NEURAL CORRELATES OF PERCEPTION FOR ACTION IN HUMANS USING TMS AND FMRI

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1 Synopsis

1.1 Introduction to sensorimotor control

Movements are humans' interface to their physical and social environment. We interact with the environment by acting within and upon it. In order to perform adequate movements within different and constantly changing environments, a range of sensory signals needs to be processed continuously and integrated into the control of our movements. The main sensory channels for movement control are vision and proprioception. Vision supplies information about the environment and also about the current state of our body, e.g. the position of our hand. Motor tasks which require precise coordination with the (visual) environment, e.g. reaching or grasping, benefit notably from visual input about the acting body part. Even though these movements can be executed without this particular visual input (Pelisson et al., 1986; Prablanc and Martin, 1992; Blouin et al., 1993), the accuracy of movements increases considerably with it (Woodworth, 1899; Bard et al., 1985; Spijkers and Lochner, 1994; Spijkers and Spellerberg, 1995; Proteau et al., 2000). Additional sensory information about the body state is provided by proprioceptive afferents. Without vision, they constitute the only sensory input about the state of our body. However, studies with a deafferented patient (Blouin et al., 1993; Sarlegna et al., 2006) have shown that even in the absence of any sensory input reasonably precise motor control is possible. The remaining information which provides information about the current body state is derived from the motor command itself (Sperry, 1950; von Holst and Mittelstaedt, 1950; Evarts, 1971)[1].

For effective movement control, the information from the different sensory channels has to be processed rapidly. Previous studies have shown that humans can react within 60 - 160 ms to recent sensory information (Crago et al., 1976; Soechting and Lacquaniti, 1983; Smeets et al., 1990; Day and Lyon, 2000). A number of theoretical models have been proposed to explain how sensory information during an ongoing movement is integrated and also how time delays

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[1] This feed-forward information derived from the motor command has first been studied on eye-movements and is called corollary discharge or efference copy as this principle has been discovered and termed by two groups in parallel.

arising from the processing of the sensory channels are handled (Andersen et al., 1997; Desmurget and Grafton, 2000; Wolpert and Ghahramani, 2000; Shadmehr, 2009; Diedrichsen et al., 2010).

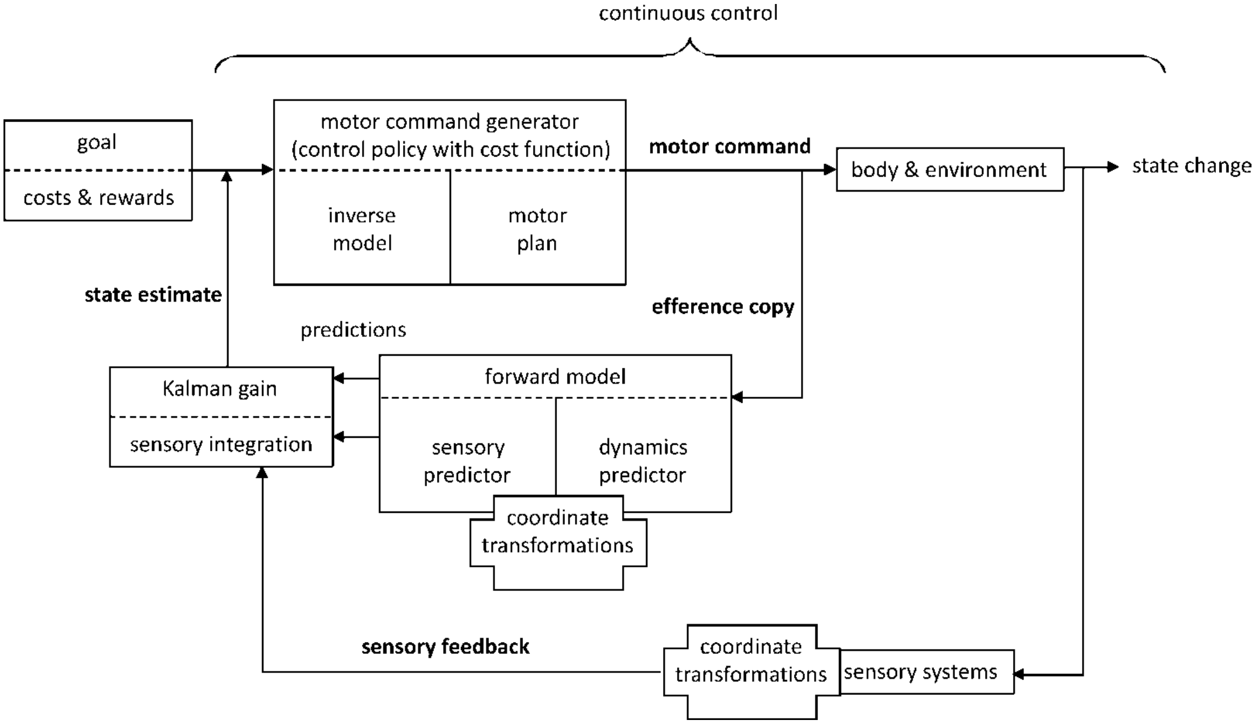

Figure 1 Sensorimotor control at a glance. This overview provides a general picture about the processes involved in sensorimotor control. It has been compiled on the basis of the theoretical models from Andersen et al. (1997), Desmurget and Grafton (2000), Wolpert and Ghahramani (2000), Shadmehr (2009), and Diedrichsen et al. (2010). **Bold** font is used to highlight noisy information.

On the motor side, an inverse problem with multiple solutions has to be solved[2]. Our motor system offers more degrees of freedom than the physical three-dimensional environment in which we act: In order to bring an effector, e.g. the hand, from one spatial position to another, a multitude of trajectories is possible to achieve the desired goal. Furthermore, for one trajectory, a multitude of joint-combinations can be activated and also numerous muscle activations accomplish the same spatial goal. Several solutions for an effective motor command generation

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[2] Known as Bernstein problem of motor control (Bernstein NA (1967) The co-ordination and regulation of movements: Pergamon Press (Oxford and New York)).

have been proposed (generalized as *control policy* in Fig. 1). One possible solution is exploiting muscle synergies (d'Avella et al., 2006), i.e. using a pre-set combination of muscles which are activated together. Another solution is minimizing kinematic descriptors such as the squared jerk (Hoff and Arbib, 1993) or the squared force. It has also been suggested that the energy expenditure is minimized, i.e. the sum of motor commands which is roughly proportional to the Adenosine-5'-triphosphate (ATP) consumption by muscle fibers (Szentesi et al., 2001). More recent work has proposed that effort and variability are minimized, which both result from the minimization of the sum of squared motor commands (Diedrichsen et al., 2010), while effort seems to play a larger role than variability (O'Sullivan et al., 2009). The executed motor command results in a change of the state of the body and eventually the environment. Additionally, an efference copy of the motor command is used to predict the consequences of the motor act by a forward model. The current state is assessed by the sensory systems. The main advantage of utilizing a forward model is that it is available much faster than the sensory feedback. The information which has to be integrated is natively available in different reference frames[3] and thus has to be transformed in some kind of common reference frames. It is a matter of ongoing debate whether the central nervous system switches between different reference frames, e.g. a “visual” frame of reference for movements where the effector is seen and a “proprioceptive” reference frame where the effector is not seen (Krakauer et al., 1999), or utilizes several reference frames in parallel (McGuire and Sabes, 2009). Also, which of the possible alternatives is implemented at which stage of the process and where in the brain is a question of ongoing research (Medendorp et al., 2003; Medendorp et al., 2005; Beurze et al., 2006; Van Pelt et al., 2010). The integration of the forward prediction with the later arriving sensory information can be conceptualized with a Kalman filter (Wolpert et al., 1995), a step-wise approach of integrating partial information arriving at different moments of time which leads to a statistically optimal integration. With this integrated information a fast and reliable prediction of the current state of the system is obtained. Sensory information and motor commands are inherently noisy signals (printed **bold** in Fig. 1). Human behavioral studies have shown that the integration of this kind of signals is described well in a Bayesian framework

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[3] e.g. retinal coordinates, head centered, body centered, or world centered coordinates

where every signal is weighted with its reliability, i.e. the inverse of its variance (Ernst and Banks, 2002).

Several neural correlates have been identified which process quickly and both sequentially and in parallel the sensory information needed for movement control (Ghez and Krakauer, 2000). Day and Brown (2001) have distinguished a sub-cortical route for the fast processing of visual information. Alongside, the posterior parietal cortex (PPC) has been outlined as an important cortical area to process sensory information for motor control. For visual information, the PPC is part of the dorsal visual stream (Goodale and Milner, 1992) where visual information *mediating the required sensorimotor transformations for visually guided actions* is processed. A growing body of literature comprising neuropsychological and neuroimaging studies (for reviews see Culham et al. (2006), Culham and Valyear (2006), Iacoboni (2006), Filimon (2010)) provides evidence that the PPC is a crucial structure for various processes sub-serving visuomotor behavior. The brain structures for the integration of proprioception into an ongoing movement plan are studied to a lesser extent so far but some studies have shown that the PPC is involved in these processes as well (Della-Maggiore et al., 2004; Blangero et al., 2009; Filimon et al., 2009). Many posterior parietal areas are part of different parieto-frontal networks for movement control (Rizzolatti et al., 1998; Tanne-Gariepy et al., 2002; Battaglia-Mayer et al., 2003; Tomassini et al., 2007). As my work presented here focuses on parietal but not frontal areas, I will also limit this introduction to the PPC areas.

The traditional view is that different PPC sub-regions are specialized for distinct processes sub-serving sensorimotor control (Andersen and Buneo, 2002). In particular, a strong effector selectivity has been found in the macaque monkey (Andersen and Buneo, 2002; Grefkes and Fink, 2005). The lateral intraparietal area (LIP), which is located in the lateral wall of the IPS, is a crucial structure for mediating saccades (Gnadt and Andersen, 1988; Duhamel et al., 1992). The anterior intraparietal area (AIP), which is located on the lateral bank of the anterior IPS, is active during the fixation and manipulation of objects (Sakata et al., 1995). Thus, this area is commonly associated with grasping movements. The medial intraparietal area (MIP), which is located on the medial bank of the medial IPS, mediates planning, execution and monitoring of reaching movements. Together with the areas V6A and the intraparietal areas of PE, MIP forms the parietal reach region (PRR; Cohen and Andersen (2002)). Additionally, MIP has been suggested as the area where coordinate transformations for the reaching target into a reference frame compatible with the motor system is performed (Andersen and Buneo, 2002). Other sub-regions have also been hypothesized to have a dominance for information processing in different coordinate frames, like head-centered coordinate frames in the ventral intraparietal area (VIP) (Colby et al., 1993) and eye-centered coordinate frames in the areas LIP and PRR (Andersen and Buneo, 2002). The search for human homologues to these areas has been moderately successful (Culham and Kanwisher, 2001; Grefkes and Fink, 2005; Culham and Valyear, 2006). In fact, a different picture for the human PPC emerges from the literature of the last decade. Instead of a modular view, sensorimotor processing seems to be largely distributed in networks with some spatial gradients and a relative dominance rather than an exclusive selectivity of some areas for specific sub-processes (Filimon, 2010). Furthermore, the distribution of processes in the human brain seems to be less effector or coordinate frame specific (Tunik et al., 2007). Whether these discrepancies stem from the different methods used (single-cell recordings in monkeys vs. whole brain imaging in humans) or whether there is a substantial difference between species remains to be uncovered, e.g. using the same methods like fMRI in both species. However, also in the macaque monkey the strict modular view begins to blur (Andersen and Cui, 2009).

In contrast to studies about different processes sub-serving sensorimotor integration in the macaque monkey (Andersen and Buneo, 2002), studies in humans are less conclusive so far. There is good evidence that substantial differences between human and monkey neuro-anatomy are present and a mapping of homologue areas between both species remains speculative (Culham and Kanwisher, 2001; Grefkes and Fink, 2005; Culham and Valyear, 2006). Several challenges have to be tackled in this field of research. In functional magnetic resonance imaging (fMRI) studies, the method used most widely for human brain mapping, the topic itself constitutes a substantial problem: Movements inside the MR scanner lead to movement artifacts and artifacts due to changes in the magnetic field – both highly correlated with the task, i.e. the movement (Friston et al., 1996; Barry et al., 2009). A common way of avoiding this problem is to restrict the movements profoundly, for instance using finger pointing or finger-reaching with a joystick instead of fully-fledged reaching movements (e.g. Simon et al. (2002), Astafiev et al. (2003), Grefkes et al. (2004)). In this special case there is good evidence that pointing activates similar brain areas - only to a lesser extent (Culham et al., 2006) - but as long as the overall effector specificity of PPC areas remains controversial (Tunik et al., 2007; Filimon, 2010), this is not a satisfactory long term solution. Also the equipment frequently used for behavioral studies (e.g. manipulanda or robots arms) is usually unsuitable for use in the MR scanner. Either special non-magnetic setups have to be built (Diedrichsen et al., 2005; Gassert et al., 2006b; Gassert et al., 2006a; Gassert et al., 2008b, a; Klare et al., 2010) or experimental paradigms with free movements have to be employed (e.g. Culham et al. (2003), Blangero et al. (2009), Filimon et al. (2009), Himmelbach et al. (2009), Cavina-Pratesi et al. (2010)), thereby limiting the amount of experimental control. Furthermore, the temporal and spatial proximity of the processes involved in motor control (e.g. planning vs. online control, eye- vs. hand-movements, coordinate transformations) challenge conventional fMRI paradigms which exploit the temporal slow blood-oxygen-level dependence (BOLD) contrast and apply spatial smoothing to the acquired data (Turner et al., 1998). These issues led to a wide variety of experimental designs and thus the results are hard to compare – one fMRI study to another as well as to studies in the macaque monkey. In order to overcome the shortcoming of fMRI on a temporal scale while using standard behavioral setups, transcranial magnetic stimulation (TMS) can be used as a "virtual lesion approach" (Cowey, 2005), i.e. temporally disturbing the brain area under study and measuring the impact on behavioral performance. A further advantage of this method is that it allows drawing causal conclusions about the involvement of the targeted brain area in the specific process under study. The drawback of this method is that it has only limited spatial resolution, especially the way used in the majority of studies where only one brain site is stimulated besides control sites. We aimed to overcome this shortcoming with parts of the work presented here (chapters 2.3 and 2.4). In short, we used a densely-spaced grid of TMS coil positions mapped to individual (functional) neuro-anatomy and demonstrated distinct TMS effects for neighboring stimulation sites. Another difficulty with TMS in higher cortical areas is that the behavioral effects are often very subtle and thus sensitive measurements of performance are required. To finish, a challenge common to all methods is that the human PPC presents high inter-individual differences (Grefkes and Fink, 2005), both in neuro-anatomy and in functional anatomy. Conventionally, group results are compiled by matching brains based on gross-anatomical landmarks (Talairach and Tournoux, 1988; Friston et al., 1995; Jenkinson et al., 2002). In one of our studies (chapter 2.3) we demonstrated a high functional variability between the participants' PPC areas using fMRI and confirmed this observation by showing spatially specific TMS effects matching the individual functional neuro-anatomy derived by fMRI. In particular, we demonstrated more robust behavioral effects for TMS sites based on individual rather than group fMRI data. This study provides an example how multi-modal neuroimaging provides real added value.

The human PPC is defined as the parietal cortex without the postcentral gyrus (PCG, Fig. 2). As mentioned above, the functional neuro-anatomy can better be described by gradients of functional preference than by specific one-to-one structure-function mappings (Filimon, 2010). One gradient spanning the PPC from anterior to posterior describes the preference for the effector (green-to-blue arrow in Fig. 2). More specifically, dominance for grasping (hand movements) to reaching (arm movements; first without and then with visual feedback about the arm) to saccades (eye movements) evolves from the anterior to the posterior parts around the intraparietal sulcus (IPS). This general pattern emerges from a number of fMRI studies on execution (Culham et al., 2003; Culham et al., 2006; Filimon et al., 2009), planning (Beurze et al., 2007; Beurze et al., 2009), and topography (Levy et al., 2007) of reaching movements and saccades and is strengthened by fMRI studies on execution (Simon et al., 2002; Astafiev et al., 2003; Medendorp et al., 2003), planning (Medendorp et al., 2005), and topography (Hagler et al., 2007) of pointing movements and saccades. Already the fact that studies report similar results for reaching and pointing , i.e. arm vs. finger, movements demonstrates the weak effector specificity within the PPC as obtained with conventional fMRI paradigms. The aIPS (highlighted green in Fig. 2) was hypothesized to be an exception to this, it is considered to be rather grasping specific (Culham et al., 2003; Tunik et al., 2005; Rice et al., 2006; Rice et al., 2007) and regarded as human homologue to the macaque AIP. Tunik et al. (2007) questioned this specificity and proposed that the aIPS is a critical node for visuomotor control in general. This opposed view is supported by two studies presented here (chapters 2.3 and 2.4), where we demonstrated the importance of aIPS for the integration of visual information during the execution of reaching movements.

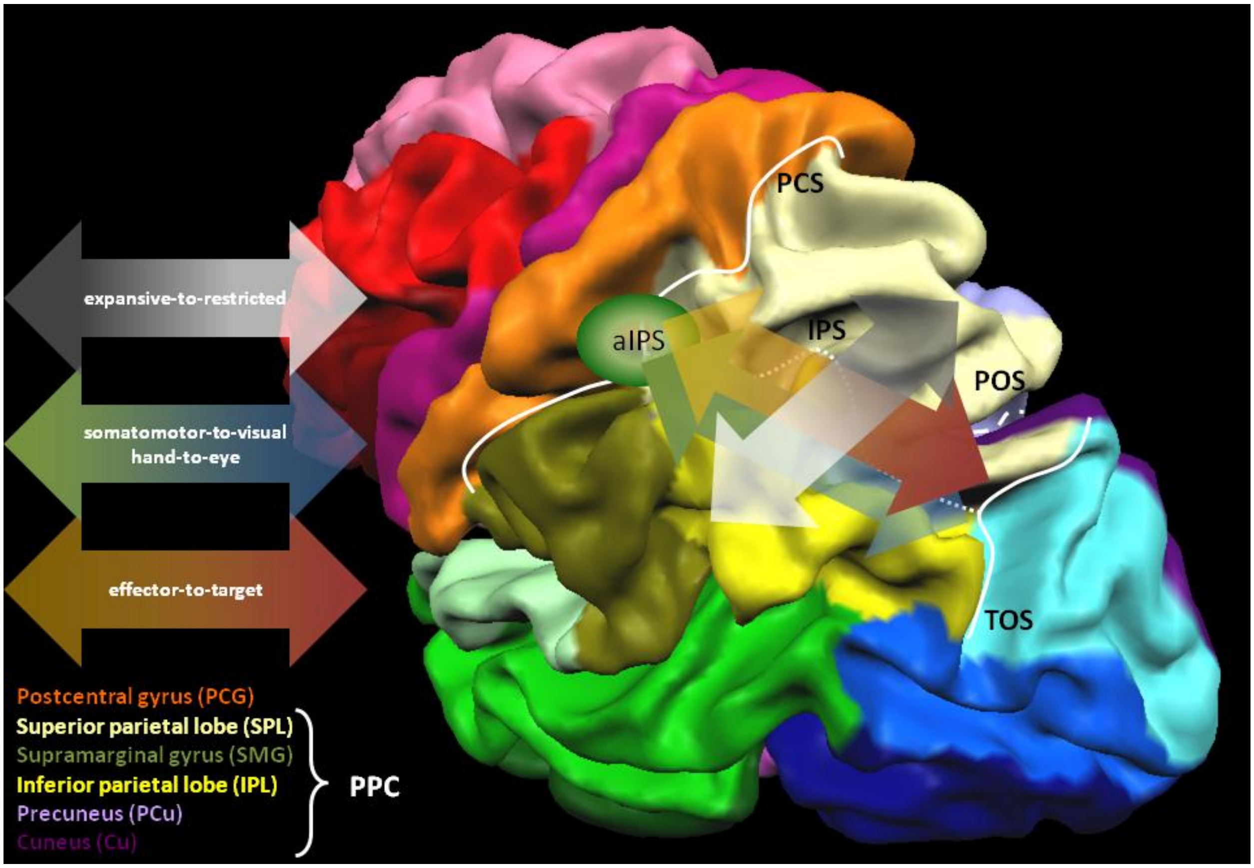

Figure 2 The human parietal cortex in a postero-lateral view on a rendered left hemisphere (BrainVoyager Brain Tutor, Brain Innovation, Maastricht, The Netherlands). Three gradients of functional preference (see text) are sketched, two spanning the PPC from anterior to posterior and one from lateral to medial. The arrows indicate only the direction of the gradients, not their spatial extent. Abbreviation of the sulci: postcentral sulcus (PCS), intraparietal sulcus (IPS), parieto-occipital sulcus (POS), transverse occipital sulcus (TOS). The anterior IPS (aIPS) is marked separately because of its prominent role for grasping movements and for its apparent importance in visuomotor processing in general, respectively.

Another gradient spanning the PPC from anterior to posterior describes the importance for the representation of the localization of the effector compared to that of the target (yellow-to-red arrow in Fig. 2). Located in between the primary motor (M1) and visual (V1) areas these gradients within the PPC seem intuitive. M1 is almost exclusively in charge of the contralateral body-half and this strong lateralization decreases the further posterior a PPC area is located. Likewise, in V1 the left and right visual hemi-field is mapped separately on the contralateral hemisphere and this strict lateralization decreases the further anterior a PPC area is located. Empirically, this picture has emerged from a number of fMRI studies. Contrasting movements to the left or right hemi-field and with the left or right arm during the planning of pointing (Medendorp et al., 2005) or reaching (Beurze et al., 2007; Beurze et al., 2009), or the execution of reaching (Blangero et al., 2009) movements has revealed these gradients. Additionally, with a series of experiments Culham et al. (2008) have highlighted the importance of the superior parietal occipital complex (SPOC) for the processing of visual target information. To conclude, an fMRI study investigating specifically online control processes (Diedrichsen et al., 2005) demonstrated higher activation in posterior PPC areas when a correction of the movement was based on a change in target position and higher activation in anterior PPC areas when a correction of the movement was based on a spatial change in the visual hand representation. The third gradient is spanning the PPC from medial to lateral (grey-to-white arrow in Fig. 2). The less expansive a movement is the more lateral fMRI activations are reported (Filimon et al., 2009). Fully-fledged reaching movements lead to stronger BOLD activations in the medial parts of the PPC whereas restricted fMRI paradigms with finger pointing activate more lateral areas. Spatially correlated to this gradient is the segmentation of the “classical” dorsal visual stream (Goodale and Milner, 1992) into a dorso-dorsal and ventro-dorsal stream (Tanne-Gariepy et al., 2002; Rizzolatti and Matelli, 2003; Verhagen et al., 2008). The dorso-dorsal stream comprises the SPL and cingulate cortex and is anatomically highly interconnected with the dorsal premotor cortex (Tomassini et al., 2007). This fronto-parietal circuit is associated with the involvement in nonstandard stimulus response mappings, online control of actions, and the processing of visuospatial parameters for grasping irrespective of the viewing conditions. The ventro-dorsal stream comprises the aIPS and anterior IPL and is anatomically highly interconnected with the ventral premotor cortex (Tomassini et al., 2007). This fronto-parietal circuit is associated with transformations of spatial object locations in motor commands and the adaptation of motor behavior to current conditions by integrating visual information from the ventral visual stream. Even though some functional principles regarding sensorimotor control begin to emerge within the PPC (as well as in frontal, cerebellar and sub-cortical areas), a lot of work remains to be done to disentangle the functional networks contributing to the individual processes which are necessary for effective motor control.

Many processes which are localized in the PPC are assumedly lateralized to either the left or the right hemisphere (Iacoboni, 2006; Busan et al., 2009). fMRI studies on sensorimotor tasks often show BOLD activation in both PPCs but a stronger activation in the left hemisphere (e.g. Culham et al. (2003), Filimon et al. (2009)). Whether this is due to a left-hemispheric dominance in these tasks or whether this reflects a contralateral activation to the dominant/used right hand/arm remains an open question. Studies which directly address the issue of lateralization deliver an inconclusive picture. In a series of studies, Rushworth et al. (2003) provide consistent evidence that motor attention is lateralized in the left PPC, irrespective of the side of the effector used. For online control of reaching, Desmurget et al. (1999) could only disrupt the correction of right handed but not of left handed movements when delivering TMS over the left PPC. Rice et al. (2007) used TMS to demonstrate that only the contralateral aIPS contributes to grasping movements. Finally, Vesia and colleagues deliver contradictory results regarding reach planning. In one study they demonstrated that left PPC TMS disturbed reach planning for both arms (Vesia et al., 2006), in another they found an effect of TMS on reaches only to the contralateral hemifield and with the contralateral arm (Vesia et al., 2008). Thus, the question of lateralization of the different processes in the context of sensorimotor control still needs to be addressed in more detail in further studies.

Tightly linked to the topic of sensorimotor control is the neuropsychological condition optic ataxia (OA) (Bálint, 1909; Perenin, 2003). OA occurs after a unilateral lesion in either hemisphere's PPC with crucial areas including the posterior part of the precuneus and the junction between the IPL and the superior occipital cortex (colored turquoise in Fig. 2) (Karnath and Perenin, 2005). This condition manifests in reaching and grasping deficits to peripheral vision in the absence of any isolated sensory or motor deficits and has thus been classified as a visuomotor deficit. Recent studies (Blangero et al., 2007; Jackson et al., 2009) have expanded this definition to a more general sensorimotor deficit. Two characteristic deficits can be distinguished (Perenin and Vighetto, 1988): The field effect (misreaching to the contralesional hemifield) is present in the majority of patients while the hand effect (misreaching with the contralesional hand) is mainly present in left-damaged patients. Future studies based on the findings outlined in this introduction might help step-by-step to understand this condition better and probably enhance therapeutic strategies. Conversely, continued work with patients suffering from OA serves as valuable complement to neuroimaging studies in healthy participants.

1.2 Summary of the presented work

Sequential processes during the execution of movements like the planning and execution phase are hard to disentangle with a method like fMRI, which has a temporal resolution of up to several seconds. Compared to the chronometry of the processes under study, usually several hundred milliseconds (Crago et al., 1976; Soechting and Lacquaniti, 1983; Smeets et al., 1990; Day and Lyon, 2000), the temporal resolution of fMRI is clearly not optimal. Furthermore, due to the technical challenges outlined in chapter 1.1, the brain processes during the execution phase of a reaching movement have been studied only coarsely so far. Additionally, most research has focused on visuomotor control, and the integration of proprioception into an ongoing movement has been studied to a lesser extent. The aim of the presented work was to characterize the chronometry of processes involved in the integration of visual and proprioceptive information during the execution of an ongoing reaching movement. Furthermore, this work aimed to contribute causal evidence for the necessity of several sub-regions on the PPC for these processes. For the experiments, we have used behavioral paradigms combined with complementary neuro-physiological and neuroimaging methods.

