Online Repetitive Transcranial Magnetic Stimulation (TMS) to the Parietal Operculum Disrupts Haptic Memory for Grasping

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Abstract: The parietal operculum (OP) contains haptic memory on the geometry of objects that is readily transferrable to the motor cortex but a causal role of OP in memory-guided grasping is only speculative. We explored this issue by using online high-frequency repetitive transcranial magnetic stimulation (rTMS). The experimental task was performed by blindfolded participants acting on objects of variable size. Trials consisted in three phases: haptic exploration of an object, delay, and reach-grasp movement onto the explored object. Motor performance was evaluated by the kinematics of finger aperture. Online rTMS was applied to the left OP region separately in each of the three phases of the task. The results showed that rTMS altered grip aperture only when applied in the delay phase to the OP. In a second experiment a haptic discriminative (match-to-sample) task was carried out on objects similar to those used in the first experiment. Online rTMS was applied to the left OP. No psychophysical effects were induced by rTMS on the detection of explicit haptic object size. We conclude that neural activity in the OP region is necessary for proficient memory-guided haptic grasping. The function of OP seems to be critical while maintaining the haptic memory trace and less so while encoding it or retrieving it. *Hum Brain Mapp 00:000–000, 2015.* © 2015 Wiley Periodicals, Inc.

Key words: dorsal stream; tactile; reaching; affordance; object; graspable; sensorimotor; premotor; parietal; somatosensory

INTRODUCTION

The parietal operculum (OP) is the cortical flap that covers the dorso-caudal part of the Sylvian fissure. From a microstructural point of view it is a highly heterogeneous region. According to recent data-driven cytoarchitectonic cortical maps [Eickhoff et al., 2006a,b] it is composed of at least four different regions referred to as OP1-OP4. The two most dorsal of these parcellations, namely OP1 (found more caudally) and OP4 (rostral to OP1) are somatosensory fields. Each contains a complete body representation and taken together they correspond to the classical definition of "secondary somatosensory area" (SII).

Also non-human primates contain in the OP region two fully independent somatosensory fields. The rostral one named Ventral Parietal area (PV) and the caudal one is referred to as SII. Odological data indicate that PV has strong efferent connections to the premotor and primary motor cortices while receiving afferents from the parietal cortex.

Additional Supporting Information may be found in the online version of this article.

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Conversely the monkey SII receives afferents from the somatosensory cortex and thalamus and does not give off efferents to the frontal lobe [Disbrow et al., 2003]. This anatomical evidence suggested that in the non-human primate the two adjacent somatosensory fields PV and SII support very different functions. Accordingly, SII would be a mainly sensory cortex, while PV would be a premotor (in the functional sense) cortex. In humans a homology has been made between OP1 and the monkey SII and between OP4 and the monkey PV. Indirect evidence for this homology has been found by means of probabilistic tractography, indicating that OP4 is connected to motor and premotor areas while OP1 is connected to sensory structures [Eickhoff et al., 2006a,b].

In a recent study we proved in the intact human, by means of dual-coil TMS, the existence of short-latency (5 ms) OP-M1 interactions [Maule et al., 2015]. The spatial resolution of TMS, however, did not allow a clear distinction between stimulation of OP1 opposite to stimulation of OP4. However, the findings were strongly suggestive, for the first time in humans, of a direct connection between the broadly intended OP and the ipsilateral primary motor cortex. The pattern of modulation of corticospinal output by conditioning TMS applied to OP showed that the OP-M1 system stored a working memory of relevant information for object-directed grasping as long as the information had been acquired in the haptic modality. Interestingly, the representation of object geometry was demonstrated in a purely pragmatic modality, i.e. in the hand posture required to grasp it, very similarly to how visual information on objects is stored in terms of potential motor acts in the ventral premotor cortex. In the present study we sought to go beyond correlational information between neural activity in OP and haptic-based grasping. We tested explicitly the hypothesis that the haptic memory trace contained in OP is *necessary* for optimal object-directed behavior.

To do so we asked blindfolded participants to perform a task consisting in three steps: exploration the variable size of an object, a delay, and a reach-grasp movement directed towards the previously explored object. Adjustment of finger aperture during the reaching movement to the size of the object was taken as a metric of how well the brain used the memorized haptic information. To assess the relation between the brain area of interest (the OP) and the specific behavior of haptically-guided grasping, we applied online high-frequency rTMS to the left OP and to a control site, the left occipital region (Occ). The rationale of such paradigm is that specific changes of grip aperture induced by TMS over OP, at any given step of the task, is causal evidence that some neural processing in OP is subserving that step of the task. The results indicated a causal role of OP in the storage of haptic memory. In a second experiment along the same line as the first, we tested whether the functional integrity of OP was necessary for an explicit haptic judgement on object size by applying TMS over the left OP during an explicit match to sample task. The results showed no effect of rTMS on the explicit task.

