response, and we thus had to discard the first 20 msec of the EEG signal (Korhonen et al., 2011). This prevented detection of early neural interactions occurring immediately after the magnetic pulse, such as the influence of the IFC over the ipsilateral motor cortex, which is known to occur within a few milliseconds (Davare et al., 2011). In this view, it is possible that the observed task-related changes in IFC effective connectivity were underpinned by indirect pathways through relay areas.

Our results show that TMS over the IFC mostly induced site-specific effects. Modulations in the control experiment tended to be smaller and less extended than those in the main experiment. However, STS-TEPs and IFC-TEPs were similar over right temporo-parietal regions at ~60 msec. This latter finding is suggestive of similar transient interactions of the IFC and the STS with posterior areas during action execution. Yet, it remains an open question whether such interactions reflect similar functional contributions of the IFC and the STS in the action task (e.g., computing sensory aspects of the movement via interactions with the parietal cortex) or, rather, non-specific factors (e.g., in both experiments, participants may have different levels of attention in the Move and Rest conditions).

Finally, IFC connectivity was investigated by comparing a simple repetitive finger movement task with a rest condition. This simple task prevents us from testing different hypotheses about the specific functions of the task-dependent changes in IFC connectivity. Nevertheless, our study was conceived to yield preliminary evidence of the temporal dynamics of effective connectivity from the IFC to the action, sensory and default-mode networks. The effectiveness of this approach paves the way for investigating effective connectivity in more complex motor tasks and experimental manipulations, which might reveal different time windows of IFC connectivity or brain structures over which the IFC exerts functional control.

5. Conclusions

Overall, the results highlighted two stages of causal influence that the posterior left IFC exerts over three different networks during execution of a hand action. In the first stage (56–67 msec), two key functional mechanisms were highlighted: the IFC influences fronto-parietal motor areas that might contribute to the generation of motor commands and action monitoring and, concurrently, feeds back the information towards posterior areas, possibly reflecting prediction of the sensory consequences of the executed actions. Subsequent effective connections between the IFC and neural regions overlapping with the DMN (77–86 msec) might reveal a cortico-cortical mechanism for maintaining anticorrelated activity between sensorimotor and defaultmode networks.

This study demonstrates a valuable use of the TMS/EEG approach to assess the temporal dynamics of task-dependent changes in effective connectivity within and beyond the human action network. The findings provide new insights into the transfer of information between the IFC and other cortical areas, and provide temporal constraints which may guide further investigations of functional relations between the areas underpinning action and cognition in healthy individuals, as well as in clinical conditions (Di Pino et al., 2014; Sato, Bergmann, & Borich, 2015).

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cortex.2018.08.004.

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