A common behavioral method to study online control processes are visual double-step (Megaw, 1974; Georgopoulos et al., 1981; Soechting and Lacquaniti, 1983; Prablanc and Martin, 1992) or other perturbation paradigms. The objective for using these paradigms is to add new, goal relevant information after the onset of a movement. This leads to an online response to the new sensory information, resulting in an accordant change of the movement. We utilized three perturbation paradigms in the work presented here. The first is the classical visual double-step paradigm in which the visual target of a reaching movement is displaced during the course of an ongoing movement. With this paradigm, the integration of visual information related to the target of the movement can be assessed. The second visual paradigm is a displacement of the visual representation of the hand position. This paradigm originates from experiments with prism goggles (Helmholtz, 1867) in which participants reached with eyes closed to a target previously seen through these prism goggles. The mismatch between the new visual scene and the proprioceptive representation of space was first used to study adaptation processes. A virtual reality (VR) environment, as used in the work presented here, allows for an exact control of the duration of this mismatch, so that it can also be used to study online control processes. Sarlegna and colleagues (Sarlegna et al., 2003; Sarlegna et al., 2004) have shown that participants reaching for a visual target respond to a displacement of the seen hand position with a correction of the movement into the opposite direction. Although the correction is not complete in respect to the visual scene (some proprioceptive influence of 30-40% still remains) this paradigm is well suited for investigating the integration of visual information about the acting body part. The final paradigm is a force or "proprioceptive" perturbation consisting of a short force impulse administered to the reaching hand by a robot arm, which was used for the movements as a manipulandum. For reaching movements without vision of the hand, the detection of the perturbation and the resulting corrective change in the movement necessarily relies on the integration of proprioceptive information. When the reaching hand is seen during the movement, the response to this perturbation can be accomplished with the integration of visual and/or proprioceptive information.

The integration of visual and proprioceptive information during an ongoing movement has previously not been studied in direct comparison in behavioral experiments. The measurements used for investigating the response onset to the two kinds of perturbations are usually different so that the results from the studies are hard to compare. For visual perturbations, mainly kinematic data like the first measurable deviation of the hand path, velocity, or acceleration is used (e.g. Prablanc and Martin (1992)). Force perturbations are frequently assessed with electromyography (EMG), measuring the onset of the muscle activity from the muscles which execute the corrective movement (Crago et al., 1976; Smeets et al., 1990). Furthermore, it has been shown repeatedly that vision of the reaching hand increases reaching accuracy (Woodworth, 1899; Bard et al., 1985; Spijkers and Lochner, 1994; Spijkers and Spellerberg, 1995; Proteau et al., 2000) but not whether this has an influence on the timing of the response onset of the corrective movement. In the first study (chapter 2.2) we investigated the effect of visual feedback about the hand position on the response time to the visual double-step and the proprioceptive perturbation. The response times to both perturbations were assessed with kinematic and EMG measurements. Interestingly, providing visual feedback about the reaching hand decreased the response latency to the visual perturbation but had no effect on the latency to the proprioceptive perturbation. Furthermore, this facilitative effect only showed for responses during an ongoing movement and not for a choice reaction time task, which we employed as a control task. We concluded that the facilitation most probably stems from the possibility to integrate the newly arriving information in the same reference frame in which the spatial sensitive movement was executed originally. Additionally, using the EMG latency measurements allowed estimating the central neural processing time for coordinate transformations to be in the range of 10 ms. With this study we also laid the foundation for the following TMS experiments. First, we provided an estimate about the neural processing times for the integration of visual and proprioceptive information during an ongoing movement, which is required for the timing of the TMS pulses. Second, we evaluated sensitive behavioral measurements for the onset of the corrective movements based on kinematic data using EMG data as reference. Such finely tuned measurements are essential for assessing the behavioral effect of TMS.

The two TMS studies (chapters 2.3 and 2.4) are inspired by the work of Desmurget and colleagues (1999), which demonstrated for the first time that applying TMS over the left PPC disrupts the corrective movement to a target displacement by. This study remained controversial as Johnson and Haggard (2005) published a non-finding using the same TMS coil positioning method and a comparable experimental procedure. In view of the high inter-individual differences in the human PPC (Grefkes and Fink, 2005) it is implausible to expect that the TMS coil placement procedure from Desmurget et al. (1999), which does not take into account any individual differences, yields in reliable behavioral effects. This was even demonstrated in the original study as only four out of five subjects showed behavioral effects. Furthermore, both studies relied on assessing the endpoint accuracy of the movements and considering the transient effects of TMS, which renders the possibility of earlier behavioral deviations more likely, this measurement might not always be sufficient to capture more subtle behavioral effects caused by TMS. In the second study (chapter 2.3) we aimed to delineate the sub-regions of the PPC which are necessary to integrate visual information into an ongoing movement. Therefore, we extended the work of Desmurget et al. (1999) in several aspects. First, we planned the TMS stimulation sites upon (individual) functional neuro-anatomy by using an fMRI localizer. The behavioral experiments were subsequently conducted with neuro-navigated TMS. Second, we conducted three experiments with different perturbation paradigms and parameters, respectively. To investigate the integration of visual information related to the target of the movement, we utilized the classical double-step paradigm, the displacement of the visual target. This paradigm was tested with vision of the reaching hand and additionally without this visual feedback. The latter is similar to the behavioral paradigm which was originally used by Desmurget et al. (1999). To investigate the integration of visual information about the acting body part, we utilized the displacement of the visual representation of the hand position as second visual perturbation paradigm. Finally, we assessed the onset of the corrective movements as behavioral measurement for the TMS effect in addition to the end accuracy. The fMRI localizer revealed partially high inter-individual differences in BOLD activation for movements with corrective responses in contrast to unperturbed movements. More superior areas on the anterior part of the PPC showed rather consistent activation while the inter-individual differences increased the more inferior an area was located. Thus, the TMS stimulation sites for the behavioral experiments were based upon group and where applicable also upon individual fMRI activations. This procedure led to a grid of TMS coil positions covering the anterior part of the PPC, spanning from the SPL to the SMG. Independent of the nature of the visual information which had to be integrated into the movement, TMS over the anterior IPS and the anterior SMG consistently delayed or attenuated the correction to the perturbation. Several controls confirmed the spatial and task-related specificity of the TMS effects. These results support the hypothesis of Tunik et al. (2007), proposing that the aIPS is a critical general node for visuomotor control. The involvement of the SMG in reaching-related activities has been reported only sporadically so far. The fMRI localizer revealed inter-individual differences in SMG activation during movement control in an order of centimeters and this is a likely cause why conventional fMRI group studies on this topic often miss the SMG region. With this study we demonstrated that localizing putative areas with fMRI and subsequently testing the individual activation pattern with TMS is a successful approach to disentangle cortical sub-areas which possess high inter-individual differences.

Finally, the last study (chapter 2.4) aimed to assess the sub-regions of the PPC required to integrate proprioceptive information into an ongoing movement and to test whether these regions are distinct from the areas necessary to integrate the corresponding visual information. For this study we utilized force perturbations with and without visual feedback about the hand position. In the former condition, the brain can exploit visual and proprioceptive information to correct for the perturbation while the latter necessitates relying on proprioceptive input alone. Applying a force perturbation paradigm in the MR scanner was not possible so we could not adopt an fMRI localizer. We used the MNI coordinates from the TMS stimulation sites of the previous study instead and extended the grid using additional stimulation sites derived from a prior TMS study about motor-adaptation in a force field (Della-Maggiore et al., 2004). This procedure led to a grid of stimulation sites which extended further medial and posterior than the one in the previous study. Dependent on the viewing condition, TMS over different sites caused distinct behavioral effects on the corrective movement to the force perturbation. When visual hand feedback was available, TMS over the aIPS prolonged reaching time. This stimulation site was the very same as used in the previous study and these results confirm once again the significance of the aIPS in visuomotor control in general. Without visual feedback about the hand position, i.e. in the pure proprioceptive condition, TMS over the middle part of the SPL interfered with the endpoint accuracy of the reaching movement when a correction to the force perturbation was necessary. This stimulation site was the same as used by Della-Maggiore et al. (2004) to interfere with motor-adaptation based on proprioceptive feedback. These results suggest that this area is a key node for processing proprioception in motor control. Both areas reported here are clearly separable as sites in between yielded no behavioral effect when stimulated with TMS.

Taken together, the results of the TMS studies presented here confirm and extend some previous (TMS) studies (Della-Maggiore et al., 2004; Tunik et al., 2007) but seem to contradict – at least partially – the general picture (mainly derived from fMRI studies) of the wide-ranging functional gradients spanning the PPC as outlined in chapter 1.1. These discrepancies clearly highlight the necessity to combine complementary techniques such as fMRI and TMS in order to disentangle the neural processes involved in sensorimotor control.

1.3 Future directions

A direct continuation of the work presented here is to investigate with TMS the contribution of the PPC to the integration of vestibular signals into an ongoing movement. When the head is fixed in space, as in the work presented here, the contribution of the vestibular system to motor control in healthy humans is negligible. As soon as the head is turned or the whole body is moving, the vestibular system is the third sensory modality contributing to the relative localization between the acting effector and the target of the movement. Studies on the cortical localization of vestibular information processing in humans are sparse. For fMRI studies, the participant has to lie still in the MR scanner and cannot rotate the head or move the body. Therefore, caloric vestibular stimulation (CVS, application of cold or warm water in either ear canal (Lidvall, 1961)) or galvanic vestibular stimulation (GVS, application of a small current between the mastoid processes (Day, 1997)) is utilized to stimulate brain regions which process vestibular information in general (Bottini et al., 1994; Lobel et al., 1998; Fasold et al., 2002; Dieterich et al., 2003; Stephan et al., 2005). These studies revealed several cortical areas within the PPC, predominantly in the temporoparietal junction (TPJ) and the anterior cingulate cortex. Additionally, involvement of the IPS, SMG, IPL, and precuneus was reported, whereby the whole PPC sparing the SPL seems to be involved in some kind of processing to vestibular input. Some studies report a lateralization dependent on the side of stimulation (Bottini et al., 1994; Dieterich et al., 2003). In contrast, other studies report either a complete right hemispheric dominance (Fasold et al., 2002), a dominance for the ipsi-handedness side (Dieterich et al., 2003), i.e. the right hemisphere for right handed participants, or a lateralization within the IPS to the left side (Lobel et al., 1998) or the right side (Suzuki et al., 2001). This inconsistent picture is complemented by a few TMS studies, underpinning the right hemispheric bias and the lateralization dependent on the side of stimulation. Administering TMS over the right TPJ interfered with embodiment[4] (Lenggenhager et al., 2006) and the authors concluded that this was due to a disturbance of vestibular and multisensory processing. The control stimulation site over the IPS showed no effect. In a series of experiments, Seemungal and colleagues (Seemungal et al., 2008b, a, 2009) investigated the effect of TMS over the PPC on path integration during

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[4] The concept of embodiment refers to the sense of being localized within one’s physical body.

passive rotation. They showed that TMS stimulation above the electrode positions P3/P4[5] decreased participants' performance in this spatial perception task when rotated to the contra-lesional side. Sensorimotor control studies on vestibular input with paradigms comparable to the work presented here have only been conducted on a behavioral level so far (Bresciani et al., 2002b; Bresciani et al., 2002a; Bresciani et al., 2005). In these studies, participants had to reach in pitch black to a remembered visual target after the onset of a passive rotation, or as a control after completion of the rotation. Successful reaching movements required therefore the integration of vestibular information during, or in the control condition before, execution of the movement (Bresciani et al., 2002a). Based on the better reaching performance when reaching during the rotation, they concluded that the processing of vestibular information during online control does not resemble spatial perception of vestibular information, which has been investigated by Seemungal and colleagues. The finding that GVS administered at rotation onset deviated the reaching trajectory towards the anode (Bresciani et al., 2002b) demonstrates that the paradigm is very sensitive to erroneous vestibular information and thus a good candidate for being utilized in TMS studies about vestibular integration in the PPC. I have implemented a comparable experimental environment and will conduct a corresponding TMS study in the near future. In view of the inconsistent fMRI findings, the stimulation sites used by Seemungal and colleagues constitute the most promising candidates for TMS stimulation sites to use for this experiment. Another putative area due to the fMRI results is the TPJ. Therefore, I will construct a grid of TMS stimulation sites between the medial IPS, the TPJ and the aIPS. The latter site is primarily added for comparability to the two TMS studies presented here. However, this area was also found by some of the fMRI studies and is therefore an interesting candidate region. As the processing of vestibular information in the PPC appears to be lateralized regarding the side of rotation and biased towards the right hemisphere, respectively, both hemispheres will be tested. In the light of the results of Seemungal and colleagues I would expect that also the online control processes for vestibular information are lateralized depending on the side of rotation.

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[5] In reference to the EEG-10-20 system. The electrodes P3/P4 are located approximately above the medial IPS but exhibit large inter-individual differences (Herwig U, Satrapi P, Schönfeldt-Lecuona C (2003) Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr 16:95-99).

This study will be the first work in healthy humans about the neural correlates of vestibular integration in goal-directed movements and round out my series of TMS studies about sensorimotor integration.

Another future field of research results directly from the current limitations in fMRI studies on sensorimotor control as outlined in chapter 1.1. fMRI is a powerful method for human brain mapping studies and sophisticated experimental setups and paradigms are needed. At the moment, studies in this field are either motivated from an engineering perspective, with highly sophisticated setups but lacking application in neuroscience research like the work by Gassert and colleagues. Some of their "simpler" devices (Gassert et al., 2006a), a 1-degree-of-freedom manipulandum and a 2-degree-of-freedom robot for hand movements, are already used in medical or neuroscience research (Bursztyn et al., 2006; Ganesh et al., 2008; Haller et al., 2009). Even though devices for natural reaching studies like a 2-degree-of-freedom manipulandum with a 25x25 cm workspace exist (Gassert et al., 2006b), to my knowledge they were never applied in neuroscience studies so far. This is possibly due to the additional challenges like movement artifacts that have to be solved to conduct such studies. The other kind of studies are motivated from a neuroscience perspective, with interesting scientific questions asked but lacking the technical means for conducting comprehensive or ecological valid studies. Examples are the "grasparatus" by Culham and colleagues (Culham et al., 2003), a simple and elegant device for investigating grasping movements but also restricted to grasping only, or the 2-degree-of-freedom robotic manipulandum from Diedrichsen et al. (2005), which was restricted to a 4x4 cm workspace in all studies. An integrative approach is needed to tackle all issues related to this research where scientists from different disciplines have to work together tightly. Sophisticated MR compatible setups have to be designed and implemented by engineers, like hydraulically or pneumatically actuated robot arms which do not cause any artifacts in the MR scanner. These manipulanda have to provide precise readout of behavioral data, manipulation of the haptic scene via force fields, and tight integration with the visual scene. Additionally, methods to handle inhomogenities in the B0 field due to participants' movements have to be developed. This issue can be addressed by MR physicists on the imaging side and by statisticians on the data analysis side. Attempts to deal with this from the imaging side include saving phase information, which serve as a good indicator of imaging stability (Menon, 2002), in addition to the signal amplitude which is usually the only information used in echo-planar imaging (EPI) data. A successful application of this principle was implemented by Barry et al. (2009) who used a navigator-corrected EPI sequence with subsequent linear regression to exploit the additional information of phase data. On the side of data analysis, several approaches have been tried but their evaluation is still missing. A relatively simple approach is to estimate the global variance of each image and weight the images inversely (Diedrichsen and Shadmehr, 2005). A related approach is to assess the time course of the signal in white matter and liquor, signal changes which occur most likely due to artifacts, and use the mean time course as additional regressor in the subsequent general linear model (GLM) analyses (Beurze et al., 2009). All these efforts of developing suitable experimental set-ups and obtaining good data quality have to be driven by neuroscientific questions and paradigms. Existing behavioral paradigms have to be adapted or new paradigms have to be developed by neuroscientists. These paradigms should be driven by the scientific questions asked and not work around what is thought to be technical feasible. For successful projects in this area I regard it essential that all these components are integrated and scientists from all disciplines work together closely.

Scientific questions which can be addressed once the suitable setups are available are also shortly touched upon in chapter 1.1. First of all, paradigms are needed to disentangle the different processes sub-serving sensorimotor control. To separate planning processes usually delayed movements are used (e.g. Astafiev et al. (2003), Medendorp et al. (2003), Medendorp et al. (2005), Beurze et al. (2007), Hagler et al. (2007), Beurze et al. (2009)). To investigate the actual execution phase of a movement and the integration of sensory information therein, perturbation paradigms as introduced in chapter 1.2 might be transferred to fit fMRI requirements. However, during execution of a movement various parallel processes (see chapter 1.1) cause brain activation at the same time and paradigms are needed to disentangle them. The isolation of areas for coordinate transformation processes has started (for a review see Medendorp et al. (2008)) but there is much left to do to disentangle all the processes which are active during sensorimotor control. One general topic which should be addressed further is the effector specificity: Do the gradients of effector-dominance as outlined in chapter 1.1 hold if different types of movements can be investigated within the same paradigm and participants? Can distinct networks be disentangled for the processing of information for specific effectors' movements? Another general question of interest is the topic of lateralization: Which sub-processes are completely lateralized or bilateral? For which processes does the lateralization depend upon the side of the effector used or the side of the sensory stimulation? But these questions are just the tip of the iceberg.

With thoroughly designed experiments and highly sophisticated setups, fMRI studies have the potential to advance the field of sensorimotor control a huge step forward within the next decade. Ideally, these studies are supplemented by experiments with complementary imaging techniques like TMS. While fMRI studies are a great technique to deliver a spatial comprehensive picture of the brain areas involved in the different processes sub-serving sensorimotor control, TMS provides insight about the causal contribution and chronometry of specific cortical areas for these processes. Therefore, research in this area should also aim to match paradigms and setups for both imaging modalities, which allows for a direct comparability and integration of experiments conducted with these techniques. Such truly multi-modal approaches are the future of neuroimaging and offer possibilities far beyond the capability of one technique alone.

1.4 References

Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. Annu Rev Neurosci 25:189-220.

Andersen RA, Cui H (2009) Intention, action planning, and decision making in parietal-frontal circuits. Neuron 63:568-583.

Andersen RA, Snyder LH, Bradley DC, Xing J (1997) Multimodal representation of space in the posterior parietal cortex and its use in planning movements. Annu Rev Neurosci 20:303-330.

Astafiev SV, Shulman GL, Stanley CM, Snyder AZ, Van Essen DC, Corbetta M (2003) Functional organization of human intraparietal and frontal cortex for attending, looking, and pointing. J Neurosci 23:4689-4699.

Bálint R (1909) Seelenlähmung des "Schauens", optische Ataxie, räumliche Störung der Aufmerksamkeit. Monatsschr Psychiatr Neurol 25:57-81.

Bard C, Hay L, Fleury M (1985) Role of peripheral vision in the directional control of rapid aiming movements. Can J Psychol 39:151-161.

Barry RL, Williams JM, Klassen LM, Gallivan JP, Culham JC, Menon RS (2009) Evaluation of preprocessing steps to compensate for magnetic field distortions due to body movements in BOLD fMRI. Magn Reson Imaging:doi:10.1016/j.mri.2009.1007.1005.

Battaglia-Mayer A, Caminiti R, Lacquaniti F, Zago M (2003) Multiple levels of representation of reaching in the parieto-frontal network. Cereb Cortex 13:1009-1022.

Bernstein NA (1967) The co-ordination and regulation of movements: Pergamon Press (Oxford and New York).

Beurze SM, Van Pelt S, Medendorp WP (2006) Behavioral reference frames for planning human reaching movements. J Neurophysiol 96:352-362.

Beurze SM, de Lange FP, Toni I, Medendorp WP (2007) Integration of target and effector information in the human brain during reach planning. J Neurophysiol 97:188-199.

Beurze SM, de Lange FP, Toni I, Medendorp WP (2009) Spatial and Effector Processing in the Human Parietofrontal Network for Reaches and Saccades. J Neurophysiol 101:3053-3062.

Blangero A, Menz MM, McNamara A, Binkofski F (2009) Parietal modules for reaching. Neuropsychologia 47:1500-1507.

Blangero A, Ota H, Delporte L, Revol P, Vindras P, Rode G, Boisson D, Vighetto A, Rossetti Y, Pisella L (2007) Optic ataxia is not only 'optic': impaired spatial integration of proprioceptive information. Neuroimage 36 Suppl 2:T61-68.

Blouin J, Bard C, Teasdale N, Paillard J, Fleury M, Forget R, Lamarre Y (1993) Reference systems for coding spatial information in normal subjects and a deafferented patient. Exp Brain Res 93:324-331.

Bottini G, Sterzi R, Paulesu E, Vallar G, Cappa SF, Erminio F, Passingham RE, Frith CD, Frackowiak RS (1994) Identification of the central vestibular projections in man: a positron emission tomography activation study. Exp Brain Res 99:164-169.

Bresciani JP, Gauthier GM, Vercher JL, Blouin J (2005) On the nature of the vestibular control of arm-reaching movements during whole-body rotations. Exp Brain Res 164:431-441.

Bresciani JP, Blouin J, Sarlegna F, Bourdin C, Vercher JL, Gauthier GM (2002a) On-line versus off-line vestibular-evoked control of goal-directed arm movements. Neuroreport 13:1563-1566.

Bresciani JP, Blouin J, Popov K, Bourdin C, Sarlegna F, Vercher JL, Gauthier GM (2002b) Galvanic vestibular stimulation in humans produces online arm movement deviations when reaching towards memorized visual targets. Neurosci Lett 318:34-38.

Bursztyn LL, Ganesh G, Imamizu H, Kawato M, Flanagan JR (2006) Neural correlates of internal-model loading. Curr Biol 16:2440-2445.

Busan P, Jarmolowska J, Semenic M, Monti F, Pelamatti G, Pizzolato G, Battaglini PP (2009) Involvement of ipsilateral parieto-occipital cortex in the planning of reaching movements: evidence by TMS. Neurosci Lett 460:112-116.

Cavina-Pratesi C, Monaco S, Fattori P, Galletti C, McAdam TD, Quinlan DJ, Goodale MA, Culham JC (2010) Functional magnetic resonance imaging reveals the neural substrates of arm transport and grip formation in reach-to-grasp actions in humans. J Neurosci 30:10306-10323.

Cohen YE, Andersen RA (2002) A common reference frame for movement plans in the posterior parietal cortex. Nat Rev Neurosci 3:553-562.

Colby CL, Duhamel JR, Goldberg ME (1993) Ventral intraparietal area of the macaque: anatomic location and visual response properties. J Neurophysiol 69:902-914.

Cowey A (2005) The Ferrier Lecture 2004: What can transcranial magnetic stimulation tell us about how the brain works? Phil Trans R Soc B 360:1185-1205.

Crago PE, Houk JC, Hasan Z (1976) Regulatory actions of human stretch reflex. J Neurophysiol 39:925-935.

Culham JC, Kanwisher NG (2001) Neuroimaging of cognitive functions in human parietal cortex. Curr Opin Neurobiol 11:157-163.

Culham JC, Valyear KF (2006) Human parietal cortex in action. Curr Opin Neurobiol 16:205-212.

Culham JC, Cavina-Pratesi C, Singhal A (2006) The role of parietal cortex in visuomotor control: what have we learned from neuroimaging? Neuropsychologia 44:2668-2684.

Culham JC, Gallivan J, Cavina-Pratesi C, Quinlan DJ (2008) fMRI Investigations of Reaching and Ego space in Human Superior Parieto-Occipital Cortex. In: Embodiment, Ego-Space and Action (Klatzky R, McWhinney B, Behrmann M, eds), pp 247-274. New York: Psychology Press.

Culham JC, Danckert SL, DeSouza JF, Gati JS, Menon RS, Goodale MA (2003) Visually guided grasping produces fMRI activation in dorsal but not ventral stream brain areas. Exp Brain Res 153:180-189.

d'Avella A, Portone A, Fernandez L, Lacquaniti F (2006) Control of fast-reaching movements by muscle synergy combinations. J Neurosci 26:7791-7810.

Day BL (1997) Galvanic vestibular stimulation: new uses for an old tool. J Physiol 517:631.

Day BL, Lyon IN (2000) Voluntary modification of automatic arm movements evoked by motion of a visual target. Exp Brain Res 130:159-168.

Day BL, Brown P (2001) Evidence for subcortical involvement in the visual control of human reaching. Brain 124:1832-1840.

Della-Maggiore V, Malfait N, Ostry DJ, Paus T (2004) Stimulation of the posterior parietal cortex interferes with arm trajectory adjustments during the learning of new dynamics. J Neurosci 24:9971-9976.

Desmurget M, Grafton S (2000) Forward modeling allows feedback control for fast reaching movements. Trends Cogn Sci 4:423-431.

Desmurget M, Epstein CM, Turner RS, Prablanc C, Alexander GE, Grafton ST (1999) Role of the posterior parietal cortex in updating reaching movements to a visual target. Nat Neurosci 2:563-567.

Diedrichsen J, Shadmehr R (2005) Detecting and adjusting for artifacts in fMRI time series data. NeuroImage 27 624 – 634.

Diedrichsen J, Shadmehr R, Ivry RB (2010) The coordination of movement: optimal feedback control and beyond. Trends Cogn Sci 14:31-39.

Diedrichsen J, Hashambhoy Y, Rane T, Shadmehr R (2005) Neural correlates of reach errors. J Neurosci 25:9919-9931.

Dieterich M, Bense S, Lutz S, Drzezga A, Stephan T, Bartenstein P, Brandt T (2003) Dominance for vestibular cortical function in the non-dominant hemisphere. Cereb Cortex 13:994-1007.

Duhamel JR, Colby CL, Goldberg ME (1992) The updating of the representation of visual space in parietal cortex by intended eye movements. Science 255:90-92.

Ernst MO, Banks MS (2002) Humans integrate visual and haptic information in a statistically optimal fashion. Nature 415:429-433.

Evarts EV (1971) Central control of movement. V. Feedback and corollary discharge: a merging of the concepts. Neurosci Res Program Bull 9:86-112.

Fasold O, von Brevern M, Kuhberg M, Ploner CJ, Villringer A, Lempert T, Wenzel R (2002) Human vestibular cortex as identified with caloric stimulation in functional magnetic resonance imaging. Neuroimage 17:1384-1393.

Filimon F (2010) Human Cortical Control of Hand Movements: Parietofrontal Networks for Reaching, Grasping, and Pointing. The Neuroscientist 16:388-407.

Filimon F, Nelson JD, Huang RS, Sereno MI (2009) Multiple parietal reach regions in humans: cortical representations for visual and proprioceptive feedback during on-line reaching. J Neurosci 29:2961-2971.

Friston KJ, Williams S, Howard R, Frackowiak RSJ, Turner R (1996) Movement-related effects in fMRI time-series. NeuroImage 25:244-252.

Friston KJ, Ashburner J, Frith CD, Poline JB, Heather JD, Frackowiak RSJ (1995) Spatial registration and normalization of images. Human Brain Mapping 3:165-189.

Ganesh G, Burdet E, Haruno M, Kawato M (2008) Sparse linear regression for reconstructing muscle activity from human cortical fMRI. Neuroimage 42:1463-1472.

Gassert R, Burdet E, Chinzei K (2008a) MRI-Compatible Robotics. IEEE Eng Med Biol Mag 27:12-14.

Gassert R, Burdet E, Chinzei K (2008b) Opportunities and challenges in MR-compatible robotics: reviewing the history, mechatronic components, and future directions of this technology. IEEE Eng Med Biol Mag 27:15-22.

Gassert R, Moser R, Burdet E, Bleuler H (2006a) MRI/fMRI-Compatible Robotoc System With Force Feedback for Interaction With Human Motion. IEEE/ASME Transactions an Mechatronics 11:9.