METHODS

Experiment 1—Participants

Fourteen healthy right-handed volunteers (six females, aged 26.9 ± 5.7 years) took part in the experiment. None of them had contraindications to TMS and all gave written informed consent in accordance with the Ethical Committee of the University of Trento (protocol n. 2009-033). All were right-handed according to the Edinburgh inventory [Oldfield, 1971].

Experiment 1—Protocol

All participants were blindfolded by means of an opaque mask. They sat comfortably on a chair with the left arm relaxed lying on the table (Fig. 1). All tasks were to be performed with the right hand. Their heads were held still with a chin-rest incorporating an additional lateral head-constrain. Each trial was made of four phases as schematized in Figure 1. (A) inter-trial phase; (B) haptic exploration of the object; (C) delay; (D) reach-grasp of the previously explored object. Please refer to the caption of Figure 1 for a detailed description of the tasks. Acoustic cues at the different phases of the trial were provided via earphones by means of pure tones. An acoustic cue (1,000 Hz pure tone, 50 ms duration) indicated to the participants the onset and offset of each phase. Experimental control was implemented by the microcontroller ArduinoUNO (www.arduino.cc).

The objects to be grasped consisted in small metal cylinders (see Target objects section) fixed to a wheel that was rotated manually by the experimenter. The rotation of the wheel occurred in each trial even if the same object was to be presented twice to ensure that the subject could not use any acoustic cue to perform the task. Two different TMS coils were permanently positioned over the stimulation sites (left OP or left V1) and held in place by means of a mechanical supports. Leaving both coils in place allowed us to interleave randomly trials with OP-TMS, trials with Occ-TMS and trials with no TMS in the same block.

The experiment had a factorial design for repeated within-subjects measures. Three factors were adopted: OBJECT DIAMETER (two levels: 19 or 23mm), TMS TARGET (two levels: OP-TMS or Occ-TMS) and PHASE of STIMULATION (three levels: EXPLORATION, DELAY and REACH-GRASP). Ten trials were run for each condition ($2 \times 2 \times 3 \times 10 = 120$ trials). In addition, 60 trials with no TMS at all were intermingled randomly with the TMS trials for a total of 180 trials. Moreover, we implemented a strategy to avoid excessive familiarity with the two diameters of interest (i.e. the 19 and 23 mm cylinders) two other cylinders of different diameter were presented in another 54 trials. These "catch trial" cylinders were 15 and 27 mm in diameter. The total number of trials was therefore of 234, though the trials that were ad-hoc planned to be used for analysis were 180.

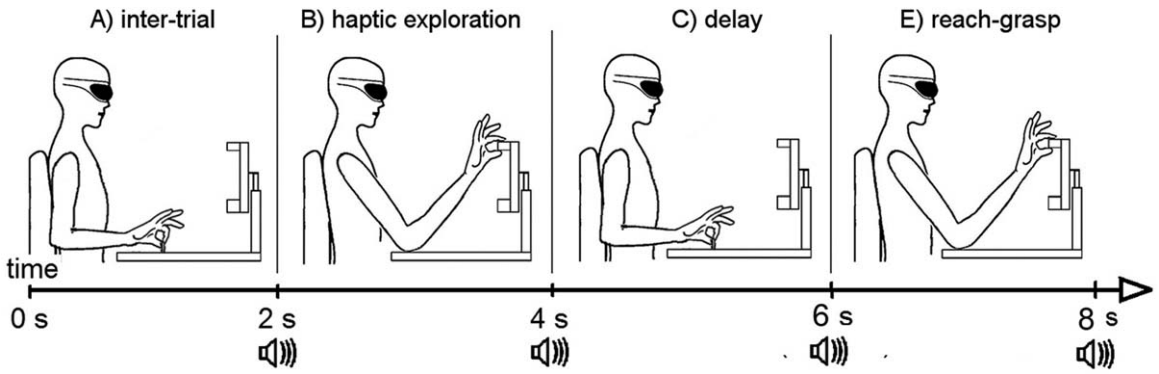

Figure 1.

Schematization of trial structure of Experiment 1.In the inter-trial phase (phase **A**) participants were required to hold a small plate fixed to the table, so that the same finger aperture was ensured at the start of the active phases of each trial. The subjects were then prompted by a sound to explore haptically the object in front of them (phase **B**). After 2 s a sound instructed the participants to go back to the resting position. They were then required to stop the haptic exploration for a delay of 2 s (phase **C**). Finally a sound prompted them to perform a thumb-and-index grasping (phase **D**) of the previously explored object.

Experiment 1—Target Objects

The graspable objects that were considered for the experimental data analysis consisted in two 30-mm long steel cylinders differing only in the diameter dimension. These were custom-made by a local lathe turner and did not have any surface feature that allowed discrimination between them besides the diameter. The smaller had a diameter of 19 mm and the larger a diameter of 23 mm. Additionally, two other cylinders of 15 and 27 mm were presented to avoid excessive familiarity with the two diameters of interest. The four cylinders were fixed perpendicularly to a wheel carousel (Fig. 1). The wheel was placed in front of the table at a suitable distance and height to allow comfortable exploration of the objects with the right hand. For each trial, the wheel was manually turned by the experimenter.

Experiment 1—Scalp Stimulation Sites and rTMS Procedure

In the present experiment we could not obtain an anatomical MRI scan of the participants to be used for neuronavigation of the TMS coil. We therefore adopted a probabilistic approach. In a previous experiment we had mapped the OP region with TMS and found that OP-M1 short-latency interactions could be elicited from one point along the postcentral sulcus around 1.5 cm above the Sylvian fissure. As stated in the introduction, this cortical location was also the target of the present experiment. We therefore localized in a series of brain MRIs the scalp projection of the OP target point, and analysed their relation to fixed scalp coordinates of the 10 to 20 system. Once the normality of the spatial distribution of the 32 spots was demonstrated, the spatial centre of the cloud of scalp points was calculated and taken as the representative scalp coordinate for stimulation over OP in the present experiment.

More in detail, we used a set of 32 brain surface and scalp three-dimensional (3D) reconstructions from healthy participants [the same that took part in Maule et al., 2015]. We localized and marked on individual 3D cortical surfaces the estimated OP target along the postcentral sulcus, 1.5 cm above the Sylvian fissure. The spot was then orthogonally projected on the corresponding 3D scalp surface on which the individual 10 to 20 system coordinates had been marked. The map that was obtained showed an extremely consistent distribution between subjects (Fig. 2). The centre point of the 2D distribution was localized at $^1/_4$ of the C5-T7 distance ventral to C5 and 1/10 of the C5-FC5 distance rostral to C5. The control stimulation was applied to the occipital region of the left hemisphere, localized on the scalp as the O1 coordinate of the 10 to 20 system (Fig. 2).

Biphasic TMS pulses over OP and the occipital region were delivered with two different stimulators (a Magpro and a Magpro compact—Magventure, Skovlunde, Denmark) each connected to a figure-of-eight coil (Magpro MFB-65). Single trains of eight stimuli at 4 Hz were delivered, at stimulation intensity of 100% of the Resting Motor Threshold (RMT) [Rossini et al., 1994], therefore keeping well within published safety limits for rTMS. (Wassermann, Rossi). By applying a 2-s train of rTMS, we ensured complete coverage of the phase during which rTMS was applied, since all three trial phases of interest were 2 s in duration (Fig. 1). The coil over OP was oriented with the handle pointing downwards similarly to previous work [Maule et al., 2015]. Conversely, the coil over the occipital region was oriented with the handle pointing backwards and therefore had a different orientation compared to the one over OP.

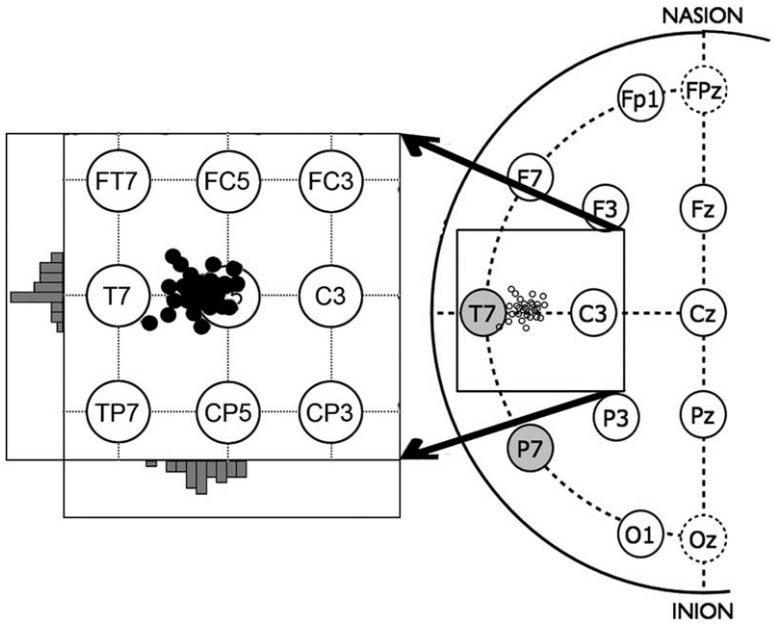

Figure 2.
Scalp positions in the 32 subjects of the projection of OP.