Gassert R, Dovat L, Lambercy O, Ruffieux Y, Chapuis D, Ganesh G, Burdet E, Bleuler H (2006b) A 2-DOF fMRI Compatible Haptic Interface to Investigate the Neural Control of Arm Movements. In: 2006 IEEE International Conference on Robotics and Automation, p 7. Orlando, Florida.

Georgopoulos AP, Kalaska JF, Massey JT (1981) Spatial trajectories and reaction times of aimed movements: effects of practice, uncertainty, and change in target location. J Neurophysiol 46:725-743.

Ghez C, Krakauer JW (2000) The Organization of Movement. In: Principles of Neural Science (Kandel ER, Schwartz J, Jessell TM, eds), pp 653-673. New York: McGraw-Hill.

Gnadt JW, Andersen RA (1988) Memory related motor planning activity in posterior parietal cortex of macaque. Exp Brain Res 70:216-220.

Goodale MA, Milner AD (1992) Separate visual pathways for perception and action. Trends Neurosci 15:20-25.

Grefkes C, Fink GR (2005) The functional organization of the intraparietal sulcus in humans and monkeys. J Anat 207:3-17.

Grefkes C, Ritzl A, Zilles K, Fink GR (2004) Human medial intraparietal cortex subserves visuomotor coordinate transformation. Neuroimage 23:1494-1506.

Hagler DJ, Jr., Riecke L, Sereno MI (2007) Parietal and superior frontal visuospatial maps activated by pointing and saccades. Neuroimage 35:1562-1577.

Haller S, Chapuis D, Gassert R, Burdet E, Klarhofer M (2009) Supplementary motor area and anterior intraparietal area integrate fine-graded timing and force control during precision grip. Eur J Neurosci 30:2401-2406.

Helmholtz H (1867) Handbuch der physiologischen Optik. Leipzig: Voss.

Herwig U, Satrapi P, Schönfeldt-Lecuona C (2003) Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr 16:95-99.

Himmelbach M, Nau M, Zundorf I, Erb M, Perenin MT, Karnath HO (2009) Brain activation during immediate and delayed reaching in optic ataxia. Neuropsychologia 47:1508-1517.

Hoff B, Arbib MA (1993) Models of Trajectory Formation and Temporal Interaction of Reach and Grasp. J Mot Behav 25:175-192.

Iacoboni M (2006) Visuo-motor integration and control in the human posterior parietal cortex: evidence from TMS and fMRI. Neuropsychologia 44:2691-2699.

Jackson SR, Newport R, Husain M, Fowlie JE, O'Donoghue M, Bajaj N (2009) There may be more to reaching than meets the eye: re-thinking optic ataxia. Neuropsychologia 47:1397-1408.

Jenkinson M, Bannister P, Brady M, Smith S (2002) Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17:825-841.

Johnson H, Haggard P (2005) Motor awareness without perceptual awareness. Neuropsychologia 43:227-237.

Karnath HO, Perenin MT (2005) Cortical control of visually guided reaching: evidence from patients with optic ataxia. Cereb Cortex 15:1561-1569.

Klare S, Peer A, Buss M (2010) Development of a 6 DoF fMRI-Compatible Haptic Interface for Finger Movements. In: Eurohaptics 2010.

Krakauer JW, Ghilardi MF, Ghez C (1999) Independent learning of internal models for kinematic and dynamic control of reaching. Nat Neurosci 2:1026-1031.

Lenggenhager B, Smith ST, Blanke O (2006) Functional and neural mechanisms of embodiment: importance of the vestibular system and the temporal parietal junction. Rev Neurosci 17:643-657.

Levy I, Schluppeck D, Heeger DJ, Glimcher PW (2007) Specificity of human cortical areas for reaches and saccades. J Neurosci 27:4687-4696.

Lidvall HF (1961) Vertigo and nystagmus responses to caloric stimuli repeated at short intervals. Acta Otolaryngol 53:33-44.

Lobel E, Kleine JF, Bihan DL, Leroy-Willig A, Berthoz A (1998) Functional MRI of galvanic vestibular stimulation. J Neurophysiol 80:2699-2709.

McGuire LM, Sabes PN (2009) Sensory transformations and the use of multiple reference frames for reach planning. Nat Neurosci 12:1056-1061.

Medendorp WP, Goltz HC, Vilis T, Crawford JD (2003) Gaze-centered updating of visual space in human parietal cortex. J Neurosci 23:6209-6214.

Medendorp WP, Goltz HC, Crawford JD, Vilis T (2005) Integration of target and effector information in human posterior parietal cortex for the planning of action. J Neurophysiol 93:954-962.

Medendorp WP, Beurze SM, Van Pelt S, Van Der Werf J (2008) Behavioral and cortical mechanisms for spatial coding and action planning. Cortex 44:587-597.

Megaw ED (1974) Possible modification to a rapid on-going programmed manual response. Brain Res 71:425-441.

Menon RS (2002) Postacquisition suppression of large-vessel BOLD signals in high-resolution fMRI. Magn Reson Med 47:1-9.

O'Sullivan I, Burdet E, Diedrichsen J (2009) Dissociating variability and effort as determinants of coordination. PLoS Comput Biol 5:e1000345.

Pelisson D, Prablanc C, Goodale MA, Jeannerod M (1986) Visual control of reaching movements without vision of the limb. II. Evidence of fast unconscious processes correcting the trajectory of the hand to the final position of a double-step stimulus. Exp Brain Res 62:303-311.

Perenin MT (2003) Optische Ataxie. In: Neuropsychologie (Karnath HO, Thier P, eds), pp 325-335. Berlin Heidelberg New York: Springer-Verlag.

Perenin MT, Vighetto A (1988) Optic ataxia: a specific disruption in visuomotor mechanisms. I. Different aspects of the deficit in reaching for objects. Brain 111 (Pt 3):643-674.

Prablanc C, Martin O (1992) Automatic control during hand reaching at undetected two-dimensional target displacements. J Neurophysiol 67:455-469.

Proteau L, Boivin K, Linossier S, Abahnini K (2000) Exploring the limits of peripheral vision for the control of movement. J Mot Behav 32:277-286.

Rice NJ, Tunik E, Grafton ST (2006) The anterior intraparietal sulcus mediates grasp execution, independent of requirement to update: new insights from transcranial magnetic stimulation. J Neurosci 26:8176-8182.

Rice NJ, Tunik E, Cross ES, Grafton ST (2007) On-line grasp control is mediated by the contralateral hemisphere. Brain Res 1175:76-84.

Rizzolatti G, Matelli M (2003) Two different streams form the dorsal visual system: anatomy and functions. Exp Brain Res 153:146-157.

Rizzolatti G, Luppino G, Matelli M (1998) The organization of the cortical motor system: new concepts. Electroencephalogr Clin Neurophysiol 106:283-296.

Rushworth MF, Johansen-Berg H, Gobel SM, Devlin JT (2003) The left parietal and premotor cortices: motor attention and selection. Neuroimage 20 Suppl 1:S89-100.

Sakata H, Taira M, Murata A, Mine S (1995) Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. Cereb Cortex 5:429-438.

Sarlegna F, Blouin J, Bresciani JP, Bourdin C, Vercher JL, Gauthier GM (2003) Target and hand position information in the online control of goal-directed arm movements. Exp Brain Res 151:524-535.

Sarlegna F, Blouin J, Vercher JL, Bresciani JP, Bourdin C, Gauthier GM (2004) Online control of the direction of rapid reaching movements. Exp Brain Res 157:468-471.

Sarlegna FR, Gauthier GM, Bourdin C, Vercher JL, Blouin J (2006) Internally driven control of reaching movements: a study on a proprioceptively deafferented subject. Brain Res Bull 69:404-415.

Seemungal BM, Rizzo V, Gresty MA, Rothwell JC, Bronstein AM (2008a) Posterior parietal rTMS disrupts human Path Integration during a vestibular navigation task. Neurosci Lett 437:88-92.

Seemungal BM, Rizzo V, Gresty MA, Rothwell JC, Bronstein AM (2008b) Cortical processing in vestibular navigation. Prog Brain Res 171:339-346.

Seemungal BM, Rizzo V, Gresty MA, Rothwell JC, Bronstein AM (2009) Perceptual encoding of self-motion duration in human posterior parietal cortex. Ann N Y Acad Sci 1164:236-238.

Shadmehr R (2009) Computational Approaches to Motor Control. In: Encyclopedia of Neuroscience (Squire LR, ed), pp 9-17. Oxford: Academic Press.

Simon O, Mangin JF, Cohen L, Le Bihan D, Dehaene S (2002) Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. Neuron 33:475-487.

Smeets JB, Erkelens CJ, Denier van der Gon JJ (1990) Adjustments of fast goal-directed movements in response to an unexpected inertial load. Exp Brain Res 81:303-312.

Soechting JF, Lacquaniti F (1983) Modification of trajectory of a pointing movement in response to a change in target location. J Neurophysiol 49:548-564.

Sperry RW (1950) Neural basis of the spontaneous optokinetic response produced by visual inversion. J Comp Physiol Psychol 43:482-489.

Spijkers W, Spellerberg S (1995) On-line visual control of aiming movements? Acta Psychol (Amst) 90:333-348.

Spijkers WA, Lochner P (1994) Partial visual feedback and spatial end-point accuracy of discrete aiming movements. J Mot Behav 26:283-295.

Stephan T, Deutschlander A, Nolte A, Schneider E, Wiesmann M, Brandt T, Dieterich M (2005) Functional MRI of galvanic vestibular stimulation with alternating currents at different frequencies. Neuroimage 26:721-732.

Suzuki M, Kitano H, Ito R, Kitanishi T, Yazawa Y, Ogawa T, Shiino A, Kitajima K (2001) Cortical and subcortical vestibular response to caloric stimulation detected by functional magnetic resonance imaging. Brain Res Cogn Brain Res 12:441-449.

Szentesi P, Zaremba R, van Mechelen W, Stienen GJ (2001) ATP utilization for calcium uptake and force production in different types of human skeletal muscle fibres. J Physiol 531:393-403.

Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Stuttgart: Georg-Thieme Verlag.

Tanne-Gariepy J, Rouiller EM, Boussaoud D (2002) Parietal inputs to dorsal versus ventral premotor areas in the macaque monkey: evidence for largely segregated visuomotor pathways. Exp Brain Res 145:91-103.

Tomassini V, Jbabdi S, Klein JC, Behrens TE, Pozzilli C, Matthews PM, Rushworth MF, Johansen-Berg H (2007) Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. J Neurosci 27:10259-10269.

Tunik E, Frey SH, Grafton ST (2005) Virtual lesions of the anterior intraparietal area disrupt goal-dependent on-line adjustments of grasp. Nat Neurosci 8:505-511.

Tunik E, Rice NJ, Hamilton A, Grafton ST (2007) Beyond grasping: representation of action in human anterior intraparietal sulcus. Neuroimage 36 Suppl 2:T77-86.

Turner R, Howseman A, Rees GE, Josephs O, Friston K (1998) Functional magnetic resonance imaging of the human brain: data acquisition and analysis. Exp Brain Res 123:5-12.

Van Pelt S, Toni I, Diedrichsen J, Medendorp WP (2010) Repetition Suppression Dissociates Spatial Frames of Reference in Human Saccade Generation. J Neurophysiol.

Verhagen L, Dijkerman HC, Grol MJ, Toni I (2008) Perceptuo-motor interactions during prehension movements. J Neurosci 28:4726-4735.

Vesia M, Monteon JA, Sergio LE, Crawford JD (2006) Hemispheric asymmetry in memory-guided pointing during single-pulse transcranial magnetic stimulation of human parietal cortex. J Neurophysiol 96:3016-3027.

Vesia M, Yan X, Henriques DY, Sergio LE, Crawford JD (2008) Transcranial magnetic stimulation over human dorsal-lateral posterior parietal cortex disrupts integration of hand position signals into the reach plan. J Neurophysiol 100:2005-2014.

von Holst E, Mittelstaedt H (1950) Das Reafferenzprinzip. Naturwissenschaften 37:464-476.

Wolpert DM, Ghahramani Z (2000) Computational principles of movement neuroscience. Nat Neurosci 3 Suppl:1212-1217.

Wolpert DM, Ghahramani Z, Jordan MI (1995) An internal model for sensorimotor integration. Science 269:1880-1882.

Woodworth RS (1899) The accuracy of voluntary movement. Psychol Rev 3:1-114.

2 Peer-reviewed publications and manuscripts for the cumulative thesis

2.1 Delineation of contribution to collective work

The thesis includes three peer-reviewed papers and manuscripts corresponding to sections 2.2 to 2.4. In the following I specify the contribution of each of the co-authors and myself.

1. Reichenbach, A., Thielscher, A., Peer, A., Bülthoff, H.H., and Bresciani, J.-P. (2009) Seeing the hand while reaching speeds up on-line responses to a sudden change in target position. The Journal of Physiology 587(19), 4605-4616.
    - I (AR) designed the experiments, acquired and analyzed the data and wrote the paper.
    - AT contributed recording methodology and wrote the paper as supervising author.
    - AP provided and set up the haptic device.
    - HHB supervised the project throughout the whole process.
    - JPB designed the experiments and wrote the paper as supervising author.
2. Reichenbach, A., Bresciani, J.-P., Peer, A., Bülthoff, H.H., and Thielscher, A. (2011) Contributions of the PPC to online control of visually guided reaching movements assessed with fMRI-guided TMS. Cerebral Cortex 21(7), 1602-1612.
    - I (AR) designed the experiments, acquired and analyzed the data and wrote the paper.
    - JPB designed the experiments and wrote the paper as supervising author.
    - AP provided and set up the haptic device.
    - HHB supervised the project throughout the whole process.
    - AT designed the experiments and wrote the paper as supervising author.
3. Reichenbach, A., Thielscher, A., Peer, A., Bülthoff H.H., and Bresciani, J.-P. (in review) Different neural substrates for proprioceptively vs. visually guided movements in the human parietal cortex.
    - I (AR) designed the experiments, acquired and analyzed the data and wrote the paper.
    - AT designed the experiments and wrote the paper as supervising author.
    - AP provided and set up the haptic device.
    - HHB supervised the project throughout the whole process.
    - JPB designed the experiments and wrote the paper as supervising author.

2.2 Reichenbach et al. (2009): Seeing the hand while reaching speeds up on-line responses to a sudden change in target position

J Physiol 587.19 (2009) pp 4605–4616

The Journal of Physiology

Seeing the hand while reaching speeds up on-line responses to a sudden change in target position

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Goal-directed movements are executed under the permanent supervision of the central nervous system, which continuously processes sensory afferents and triggers on-line corrections if movement accuracy seems to be compromised. For arm reaching movements, visual information about the hand plays an important role in this supervision, notably improving reaching accuracy. Here, we tested whether visual feedback of the hand affects the latency of on-line responses to an external perturbation when reaching for a visual target. Two types of perturbation were used: visual perturbation consisted in changing the spatial location of the target and kinesthetic perturbation in applying a force step to the reaching arm. For both types of perturbation, the hand trajectory and the electromyographic (EMG) activity of shoulder muscles were analysed to assess whether visual feedback of the hand speeds up on-line corrections. Without visual feedback of the hand, on-line responses to visual perturbation exhibited the longest latency. This latency was reduced by about 10% when visual feedback of the hand was provided. On the other hand, the latency of on-line responses to kinesthetic perturbation was independent of the availability of visual feedback of the hand. In a control experiment, we tested the effect of visual feedback of the hand on visual and kinesthetic two-choice reaction times – for which coordinate transformation is not critical. Two-choice reaction times were never facilitated by visual feedback of the hand. Taken together, our results suggest that visual feedback of the hand speeds up on-line corrections when the position of the visual target with respect to the body must be re-computed during movement execution. This facilitation probably results from the possibility to map hand- and target-related information in a common visual reference frame.

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When reaching for a target object, the afferent signals provided by different sensory channels are continuously processed to supervise the ongoing movement (Wolpert *et al.* 1995; Desmurget & Grafton, 2000). If a discrepancy is detected between the predicted end-point of the movement and the target location – e.g. caused by motor errors or unexpected perturbations – the arm trajectory is modulated on-line to compensate for the detected error and preserve reaching accuracy. For instance, visually detected changes of the target location occurring during movement execution (Soechting & Lacquaniti, 1983; Goodale *et al.* 1986; Prablanc & Martin, 1992; Day & Lyon, 2000; Day & Brown, 2001; Johnson *et al.* 2002; Sarlegna *et al.* 2003) or a load perturbation unexpectedly applied to the reaching arm (Vince, 1948; Crago *et al.* 1976; Cordo, 1990; Smeets *et al.* 1990) can trigger on-line corrections of the hand trajectory. Visual feedback of the hand position plays an important role in this control. In particular, it increases the reaching accuracy (Woodworth, 1899; Bard *et al.* 1985; Spijkers & Lochner, 1994; Spijkers & Spellerberg, 1995; Proteau *et al.* 2000). Also, when the mapping between the viewed and the actual hand position is altered, the hand trajectory is modulated according to the viewed position (Sarlegna *et al.* 2003, 2004; Saunders & Knill, 2003, 2004; Sober & Sabes, 2003, 2005; Sarlegna & Sainburg, 2007). Here, we tested whether visual feedback of the hand affects the latency of on-line responses to an external perturbation when reaching for a visual target.

In most reaching situations, both kinesthetic and visual information about the hand are used to control the movement (Sarlegna *et al.* 2003). However, visual and kinesthetic signals can also be processed separately to control reaching movements. Indeed, accurate reaching movements can be performed without visual feedback

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of the hand (Pelisson *et al.* 1986; Prablanc & Martin, 1992; Blouin *et al.* 1993; Sarlegna *et al.* 2006) as well as in the absence of proprioception (Blouin *et al.* 1993). In line with this, several studies suggested that visual and kinesthetic afferents might underlie two 'parallel' modes of controlling reaching movements: a kinematic mode for the reaching trajectory – mainly relying on visual information, and a dynamic mode for muscle forces – mainly relying on kinesthetic information (Krakauer *et al.* 1999). For instance, visual feedback of the hand is not necessary for learning novel dynamics (DiZio & Lackner, 2000; Tong *et al.* 2002; Osu *et al.* 2004; Scheidt *et al.* 2005; Franklin *et al.* 2007). Along the same line, kinematic and dynamic internal models can be learned independently from each other, based on errors computed in different coordinate frames (e.g. visual and kinesthetic reference frames, respectively; Krakauer *et al.* 1999). Yet, if two such modes of control are used by the central nervous system, then the availability of visual information about the hand should affect the mode in which the movement is controlled. Specifically, when reaching for a visual target with visual feedback of the hand, the relative positions of the hand and target can be computed in a unique, visual coordinate frame. On the other hand, when visual feedback of the hand is not available, kinesthetic signals about the hand/arm and visual signals about the target have to be mapped into a common coordinate frame. Such mapping between coordinates might have processing costs, in which case on-line responses to a detected reaching error should take place with a delay when no visual information about the hand is available. In line with this, we tested here whether the latency of on-line responses to external perturbation depends on the presence of visual feedback of the hand.

On-line corrections take place with a latency with respect to the perturbation because of the time required to process the afferent signals and trigger the appropriate response. Therefore, the latency of on-line responses can be used as a behavioural indicator of the underlying sensorimotor processes. In particular, given that the mechanical constraints of the motor output are identical, different response latencies for two types of stimulus would suggest that the sensory information is processed differently for the two stimuli. We used a protocol in which reaching movements for a visual target were perturbed, and we measured both the first observable corrections of the hand trajectory and the electromyographic (EMG) latency of the responses to the perturbation. Trajectory corrections and EMG latencies were compared with and without visual feedback of the hand. As mentioned above, we reasoned that if the mode of control of reaching movements is affected by visual information about the hand, then the responses to perturbation should occur faster with visual feedback of the hand. We used two different types of perturbation: a pure visual perturbation and a kinesthetic perturbation. This allowed us to test whether visual feedback of the hand similarly affects the latency of the corrections, irrespective of the modality in which the perturbation is detected. The visual perturbation was a target jump, i.e. a sudden change of the spatial location of the target, whereas the kinesthetic perturbation consisted of a force step applied to the reaching hand. The two types of perturbation occurred at identical times during movement execution, and required comparable on-line corrections of the hand trajectory. Both types of perturbation were tested with and without visual feedback of the hand.

In addition to the main experiment, we conducted a control experiment in which we measured the latencies of two-choice reaction times (see online Supplemental material). As in the main experiment, we used visual and kinesthetic stimuli and tested whether the response latencies were affected by the visual feedback of the hand. However, whereas in the main experiment the perturbation occurred while the subject was performing reaching movements, in the control experiment the stimuli occurred while the subject was holding the hand stationary in space. So the main difference between the two experiments was the task in which the subject was engaged at the time of the perturbation/stimulation. The control experiment was aimed at contrasting the role of visual information about the hand in motor control with its role in a standard reaction time task. In particular, because coordinate frame transformations are not critical in a two-choice reaction time task, we expected that the visual feedback of the hand would not affect the latency of the responses in the control experiment.

Methods

Participants

Eleven right-handed subjects (age 20–37, 5 female) completed the full set of conditions of the experiment. None of them had a history of sensorimotor disorder, and all had normal or corrected-to-normal vision and good stereo vision. All participants gave their informed consent before taking part in the experiment, which was approved by the Ethics Committee of the University Clinic of Tübingen, and conformed with the Declaration of Helsinki.

Experimental set-up

The experimental set-up is shown in Fig. 1. The subjects were seated with their head resting on a chin and forehead rest. In their right hand, they held a vertical handle mounted on a haptic device with four degrees of freedom (DekiFeD, Technische Universität München, München, Germany, Buss & Schmidt, 1999). The haptic device recorded the subject's hand position and rendered the haptic scene, which was restricted to a 37 cm × 50 cm horizontal plane at the height of the subject's navel. The visual scene was rendered on a CRT monitor mounted with the screen tilted downwards, and the subjects viewed its reflection binocularly in an opaque mirror through liquid-crystal shutter glasses (StereoGraphics/REAL D, Beverly Hills, CA, USA). The 3D visual and haptic scenes matched spatially. The visual scene consisted of three spheres of 5 mm radius. Two spheres were magenta and represented the starting position for the reaching movements and the target to reach, respectively. The third sphere was red and provided feedback of the hand position – i.e. position of the top of the handle.

EMG recordings

EMG activity of the right pectoralis major (arm adductor) and posterior deltoid (arm abductor) muscles were recorded using surface cup-electrodes of 10 mm diameter. Two pairs of electrodes were placed near the middle third of the muscles after cleaning the skin with alcohol, along a line parallel to the muscle fibre orientation (Cram, 2003; Brindle *et al.* 2006). A ground electrode was attached to the subject's right wrist. These electrodes were connected to an amplifier (Psylab EEG8, Contact Precision Instruments Inc., Boston, MA, USA) and afterwards via an AD converter (5 kHz sampling rate, DAQ2205, Adlink Technology Inc., Taiwan) to a PC. The signal was band-pass filtered from 3 Hz to 400 Hz from the amplifier. A custom-made MATLAB (The MathWorks, Natick, MA, USA) program on the PC saved the potentials from both muscles separately, from 300 ms before until 1000 ms after a trigger indicating the perturbation.

Procedure

At the beginning of each trial, the starting position and visual feedback of the hand position appeared simultaneously. The starting position was randomly jittered in a 2 cm × 2 cm area located 10 cm in front of the subject about body midline. After the visual feedback of the hand position had been maintained in the starting position for about 1 s, the target appeared and the starting position disappeared. The subject's task was to reach for the target as quickly and precisely as possible. For the trials without visual feedback of the hand, the red sphere representing the top of the handle disappeared as soon as the target appeared. The target was located 20 cm from the starting position, either straight ahead or 30 deg on either side of body midline. For some trials, the reaching movement was perturbed, forcing the subject to modify the hand trajectory on-line. Two types of perturbation were used: the visual perturbation consisted of suddenly displacing the target by 7.5 deg, either rightward or leftward with respect to its original location (Fig. 2*A*). The kinesthetic perturbation was a force of 10 N applied perpendicularly to the reaching direction over a path length of 10 cm (Fig. 2*B*). The force could come either from the right or from the left. The perturbation occurred either 1 or 5 cm after the starting point of the reaching movement, for the rest of the paper referred to as early and late perturbation, respectively. The time at which the velocity of the hand

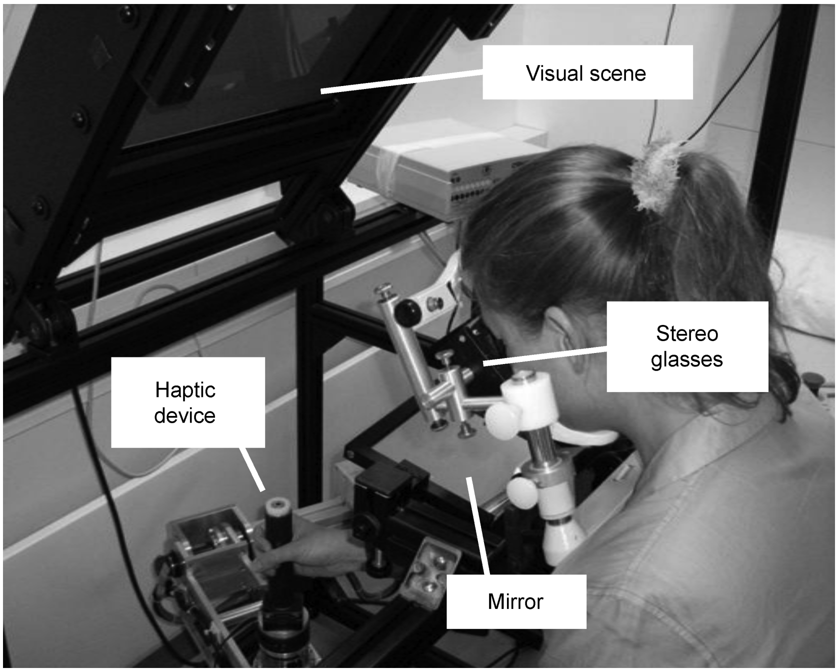

Figure 1
Experimental set-up.

dropped below 1 cm s^{-1} was defined as the end of the trial. At that time, the visual scene disappeared.

Blocks and duration

Each subject first conducted a training block of 96 trials to familiarize himself with the set-up and the perturbations. Then, the four blocks of the main experiment (192 trials each) and the block of the control experiment (64 trials, see Supplemental material) were performed. Half of the subjects performed the main experiment first whereas the other half started with the control experiment. Each experimental block consisted of two repetitions of the full permutation of all independent variables: two perturbation types (visual; kinesthetic), two feedback types (visual feedback of the hand; no visual feedback), two perturbation onsets (1 cm, early; 5 cm, late), three target locations (30 deg to the left; 30 deg to the right, or straight to the middle) and two perturbation directions (right; left). An equal number of unperturbed trials was also performed, resulting in a 50% chance for a perturbation to occur. In each block, the order of presentation of the trials was fully randomized. Mixing all conditions in each block prevented any predictability or anticipation concerning the perturbation of the reaching movements. Two seconds separated each trial from the next one. Overall, each subject performed 928 trials and the experiment lasted between 90 and 120 min, with a 3 min pause every 20–25 min.

Measured variables

We measured the reaching accuracy and the latency of on-line responses to perturbations. The reaching accuracy was used as an indicator of the functional efficiency of the corrections. However, the latency constituted our main focus of interest since we wanted to determine whether visual feedback of the hand speeds up the occurrence of on-line responses. The latency of the responses was assessed measuring both the kinematic of the hand trajectory and the neuro-muscular activity (EMG latency) correlated to the reaching movements. All reported latencies, whether kinematic or EMG, are relative to perturbation onset.