Experiment 1—Recordings and Analysis of Finger Aperture

The aperture of the thumb and finger was measured by means of a fleximeter, i.e. a transducer embedded in a plastic strip that changes its resistance with the bending/flexion of the strip. By injecting a constant voltage in the fleximeter, the output voltage is proportional only to the amount of flexion and therefore the output voltage is a reliable indicator of the strip's flexion state. The strip was 70 × 5 mm with flat resistance = 25 KΩ and a bend resistance range of 45 to 125 KΩ. It was attached tightly to the palmar aspect of the right hand's thumb and index fingers (as shown in Fig. 3, upper left illustration). The signal produced by the fleximeter in such position was representative of the thumb and index fingers' aperture (see Fig. 3). The analog fleximeter's output was digitized by means of a CED 1401 micro Mk-II unit (Cambridge Electronic Design, Cambridge, UK) at a sampling frequency of 100 Hz and recorded by means of the Signal software (Cambridge Electronic Design, Cambridge, UK). As a first step we investigated whether the fleximeter was producing an output that was linearly correlated to the grip aperture and how noisy was the signal. The results are shown in Supporting Information Figure 1 and show a clear linearity in the relation between the thumb-index distance and the fleximeter's resistance. However, the initial offset of the fleximeter's output was dependent on the subject's anatomy and on minimal variations in the points of attachment of the fleximeter to the hand (Supporting Information Fig. 1). We therefore opted for a normalization procedure of data from individual experimental sessions. In each subject, after the fleximeter was mounted on the thumb and index fingers, we measured its output values in the minimum finger aperture (F_{min}) and maximum aperture (F_{max}) positions, to calibrate the signal. All further measurements of fleximeter output (F_x) were referred to the two extreme values by the following normalization procedure: F_x (normalized) = $(F_x - F_{min})/(F_{max} - F_{min})$.

For each trial, the datum of interest was the amplitude of the maximal finger aperture during the reach, because it was the part of the fleximeter's signal that actually indicated the use of the memorized haptic information on object size (see Fig. 3). To automate the procedure of baseline-peak amplitude extraction we considered as baseline the value of fleximeter output at time = 6 s. The first peak occurring after 6 s was automatically identified provided that a hysteresis of 0.2 s was preserved. In this way one single number (i.e. the baseline-peak amplitude of the reach-grasp-phase) was taken as representative of the whole trial.

Experiment 1—Statistical Analysis

Trials were grouped in 18 cells according to a 2 × 3 × 3 factorial design with the factors: DIAMETER (two levels: 19 and 23 mm), TMS (three levels: OP, V1, NO-TMS), and PHASE (three levels: during exploration, during delay, and during grasping). Given the small number of repetitions per cell (10 repetitions) the normality of the distribution of

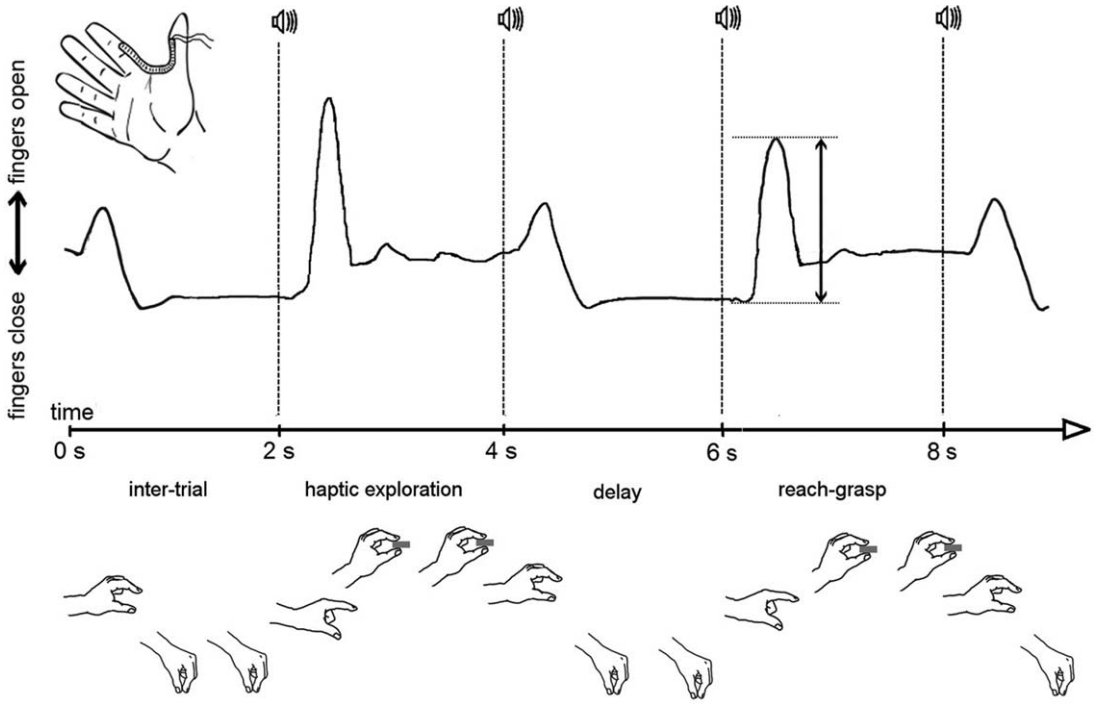

Figure 3.

Example of the fleximeter's output in a representative trial. On the upper part of the figure the electrical signal obtained by the fleximeter during a whole trial is represented. On the lower part of the figure, the corresponding hand configuration producing the signal is reported. In the upper left corner the fleximeter is schematized. The fleximeter was sticked to the hand as showed in order to obtain an electrical signal variable according to the hand aperture indicating the hand preshaping during the thumb-index grasping (phase D). The baseline-peak amplitude of the finger aperture that was measured in phase D and then used for further analysis is indicated by a double arrow.

single trial data within each cell was not guaranteed. We decided therefore to use a measure of central tendency of data and adopted the median rather than the mean values. Median values were then used as dependent variable in an ANOVA analysis with the three within-subject factors described above (DIAMETER, TMS, and PHASE). All post-hoc tests were made with Bonferroni-corrected *t*-tests.