Reaching accuracy

The onset and the end of the movement were defined as the first time the velocity of the hand raised above and dropped below 2 cm s^{-1}, respectively. For unperturbed trials, the reaching accuracy was defined as the angle in degrees between the top of the handle at the end of the movement and the reached target. For perturbed trials, the reaching accuracy was the reaching error in degrees with respect to the unperturbed reaching movements for the corresponding target.

Kinematic latency of on-line corrections

We assessed the first correction-specific changes of the hand trajectory. For that, we measured the first deviations of the hand path ('PATH') as well as the first changes of hand velocity ('VEL'). We focused on the component of the reaching trajectory perpendicular to the vector between the starting position of the hand and the initial position of the target (illustrated in Figs S1 and S2 of the Supplemental material).

For each subject and condition, the PATH latencies were defined as the first time the mean trajectory reached a fixed threshold. Before that, for each condition, the mean of the unperturbed trials was subtracted from each trial to circumvent constant reaching biases. For visual perturbation, the threshold was one quarter of the way to the displaced target. For kinesthetic perturbation, the threshold was one quarter of the way from the maximum displacement until the end of the movement.

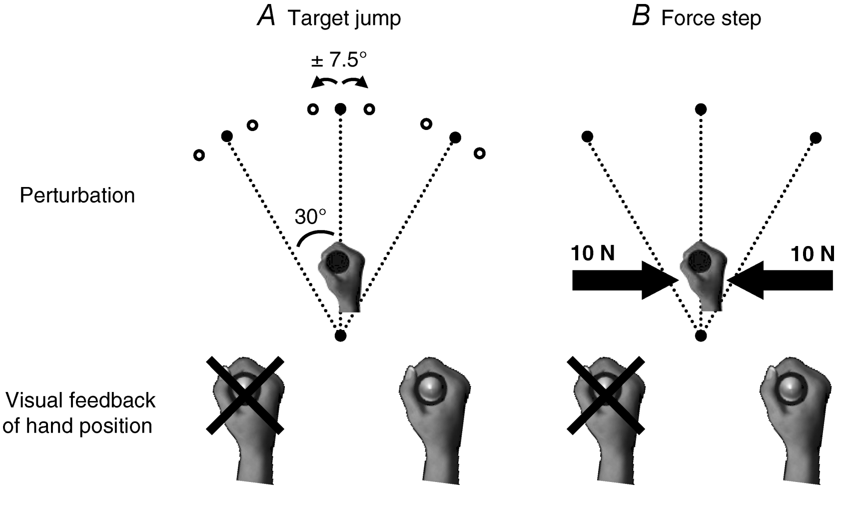

Figure 2. Experimental conditions
Two types of reaching perturbation were used: *A*, displacement of the visual target, and *B*, force step applied to the reaching arm. For both types of perturbation, half of the trials were performed with visual feedback of the hand position and the other half without.

This threshold was chosen to identify hand deviation as early as possible. Some studies (Day & Lyon, 2000; Day & Brown, 2001) used measurements more comparable to a 10% threshold. However, in our study, a 10% threshold yielded in many invalid onset times because of the initial variability of the data.

Concerning VEL latencies, the first changes of hand velocity were computed using half the maximum velocity as threshold for visual perturbation, and half the difference between maximum and minimum velocity as threshold for kinesthetic perturbation. These thresholds were chosen because lower thresholds (e.g. a quarter or 10%) provided more variable data and many invalid onset times.

To limit the dependency of the results on the threshold values, PATH and VEL latencies were also determined with two other fixed thresholds as well as using the unperturbed trials as baseline. More details about these additional measurements are provided in the Supplemental material.

EMG latency of on-line corrections

We assessed the first correction-specific changes of EMG activity (i.e. first excitatory bursts). We focused on the shoulder muscles agonistic to the corrective movement, namely the posterior deltoid for trials in which a rightward correction (arm abduction) was required, and the pectoralis major for trials in which a leftward correction (arm adduction) was required. We chose these two muscles because d'Avella *et al.* (2006) showed that they are involved at an early stage in the muscle synergies producing medial and lateral movements of the arm when reaching. We did not measure the activation of elbow muscles since, for on-line responses to both visual and kinesthetic perturbation, the EMG activation of shoulder and elbow muscles is similar (Soechting & Lacquaniti, 1983; Smeets *et al.* 1990). Also, we did not measure the latency of inhibition of the antagonistic muscle because early inhibitions were very difficult to detect.

For each EMG trace, the AC component of the signal was rectified and then smoothed using a rectangular moving window of 25 ms to reflect the low pass characteristics of muscle (Hammond, 1960; Eklund *et al.* 1982). The EMG latencies were determined using the mean activation of unperturbed trials as baseline (Fig. 3 shows some exemplary EMG traces). To define correction onset, the EMG trace of the perturbed trials had to stay for 25 ms above the threshold which was set to 110% of the baseline. This procedure resulted in a detection rate of 64.7% and 71.4% for visual and kinesthetic perturbation, respectively.

To avoid a dependency of the results on the threshold values, the data were also analysed with a threshold set at 120% of the baseline. Moreover, in order to limit the dependency of the results on the method chosen, we used an additional and independent EMG measurement to assess the latency of the responses. More details about these additional thresholds and measurements can be found in the Supplemental material.

Data analysis and statistics

Reported values are mean ± standard error unless stated otherwise. All statistical tests were conducted using analyses of variance (ANOVA). For all measurements, there were no significant interactions between our main variable of interest, i.e. visual feedback of the hand, and target location or perturbation direction.

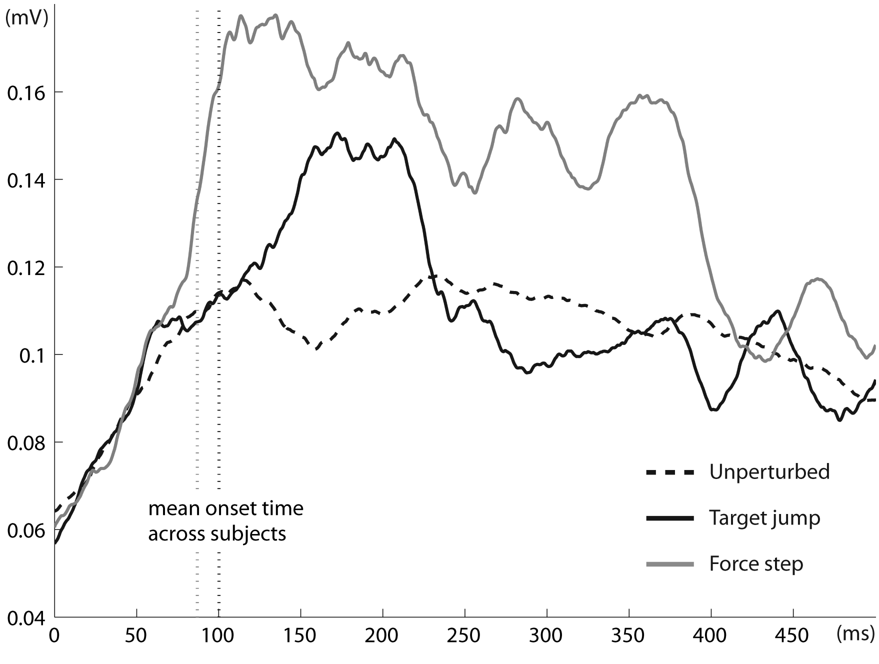

Figure 3. Group EMG traces of the posteriod deltoid muscle for one condition with visual and kinesthetic perturbation, and their corresponding unperturbed trials (target to the left, correction to the right, early onset, with visual feedback of hand position)
Time point 0 is the onset time of the perturbation. The dashed lines indicate the mean response latency for these conditions.

Therefore, we pooled the data over target location and perturbation direction. This resulted in 2 × 2 × 2 [type of perturbation (visual, kinesthetic) × visual feedback of the hand position (without, with) × onset of perturbation (early, late)] repeated-measures ANOVAs, unless stated otherwise. Also, pre-planned comparisons between corresponding conditions with and without visual feedback about the hand were systematically conducted. Corrections for multiple comparisons were conducted with Newman–Keuls tests for the ANOVAs, or Bonferroni corrected paired *t* tests ($P < 0.05$) when necessary.

Results

Movement time and time of perturbation onset

Movement times with the two types of perturbation were not significantly different (797.9 ± 38.5 and 809.3 ± 32.1 ms for visual and kinesthetic perturbation, respectively) but were both significantly longer than unperturbed reaching movements (665.2 ± 35.6 ms, $P < 0.001$). Early and late perturbations occurred on average 78.0 ± 22.4 and 180.3 ± 40.2 ms after movement onset, respectively. From perturbation to maximum velocity, 170.8 ± 50.4 ms elapsed for early perturbations and 68.2 ± 44.2 ms for late perturbations. From perturbation to maximum acceleration, 143.4 ± 64.5 ms elapsed for early perturbations and 40.8 ± 58.5 ms for late perturbations. None of the early perturbations occurred after maximum velocity or maximum acceleration had been reached. As for late perturbations, 2.4% occurred after maximum velocity had been reached (following for 62 ms at most) and 19.2% after maximum acceleration had been reached (following for 215 ms at most). For all those measurements, no difference was found between trials with and without visual feedback of the hand.

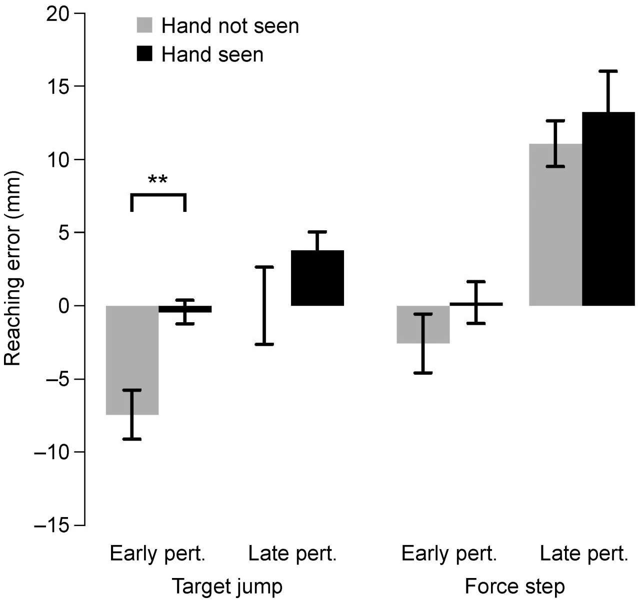

Figure 4. Reaching accuracy with and without visual feedback of the hand, for all combinations between perturbation type and perturbation onset

For early visual perturbation, the trials without visual feedback of the hand exhibited an overcompensation as compared to the trials with visual feedback of the hand. For the late kinesthetic perturbation there was no difference between the trials with and without visual feedback of the hand, the corrections being incomplete in both conditions.

Reaching accuracy

When the reaching movements were unperturbed, the subjects reached on average 1.50 ± 0.91 deg to the left of the target without visual feedback of the hand, and 0.17 ± 0.09 deg to the right with feedback (1 deg = 3.5 mm). For perturbed reaching movements, corrections were less complete for kinesthetic *vs.* visual perturbation ($F_{1,10} = 20.54$; $P < 0.01$), less complete with visual feedback of the hand *vs.* without ($F_{1,10} = 12.019$; $P < 0.01$), and less complete for late *vs.* early perturbation ($F_{1,10} = 67.51$; $P < 0.0001$). The comparisons between the corresponding conditions with and without feedback about the hand revealed that for early visual perturbation, the subjects were more accurate when visual feedback of the hand was provided ($P < 0.01$; see Fig. 4).

Kinematic latency of on-line corrections

Kinematic analyses did not allow us to compare directly the latency of visual and kinesthetic perturbation. Specifically, whereas for visual perturbation the initial path deviation resulted from the correction, it was produced by the perturbation itself for kinesthetic perturbation. Therefore, our analyses focused on the effect of visual feedback of the hand, which was assessed with Bonferroni corrected paired *t* tests for each combination between perturbation type and perturbation onset. Both PATH and VEL analyses showed that on-line corrections to early visual perturbation occurred earlier with visual feedback of the hand (see Figs 5 and 6*A* and *B*). This pattern of results was identical irrespective of the method of measurement used and the threshold selected (see Supplemental material).

EMG latency of on-line corrections

On-line corrections took place earlier when a force was applied to the arm than when the target position changed ($F_{1,10} = 16.80$; $P < 0.01$). More importantly, the comparisons between corresponding conditions with and without feedback about the hand revealed that visual feedback of the hand sped up the latency of on-line corrections for early visual perturbation (8.9 ± 3.5 ms;

$P < 0.05$). These results are shown in Fig. 7. The same pattern of results was observed with the other method of measurement and with all selected thresholds (see Supplemental material).

Discussion

The main result of the present experiment is that when reaching for a visual target, visual feedback of the hand speeds up the latency of on-line responses to a sudden change of target position. Such latency facilitation was observed only when the change of target position occurred at an early stage of reaching movement execution. Also, visual feedback of the hand did not affect the latency of on-line responses to kinesthetic perturbation. Finally, visual feedback of the hand failed to alter the latency of visual and kinesthetic two-choice reaction times, suggesting that the facilitation observed in the main experiment is specific to on-line responses.

Latency and accuracy of on-line responses in humans

In humans, the reported latencies for on-line responses are very variable, depending on the task and method of measurement used. Kinematic latencies, i.e. the first measured changes of hand path, velocity or acceleration are the most commonly reported for responses to visual perturbations, and they are usually in the range 280–350 ms for path deviations and 190–280 ms for velocity changes (e.g. Prablanc & Martin, 1992; Johnson *et al.* 2002; Sarlegna *et al.* 2003). The latencies we measured compare well with those values, though slightly longer. Observing such a slight delay in our experiment was to be expected considering the mass/inertia added by the haptic device with which the reaching movements were

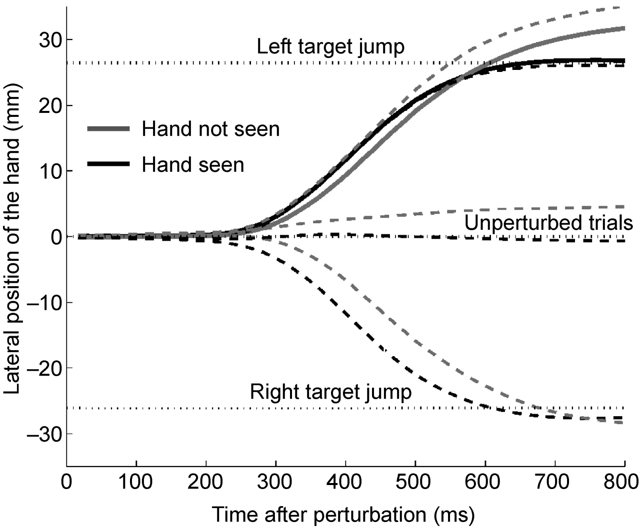

Figure 5. Mean hand trajectories (averaged across subjects and initial target position) for unperturbed reaching movements and 'early' target jumps in both directions (left and right)
The dashed lines represent the uncorrected trajectories, whereas the continuous lines represent the averaged trajectories for on-line responses to left and right target jumps (unsigned). On-line corrections take place earlier when visual feedback of the hand is provided.

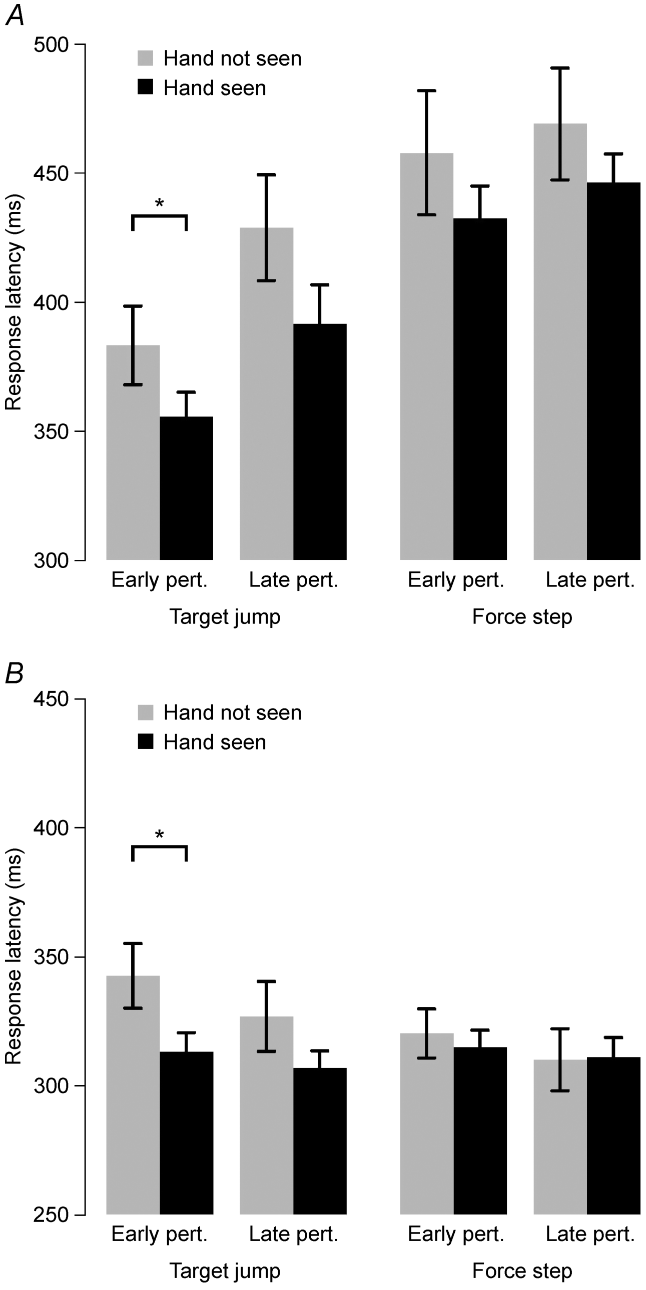

Figure 6. Average onset times of path (*A*) and velocity deviations (*B*) based on a fixed threshold with and without visual feedback of the hand, for all combinations between perturbation type and perturbation onset
For the responses to early visual perturbation, both measurements show significantly shorter latencies when visual feedback of the hand was provided.

performed. Remarkably, Day & Lyon (2000) measured very short latencies (125–160 ms). This corresponds to what we observed setting the VEL threshold at 10% of the maximum velocity (see Supplemental material). Such a threshold is well suited to detect very early responses but, in our case, it resulted in many invalid onset times. Since we were mostly interested in comparing trials with and without visual feedback of the hand, we opted for a more conservative threshold which allowed more robust comparisons. Concerning responses to kinesthetic perturbation, kinematic latencies are quite variable and little reliable since the first changes of hand path/velocity usually result from the perturbation itself. Therefore, they are difficult to compare between studies when the nature of the kinesthetic perturbation differs. On the other hand, because they constitute a direct measurement of the activity of the muscles producing the movement, EMG recordings constitute a reliable indicator of the latency of responses to kinesthetic perturbation. Also, for both visual and kinesthetic perturbation, EMG recordings allow early detection of on-line responses, which is not possible with kinematic analyses. In humans, the reported EMG latencies for on-line responses to kinesthetic perturbation lie in the range 60–100 ms (Crago *et al.* 1976; Smeets *et al.* 1990). This is similar to what we measured in our experiment. As for responses to visual perturbation, only few studies used EMG measurements to determine their latency. Using a method comparable to ours, Soechting & Lacquaniti (1983) reported latencies of 110–120 ms, which is similar to what we measured.

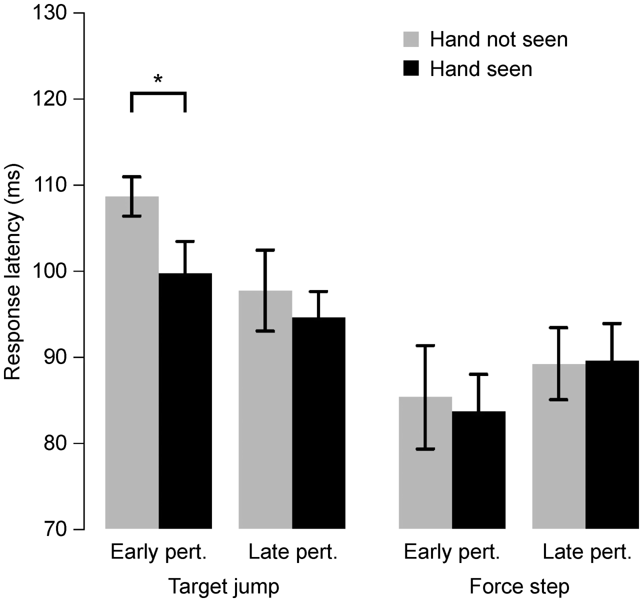

Figure 7. Average EMG response latencies with and without visual feedback of the hand, for all combinations between perturbation type and perturbation onset
For the responses to early visual perturbation, the latency was significantly shorter with visual feedback of the hand.

Regarding reaching accuracy, we observed mean deviations of less than 3 deg for on-line responses to visual perturbation. This corresponds to the accuracy reported in previous studies using similar perturbations (Cordo, 1990; Prablanc & Martin, 1992; Bard *et al.* 1999; Sarlegna *et al.* 2003). Also, providing visual feedback of the hand increased the reaching accuracy, which is in agreement with previous studies (Woodworth, 1899; Bard *et al.* 1985; Spijkers & Lochner, 1994; Spijkers & Spellerberg, 1995; Proteau *et al.* 2000). The accuracy we measured for on-line responses to kinesthetic perturbation is more difficult to compare with other studies since, to our knowledge, this particular task was used here for the first time. Responses to early perturbations preserved the reaching accuracy, which was similar to that measured for responses to visual perturbation. On the other hand, the corrections taking place with late kinesthetic perturbation were consistently incomplete, and this irrespective of the availability of visual feedback of the hand. In that condition, the force field ended only 5 cm ahead of the target. Our results suggest that this distance is too short for an efficient on-line correction to take place.

Visual feedback of the hand position speeds up on-line responses to early visual perturbation

For both kinematic and EMG measurements, providing visual feedback of the hand during reaching movements significantly shortened the latency of on-line responses to early visual perturbation. Specifically, EMG latencies were about 10 ms shorter and response-specific changes of the hand trajectory were observed about 30 ms earlier with vision of the hand. This consistency in the pattern of response latencies reinforces the hypothesis that the mode of control of reaching movements depended on the availability of visual feedback about the hand. Previous research suggested that the mode in which goal-directed movements are both planned (Sober & Sabes, 2003, 2005; Sarlegna & Sainburg, 2007) and controlled (van Beers *et al.* 1999, 2002) can change as a function of the modality of the target and the nature of the available information about the reaching hand/arm. Our results confirm this hypothesis. In particular, when visual information about the hand position is not available, the kinesthetic signals about the arm position and the visual signals about the target position have to be mapped into a common coordinate frame. On the other hand, when visual information about the hand is available, the relative positions of the hand and target can be computed in a unique, visual coordinate frame. Our results show for the first time that the latter scenario allows faster responses to a change of target position, providing an important insight into the mechanisms underlying the on-line control of reaching movements.

In contrast to what we observed for early visual perturbation, visual feedback of the hand did not speed up on-line responses to target displacements occurring at a later point of the hand trajectory. This difference can be explained by the temporal relationship between the perturbation and the saccade to the target. In particular, early perturbations occur around the time point of the initial saccade to the target (Prablanc & Martin, 1992). Therefore, the corrective saccade to the displaced target falls into the corrective saccade that is 'pre-packaged' with the initial saccade (Becker & Fuchs, 1969). In this case, there is a stable visual reference frame with respect to the target available very early. Within this visual reference frame, the visual feedback of the hand position is profitable. On the other hand, late perturbations trigger an extra saccade (Becker & Fuchs, 1969), which needs time to initiate and draws attention to the new target. The visual reference frame is shifted and remains unstable for a longer time. In this case, the visual feedback of the hand does not provide any benefit. Also, saccadic suppression might occur during the time-point of correction, preventing the processing of the visual feedback of the hand position.

Most studies using visual perturbation protocols are more comparable to our early perturbation condition as the initial saccade is often used to trigger the perturbation. Our results show that there is an influence of the time point of perturbation that cannot be disregarded. In that respect, investigating the influence of perturbation time point and its interaction with other parameters, such as the availability of sensory information or the modality of perturbation might be an interesting direction for future research.

Visual feedback of the hand position does not affect on-line responses to a force applied to the reaching arm

Visual feedback of the hand did not affect the latency of on-line responses to a force applied to the reaching hand. This result might seem surprising for two reasons. First, since the target was always visual, one could expect visual information about the hand to have the same beneficial influence on the responses to both types of perturbation. Indeed, irrespective of the perturbation type, when visual feedback of the hand is available the relative positions of the hand and target can be coded in a unique visual coordinate frame. In addition, for kinesthetic perturbation, visual information about the hand provided a second sensory cue about the arm deviation. With visual feedback, the subjects could feel their hand position via proprioceptive afferents, and additionally see their hand deviating from the initial trajectory. This additional sensory cue about the perturbation could have contributed to speed up the responses since previous research has shown facilitation of response times when more sensory channels provide redundant information about the same event (Hershenson, 1962; Morrell, 1968; Bernstein *et al.* 1969; Nickerson, 1973; Gielen *et al.* 1983). This was not the case. The latency of the responses to the force perturbation was identical irrespective of the presence of visual feedback of the hand position.

One notable difference between the two types of perturbation was the spatial relationship between the target and the body. Specifically, as opposed to visual perturbation, kinesthetic perturbation did not alter the spatial position of the target. This implies that the central nervous system did not have to re-compute on-line the target position with respect to the body. The kinesthetic perturbation only required a quick reaction to the force detected by the kinesthetic sensors by sending a motor command to counteract this force. Such a response could be triggered within a 'pure' kinesthetic reference frame (Krakauer *et al.* 1999). In the latter case, no re-mapping between visual and kinesthetic reference frames would be required, which means that no extra processing time would be needed before triggering an on-line response when visual feedback of the hand is not available. In line with this, our results suggest that visual information about the hand reduces the latency of on-line corrections only when the position of the visual target has to be re-coded in a body-centred reference frame during the execution of the reaching movement.

The response facilitation evoked by the visual feedback of the hand is specific to on-line corrections

Although the neural mechanisms underlying the on-line control of reaching movements are not completely known, several experiments suggested that this control relies on automatic, fast feedback loops, that are distinct from the processes involved in 'classic' reaction times. Specifically, on-line corrections of the hand trajectory can occur without awareness (Goodale *et al.* 1986; Prablanc & Martin, 1992; Sarlegna *et al.* 2003) and are difficult to prevent (Day & Lyon, 2000; Pisella *et al.* 2000). Also, the reported latencies of on-line corrections to visual (Carlton, 1981; Soechting & Lacquaniti, 1983; Prablanc & Martin, 1992; Day & Lyon, 2000; Day & Brown, 2001) and proprioceptive perturbations (Vince, 1948; Crago *et al.* 1976; Smeets *et al.* 1990) are much shorter than the latencies of visual (Evarts *et al.* 1981; Day & Brown, 2001; Jaskowski & Sobieralska, 2004) and proprioceptive reaction times (Evarts *et al.* 1981). This is confirmed by our experiment, in which on-line responses to visual and kinesthetic perturbations occurred almost twice as fast as two-choice reaction times to similar stimuli. Finally, a recent study by Day & Brown (2001) with a split-brain patient suggested that, in contrast to classical reaction times, on-line control of reaching movements might partly be mediated by sub-cortical structures.

In our experiment, visual feedback of the hand facilitated on-line responses to early visual perturbation but did not affect the latency of two-choice reaction times. This constitutes additional evidence that the neural processes underlying on-line responses differ from those underlying mainly preparatory motor processes like classic reaction times (Day & Lyon, 2000). More importantly, it highlights the specificity of the facilitation observed for the on-line responses to early visual perturbation. Since on-line corrections of reaching movements present strong spatial accuracy constraints, coordinate frame transformations constitute a critical issue when performing such corrections. On the other hand, the two-choice reaction time task that we used had very low spatial accuracy constraints. Indeed, the subjects were only instructed to move as fast as possible in the correct direction (i.e. right *vs.* left). As a consequence, coordinate transformation was critical to perform on-line corrections but not to perform the two-choice reaction time task. In line with this, the absence of a difference in the two-choice reaction time task supports the idea that the facilitation of on-line responses indeed resulted from the availability of sensory information about the hand and the new target in the same coordinate frame.

Neural processing of visual feedback for controlling action

As kinematic measurements also depend on external factors like inertia of the system moved, our discussion will focus here on EMG latencies, which better represent the actual timing of on-line corrections and are therefore more suitable for making inferences about neural processing times. In our experiment, the EMG latency of the responses to early visual perturbation decreased on average from 110 ms when no visual feedback of the hand was available to 100 ms or even less with visual feedback. This constitutes a rough 10% reduction of the gross response latency. In terms of neural processing time actually devoted to sensorimotor integration, however, it represents a much larger reduction. Specifically, the sensorimotor processes underlying the on-line control of reaching movements can be subdivided into three stages. First, the afferent signals are conveyed from the peripheral sensors to the cerebral cortex. Then, the information can be integrated (e.g. in the posterior parietal cortex) and a motor response is selected (e.g. in the supplementary motor areas). This is the stage where coordinate transformation occurs when necessary (Andersen *et al.* 1997; Colby, 1998). Finally, a motor command is sent from the primary motor cortex to the effectors (muscles). Concerning the sensory processing of visual signals, visual afferents need about 60 ms to reach the cerebral cortex in monkeys (Bullier & Nowak, 1995; Schmolesky *et al.* 1998; Bullier, 2001), whereas the first visual-evoked potentials in humans are usually observed after 70–75 ms (Odom *et al.* 2004). Regarding the time needed for motor commands sent by the primary motor cortex to reach shoulder muscles in humans, transcranial electric and magnetic stimulation studies indicate that it takes about 10–15 ms (Merton & Morton, 1980; Hess *et al.* 1987; Di Lazzaro *et al.* 1998; Bawa *et al.* 2004). Therefore, 'pure' visual and motor processes probably add up to about 80 ms. Subtracting these 80 ms from the response latencies we measured, the time actually allotted to sensorimotor integration and motor selection in our experiment decreased from 30 ms without visual feedback of the hand to about 20 ms with feedback. In other words, when the target position changed during movement execution, providing visual feedback of the hand (thereby enabling target- and hand-related information to be mapped in a common visual reference frame) reduced the 'cortical' processing time by about 35%. Note that Reynolds & Day (2007) made an analogous but much more conservative estimate of the visuo-motor processing time, evaluating that a minimum of 40 ms is required (rather than 80 ms with our estimate). With such a conservative estimate, the net reduction of cortical processing time allowed by visual feedback of the hand would amount to 15%. Overall, our results suggest that when a coordinate transformation between visual and proprioceptive signals must be performed on-line to re-code the target position in a body-centred reference frame, the neural processing time needed to integrate sensory information and select an appropriate response is notably increased.

Conclusion

Using a task in which reaching movements for a visual target were perturbed by either a change of target location (visual perturbation) or a force applied to the reaching hand (kinesthetic perturbation), we showed that providing visual feedback of the hand reduces the latency of on-line responses to early visual perturbation. On the other hand, when the perturbation was kinesthetic and did not alter the position of the target with respect to the body, the latency of on-line responses remained unaffected by the visual feedback of the hand. A control experiment showed that visual feedback of the hand never speeds up two-choice reaction times, indicating that the facilitation is specific to on-line responses. Taken together, our results suggest that when the position of the target with respect to the body must be re-computed during movement execution, providing visual feedback of the hand speeds up on-line corrections by enabling hand- and target-related information to be mapped in a common visual reference frame.

References

Andersen RA, Snyder LH, Bradley DC & Xing J (1997). Multimodal representation of space in the posterior parietal cortex and its use in planning movements. *Annu Rev Neurosci* **20**, 303–330.

Bard C, Hay L & Fleury M (1985). Role of peripheral vision in the directional control of rapid aiming movements. *Can J Psychol* **39**, 151–161.

Bard C, Turrell Y, Fleury M, Teasdale N, Lamarre Y & Martin O (1999). Deafferentation and pointing with visual double-step perturbations. *Exp Brain Res* **125**, 410–416.

Bawa P, Hamm JD, Dhillon P & Gross PA (2004). Bilateral responses of upper limb muscles to transcranial magnetic stimulation in human subjects. *Exp Brain Res* **158**, 385–390.

Becker W & Fuchs AF (1969). Further properties of the human saccadic system: eye movements and correction saccades with and without visual fixation points. *Vision Res* **9**, 1247–1258.

Bernstein IH, Clark MH & Edelstein BA (1969). Effects of an auditory signal on visual reaction time. *J Exp Psychol* **80**, 567–569.

Blouin J, Bard C, Teasdale N, Paillard J, Fleury M, Forget R & Lamarre Y (1993). Reference systems for coding spatial information in normal subjects and a deafferented patient. *Exp Brain Res* **93**, 324–331.

Brindle TJ, Nitz AJ, Uhl TL, Kifer E & Shapiro R (2006). Kinematic and EMG characteristics of simple shoulder movements with proprioception and visual feedback. *J Electromyogr Kinesiol* **16**, 236–249.

Bullier J (2001). Integrated model of visual processing. *Brain Res Brain Res Rev* **36**, 96–107.

Bullier J & Nowak LG (1995). Parallel *versus* serial processing: new vistas on the distributed organization of the visual system. *Curr Opin Neurobiol* **5**, 497–503.

Buss M & Schmidt G (1999). Control problems in multimodal telepresence systems. In *Advances in Control, Highlights of ECC'99*, pp. 65–101. Springer-Verlag, London.

Carlton LG (1981). Processing visual feedback information for movement control. *J Exp Psychol Hum Percept Perform* **7**, 1019–1030.

Colby CL (1998). Action-oriented spatial reference frames in cortex. *Neuron* **20**, 15–24.

Cordo PJ (1990). Kinesthetic control of a multijoint movement sequence. *J Neurophysiol* **63**, 161–172.

Crago PE, Houk JC & Hasan Z (1976). Regulatory actions of human stretch reflex. *J Neurophysiol* **39**, 925–935.

Cram JR (2003). The history of surface electromyography. *Appl Psychophysiol Biofeedback* **28**, 81–91.

d'Avella A, Portone A, Fernandez L & Lacquaniti F (2006). Control of fast-reaching movements by muscle synergy combinations. *J Neurosci* **26**, 7791–7810.

Day BL & Brown P (2001). Evidence for subcortical involvement in the visual control of human reaching. *Brain* **124**, 1832–1840.

Day BL & Lyon IN (2000). Voluntary modification of automatic arm movements evoked by motion of a visual target. *Exp Brain Res* **130**, 159–168.

Desmurget M & Grafton S (2000). Forward modelling allows feedback control for fast reaching movements. *Trends Cogn Sci* **4**, 423–431.

Di Lazzaro V, Oliviero A, Profice P, Saturno E, Pilato F, Insola A, Mazzone P, Tonali P & Rothwell JC (1998). Comparison of descending volleys evoked by transcranial magnetic and electric stimulation in conscious humans. *Electroencephalogr Clin Neurophysiol* **109**, 397–401.

DiZio P & Lackner JR (2000). Congenitally blind individuals rapidly adapt to coriolis force perturbations of their reaching movements. *J Neurophysiol* **84**, 2175–2180.

Eklund G, Hagbarth KE, Hagglund JV & Wallin EU (1982). Mechanical oscillations contributing to the segmentation of the reflex electromyogram response to stretching human muscles. *J Physiol* **326**, 65–77.

Evarts EV, Teravainen H & Calne DB (1981). Reaction time in Parkinson's disease. *Brain* **104**, 167–186.

Franklin DW, So U, Burdet E & Kawato M (2007). Visual feedback is not necessary for the learning of novel dynamics. *PLoS One* **2**, e1336.

Gielen SC, Schmidt RA & Van Den Heuvel PJ (1983). On the nature of intersensory facilitation of reaction time. *Percept Psychophys* **34**, 161–168.

Goodale MA, Pelisson D & Prablanc C (1986). Large adjustments in visually guided reaching do not depend on vision of the hand or perception of target displacement. *Nature* **320**, 748–750.

Hammond PH (1960). An experimental study of servo action in human muscular control. *Proc III Int Conf Med Electron*, 190–199.

Hershenson M (1962). Reaction time as a measure of intersensory facilitation. *J Exp Psychol* **63**, 289–293.

Hess CW, Mills KR & Murray NMF (1987). Responses in small hand muscles from magnetic stimulation of the human brain. *J Physiol* **388**, 397–419.

Jaskowski P & Sobieralska K (2004). Effect of stimulus intensity on manual and saccadic reaction time. *Percept Psychophys* **66**, 535–544.

Johnson H, Van Beers RJ & Haggard P (2002). Action and awareness in pointing tasks. *Exp Brain Res* **146**, 451–459.

Krakauer JW, Ghilardi MF & Ghez C (1999). Independent learning of internal models for kinematic and dynamic control of reaching. *Nat Neurosci* **2**, 1026–1031.

Merton PA & Morton HB (1980). Stimulation of the cerebral cortex in the intact human subject. *Nature* **285**, 227.

Morrell LK (1968). Temporal characteristics of sensory interaction in choice reaction times. *J Exp Psychol* **77**, 14–18.

Nickerson RS (1973). Intersensory facilitation of reaction time: energy summation or preparation enhancement? *Psychol Rev* **80**, 489–509.

Odom JV, Bach M, Barber C, Brigell M, Marmor MF, Tormene AP, Holder GE & Vaegan (2004). Visual evoked potentials standard (2004). *Doc Ophthalmol* **108**, 115–123.

Osu R, Hirai S, Yoshioka T & Kawato M (2004). Random presentation enables subjects to adapt to two opposing forces on the hand. *Nat Neurosci* **7**, 111–112.

Pelisson D, Prablanc C, Goodale MA & Jeannerod M (1986). Visual control of reaching movements without vision of the limb. II. Evidence of fast unconscious processes correcting the trajectory of the hand to the final position of a double-step stimulus. *Exp Brain Res* **62**, 303–311.

Pisella L, Grea H, Tilikete C, Vighetto A, Desmurget M, Rode G, Boisson D & Rossetti Y (2000). An 'automatic pilot' for the hand in human posterior parietal cortex: toward reinterpreting optic ataxia. *Nat Neurosci* **3**, 729–736.

Prablanc C & Martin O (1992). Automatic control during hand reaching at undetected two-dimensional target displacements. *J Neurophysiol* **67**, 455–469.

Proteau L, Boivin K, Linossier S & Abahnini K (2000). Exploring the limits of peripheral vision for the control of movement. *J Mot Behav* **32**, 277–286.

Reynolds RF & Day BL (2007). Fast visuomotor processing made faster by sound. *J Physiol* **583**, 1107–1115.

Sarlegna F, Blouin J, Bresciani JP, Bourdin C, Vercher JL & Gauthier GM (2003). Target and hand position information in the online control of goal-directed arm movements. *Exp Brain Res* **151**, 524–535.

Sarlegna F, Blouin J, Vercher JL, Bresciani JP, Bourdin C & Gauthier GM (2004). Online control of the direction of rapid reaching movements. *Exp Brain Res* **157**, 468–471.

Sarlegna FR, Gauthier GM, Bourdin C, Vercher JL & Blouin J (2006). Internally driven control of reaching movements: a study on a proprioceptively deafferented subject. *Brain Res Bull* **69**, 404–415.

Sarlegna FR & Sainburg RL (2007). The effect of target modality on visual and proprioceptive contributions to the control of movement distance. *Exp Brain Res* **176**, 267–280.

Saunders JA & Knill DC (2003). Humans use continuous visual feedback from the hand to control fast reaching movements. *Exp Brain Res* **152**, 341–352.

Saunders JA & Knill DC (2004). Visual feedback control of hand movements. *J Neurosci* **24**, 3223–3234.

Scheidt RA, Conditt MA, Secco EL & Mussa-Ivaldi FA (2005). Interaction of visual and proprioceptive feedback during adaptation of human reaching movements. *J Neurophysiol* **93**, 3200–3213.

Schmolesky MT, Wang Y, Hanes DP, Thompson KG, Leutgeb S, Schall JD & Leventhal AG (1998). Signal timing across the macaque visual system. *J Neurophysiol* **79**, 3272–3278.

Smeets JB, Erkelens CJ & Denier Van Der Gon JJ (1990). Adjustments of fast goal-directed movements in response to an unexpected inertial load. *Exp Brain Res* **81**, 303–312.

Sober SJ & Sabes PN (2003). Multisensory integration during motor planning. *J Neurosci* **23**, 6982–6992.

Sober SJ & Sabes PN (2005). Flexible strategies for sensory integration during motor planning. *Nat Neurosci* **8**, 490–497.

Soechting JF & Lacquaniti F (1983). Modification of trajectory of a pointing movement in response to a change in target location. *J Neurophysiol* **49**, 548–564.

Spijkers W & Spellerberg S (1995). On-line visual control of aiming movements? *Acta Psychol (Amst)* **90**, 333–348.

Spijkers WA & Lochner P (1994). Partial visual feedback and spatial end-point accuracy of discrete aiming movements. *J Mot Behav* **26**, 283–295.

Tong C, Wolpert DM & Flanagan JR (2002). Kinematics and dynamics are not represented independently in motor working memory: evidence from an interference study. *J Neurosci* **22**, 1108–1113.

van Beers RJ, Sittig AC & Gon JJ (1999). Integration of proprioceptive and visual position-information: An experimentally supported model. *J Neurophysiol* **81**, 1355–1364.

van Beers RJ, Wolpert DM & Haggard P (2002). When feeling is more important than seeing in sensorimotor adaptation. *Curr Biol* **12**, 834–837.

Vince MA (1948). Corrective movements in a pursuit task. *Q J Exp Physiol Cogn Med Sci* **1**, 85–103.

Wolpert DM, Ghahramani Z & Jordan MI (1995). An internal model for sensorimotor integration. *Science* **269**, 1880–1882.

Woodworth RS (1899). The accuracy of voluntary movement. *Psychol Rev* **3**, 1–114.

Author contributions

A.R. and J.-P.B. conceived and designed the experiments. A.R. analysed the data and all authors contributed to their interpretation. A.R. and J.-P.B. wrote the article. A.T., A.P. and H.H.B. contributed to the revision of the draft. All authors approved the final version of the article.

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PATH, VEL and EMG latencies with other thresholds

Results

The kinematic latencies measured with other thresholds are shown in Table S1 and illustrated in the figures S1 and S2. They confirm the general pattern of the results. In particular, on-line corrections to early visual perturbation occurred consistently earlier when visual feedback of the hand was provided.

The EMG latencies with the additional threshold are shown in Table S2 (EMG120). Fixing the threshold at 120% of the unperturbed data shifted the latencies to a later time point, but the pattern of results remains the same, responses to early visual perturbation taking place earlier with visual feedback of the hand (even though the difference failed to reach significance in this latter case). In other words, the response facilitation induced by the visual feedback of the hand was observed irrespective of the thresholds chosen.

Kinematic latencies using unperturbed trials as baseline (PATHb and VELb)

PATHb: For each subject and condition, the latencies were determined by conducting paired t-tests (α = .05) between perturbed trials and the corresponding unperturbed trials for each time sample. For visual perturbation, the first time a significant difference was detected and maintained throughout the rest of the trial was chosen as deviation onset. For kinesthetic perturbation, the initial deviation resulted from the force applied to the reaching arm. Therefore, deviation onset was defined as the first time the hand path was not significantly different any more from the baseline. This method did not allow the early detection of on-line corrections but nonetheless allowed the comparison between trials with and without visual feedback of the hand. To account for possible outliers, the mean of each subject and condition was re-calculated, taking into account only onset times in the range ‘mean onset time ± 2 standard deviations’.

VELb: The latencies were computed by comparing the hand velocity of perturbed and unperturbed trials for each time sample (paired t-tests, α = .05). For visual perturbation, the onset of the correction was defined as the first time the hand velocity was significantly larger than the baseline and then maintained larger until the maximum velocity was reached. For kinesthetic perturbation, correction onset was defined as the first time the hand velocity was not significantly different any more from the baseline. To account for possible outliers, the mean of each subject and condition was re-calculated, taking into account only onset times in the range ‘mean onset time ± 2 standard deviations’.

Results

PATHb and VELb analyses showed that corrections of the hand trajectory occurred significantly earlier with visual feedback of the hand, for both early and late visual perturbations (see Table S1). However, both measurements depended on the variability of the data, and hand path variance was significantly higher without visual feedback of the hand (correlation between PATHb latency and the standard deviation of the path at the corresponding time point, $R^2 = .36$; $p < .0001$). Therefore, these results should be considered with caution.

EMG latencies using the mean EMG activity before perturbation as baseline (EMGb)

For each EMG trace, the onset of the corrective response was assessed using an extended threshold method (Figure S3, parameters adjusted after Hodges & Bui, 1996). For each trial, the threshold was set to baseline plus two standard deviations. The first time point at which the trace stayed above the threshold for at least 25 msec was defined as the onset of the on-line correction. The average response latency per subject and condition was calculated leaving out latencies shorter than 20 and longer than 300 msec. Manual inspection of pretest data indicated that no valid onset was to find outside this time range. Invalid onsets resulted from the low signal-to-noise-ratio of some trials. Specifically, the onset of correction-specific EMG activation was sometimes difficult to detect because it was superimposed on the baseline activation resulting from the initial reaching movement. After discarding onset times outside the range of ‘baseline ± 2 standard deviations’ as outliers, the mean of each subject and condition was re-calculated. With this procedure, the detection rate (i.e., percentage of trials with valid onset) was 58.7% for visual perturbation and 66.5% for kinesthetic perturbation. To avoid a dependency of the results on the threshold values, the data were also analyzed with a threshold set at baseline plus/minus one and baseline plus/minus three standard deviations.

Results

The pattern of results is identical to that of EMG latencies determined using unperturbed trials as baseline. In particular, visual feedback of the hand sped up the latency of on-line corrections for early visual perturbation (12.4 ± 4.1 msec; $p < .05$). Fixing the threshold at one and three standard deviations of the baseline shifted the latencies to an earlier and later time point, respectively, but in both cases, the latency of the responses to an early perturbation was significantly shorter with visual feedback of the hand ($p < .05$). The EMG latencies determined using the different thresholds are reported in Table S2.

The trials in which the corrective movement was in the direction opposite to the initial reaching movement presented a higher signal-to-noise ratio. Indeed, these trials exhibited a higher contrast between the baseline activity induced by the initial reaching movement (i.e., before correction) and the EMG burst resulting from the corrective movement. Therefore, those trials provided more power to detect the response onset reliably. Interestingly, this subset of data revealed that for early visual perturbation the response facilitation induced by the visual feedback of the hand was even larger, on-line responses taking place on average 19.6 ± 5.8 msec earlier with feedback, which constitutes a 23% facilitation ($p < .05$).

Control experiment

Procedure

The task was a two-choice reaction time task in which the subject had to react as fast as possible to either a visual or a kinesthetic stimulus. The beginning of a trial was identical to the main experiment, with the subject having to maintain the visual feedback of the hand in the starting position for about one second. After a random period of 0 to 4 seconds, the starting position disappeared and either a visual target appeared or a short force step was applied to the hand with the haptic device. The visual stimulus was located 10 cm on either side of body midline at the height of the starting position. The force step of 10 N was delivered for 500 ms, coming from either the right or the left side. The subject was instructed to move the arm in the direction of the stimulus, i.e., to the side where the visual target appeared, or to the side counteracting the force step. As in the main experiment, visual feedback of the hand was an independent variable, i.e., it was randomly available in half of the trials, and not absent the other half.

Kinematic analyses of the reaching trajectories

The onset of the response to the visual stimulus was defined as the time point at which the hand covered a distance of 1 cm towards the target. For the kinesthetic stimulus, the onset of the response was defined as the time point at which the maximum distance from the starting position was reached, thus marking the start of the effective counter movement.

EMG latency of the responses

EMG latencies were determined using the mean EMG activity before stimulus presentation as baseline. Here, the onset of the response-specific EMG activation was relatively easy to detect because the baseline activation was much lower (the arm was kept still before stimulus presentation). Those data were analyzed using only a threshold set at baseline plus/minus two standard deviations.

Results of two-choice reaction times

In contrast to what we observed for on-line corrections, both the kinematic and EMG latencies of the responses remained unaffected by visual information about the hand (see Figure S4). It is worth mentioning here that kinematic latencies we measured are relatively long, mostly due to the inertia of the haptic device. In addition, the actual kinematic latency of the responses to the kinesthetic stimulus is probably a bit shorter than the latency we measured. Specifically, when a force step is applied to the arm, the actual response first acts to decelerate the limb before it is able to reverse its direction. Since response onset was define as the time point at which the maximum distance from the starting position was reached, the latencies we measured are probably a bit overestimated.

References

Hodges PW & Bui BH. (1996). A comparison of computer-based methods for the determination of onset of muscle contraction using electromyography. *Electroencephalogr Clin Neurophysiol* **101,** 511-519.

Table S1: Kinematic latencies [ms] measured with other thresholds and determining response onset with another method (PATHb and VELb). Significant differences ($p < .05$) between conditions with and without visual feedback about the hand position are marked bold.

		Visual perturbation				Kinesthetic perturbation			
		Early onset		Late onset		Early onset		Late onset	
		nHF	HF	nHF	HF	nHF	HF	nHF	HF
PATH 50%	Mean	**461.4**	**426.6**	**548.3**	**470.8**	533.6	498.2	547.1	514.6
	SE	**19.0**	**12.1**	**35.0**	**14.7**	31.1	16.2	29.3	13.4
VEL 25%	Mean	277.0	260.2	229.5	235.6	266.3	260.9	**249.7**	**262.9**
	SE	10.2	11.4	15.7	9.4	7.1	5.5	**9.7**	**7.6**
PATHb	Mean	**399.5**	**346.2**	**458.4**	**382.5**	562.5	570.7	628.5	590.0
	SE	**17.4**	**12.3**	**23.1**	**16.0**	30.3	19.7	28.99	21.4
VELb	Mean	**312.7**	**273.8**	**342.9**	**297.6**	296.8	293.3	295.1	313.3
	SE	**14.4**	**8.7**	**13.7**	**12.3**	11.6	7.8	9.1	8.8

Table S2: EMG latencies [ms] measured with another threshold (EMG120) and determining response onset with another method (EMGb) and different thresholds. Significant differences (*p* < .05) between conditions with and without visual feedback about the hand position are marked bold.

		Visual perturbation				Kinesthetic perturbation			
		Early onset		Late onset		Early onset		Late onset	
		nHF	HF	nHF	HF	nHF	HF	nHF	HF
EMG 120%	Mean	113.9	109.8	106.3	108.5	94.2	89.5	97.0	95.3
	SE	3.5	4.0	5.1	3.6	6.5	4.6	5.4	4.5
EMGb 1*STDEV	Mean	**99.2**	**88.3**	98.1	98.6	82.6	79.5	84.5	89.0
	SE	**5.2**	**5.0**	4.5	5.6	3.8	3.6	4.5	4.0
EMGb 2*STDEV	Mean	**115.6**	**103.1**	107.4	107.5	87.6	94.6	97.1	102.9
	SE	**5.8**	**6.0**	5.4	5.7	3.7	4.4	4.7	5.5
EMGb 3*STDEV	Mean	**127.9**	**109.3**	117.7	115.2	98.2	106.3	112.0	113.9
	SE	**7.2**	**5.5**	8.4	5.7	4.9	4.9	4.3	7.1

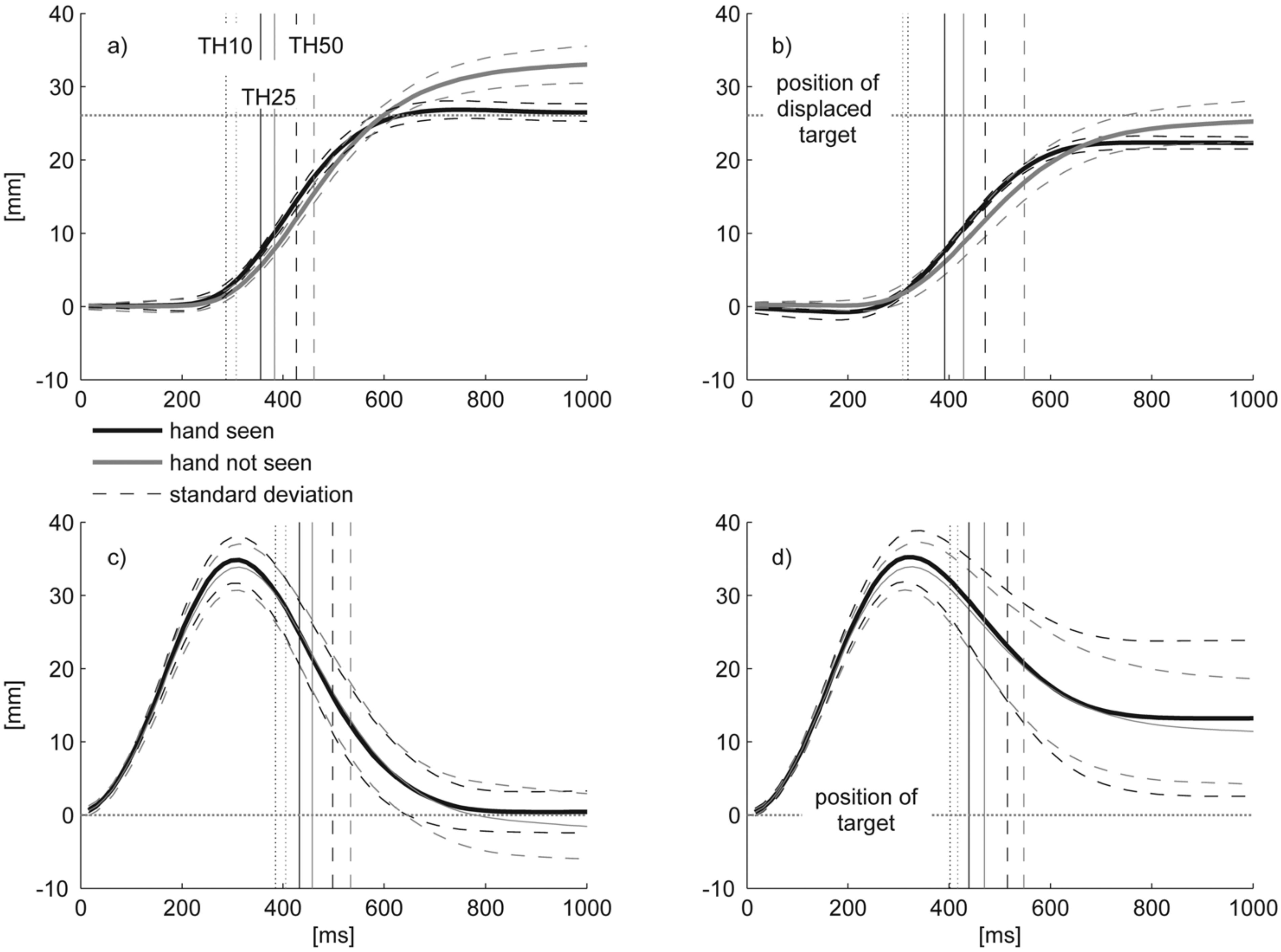
Figures captions

Figure S1: Mean path of trajectory perpendicular to the original target direction. Beforehand, the corresponding mean unperturbed trajectory was subtracted from the perturbed ones. A) and B) depict the visual perturbations, C) and D) the kinesthetic perturbations. A & C) show the early onsets, B & D) the late onsets. Time point 0 is the onset time of the perturbation. The straight vertical lines indicate the mean response latency with PATH measurement (threshold 25%), the dashed and dotted vertical lines illustrate the corresponding latencies for threshold 50% and 10%, respectively.