Experiment 2—Participants and Protocol

Participants were 12 healthy right-handed volunteers (nine females, aged 26.6 ±3.4 years) with no contraindications to TMS [Rossi et al., 2009]. All gave written informed consent in accordance with the Ethical Committee of the University of Trento (protocol n. 2009-033). All participants were required to perform a haptic match-to-sample task. After a training block of 40 trials without TMS, participants underwent the main experimental session in which three trial types were randomly intermixed: trials with OP-TMS, trials with OCC-TMS and trials with no TMS. Each trial type was repeated 80 times.

Trial structure is summarized in Figure 4. In each trial the blindfolded participants were asked to explore haptically for 2 s the first of two cylinders that were presented. They were then required to stop the exploration and after 2 s, they were asked to explore the second of the two cylinders. At this point they had to state verbally if the second cylinder was the same as the first one and their answer was recorded for following analysis. Each trial consisted therefore in three phases: (A) haptic object exploration phase; (B) delay phase; (C) haptic object exploration phase and response. An acoustic cue (1,000 Hz, 50 ms duration) indicated the beginning and the end of each phase. The objects explored consisted in two purpose-made steel cylinders differing only in the diameter dimension (cylinder 1: height = 30 mm, diameter = 17 mm; cylinder 2: height =30 mm, diameter = 19 mm). The size of the cylinders was different from that of Experiment 1. The reason for this is that in a pilot study (data not shown) we tested the capacity of some participants to discriminate explicitly between cylinders of different sizes. All pilot participants were extremely efficient (100% of accuracy) in differentiating between the 19 mm cylinder from the 23 mm cylinder. We therefore reduced the difference between the two cylinder sizes to make the task more difficult and avoid ceiling effects.

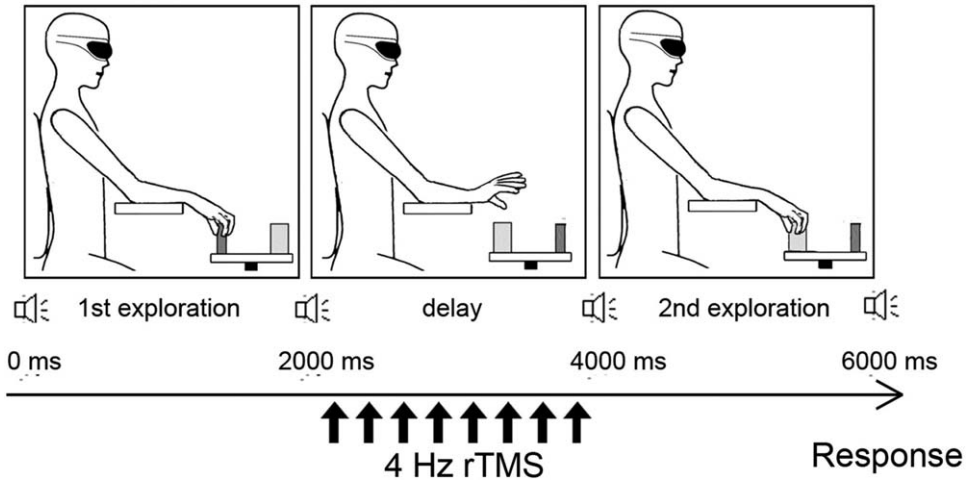

Figure 4.
Schematization of trial structure of Experiment 2.

The two cylinders were fixed on the two opposite points of a plastic wheel mounted horizontally on a vertical axis. The wheel was placed in front of the table at a suitable distance and height to allow comfortable exploration of the objects with the right hand with minimal reach movements. For each trial, the wheel was manually turned by the researcher. A complete rotation of the wheel occurred in each trial, even when the second cylinder was the same as the first one so that no acoustic cue was given to the participant. Each of the four combinations of the two cylinders (cylinder 1 + cylinder 1; cylinder 1 + cylinder 2; cylinder 2 + cylinder 1; cylinder 2 + cylinder 2) occurred in 25% of trials, and were presented in random order. Therefore in 50% of trials the second cylinder was the same as the first one. During all trials, both the training and the experimental ones, after the subject's response, a feedback on the correctness was provided by the experimenter. The control and the synchronization of cue sounds with the TMS triggers were implemented by the microcontroller ArduinoUNO (www.arduino.cc). Only the start of each trial was controlled manually by the experimenter. The training session was 7 min long and the experimental block lasted for around 45 min.

Experiment 2—TMS

The stimulation setup and apparatus was the same as in Experiment 1, with the two TMS coils simultaneously present on the participant's scalp on the OP O1 spots so that different trial types could be randomly interleaved in the same block. TMS was applied at 100% of the RMT [Rossini et al., 1994] computed for ID1 at a frequency of 4 Hz during the delay phase (phase B) of OP-TMS, trials with OCC-TMS trials.