Figure S2: Mean velocity of trajectory perpendicular to the original target direction. Beforehand, the corresponding mean unperturbed trajectory was subtracted from the perturbed ones. A) and B) depict the visual perturbations, C) and D) the kinesthetic perturbations. A & C) show the early onsets, B & D) the late onsets. Time point 0 is the onset time of the perturbation. The straight vertical lines indicate the mean response latency with VEL measurement (threshold 50%), the dashed and dotted vertical lines demonstrate the corresponding latencies for threshold 25% and 10%, respectively.

Figure S3: Two representative single EMG traces for one subject (AC component rectified and smoothed). The EMGb response latency (black arrows) is determined where the EMG signal stays over its individual threshold (TH) for at least 25 msec. Each TH was set to baseline ± 2 standard deviations.

Figure S4: Kinematic (A) and EMG latency (B) of two-choice reaction times. EMG Reaction times to a kinesthetic stimulus were significantly faster than those to a visual stimulus, but for both types of stimulus, the reaction times remained unaffected by the visual feedback of the hand.


a)
b)
c)
d)
TH10
TH25
TH50
position of displaced target
position of target
hand seen
hand not seen
standard deviation
[mm]
[ms]
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30
20
10
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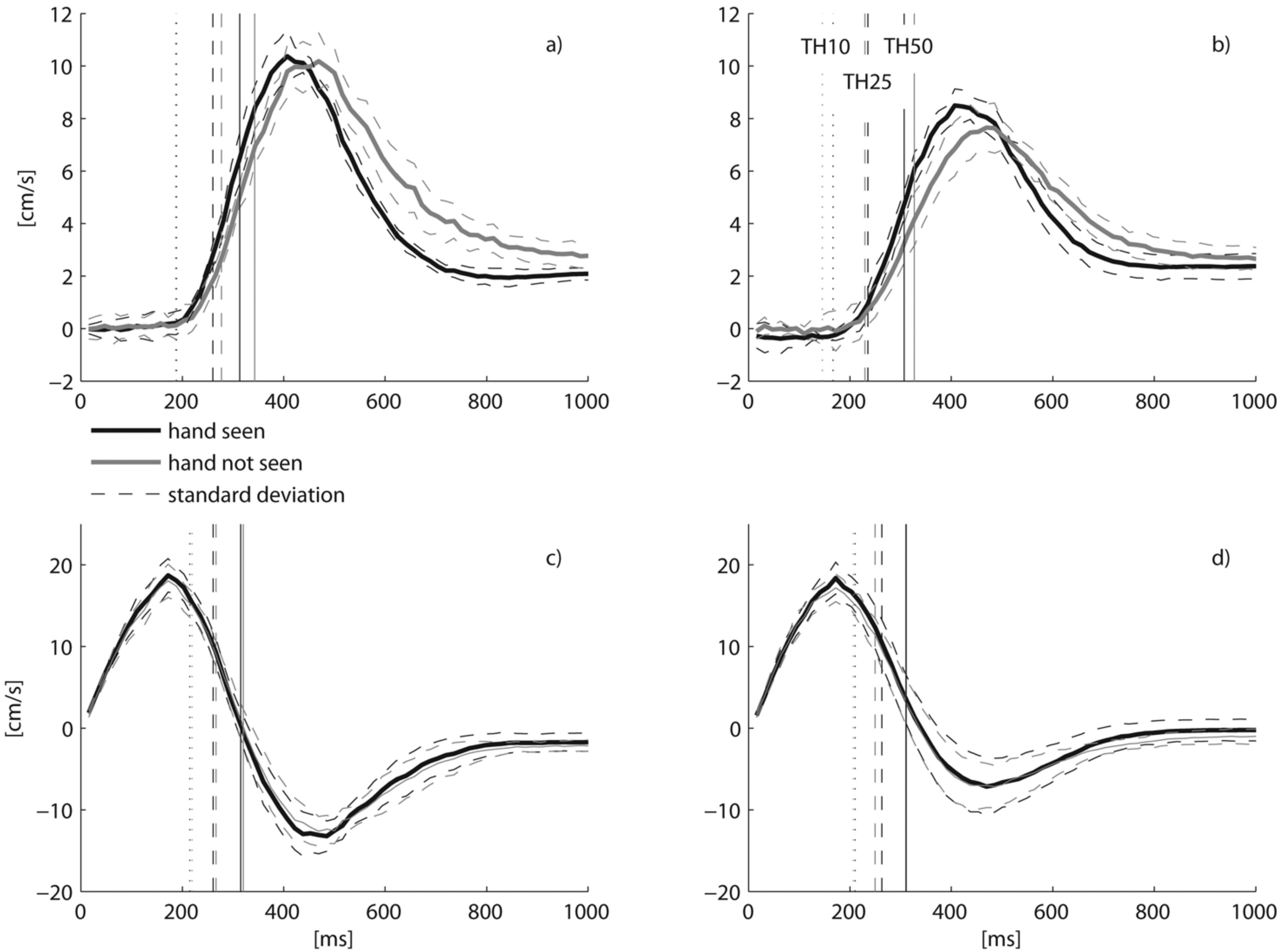
-10
0
200
400
600
800
1000

a)
b)
c)
d)
[cm/s]
[ms]
TH10
TH25
TH50
hand seen
hand not seen
standard deviation
12
10
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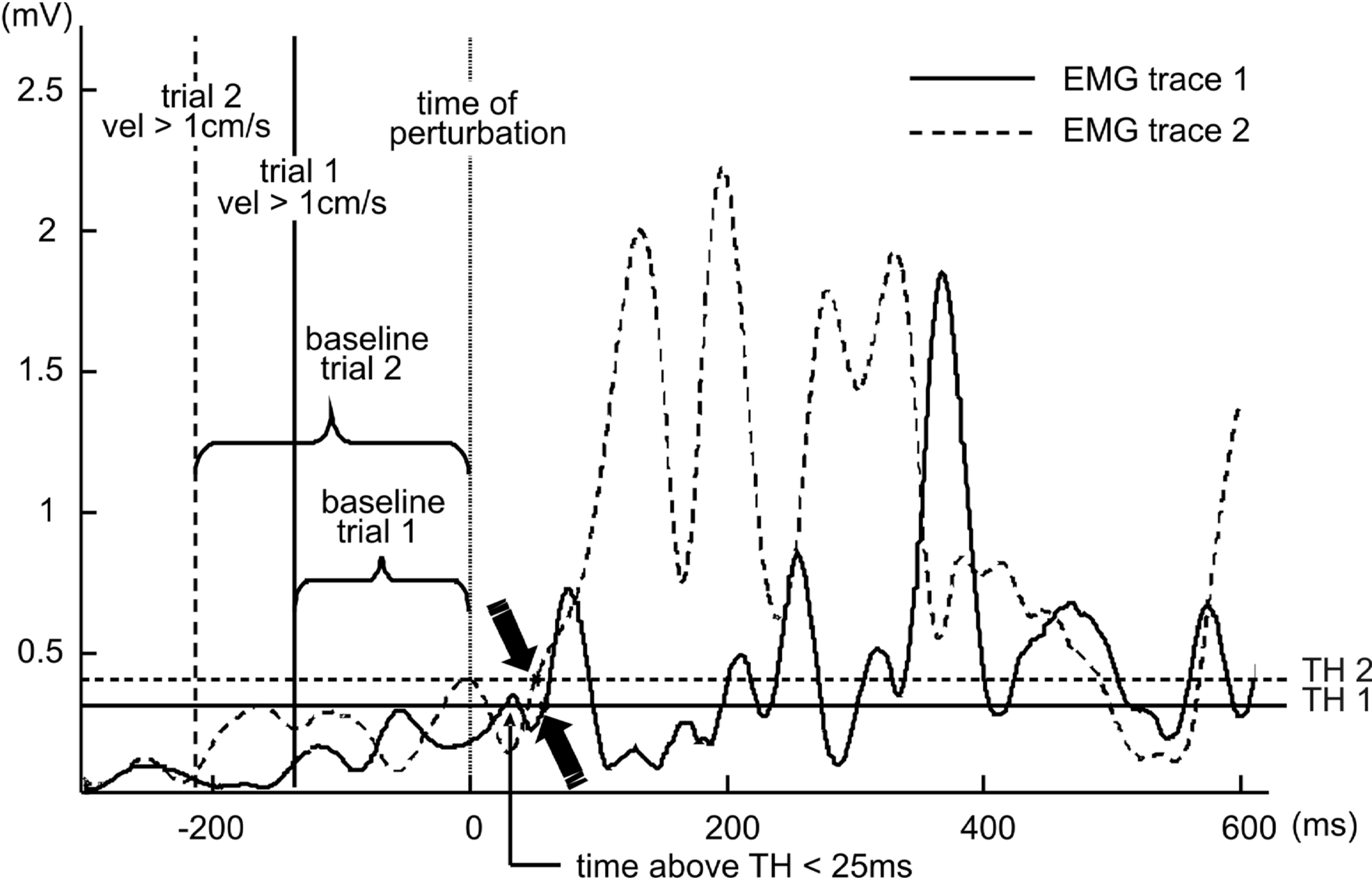
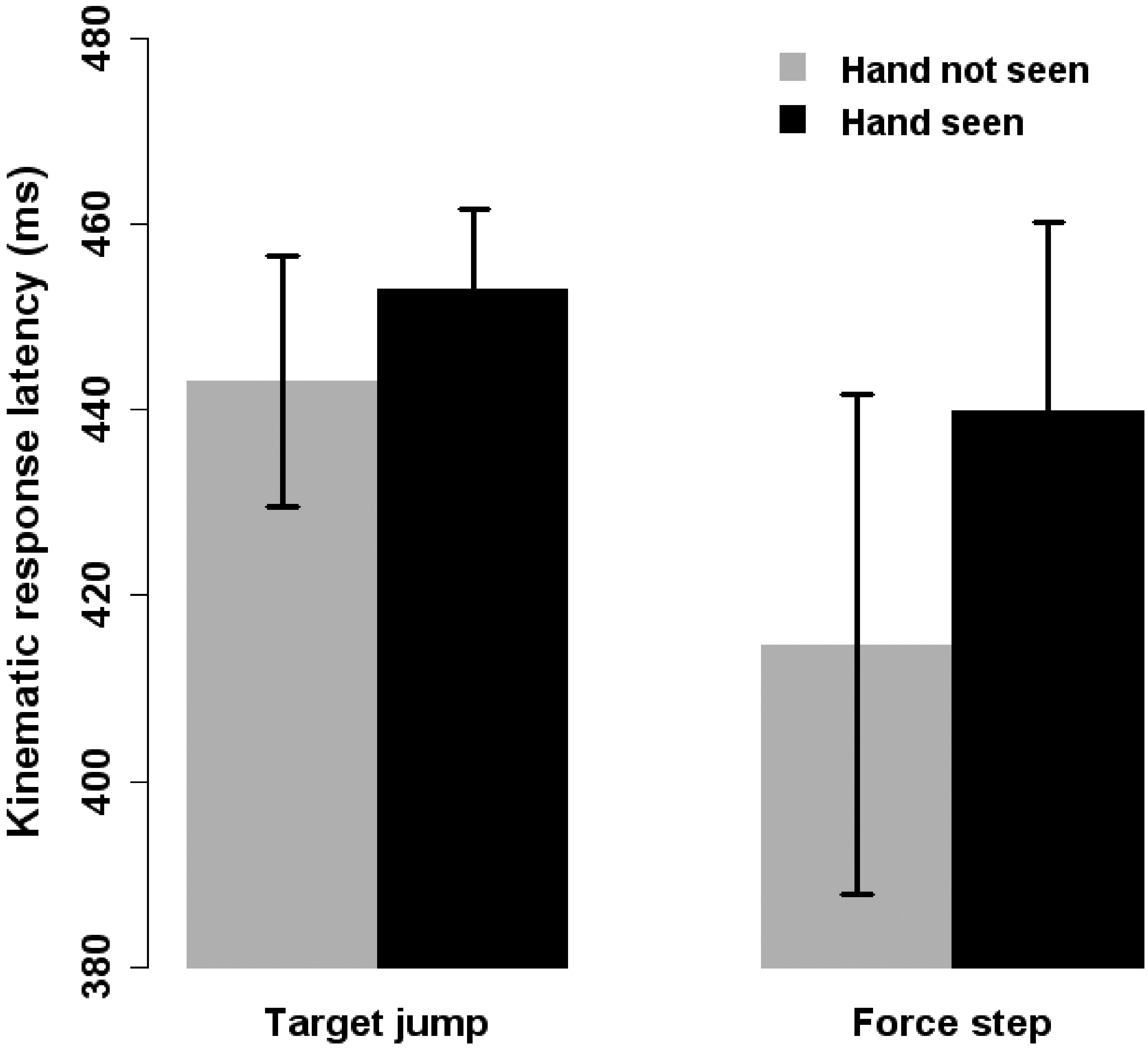
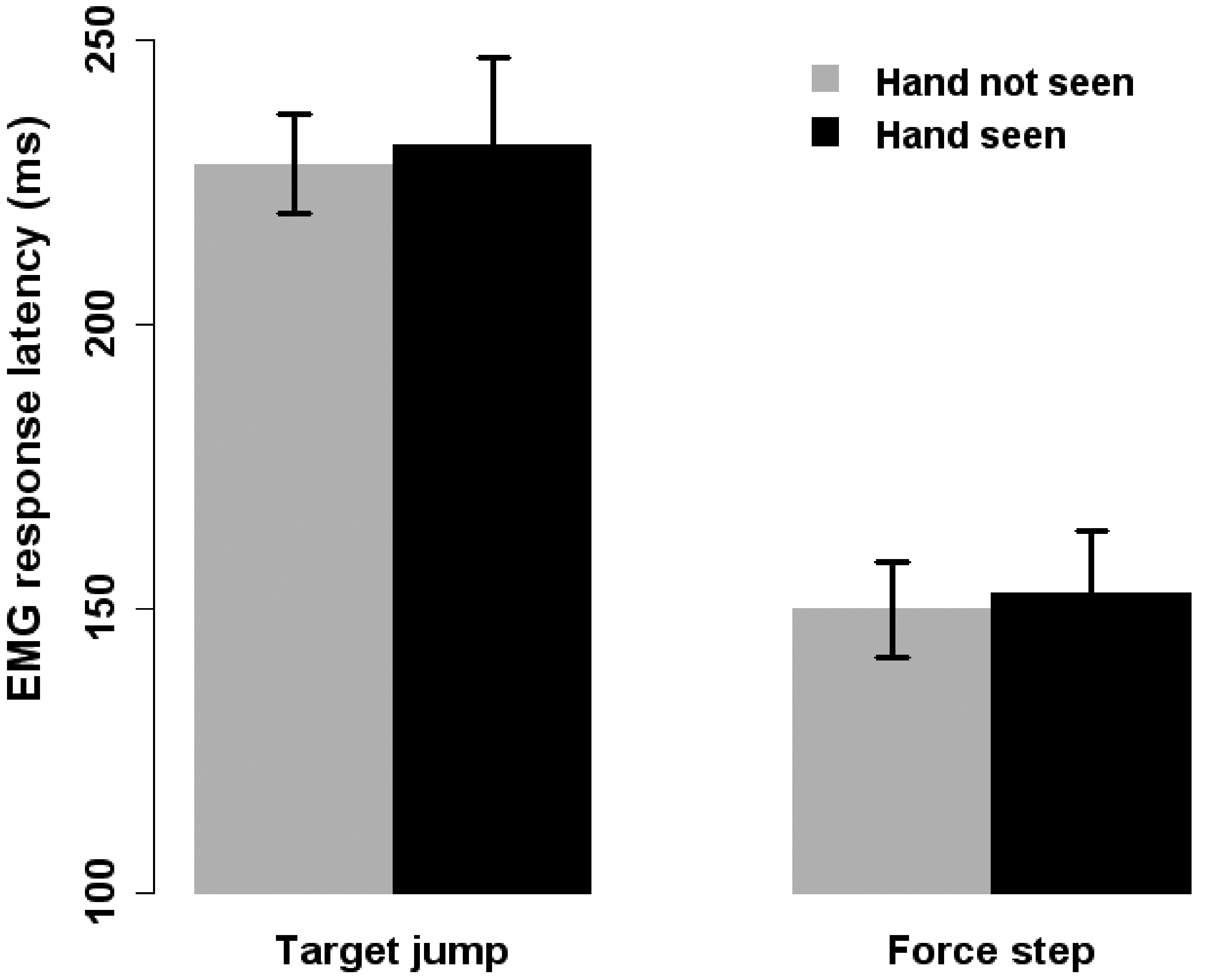
0
200
400
600
800
1000


(mV)
2.5
2
1.5
1
0.5
trial 2
vel > 1cm/s
trial 1
vel > 1cm/s
time of
perturbation
baseline
trial 2
baseline
trial 1
EMG trace 1
EMG trace 2
TH 2
TH 1
-200
0
200
400
600
(ms)
time above TH < 25ms


Hand not seen
Hand seen
Kinematic response latency (ms)
480
460
440
420
400
380
Target jump
Force step



EMG response latency (ms)
250
200
150
100
Target jump
Force step
Hand not seen
Hand seen

2.3 Reichenbach et al. (2011): Contributions of the PPC to online control of visually guided reaching movements assessed with fMRI-guided TMS

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Contributions of the PPC to Online Control of Visually Guided Reaching Movements Assessed with fMRI-Guided TMS

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The posterior parietal cortex (PPC) plays an important role in controlling voluntary movements by continuously integrating sensory information about body state and the environment. We tested which subregions of the PPC contribute to the processing of target- and body-related visual information while reaching for an object, using a reaching paradigm with 2 types of visual perturbation: displacement of the visual target and displacement of the visual feedback about the hand position. Initially, functional magnetic resonance imaging (fMRI) was used to localize putative target areas involved in online corrections of movements in response to perturbations. The causal contribution of these areas to online correction was tested in subsequent neuronavigated transcranial magnetic stimulation (TMS) experiments. Robust TMS effects occurred at distinct anatomical sites along the anterior intraparietal sulcus (aIPS) and the anterior part of the supramarginal gyrus for both perturbations. TMS over neighboring sites did not affect online control. Our results support the hypothesis that the aIPS is more generally involved in visually guided control of movements, independent of body effectors and nature of the visual information. Furthermore, they suggest that the human network of PPC subregions controlling goal-directed visuomotor processes extends more inferiorly than previously thought. Our results also point toward a good spatial specificity of the TMS effects.

Keywords: functional magnetic resonance imaging localizer, motor control, online responses, posterior parietal cortex, transcranial magnetic stimulation

Introduction

Every day, humans reach for objects in the environment with an incredible high degree of precision. Such behavior is seemingly effortless, even when sudden perturbations such as object relocations occur (Prablanc and Martin 1992; Pisella et al. 2000). This skill necessitates the fast processing of sensory information about our body and the environment in order to continuously control our movement (Desmurget and Grafton 2000). The sensory information available is usually composed of visual information about the object to reach for (called external visual information in the following), visual information about the body's effectors (called body-related visual information in the following), and proprioceptive information about the body's effectors.

The brain regions integrating information from different sensory channels for motor control have been investigated in humans using functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS; for reviews, see Culham and Valyear 2006; Iacoboni 2006; Filimon 2010). Although there is agreement that the posterior parietal cortex (PPC) contributes to many processes for online control of reaching movements, like coordinate transformations, the reported subregions vary substantially between studies. This might be due, on the one hand, to the wide variety of tasks used in the different studies and on the other hand to the high interindividual variance in neuroanatomy within the PPC (Grefkes and Fink 2005). Therefore, a consensus on the functional neuroanatomy of the human PPC in motor control is still missing. While studies on nonhuman primates deliver a more clear-cut view on this topic, applying this knowledge to humans remains a challenge, as pointed out by recent comparative work (Culham and Kanwisher 2001; Grefkes and Fink 2005).

The goal of the present study was to identify subregions of the PPC that contribute to the integration of visual information during online control of reaching movements. In order to distinguish between the processing of external and body-related visual information, 2 types of perturbations were investigated in a reach-to-target paradigm: displacement of the visual target (corresponding to external visual information; Prablanc and Martin 1992) and displacement of the visual feedback of the hand position (corresponding to body-related visual information; Sarlegna et al. 2003). The former perturbation was investigated both with and without visual feedback about the hand position as the "mode" of motor control might differ as a function of the available visual information about the hand (Krakauer et al. 1999; Reichenbach et al. 2009). Consequently, different processes and brain regions might be recruited to some extent. Furthermore, when visual information about the target and proprioceptive information from the body effectors has to be integrated, extra coordinate transformations are necessary to bring this information into a common frame of reference.

In contrast to prior studies (Desmurget et al. 1999; Johnson and Haggard 2005; Chib et al. 2009), we combined an fMRI localizer task with subsequent neuronavigated TMS experiments for the same subjects. The fMRI localizer gave an approximate overview over the areas generally involved in online control during visuomotor processing. This enabled accurate selection of individual TMS stimulation sites. Our approach therefore took into account interindividual differences in (functional) neuroanatomy of the human PPC. The fMRI localizer yielded a better spatial localization of the TMS results, while TMS allowed us to causally disentangle necessary from coactivated brain areas, thus underpinning the importance of a subset of the areas detected by fMRI.

Materials and Methods

General Procedure

Nine healthy volunteers (aged 23–34 years, 5 females) including 2 of the authors participated in the study. Besides the authors, all subjects were naive to the purpose of the study. They had normal or corrected-to-normal vision and no history of neurological disorders. Written informed consent was obtained for each subject prior to the first experiment. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee of the Medical Faculty of the University of Tübingen. Each subject participated in several experimental sessions in which he/she was first familiarized with the overall procedure, then the fMRI data were recorded, and finally the different TMS experiments were performed. Successive sessions were separated by 1 week or more. During the MRI scan and the TMS experiments, subjects wore earplugs to prevent hearing damage and auditory influence on task performance. One subject dropped out in the course of the study due to personal reasons unrelated with the experiment.

Two different visual perturbations were applied in order to investigate the subregions of the PPC contributing to the integration of external and body-related visual information during reaching: the displacement of the visual target (abbreviated TD indicating “target displacement,” Fig. 1*a*) and the displacement of the visual feedback about the hand position (abbreviated HD indicating “hand displacement,” Fig. 1*b*) after onset of the reaching movement.

In the fMRI localizer task, brain regions were identified that were robustly activated during reaching (compared with fixation with matched visual input) and, in addition, were more active during perturbed than during unperturbed reaching (Fig. 2*a–c*). Brain region identification was done separately for TD and HD. These regions, and additionally some control sites, provided the basis for selecting the stimulation sites of the subsequent (causal) TMS experiments. The paradigms for the TMS and fMRI experiments were matched apart from one detail, in order to prevent artifacts in the fMRI images. In the fMRI localizer, we used finger reaching with the tip of the index finger attached to an MR-compatible joystick placed beside the hip and the visual scene projected onto a coil mounted mirror. The TMS experiments were conducted in a virtual reality environment with spatially matched visual and haptic scenes where the subjects had to perform fully fledged reaching movements with their right arm using a robot arm as manipulandum (Supplementary Fig. S1). Importantly, however, the type and extent (in degrees) of the visual perturbations were the same for both imaging modalities.

In the TMS main experiments, we tested whether the subjects' ability to correct for visual perturbations was reduced when magnetic pulses were applied to the brain regions previously identified by fMRI but not when applied to control sites. The first 2 TMS experiments investigated the responses to visual TDs, first with and then without visual feedback about the hand position (TMS experiment 1: TD_HF and TMS experiment 2: TD_nHF, Fig. 1*a*). In the third experiment, the effects of displacing the visual feedback about the hand position were tested (TMS experiment 3: HD, Fig. 1*b*).

Details on the fMRI localizer experiment can be found in the Supplementary Data B. The following paragraphs first describe how the TMS stimulation sites were derived from the fMRI results and then depict the methods of the TMS experiments. The Results section is identically organized.

TMS Stimulation Sites

The peak activations within the regions that exhibited higher blood oxygen level–dependent (BOLD) activity during perturbed than during unperturbed reaching in the fMRI localizer task (Fig. 2*b*,*c*) were used to determine the TMS stimulation sites. Most TMS stimulation sites were based on group results. The statistical group maps were transformed back from Montreal Neurological Institute (MNI) space to the space of the individual structural images, and the closest coil position on the skull was determined for each activation peak using custom-written MATLAB routines (The MathWorks). The routines used the surface reconstruction of the skull as obtained with BrainVoyager 2000 (Brain Innovation). Additional individual stimulation sites were defined whenever the individual activation peak within a given anatomical region was spatially offset from the corresponding peak in the group map, that is, when planning the coil position based on the individual activation peak resulted in a coil position >10 mm apart from the position planned on the peak of the group activation. In the TMS experiments, these individual sites were tested in addition to the sites derived from the fMRI group activations. An additional level for the factor “stimulation site” was defined for the statistical group analyses whenever an anatomical region included individual stimulation sites: The first level representing a particular region was based solely on the TMS data gathered at the fMRI group site (indicated by the subscript “group” in the following). The additional level was used to represent the individual test sites. It contained the data from the individual sites whenever they existed and the data acquired at the group site for the remaining subjects (indicated by the subscript “indiv” in the following). In each case, data from all 9 subjects (8 subjects for experiment 2) were used to compile the TMS results at the group level.

TMS Experiments: Technical Setup

A mirror-setup with a top-mounted CRT monitor and shutter glasses (StereoGraphics/REAL D) was used to render the 3D visual scene in spatial congruence to the haptic scene (Supplementary Fig. S1). The latter was controlled by a robot arm (DekiFeD, Technische Universität München, Germany; Buss and Schmidt 1999) used as manipulandum that restricted the hand movements to a horizontal plane. The subjects kept the handle that was mounted on the robot arm grasped with the right-hand throughout an experimental block, and the visual feedback about the hand position (represented by a red sphere), whenever given, corresponded spatially to the top of this handle. The robot arm actively followed the hand movements to minimize its inertia as felt by the subject. Visual scene presentation and acquisition of the kinematic data were performed at 120 Hz. For additional details, please refer to Reichenbach et al. (2009).