Experiment 2—Data Analysis

The simple match to sample task employed here was assimilated to a signal detection ("Yes/No") task, thus allowing us to use the measures of accuracy (Acc) and sensitivity (d'), from Signal Detection Theory [Green and Swets, 1966], to quantify the subject's ability to discriminate between the two cylinders. Acc and d' have been calculated as follows: $\text{Acc} = (H + 1 - F)/2$; $d' = z(H) - z(F)$, where H (hit rate) and F (false alarm rate) are the two SDT independent conditional probabilities of "Yes" answer, while z represents the inverse cumulative Gaussian distribution. Acc and d' were computed separately for each of the three trial types. These were compared in an ANOVA analysis with a single within-subjects factor, the target of TMS, made of three levels (left OP, left V1, no TMS). Post-hoc analyses were carried out with pairwise t-tests and Bonferroni correction was applied when appropriate.

RESULTS

Experiment 1

None of the participants reported undesired side effects of TMS aside from occasional mild local pain during stimulation. The analysis of fleximeter's output in the No_TMS condition showed a significant difference between the two diameters ($t_{(15)} = -5.48$, $P = 0.00006$). Subjects showed larger potentiometer outputs, corresponding to wider maximum grip apertures, when grasping the larger diameter object (0.356; SD = 0.086) than when grasping the smaller diameter object (0.320; SD = 0.088) (Fig. 5).

The ANOVA produced a significant main effect of DIAMETER ($F_{(1,15)} = 69.8$, $P < 0.000001$) and a significant PHASE × TMS × DIAMETER interaction ($F_{(2,30)} = 4.66$, $P = 0.017$). All other effects or interactions had a $P > 0.14$. To explore

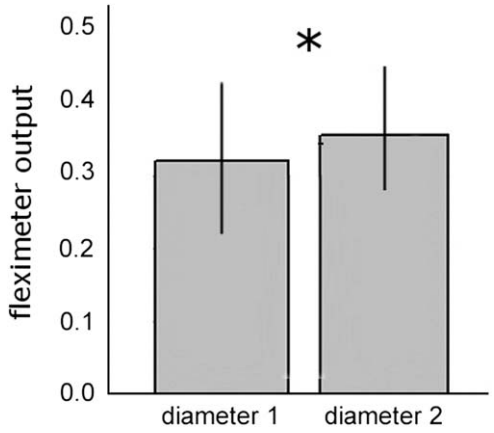

Figure 5.

Results of Experiment 1: mean fleximeter outputs for the two diameters in the trials without TMS. Error bars indicate 95% confidence intervals of the mean.

this three-way interaction we performed on the omnibus ANOVA a series of planned comparisons so that all data from the same cylinder were compared between conditions and data from different cylinders were compared only within the same condition (e.g. cylinder 1 in the OP-TMS and reach PHASE condition was compared with cylinder 2 only in the corresponding OP-TMS and reach PHASE condition) for a total of 36 planned comparisons. The results and *P* values are represented in Figure 6. We found significant differences between data from cylinder 2 only between the OP-TMS/delay PHASE condition and all the remaining conditions. Regarding the data from cylinder 1 we similarly found significant differences between the OP-TMS/delay PHASE condition and all the remaining conditions aside from the OCC-TMS/delay PHASE condition ($P = 0.08$). The comparisons between cylinder 1 and cylinder 2 within conditions indicated a significant difference in grip aperture in all conditions aside from the OP-TMS/delay PHASE one ($P = 0.49$). Altogether the data were interpreted as TMS over OP inducing a loss of specificity of the grip aperture to the size of the object to be grasped. To further investigate the origin of the three-way interaction and corroborate our interpretation by pinpointing the interaction to the OP-TMS condition in the delay PHASE, we split the three-way ANOVA into two symmetrical ANOVAs, one for each of the TMS targets, with PHASE and DIAMETER as within-subjects factors. In these two ANOVAs a main effect of diameter was found (all $P < 0.038$). A significant PHASE × DIAMETER interaction was found only for the OP_TMS condition ($F_{(1,15)} = 5.69$, $P = 0.03$), as illustrated in Figure 6. The interaction was further analyzed by post-hoc comparisons between the two diameters in each of the three conditions. The significance threshold for *P* was therefore set at $0.05/3 = 0.016$. The comparisons indicated that the maximum finger aperture was significantly higher for the large than the small cylinder only when TMS had been delivered in the exploration or in the reach phases, but not so in the delay phase (see Fig. 6 for *P* values). Summarizing the results, the participants failed to scale properly the fingers to the object's diameter if TMS had been delivered over OP and only during the delay phase of the trial.