Saccade detection was realized online via electrooculography (EOG) on a separate computer. Three small cup electrodes were placed on the subject's face, above and below the right eye, and the reference in the center of the forehead. The electrodes were connected to the AD-converter (DAQ2205; Adlink Technology Inc., sampling rate 10 kHz) of the computer via an amplifier (Psylab, Contact Precision Instruments Inc.). A custom-written MATLAB program reported the saccades to the computer that controlled the experiment. The EOG threshold was adjusted for each subject so that the saccade triggers corresponded to the initial acceleration period of the eye movement.

Biphasic TMS stimuli were applied using a Medtronic MagPro X100 stimulator (MagVenture) with a MC-B70 butterfly coil. The coil position was monitored using a neuronavigation system (BrainView, Fraunhofer IPA; for a description of the system, see Kammer et al. (2007)). The spatial accuracy of the registration between the subject's real head and his anatomical MR image in the neuronavigation system was established at the beginning and checked again at the end of each session using the positions of clearly visible landmarks (e.g., nasion and inion). The coil was held manually by a trained investigator, keeping the coil position in a range of 2 mm to the preplanned stimulation sites. Blocks were repeated whenever the distance of the coil to the stimulation site exceeded 2 mm. The stimulation intensity was chosen to meet 2 competing goals: It should be as high as possible to maximize the impact on the stimulation site without eliciting direct effects on M1. For this purpose, the coil was placed at the most anterior stimulation site at the beginning of each session, and the intensity was gradually decreased until no motor responses were elicited in the finger muscles any more for at least 10 consecutive trials (tested by recording surface electromyography from the relaxed first dorsal interosseus). Subsequent control measurements confirmed that this procedure resulted

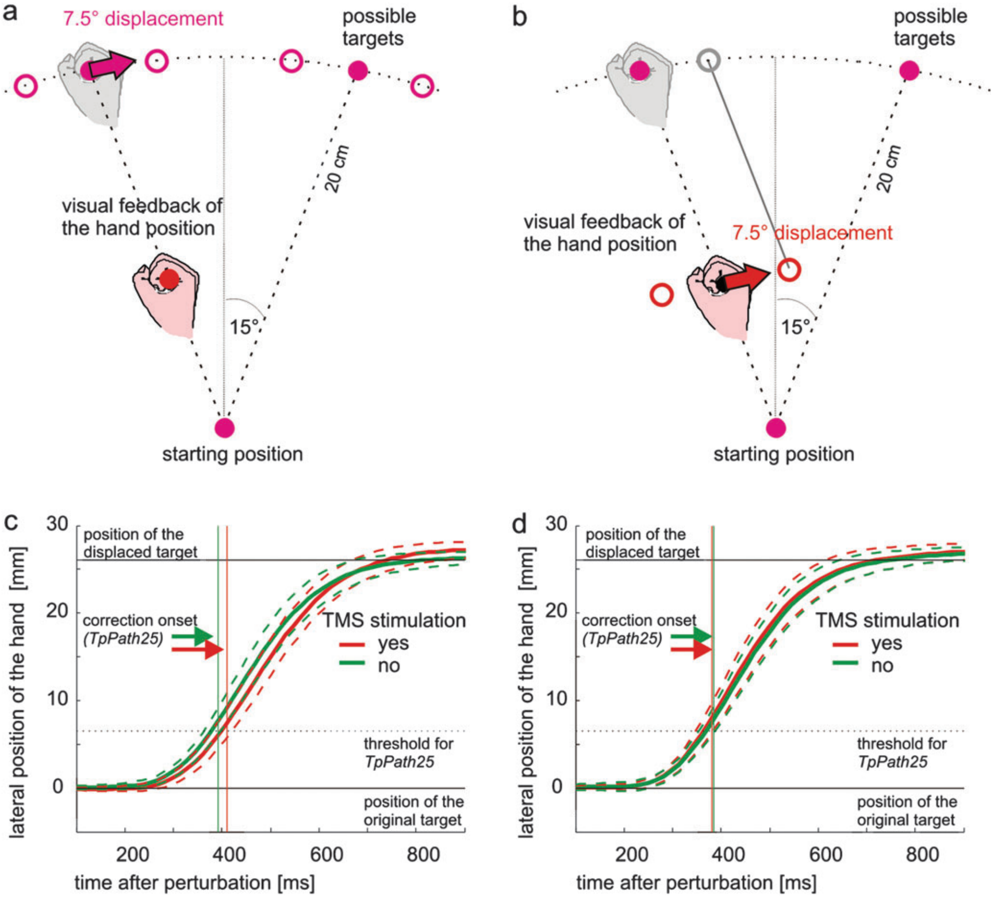

Figure 1. Upper panel: schematic sketch of the arrangement of the visual scene for both the fMRI and the TMS experiments. The locations of the starting position and of the visual targets are shown as filled magenta circles. The grayed out components illustrate the scenario at the end of the perturbed movements if the subject had not corrected for the corresponding perturbation. All perturbations required an amendment of the hand by 7.5° (rotated relative to the starting circle) from the original target direction at the end of the reaching movement. (*a*) The spatial displacements of the visual target (TD) are depicted as open circles (fMRI condition 2 and TMS experiments 1 and 2). (*b*) The open circles indicate the displacements of the visual feedback about the hand position (HD) (fMRI condition 3 and TMS experiment 3). Lower panel: mean kinematic data (dashed lines: SE across subjects) for illustration of TpPath25 for $\text{IPS}_{\text{group}}$ (*c*) and reach (*d*) for the first TMS experiment (TD_HF). Data of all perturbed conditions are collapsed and only the lateral position of the hand (i.e., the component perpendicular to the original reaching direction) is plotted against time. As long as the hand is heading straight to the original target, no lateral displacement is visible on the *y*-axis. The displacement of 7.5° in a distance of 20 cm corresponds to a lateral displacement of 26.1 mm. Corresponding spatial 2D trajectories can be found in the Supplementary Data (Supplementary Fig. S2).

in a stimulation intensity of ~90% relative to the individual motor threshold. Finger muscles were used for this purpose as it is known that these muscles exhibit the lowest TMS thresholds. The coil was initially oriented parallel to the central sulcus and adjusted when necessary. This procedure resulted in stimulation intensities of 48–61% of maximum stimulator output.

TMS Experiments: Procedure and Behavioral Task

In separate sessions, 3 different visual conditions were tested: displacement of the visual target, first with and then without visual feedback about the hand position (TMS experiment 1: TD_HF and TMS experiment 2: TD_nHF, Fig. 1*a*), and displacement of the visual feedback about the hand position (TMS experiment 3: HD, Fig. 1*b*). The independent variables tested that were common to all 3 experiments were position of the target (15° to the left/15° to the right), visual perturbation (7.5° to the right/7.5° to the left/none), and TMS (yes/no). The number of trials without TMS was equated to the number of TMS trials. The timing between the initial saccade to the visual target and the magnetic pulses (called TMS stimulus onset asynchrony (SOA) in the following) was 40 ms. For experiment 2 (TD_nHF), an additional later TMS SOA of 80 ms was used, resulting in 3 levels for the variable TMS in this case (80 ms/40 ms/no). The additional TMS SOA was based on results from a prior psychophysical study (Reichenbach et al. 2009) which indicated that online corrections to displaced targets are slower when visual feedback about the hand position was not available.

A session proceeded in complete darkness and consisted of several blocks, including an initial training block to familiarize the subject with the task. One block lasted 10–15 min and contained 72 trials, covering all possible combinations of the independent variables. The order of presentation was fully randomized to prevent any predictability or anticipation of the visual perturbation and the administration of TMS. Altogether, 12 repetitions were recorded for each combination of independent variables, resulting in 2 (TMS experiments 1 and 3) or 4 (TMS experiment 2) blocks per TMS stimulation site. The order of stimulation sites was randomized to prevent training or fatigue effects from biasing the results. With exception of the right hemispheric control site, the stimulation positions were undistinguishable for the subjects. Depending on the experiment and the subject (having individual test sites or not), the number of stimulation sites varied between 3 and 8. The highest number of sites was tested for TD_HF so that some of the control sites were tested in a separate session for this visual condition.

A trial started with the presentation of the starting position with the visual feedback about the hand position present. The starting position was randomly jittered in a 2 × 2 cm area located 10 cm in front of the subject about the body midline. After the hand had been maintained in the starting position for about 1 s, the target appeared and the starting position disappeared. The target was displayed at 20 cm distance from

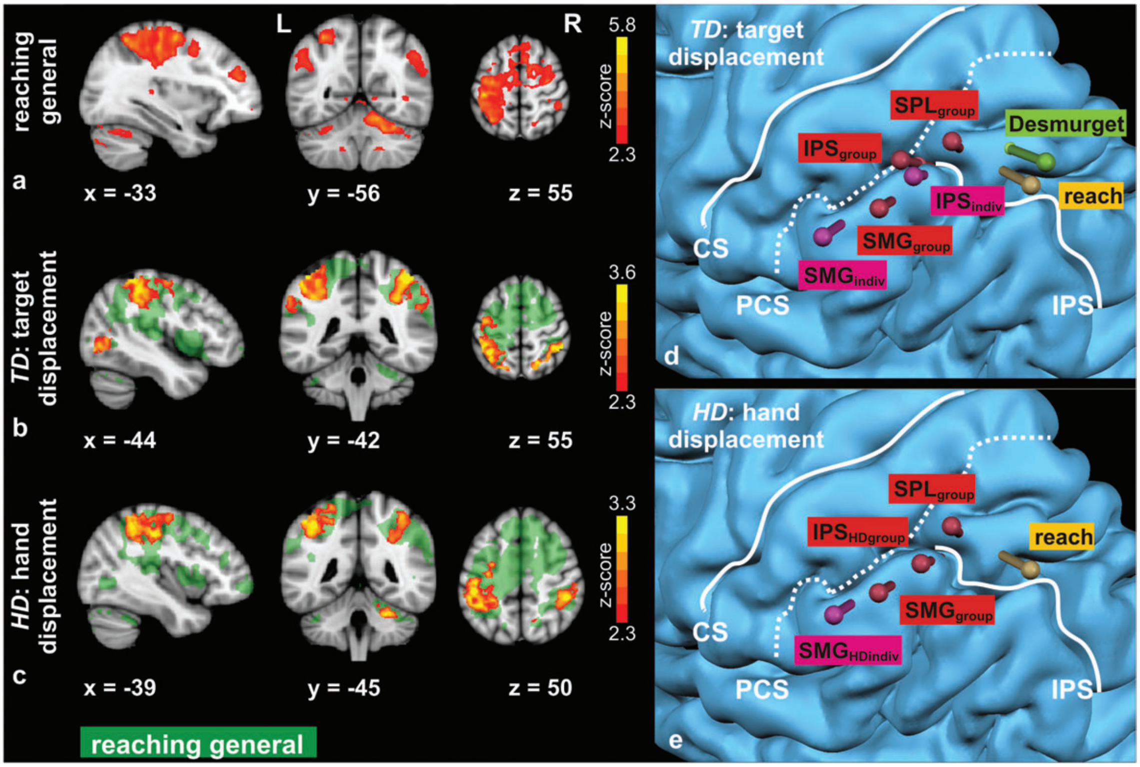

Figure 2. Left panel: fMRI activation patterns for the group analysis (all maps were thresholded using $Z = 2.3$ at voxel level and $P = 0.05$ corrected at cluster level; MNI space). The entire fMRI experiment was conducted with visual feedback about the cursor position present. (*a*) Activation pattern for general reaching compared with fixation. The depicted slices were selected using the MNI coordinates of the local peak activation in the left PPC. This contrast was used as mask for the subsequent fMRI analyses. (*b*) Activation pattern for displacement of the visual target (TD) compared with unperturbed reaching. The depicted slices were selected according to the position of the absolute peak activation, the latter residing within the left PPC. This activation map served as basis for planning the stimulation sites of TMS experiments 1 and 2 (Fig. 2*d*). (*c*) Activation pattern for displacement of the visual feedback of the "hand" position, that is, the cursor position on the screen (HD) compared with unperturbed reaching. The slices were selected according to the local peak activation in the left PPC. This activation map was used to plan the stimulation sites of TMS experiment 3 (Fig. 2*e*). Right panel: (*d*) stimulation sites for TMS experiments 1 and 2 with displacement of the visual target (TD) as derived from the fMRI activations. (*e*) Stimulation sites for TMS experiment 3 with displacement of the visual feedback about the hand position (HD). The MNI group coordinates were transformed in one subject's individual space and then projected onto the rendered 3D reconstruction of this subjects' left hemisphere. The "needles" indicate the different coil positions: Their direction is aligned perpendicular to the TMS coil and their head is located directly at the center of the coil on the skull. The white lines highlight the principle sulci: central sulcus (CS), postcentral sulcus (PCS), IPS.

the starting position, and its location was 15° on either side of the body midline. The subject's task was to look at and reach for the target as quickly and precisely as possible. In experiment 2 (TD_nHF), the visual feedback about the hand position disappeared as soon as the target appeared. The time at which the velocity of the hand dropped below 1 cm/s again was defined as the end of the trial. In between trials, the visual scene disappeared for 2 s.

Visual perturbations were set to occur while the subject performed the saccade to the target to prevent them being consciously perceived (Zuber and Stark 1966). In the first 2 experiments (TD_HF and TD_nHF), the visual target was displaced 7.5° on either side of its original location (Fig. 1*a*). In the third experiment (HD), the visual feedback about the hand position was translated perpendicular to the original reaching direction on either side of its original location to yield in an offset of 7.5° at the end of the movement (Fig. 1*b*).

In TMS trials, 3 magnetic pulses were applied at a frequency of 60 Hz. The first pulse was delivered at a fixed delay of 40 ms (or 80 ms for the later SOA in experiment 2) with respect to the time of the visual perturbation (i.e., after the saccade). The 3 pulses of the 40 ms SOA covered a period of 33 ms after hand movement onset (Desmurget et al. 1999).

In order for participants to remain naive throughout the complete duration of the study, no explicit questions about the subject's awareness of the applied perturbations were asked. Instead, after each session, the subjects were encouraged to disclose any oddity they encountered during the course of the experiment. Some subjects reported that sometimes it "felt weird" or about "being worse than expected" but all clearly missed the real reason for it.

TMS Experiments: Behavioral Measures and Data Analysis

The onset and offset of the movement were defined as the time at which the velocity of the robot arm exceeded and fell below 2 cm/s, respectively. Trials were excluded from further analysis if total time, total path length, or peak velocity were outside the range of the subject's mean ± 3 × standard deviation. The impact of TMS on the online corrections to the visual perturbations was assessed by applying 2 different measures to the kinematic data. The time point at which the mean trajectory first exceeded 25% of the distance necessary to fully compensate for the perturbation was used as temporal measure of the correction onset (TpPath25; Fig. 1*c*,*d*; Reichenbach et al. 2009). The absolute value of the maximum deviation between the recorded trajectory and an "ideal trajectory" (i.e., a straight line between the starting position and the final target) was used as the spatial measure for the amount of incorrect reaching (MaxDev). Additionally, measurements of the overall reaching time (ReachTime) and endpoint accuracy (EndAcc) were assessed. The latter was defined as the distance of the final hand position to the final target, whereby the evaluation was restricted to the component perpendicular to the original reaching direction (a displacement of 7.5° in the distance of 20 cm yields in a lateral displacement of 26.1 mm). Group analyses for each TMS experiment were conducted with repeated-measures analyses of variance (ANOVAs) on the factors TMS (TMS SOA(s)/TMS not applied) and stimulation site. Subsequently, for each stimulation site, preplanned comparisons between each TMS SOA versus TMS not applied were conducted. Fisher's least significant difference tests were used for multiple comparisons correction when the interaction of the ANOVA was significant. Reported values are mean ± standard error (SE) across subjects, unless stated otherwise.

Results

TMS Stimulation Sites: Results of the fMRI Localizer Task

General reaching-related activity compared with fixation mainly clustered in the left hemisphere (Fig. 2*a*), spanning from motor cortex over somatosensory cortex to the PPC. Additional strong activations occurred bilaterally in the frontal lobes (including premotor areas) and the right cerebellum. A smaller cluster was present in the right PPC. The peak activation within the left PPC was used to plan a TMS control site ("reach"; see Tables 1–3 for the MNI coordinates on which all stimulation sites are based upon). Evaluation of the behavioral data confirmed that the subjects corrected for the visual perturbations, even though the overall movements were small (data not shown).

The stimulation sites for TMS experiment 1 (TD_HF; Fig. 2*d*) were based on the comparison of reaching trials with displacement of the visual target (TD) versus unperturbed trials (Fig. 2*b*). A large left-lateralized cluster exhibited enhanced BOLD activity during perturbed versus unperturbed reaching. The peak difference was observed in the anterior part of the intraparietal sulcus (resulting in stimulation site $\text{IPS}_{\text{group}}$) and additional local peaks occurred on the anterior supramarginal gyrus (aSMG) and the anterior superior parietal lobe (resulting in sites $\text{SMG}_{\text{group}}$ and $\text{SPL}_{\text{group}}$). Additionally, 3 subjects had robust individual peaks more posteriorly within the IPS (resulting in individual TMS stimulation sites displaced by 11–17 mm from $\text{IPS}_{\text{group}}$), and 5 subjects had robust individual peaks more inferiorly on the SMG (resulting in individual TMS stimulation sites having a distance of 19–39 mm to $\text{SMG}_{\text{group}}$). These positions were included as additional individual TMS stimulation sites ($\text{IPS}_{\text{indiv}}$ and $\text{SMG}_{\text{indiv}}$). At the group level, the comparison revealed an additional small peak in the right PPC that approximately mirrored the position of $\text{IPS}_{\text{group}}$ and that was therefore selected as control stimulation site over the right hemisphere ($\text{IPS}_{\text{right}}$). One additional test site was obtained using the procedure of Desmurget et al. (1999), independent of the fMRI localizer results. For TMS experiment 2 (TD_nHF), which served as an addendum to test whether the observed TMS effects (as described below) depended on visual feedback about the hand position, we used a subset of these sites ($\text{IPS}_{\text{indiv}}$, $\text{SMG}_{\text{indiv}}$, and $\text{SPL}_{\text{group}}$).

The sites for TMS experiment 3 (HD; Fig. 2*e*) were based on regions that exhibited enhanced BOLD activity for reaching trials with displacement of the visual feedback about the hand position (HD) versus unperturbed trials (Fig. 2*c*). The peak difference within the PPC was located in the anterior part of the IPS (resulting in site $\text{IPS}_{\text{HDgroup}}$). Six subjects had robust individual peaks on the inferior SMG (resulting in individual TMS stimulation sites 11–33 mm distant to $\text{SMG}_{\text{group}}$) that were used as additional stimulation sites ($\text{SMG}_{\text{HDindiv}}$). At the group level, a peak was present in the right IPS that served as control site over the right hemisphere ($\text{IPS}_{\text{HDright}}$). Positions $\text{SMG}_{\text{group}}$ (situated between $\text{IPS}_{\text{HDgroup}}$ and $\text{SMG}_{\text{HDindiv}}$) and $\text{SPL}_{\text{group}}$ were included as additional test sites in order to cover the complete region ranging from SMG to SPL comparable with the preceding 2 experiments. At both positions, BOLD activity for HD trials was clearly enhanced compared with unperturbed reaching, even though it did not peak there.

TMS Experiment 1: Displacement of the Visual Target with Visual Feedback of the Hand Position (TD_HF)

For trials with displacement of the visual target, overall reaching times were selectively prolonged by TMS stimulation over sites $\text{IPS}_{\text{group}}$, $\text{SMG}_{\text{group}}$, and $\text{SMG}_{\text{indiv}}$ (ReachTime in Table 1; interaction TMS × stimulation site: $F_{7,56} = 3.77$; $P < 0.01$). Endpoint accuracy was generally good and not affected by TMS stimulation (EndAcc in Table 4). The online correction for the perturbation started significantly later when TMS was applied over sites $\text{IPS}_{\text{group}}$, $\text{IPS}_{\text{indiv}}$, and $\text{SMG}_{\text{indiv}}$ (TpPath25 in Table 1; interaction TMS × stimulation site: $F_{7,56} = 2.85$; $P < 0.05$). Accordingly, the maximum deviation was enhanced when TMS was applied over these sites (MaxDev in Table 1; interaction TMS × stimulation site: $F_{7,56} = 2.21$; $P < 0.05$).

Including test sites based on individual fMRI data shifted the mean position of the IPS stimulation site only 4 mm posteriorly. Accordingly, the TMS effects were comparable in both cases ($\text{IPS}_{\text{indiv}}$ vs. $\text{IPS}_{\text{group}}$ in Table 1). In contrast, the inclusion of individual sites shifted the mean stimulation site over the SMG 12 mm lateral-inferiorly and resulted in markedly more stable TMS effects ($\text{SMG}_{\text{indiv}}$ vs. $\text{SMG}_{\text{group}}$ in Table 1). As the usage of individual sites tended to stabilize the TMS effects, we used $\text{IPS}_{\text{indiv}}$ and $\text{SMG}_{\text{indiv}}$ rather than the corresponding group sites in TMS experiment 2.

TMS Experiment 2: Displacement of the Visual Target without Visual Feedback of the Hand Position (TD_nHF)

Compared with the preceding experiment, reaching times were generally slightly shorter (4 ms, Table 4) but were not affected by TMS at any of the 3 stimulation sites (Table 4; main effect of TMS on ReachTime: $P > 0.5$; interaction TMS × stimulation site: $P > 0.05$). The spatial accuracy of the reaching movements was reduced compared with the preceding experiment, as reflected by larger SEs for EndAcc (Table 4).

When separately analyzing the data for the TMS SOAs 40 and 80 ms, the results revealed a tendency toward later correction onsets and enhanced maximum deviation for stimulation sites $\text{IPS}_{\text{indiv}}$ and $\text{SMG}_{\text{indiv}}$ compared with $\text{SPL}_{\text{group}}$ (data not shown). This pattern is similar to the data obtained with visual feedback about the hand position. However, they did not reach statistical significance due to the generally large variability of the movements. We therefore pooled the 2 TMS SOAs in each subject before performing the group analysis. For site $\text{SMG}_{\text{indiv}}$, this helped to confirm longer general reaching times (ReachTime in Table 2; interaction TMS × stimulation site: $F_{2,14} = 3.56$; $P = 0.05$) and a later correction onset (TpPath25 in Table 2; interaction TMS × stimulation site: $F_{2,14} = 3.69$; $P = 0.05$) for trials with versus without TMS. The endpoint accuracy was selectively affected by TMS over site $\text{IPS}_{\text{indiv}}$ (EndAcc in Table 2; interaction TMS × stimulation site: $F_{2,14} = 4.82$; $P < 0.05$).

TMS Experiment 3: Displacement of the Visual Feedback of the Hand Position (HD)

For trials where the visual feedback about the hand position was displaced, the overall reaching time was selectively prolonged by TMS stimulation over sites $\text{SMG}_{\text{group}}$ and $\text{SMG}_{\text{HDindiv}}$ (Table 3). As expected from the results of prior studies (Sarlegna et al. 2003, 2004), the correction for the visual perturbation was generally incomplete due to some remaining proprioceptive influence, resulting in negative values for EndAcc (Table 4). This general tendency was not affected by

Table 1
Results for TMS experiment 1 (TD_HF)

Stimulation site	MNI coordinates, *x*, *y*, *z* in [mm], (±SD)	TpPath25, [ms], (*P* values)	MaxDev, [mm], (*P* values)	ReachTime, [ms], (*P* values)	EndAcc, [mm], (*P* values)
$\text{SPL}_{\text{group}}$	−36, −49, 57	9.4 ± 6.5	0.6 ± 0.5	−1.3 ± 5.3	−0.6 ± 0.3
$\text{IPS}_{\text{group}}$	−44, −42, 55	**18.0 ± 7.9, (<0.01)**	**0.8 ± 0.4, (<0.05)**	**26.3 ± 16.5, (<0.01)**	0.9 ± 0.6
$\text{IPS}_{\text{indiv}}$	−42.9/−45.0/52.9, (±1.9 4.7 4.3)	**13.2 ± 6.5, (<0.05)**	**0.7 ± 0.3, (<0.05)**	16.2 ± 15.4	0.1 ± 0.4
$\text{SMG}_{\text{group}}$	−45, −40, 45	9.5 ± 4.8	0.1 ± 0.2	**46.0 ± 9.7, (<0.001)**	0.6 ± 0.5
$\text{SMG}_{\text{indiv}}$	−53.4, −32.5, 40.3, (±8.3 7.5 5.2)	**19.3 ± 8.3, (<0.01)**	**0.8 ± 0.4, (<0.05)**	**36.0 ± 7.8, (<0.001)**	0.4 ± 0.4
$\text{IPS}_{\text{right}}$	44, −42, 57	−3.2 ± 4.4	−0.2 ± 0.3	2.8 ± 8.4	0.1 ± 0.4
Reach	−33, −56, 55	−3.4 ± 5.6	−0.2 ± 0.4	−3.8 ± 4.9	0.4 ± 0.4
Desmurget	−33.9, −59.4, 62.8, (±3.8 3.4 2.3)	−9.9 ± 4.8	−0.5 ± 0.5	5.9 ± 5.6	0.1 ± 0.2

Note: The MNI coordinates upon which the TMS stimulation sites were planned are given and for TpPath25, MaxDev, ReachTime and EndAcc, the difference ± SE between trials with versus without TMS is given for each TMS stimulation site. Statistically significant differences are marked bold.

Table 2
Results for TMS experiment 2 (TD_nHF)

Stimulation Site	MNI coordinates, *x*, *y*, *z* in [mm], (±SD)	TpPath25, [ms], (*P* values)	MaxDev, [mm], (*P* values)	ReachTime, [ms], (*P* values)	EndAcc, [mm], (*P* values)
$\text{SPL}_{\text{group}}$	−36, −49, 57	−12.9 ± 10.3	−0.4 ± 0.6	−4.1 ± 2.8	0.9 ± 0.6
$\text{IPS}_{\text{indiv}}$	−42.9, −45.0, 52.9, (±1.9 4.7 4.3)	18.3 ± 13.6	1.0 ± 0.9	−9.2 ± 7.2	**−1.8 ± 0.9, (<0.05)**
$\text{SMG}_{\text{indiv}}$	−53.4, −32.5, 40.3, (±8.3 7.5 5.2)	**22.4 ± 8.6, (<0.05)**	0.9 ± 0.3	**12.4 ± 6.2, (0.05)**	0.0 ± 0.8

Note: The MNI coordinates upon which the TMS stimulation sites were planned are given and for TpPath25, MaxDev, ReachTime, and EndAcc, the difference ± SE between trials with versus without TMS is given for each TMS stimulation site—the data of both TMS SOAs is collapsed. Statistically significant differences are marked bold.