Experiment 2

The one-way ANOVA performed on the sensitivity data did not produce any significant effect ($F_{(3,33)} = 7.089$ $P = 0.6212$) nor

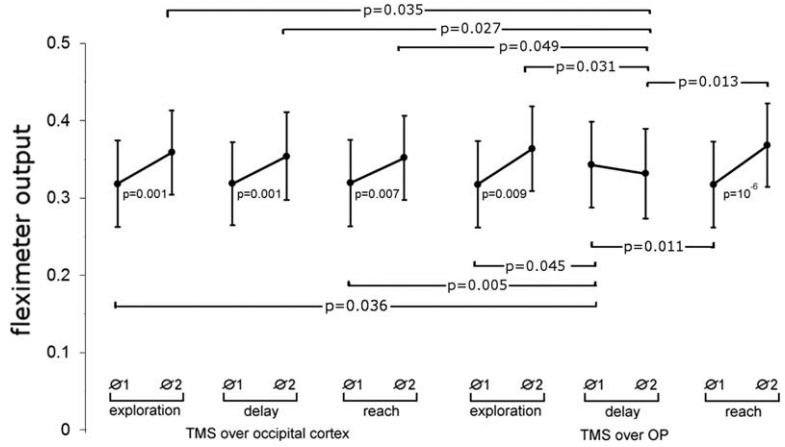

Figure 6.

Results of Experiment 1: mean fleximeter outputs in the different experimental conditions. *P* values refer to pairwise planned contrasts. Only significant *P* values are shown. Note that the condition in which TMS had been delivered to OP in the delay period was the only one in which no differentiation was observed between the two cylinders. Error bars indicate 95% confidence intervals of the mean.

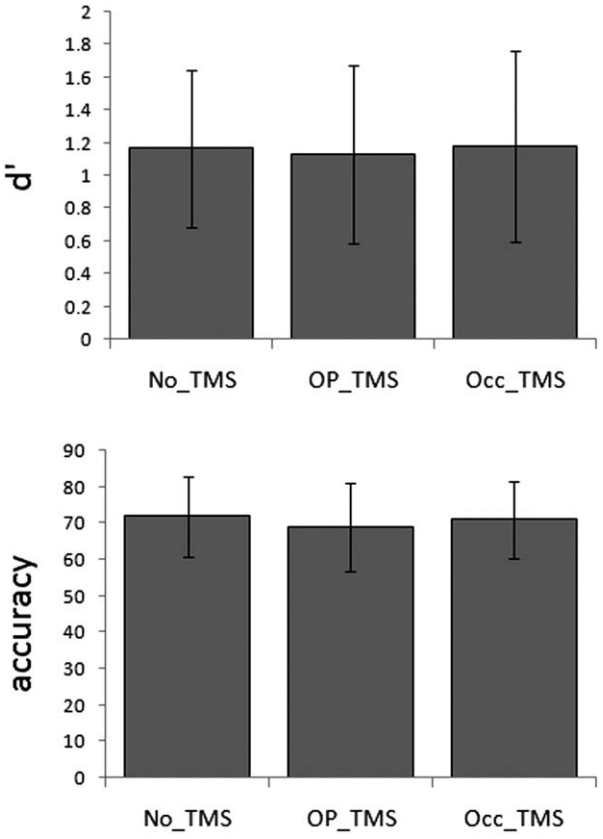

Figure 7.
Results of Experiment 2. Error bars indicate 95% confidence intervals of the mean.

did the ANOVA on the accuracy ($F_{(3,33)} = 7.089$, $P = 0.87$) as illustrated in Figure 7.

DISCUSSION

In this experiment we aimed to study whether rTMS delivered over left OP produced a significant perturbation of performance in two different tasks that both relied on the formation of an internal representation of the 3D properties of an object acquired in the haptic modality. Specifically, Experiment 1 aimed to assess whether rTMS induced significant modification in the kinematics of hand pre-shaping when reaching for a previously haptically explored object. Experiment 2 aimed to study the effects of rTMS on the participant's accuracy when performing an explicit discrimination task of an object's size.

The first result that requires brief discussion is the effect of the target diameter on finger peak apertures in the No_TMS condition. The larger was the diameter of the cylinder previously explored, the higher was the fleximeter's output, indicating a larger finger aperture while reaching for the target. This expected result is in accordance with the well-known principle of reach-grasp kinematic stating that the hand is preshaped during the reach phase to fit the object size [Bootsma et al., 1994]. This finding validates the main theoretical assumption for Experiment 1, i.e. the use by the motor system of haptically-obtained information in an open loop manner, to guide hand shape during reaching. The main result of Experiment 1 is that TMS applied over OP but not over a control (visual) area produced impaired scaling of fingers when participants reached for the target object (Fig. 6). The effect of TMS was temporally specific because it occurred only if rTMS was applied during the delay phase of the trial, i.e. when the object size was to be held in memory. The results are at first sight puzzling. If the OP was the storage site of a sensory memory, it could be expected that its inactivation would equally perturbed the acquisition and storage of the haptic information. The dissociation between the effects of rTMS during the encoding and the delay phases can be explained in reference with the model of the phonological loop in working memory [Baddeley, 2003]. In this model two systems interact for verbal working memory: a memory buffer and a rehearsal system. If we apply to haptic working memory a similar model, our data fit well with a role of the OP in the motor rehearsal module rather than in the pure memory buffer module. The analogy between haptic and phonological working memory is however limited. The haptic system is special in the sense that in order to acquire sensory information for grasping, voluntary movement is required from the very same effector that will use that information, while listening to sounds can be performed in the absence of voluntary movement. In this respect, the fact that TMS did not deteriorate later memory-guided grasping performance when applied during the exploration phase indicates that the OP doesn't have a general role in whatever behavior requiring active manipulation; on the contrary the present data indicate a very specific role of OP in the storage of haptic memory for grasping. The role of OP as tested in the present paradigm would therefore be more similar to that of a premotor cortex, but with high functional specialization. By all means this partial conclusion does not exclude that the OP contains purely sensory representations. However, as we have previously stated [Maule et al., 2015] at least some neuronal populations in the OP region are part of a premotor network rather than of a sensory one. From this point of view the present work goes well beyond our previous observations on functional connectivity between OP and hand-M1. While the previous data were mainly correlative, here we establish an unequivocal causal link between the OP-associated cortex and the capacity of the motor system to retain a haptic memory of graspable objects.

In general the present data together with our previous description of OP-M1 connectivity [Maule et al., 2015] support the idea that part of the OP cortex plays a major role in motor behavior rather than being a purely sensory area. Data obtained in non-human primates share a striking

similarity with the present findings. Several neurons in the OP region have been found to be specifically linked to active manipulation movements rather than simply reflecting somatosensory information [Ishida et al., 2013]. In particular, it was found that a majority of recorded neurons fired only during active manipulation and not during passive limb movements. Our data actually move one step forward. We show that neural coding in OP represents not only somatosensory stimulation during active movements but can store haptic memories to be used in feed-forward, open loop process. These sensorimotor memories are assumed to be a key component of the sensorimotor control of reach-to-grasp movements. Recent studies have revealed the influential role of haptic information acquired in the immediate past on current actions [Tang et al., 2015]. The use of past haptic information for movement preparation is highly dependent upon the reliability of other sources of information due to contextual manipulation [Brydges and Dubrowski, 2009] or brain damage [Schenk, 2012].

Unlike Experiment 1, Experiment 2 did not provide any significant result. TMS over OP delivered during the delay phase of the explicit haptic match-to-sample task failed to impact in any way our psychophysical measures of performance. The dissociation between the results of the two experiments deserves further discussion. Both of the tasks required the short-term retention of the geometrical feature of the object (e.g. size), however, the use of such information for the task accomplishment was different. In Experiment 1 the sensory information was implicitly used to act upon the object. In Experiment 2 the sensory information was to be encoded as an explicit memory of object size.

Our main interpretation of the dissociation between the two tasks is that OP might actually not be involved in the storage of explicit haptic memories at all. It has been proposed that, pretty much like in the visual system [Goodale and Milner, 1992], also haptic information takes two separate routes in the brain, one subserving movement and the other subserving conscious perception [Dijkerman and de Haan, 2007; Mishkin, 1979; Murray and Mishkin, 1984]. Such model is indirectly supported by imaging data [Stoeckel et al., 2003]. More interestingly, also the study of tactile illusions [Westwood and Goodale, 2003] as well as patient studies [Caselli, 1991; Reed and Caselli, 1994] indicate a dissociation between explicit and implicit haptic processing. In this respect, our data are once again strongly corroborated by previous descriptions of neuronal activity in non-human primates. The study by Romo et al. [2002] employed a delayed match-to-sample task very similar to the one employed here in Experiment 2, with the difference that stimuli were simple vibrations instead of 3D objects as in our case. Significantly, the authors failed to find delay-related activity in the secondary somatosensory cortex, similarly to our finding of absence of interference by rTMS over OP during the delay phase of the task. An alternative and more speculative explanation for the dissociation between the two experiments is that premotor neurons in OP probably access only the ipsilateral M1 (though their unilaterality has never been the object of direct ad-hoc investigation in neither monkeys nor humans), thus accounting for the motor effects of unilateral rTMS. On the contrary, it is well-known that sensory representations in S2 are bilateral, therefore compensatory activity of the contralateral non-stimulated OP could account for the lack of effects in the encoding phase of Experiment 1 and even for the negative result of Experiment 2 [Cipolloni and Pandya, 1999; Cusick et al., 1989; Disbrow et al., 2003; Krubitzer and Kaas, 1990; Mesulam and Mufson, 1982; Mufson and Mesulam, 1982; Pandya and Seltzer, 1982; Qi et al., 2002; Stepniewska et al., 1993].

In conclusion, the results of our own Experiment 1 support the involvement of left OP in an "object-directed action" network for the haptic modality, as shown by the significant variation in grasping behavior obtained by rTMS. Our data further corroborate the concept that the OP is a highly heterogeneous portion of cortex and that part of it supports highly specialized "premotor" functions linked to the haptic modality.

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