Table 3
Results for TMS experiment 3 (HD)

Stimulation Site	MNI coordinates, *x*, *y*, *z* in [mm], (±SD)	TpPath25, [ms], (*P* values)	MaxDev, [mm], (*P* values)	ReachTime, [ms], (*P* values)	EndAcc, [mm], (*P* values)
$\text{SPL}_{\text{group}}$	−36, −49, 57	1.9 ± 7.4	0.2 ± 0.3	5.0 ± 10.3	0.3 ± 0.5
$\text{IPS}_{\text{HDgroup}}$	−39, −45, 50	**15.2 ± 6.3, (<0.05)**	1.2 ± 0.4	21.2 ± 9.1	0.1 ± 0.4
$\text{SMG}_{\text{group}}$	−45, −40, 45	**26.8 ± 5.6, (<0.001)**	0.5 ± 0.6	**33.2 ± 5.6, (<0.01)**	0.1 ± 0.3
$\text{SMG}_{\text{HDindiv}}$	−48.2, −34.2, 38.5, (±8.3 6.3 7.0)	**16.3 ± 10.8, (<0.05)**	−0.2 ± 0.4	**31.3 ± 12.3, (<0.01)**	0.5 ± 0.7
$\text{IPS}_{\text{HDright}}$	45, −39, 52	1.0 ± 10.0	0.2 ± 0.7	11.4 ± 8.8	0.6 ± 0.6
Reach	−33, −56, 55	1.2 ± 6.5	−0.2 ± 0.5	13.6 ± 8.5	0.7 ± 0.3

Note: The MNI coordinates upon which the TMS stimulation sites were planned are given and for TpPath25, MaxDev, ReachTime, and EndAcc, the difference ± SE between trials with versus without TMS is given for each TMS stimulation site. Statistically significant differences are marked bold. For ReachTime, the interaction TMS × stimulation site did not reach significance. Newman–Keuls rather than Fisher least significant difference was therefore used for multiple comparisons correction in this case.

Table 4
Average absolute values across stimulation sites for all experiments

		TpPath25 [ms]	MaxDev [mm]	ReachTime [ms]	EndAcc [mm]	PeakAcc [cm/s^2]	Time2peakAcc [ms]
Exp. 1: TD_HF	TMS	404 ± 21	12.5 ± 0.9	669 ± 26	0.8 ± 0.5	642 ± 95	182 ± 11
	No TMS	397 ± 20	12.2 ± 1.0	653 ± 26	0.5 ± 0.4	643 ± 95	181 ± 9
Exp. 2: TD_nHF	TMS 40	398 ± 22	20.1 ± 2.0	654 ± 27	−0.1 ± 2.3	771 ± 74	174 ± 8
	TMS 80	403 ± 25	20.9 ± 2.0	659 ± 30	−1.8 ± 2.4	805 ± 83	179 ± 9
	No TMS	391 ± 20	20.0 ± 2.0	658 ± 28	−0.3 ± 2.1	779 ± 71	176 ± 10
Exp. 3: HD	TMS	476 ± 26	19.4 ± 1.0	718 ± 35	−1.1 ± 0.6	709 ± 84	177 ± 12
	No TMS	466 ± 22	19.1 ± 1.1	699 ± 32	−1.5 ± 0.7	727 ± 80	176 ± 13

Note: TpPath25, MaxDev, ReachTime, EndAcc, PeakAcc, and Time2peakAcc are listed separately for trials with TMS (for experiment 2 also separately the TMS SOAs) and without TMS, respectively. The mean ± SE across subjects is given. Positive values of EndAcc represent overcompensation for the perturbation, negative values represent incomplete compensation.

TMS (main effect of TMS: $P > 0.05$) nor did it depend on the stimulation site (Table 3; interaction TMS × stimulation site: $P > 0.9$). TMS over $\text{IPS}_{\text{HDgroup}}$, $\text{SMG}_{\text{group}}$, and $\text{SMG}_{\text{HDindiv}}$ selectively delayed the onset of the correction to the perturbation (TpPath25 in Table 3; interaction TMS × stimulation site: $F_{5,40} = 2.48$; $P < 0.05$). Maximum deviation (MaxDev in Table 3) was not affected by TMS when correcting for multiple comparisons. The apparent large TMS effect for $\text{IPS}_{\text{HDgroup}}$ stimulation manifested as trend ($P = 0.02$ uncorrected; paired *t*-test).

Correlations between TMS Effects and fMRI Activation

For both conditions with visual feedback about the hand position (TMS experiments 1 and 3), we tested whether the size of TMS effects correlated with the individual fMRI activation strengths across the different stimulation sites (Fig. 3). A condition corresponding to TD_nHF was not tested in the fMRI experiment and could therefore not be used for a correlation analysis. For every stimulation site, the individual fMRI effect strength was determined in each subject as the mean *Z* value of the corresponding fMRI contrast in a cylindrical mask with radius 5 mm and height 3 cm beneath the TMS coil center. Subsequently, we tested whether the individual TMS effect, as assessed by TpPath25 and MaxDev, correlated with the fMRI effect strength across sites and subjects. The TMS and fMRI effects were ranked across all stimulation sites in each subject in order to prevent that absolute differences between

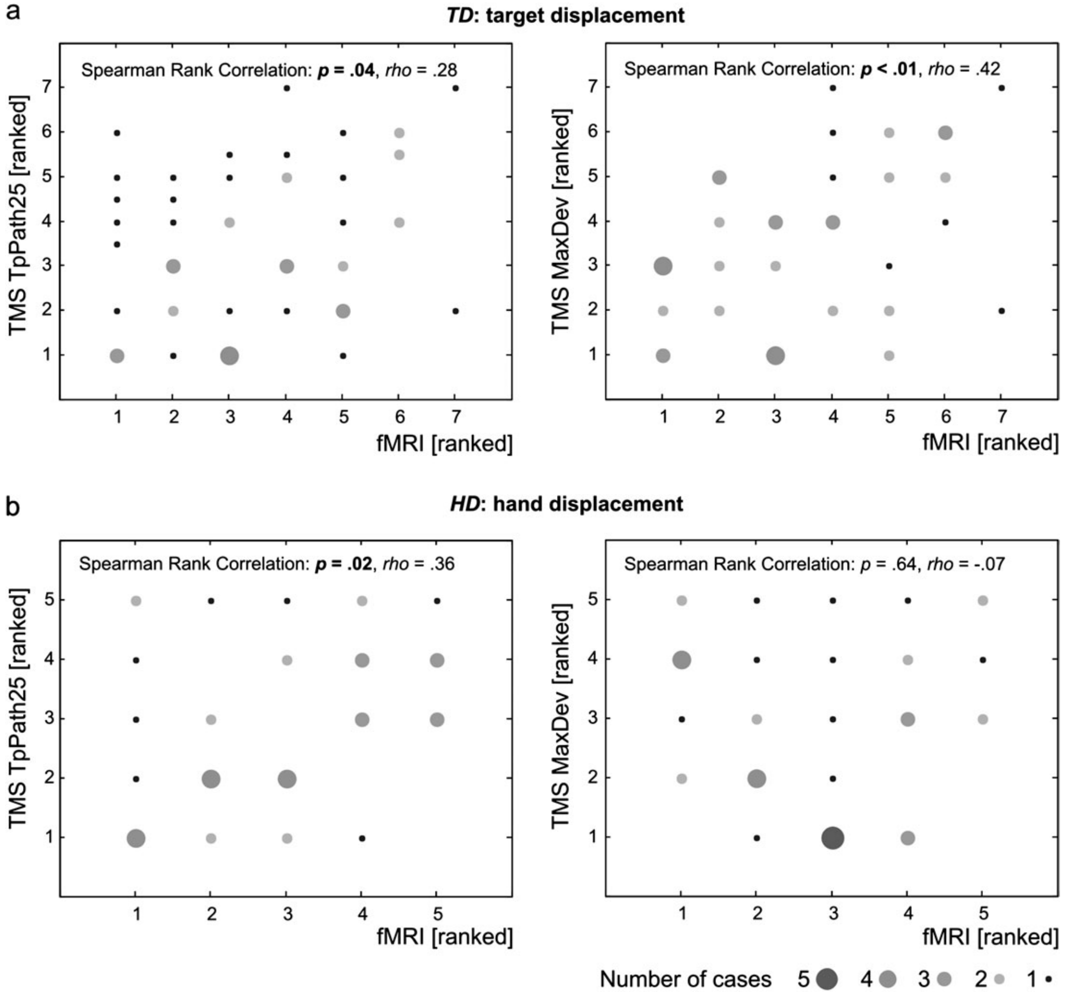

Figure 3. Correlations between ranked fMRI and TMS effects. In the left panels, the TMS effect is measured with TpPath25 on the right panels with MaxDev. (*a*) Correlations for the displacement of the visual target (TD, TMS experiment 1). (*b*) Correlations for the displacement of the visual feedback of the hand position (HD, TMS experiment 3).

subjects, both in BOLD activation and for the TMS measurements, affected the results. Subsequently, Spearman rank correlation tests were conducted on the ranked data across subjects. For TD_HF, both TMS measures were significantly correlated with the fMRI effect (Fig. 3*a*; $P < 0.05$, $\rho = 0.28$ for TpPath25; $P < 0.01$, $\rho = 0.42$ for MaxDev). For HD, TpPath25 correlated well with the fMRI effect (Fig. 3*b*; $P < 0.05$, $\rho = 0.36$). *MaxDev* did not show any correlation (Fig. 3*b*; $P = 0.64$; $\rho = -0.07$), just as this measurement did not reveal strong effects for TMS stimulation as well.

Discussion

We have demonstrated that TMS applied over the anterior IPS (aIPS) and aSMG, but not over other sites on the PPC, reduced the subjects' ability to correct for visual perturbations during reaching movements. This was clear for perturbations of both external and body-related visual information (TMS experiments 1 and 3). Additionally, the cortical sites exhibiting TMS effects remained the same when visual feedback about the hand position was absent (TMS experiment 2). Taken together, our results provide the first causal demonstration that the human aIPS and aSMG are engaged in the integration of sensory information for online control of reaching, independent of the nature of the visual perturbation.

Our results provide support for the existence of 2 distinct, but neighboring parietal regions (aIPS and aSMG): First, the TMS effects consistently occurred over positions that exhibited specific BOLD activity increases for perturbed versus unperturbed reaching in the fMRI experiment. The correlations between fMRI and TMS results support the hypothesis of 2 distinct regions, even though this alone is not sufficient evidence. Second, in TMS experiment 1, the effects at site $\text{SMG}_{\text{group}}$ were very weak, while a stable impact of TMS occurred at the more inferior position $\text{SMG}_{\text{indiv}}$. That is, moving the SMG site further away from the aIPS stabilized (rather than attenuated) the TMS effects. Third, in TMS experiment 2, stimulation over aIPS and $\text{SMG}_{\text{indiv}}$ yielded opposite behavioral effects: impact on reaching accuracy versus timing of the corrective movement. Fourth, in all experiments, TMS effects were observed at the aIPS and $\text{SMG}_{\text{indiv}}$ with an average distance of ~20 mm. In contrast, sites closer to the aIPS (SPL, reach, and Desmurget; average distance ~12 mm to the aIPS sites) consistently lacked any effect. Taken together, these findings suggest 2 distinct target sites during the experiments with visual TDs. TMS experiment 3 is less conclusive in this respect as site $\text{SMG}_{\text{group}}$ between $\text{IPS}_{\text{HDgroup}}$ and $\text{SMG}_{\text{indiv}}$ also showed strong effects, and the effects were similar across all 3 sites. However, the consistent spatial pattern found in all experiments (including the fMRI localizer) at least supports different anatomical sites also for TMS experiment 3. It should be noted that similar spatial resolutions of TMS have previously been observed, for example, in motormapping studies investing the separation between muscle representations (Wilson et al. 1993; Krings et al. 1998), visual suppression studies with 7-mm grids (Thielscher et al. 2010), studies investigating the dependence of phosphenes on coil position (Cowey 2005), and TMS hunting procedures to localize PPC target sites (Ashbridge et al. 1997). Clearly, TMS experiments generally do not qualify for drawing conclusions about the 3D position of the stimulated anatomical location. TMS solely provides a 2D focus and always yields in stronger electric fields in more superficial areas, even when they are not perfectly beneath the center of the coil. However, a rigorous design as pursued in this study provides additional information to control for this problem: Demonstrating that optimal stimulation of adjacent, more superficial sites does not result in behavioral impairment helps to rule out that the TMS effect was caused by disruption of these areas rather than the targeted area. In addition, the distances between the fMRI peak activations and the TMS coil were not significantly different between sites SPL and aIPS/aSMG (data not shown).

Using individually adjusted stimulation intensities, we excluded that TMS caused direct motor impairments that would have biased our results. This was confirmed by the absence of TMS effects when stimulating over the anterior SPL (aSPL), which had a similar distance to the motor cortex (M1) as the sites over the aIPS and aSMG. The correlation between the individual TMS and fMRI effect strengths further argues against any direct TMS effects on M1, just as the observation that the initial movement period was unaffected by TMS (Supplementary Data C.1). Likewise, for TMS experiments 1 and 2, putative effects of the magnetic stimuli on corrective eye movements rather than reaching-related activity were carefully ruled out (Supplementary Data C.2 and C.3). The magnetic pulses were applied after the main saccade to the visual target in all 3 TMS experiments. As TMS experiment 3 did not require compensatory saccades, the reported results could not stem from unintended effects on saccadic activity in first place. Finally, also the spatial pattern of the observed TMS effects (impact on the aIPS and aSMG but not on more posterior control sites) argues against putative TMS effects on saccades as a large body of literature shows that more posterior parts of the PPC are involved in saccade processing (Simon et al. 2002; Konen et al. 2004). The TMS studies in this field always tested more posterior positions compared with our sites and offer inconsistent results on whether left PPC TMS does affect saccades processing (Van Donkelaar et al. 2000; Yang and Kapoula 2004).

Desmurget et al. (1999) were the only group to date demonstrating that TMS over the left IPS largely disturbed online corrections in a visually perturbed reaching paradigm. Using the coil positioning method reported in their study, we stimulated sites over the aSPL and did not find any TMS effect. The effects reported here for the neighboring sites aIPS and aSMG are generally weaker, though in the usual range of TMS studies targeting the PPC. However, there are several methodological differences between the studies that might have contributed to the different results (e.g., spatial extent of the magnetic field induced by the coil, direction of eye movements, and restriction of movement). Importantly, in contrast to their coil positioning strategy which did not take into account interindividual differences in (functional) anatomy, our usage of several stimulation sites allows for a spatially specific mapping to neuroanatomy in respect to the cortical surface. Furthermore, testing different perturbation paradigms enabled us to functionally disentangle the identified regions.

Due to the specificity of area aIPS for actions related to grasping objects that was found in some studies (Binkofski et al. 1998; Tunik et al. 2005; Culham et al. 2006; Rice et al. 2006), this area is commonly regarded as a likely candidate for the human homologue to the macaque's anterior intraparietal area, where neurons respond selectively to hand manipulation tasks (Sakata et al. 1995). Apart from grasping studies, the involvement of area aIPS has also been demonstrated in reaching tasks, both with and without vision of the hand (Desmurget et al. 2001; Filimon et al. 2007, 2009; Taubert et al. 2010). Tunik et al. (2007) recently suggested that the aIPS is more generally involved in online control of motor actions, independent of the effectors that they demonstrated for finger position and wrist orientation in grasping. Our results support this hypothesis by providing direct evidence that it also applies to the hand positioning for reaching, as demonstrated for both external and body-related visual information. For displacement of the visual target without visual feedback about the hand position, TMS over the aIPS significantly impaired the end accuracy of reaching. This suggests that TMS induced relatively long-lasting effects in this specific task that required intact coordinate transformations between the external visual and the body-related proprioceptive information to be continuously maintained throughout the reaching movement. Anatomically, area aIPS is part of the ventro-dorsal stream (Tanne-Gariepy et al. 2002; Rizzolatti and Matelli 2003; Verhagen et al. 2008) and highly interconnected with the ventral premotor cortex (Tomassini et al. 2007). This fronto-parietal circuit is associated with transformations of spatial object locations in motor commands and the adaptation of motor behavior to current conditions by integrating visual information from the ventral stream. This further supports a role of the aIPS in "dynamic, goal-based, sensorimotor transformations" as suggested by Tunik et al. (2007), in addition to the more short-termed TMS effects over the aIPS with visual feedback of the hand position.

Area aSMG has been mainly associated with tasks relying on the integration of visual and proprioceptive/somatosensory information such as hand-object interactions, grasping (Nickel and Seitz 2005; Naito and Ehrsson 2006), and tool use (Johnson-Frey 2004). Fewer studies demonstrated a role of the SMG in reaching (Diedrichsen et al. 2005; Filimon et al. 2007). Diedrichsen et al. (2005) showed that parts of the aSMG exhibited enhanced BOLD activity during the processing of execution errors stemming from miscalibrated internal models of body effectors (e.g., visual-proprioceptive mismatch or altered limb dynamics). Thus, the aSMG might contribute to maintaining coherent representations of body effectors, including resolving discrepancies between expected and actual states. Consistently, in our study, displacement of the visual hand representation created a visual-proprioceptive conflict and TMS disturbance of the aSMG might have delayed the resolution of this conflict, thus causing later online corrections. Alternatively, aSMG stimulation might have interfered with bottom-up proprioceptive information, which is conceptually distinct from disturbing visual–somatosensory interactions. However, this would rather lead to an attenuation of the visual-proprioceptive conflict and thus a reverse result pattern. Additionally, visual-plus-somatosensory areas were found near the SMG (Bremmer et al. 2001). Unlike Diedrichsen et al. (2005), we found that the aSMG also contributed to the online corrections for displacements of the visual targets. This discrepancy might stem from methodological differences such as different workspaces, or the restriction to fMRI group results versus the assessment of interindividual differences in the aSMG activations. Importantly, our TMS experiments confirmed the causal contribution of aSMG for the correction to all visual perturbations that we tested within the individual subject.

The enhanced BOLD activity for perturbed versus unperturbed reaching extended into the SPL. General reaching (versus fixation) induced activations extending even more medially and posteriorly in the PPC. Even though saccades might have contributed to the more posterior SPL activations in the latter case (Simon et al. 2002), this is consistent with the common view that the SPL is involved in the planning and control of reaching (Nickel and Seitz 2005; Culham et al. 2006; Blangero et al. 2009; Chib et al. 2009). Using fMRI and a joystick task adapted from macaque studies investigating the role of the PPC in visuomotor coordinate transformations (Eskandar and Assad 1999, 2002), Grefkes et al. (2004) suggested the medial parts of the SPL and IPS to be the putative human homologues to the macaque medial intraparietal area, which is part of the parietal reach region. Anatomically, the SPL is part of the dorso-dorsal stream (Tanne-Gariepy et al. 2002; Rizzolatti and Matelli 2003; Verhagen et al. 2008) and highly interconnected with the dorsal premotor cortex (Tomassini et al. 2007). This fronto-parietal circuit is associated with the involvement in non-standard stimulus response mappings, online control of actions, and the processing of visuospatial parameters for grasping irrespective of the viewing conditions (please see Filimon (2010) for a comprehensive review also covering the relation between human and macaque data). Interestingly, in our case, the absence of TMS effects above the SPL indicates that this area might be more important for planning (Vesia et al. 2008) than for online control. An alternative explanation could be that areas contributing to the planning of reaching movements are more superficial in the SPL than areas involved in online control so that planning processes could be more easily disturbed by TMS (Vesia et al. 2008). Regarding the differences in TMS results in this study between SPL and aIPS/aSMG despite similar distances between the fMRI peak activations and the TMS coil (as already mentioned above) argues against this. Furthermore, a recent fMRI study pointed out that the use of finger pointing (as used in some fMRI studies in this field) rather than normal reaching likely shifted the activations more laterally in prior studies (Filimon et al. 2009). Both our fMRI and TMS results indicate more lateral regions when comparing perturbed versus unperturbed reaching but not for general reaching. Thus, the differences between their and our results likely stem from comparing online control versus reaching in general, especially our TMS experiments demonstrate a specific interference during the execution phase.

A number of studies report posterior parts of the PPC close to the parieto-occipital junction being involved in reaching (Diedrichsen et al. 2005; Karnath and Perenin 2005; Culham et al. 2008). The use of simplified finger "reaching" without arm transport (Culham et al. 2008) during fMRI is the likely cause of why we missed these areas. It should be noted, however, that the usage of finger "reaching" during fMRI does not confound the results for the areas that we actually do report (aIPS and aSMG), as TMS confirmed their involvement in fully fledged reaching movements. In fact, our study strengthens the view that these areas are involved in online control of movements rather independent of the body effectors (hand for grasping, arms for reaching, and fingers for "finger-reaching" or pointing), for example, to fine-tune movements in general.

To conclude, using a combination of fMRI localizer task followed by TMS experiments, we demonstrated for the first time a causal contribution of the aIPS and the aSMG to online control of reaching. This underpins the hypothesis that a large network forms the human functional equivalent to the macaque's network of "parietal reach regions" and that this network extends even further inferior than previously thought. Furthermore, we demonstrated that accounting for interindividual differences when investigating the human PPC can reveal the involvement of subregions that are otherwise missed on the group level and that deriving TMS stimulation sites based on individual functional neuroanatomy is a more effective approach than other selection of stimulation sites. In future, this approach can be used to further disentangle the PPC subregions integrating different sensory modalities in reaching and grasping. fMRI allows to localize putative key areas with high spatial resolution, while subsequent individualized TMS can be used to confirm their causal contribution to the task under study.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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References

Ashbridge E, Walsh V, Cowey A. 1997. Temporal aspects of visual search studied by transcranial magnetic stimulation. Neuropsychologia. 35:1121–1131.

Binkofski F, Dohle C, Posse S, Stephan KM, Hefter H, Seitz RJ, Freund HJ. 1998. Human anterior intraparietal area subserves prehension: a combined lesion and functional MRI activation study. Neurology. 50:1253–1259.

Blangero A, Menz MM, McNamara A, Binkofski F. 2009. Parietal modules for reaching. Neuropsychologia. 47:1500–1507.

Bremmer F, Schlack A, Shah NJ, Zafiris O, Kubischik M, Hoffmann K, Zilles K, Fink GR. 2001. Polymodal motion processing in posterior parietal and premotor cortex: a human fMRI study strongly implies equivalencies between humans and monkeys. Neuron. 29:287–296.

Buss M, Schmidt G. 1999. Control problems in multimodal telepresence systems. In: Frank P, editor. Advances in control, highlights of ECC '99. London: Springer-Verlag. p. 65–101.

Chib VS, Krutky MA, Lynch KM, Mussa-Ivaldi FA. 2009. The separate neural control of hand movements and contact forces. J Neurosci. 29:3939–3947.

Cowey A. 2005. The Ferrier Lecture 2004: what can transcranial magnetic stimulation tell us about how the brain works? Philos Trans R Soc B Biol Sci. 360:1185–1205.

Culham JC, Cavina-Pratesi C, Singhal A. 2006. The role of parietal cortex in visuomotor control: what have we learned from neuroimaging? Neuropsychologia. 44:2668–2684.

Culham JC, Gallivan J, Cavina-Pratesi C, Quinlan DJ. 2008. fMRI investigations of reaching and ego space in human superior parieto-occipital cortex. In: Klatzky R, McWhinney B, Behrmann M, editors. Embodiment, ego-space and action. New York: Psychology Press. p. 247–274.

Culham JC, Kanwisher NG. 2001. Neuroimaging of cognitive functions in human parietal cortex. Curr Opin Neurobiol. 11:157–163.

Culham JC, Valyear KF. 2006. Human parietal cortex in action. Curr Opin Neurobiol. 16:205–212.

Desmurget M, Epstein CM, Turner RS, Prablanc C, Alexander GE, Grafton ST. 1999. Role of the posterior parietal cortex in updating reaching movements to a visual target. Nat Neurosci. 2:563–567.

Desmurget M, Grafton S. 2000. Forward modeling allows feedback control for fast reaching movements. Trends Cogn Sci. 4:423–431.

Desmurget M, Grea H, Grethe JS, Prablanc C, Alexander GE, Grafton ST. 2001. Functional anatomy of nonvisual feedback loops during reaching: a positron emission tomography study. J Neurosci. 21:2919–2928.

Diedrichsen J, Hashambhoy Y, Rane T, Shadmehr R. 2005. Neural correlates of reach errors. J Neurosci. 25:9919–9931.

Eskandar EN, Assad JA. 1999. Dissociation of visual, motor and predictive signals in parietal cortex during visual guidance. Nat Neurosci. 2:88–93.

Eskandar EN, Assad JA. 2002. Distinct nature of directional signals among parietal cortical areas during visual guidance. J Neurophysiol. 88:1777–1790.

Filimon F. 2010. Human cortical control of hand movements: parietofrontal networks for reaching, grasping, and pointing. Neuroscientist. 16:388–407.

Filimon F, Nelson JD, Hagler DJ, Sereno MI. 2007. Human cortical representations for reaching: mirror neurons for execution, observation, and imagery. Neuroimage. 37:1315–1328.

Filimon F, Nelson JD, Huang RS, Sereno MI. 2009. Multiple parietal reach regions in humans: cortical representations for visual and proprioceptive feedback during on-line reaching. J Neurosci. 29:2961–2971.

Grefkes C, Fink GR. 2005. The functional organization of the intraparietal sulcus in humans and monkeys. J Anat. 207:3–17.

Grefkes C, Ritzl A, Zilles K, Fink GR. 2004. Human medial intraparietal cortex subserves visuomotor coordinate transformation. Neuroimage. 23:1494–1506.

Iacoboni M. 2006. Visuo-motor integration and control in the human posterior parietal cortex: evidence from TMS and fMRI. Neuropsychologia. 44:2691–2699.

Johnson H, Haggard P. 2005. Motor awareness without perceptual awareness. Neuropsychologia. 43:227–237.

Johnson-Frey SH. 2004. The neural bases of complex tool use in humans. Trends Cogn Sci. 8:71–78.

Kammer T, Vorwerg M, Herrnberger B. 2007. Anisotropy in the visual cortex investigated by neuronavigated transcranial magnetic stimulation. NeuroImage. 36:313–321.

Karnath HO, Perenin MT. 2005. Cortical control of visually guided reaching: evidence from patients with optic ataxia. Cereb Cortex. 15:1561–1569.

Konen CS, Kleiser R, Wittsack HJ, Bremmer F, Seitz RJ. 2004. The encoding of saccadic eye movements within human posterior parietal cortex. Neuroimage. 22:304–314.

Krakauer JW, Ghilardi MF, Ghez C. 1999. Independent learning of internal models for kinematic and dynamic control of reaching. Nat Neurosci. 2:1026–1031.

Krings T, Naujokat C, Graf v. Keyserlingk D. 1998. Representation of cortical motor function as revealed by stereotactic transcranial magnetic stimulation. Electroencephalogr Clin Neurophysiol. 109:85–93.

Naito E, Ehrsson HH. 2006. Somatic sensation of hand-object interactive movement is associated with activity in the left inferior parietal cortex. J Neurosci. 26:3783–3790.

Nickel J, Seitz RJ. 2005. Functional clusters in the human parietal cortex as revealed by an observer-independent meta-analysis of functional activation studies. Anat Embryol (Berl). 210:463–472.

Pisella L, Grea H, Tilikete C, Vighetto A, Desmurget M, Rode G, Boisson D, Rossetti Y. 2000. An 'automatic pilot' for the hand in human posterior parietal cortex: toward reinterpreting optic ataxia. Nat Neurosci. 3:729–736.

Prablanc C, Martin O. 1992. Automatic control during hand reaching at undetected two-dimensional target displacements. J Neurophysiol. 67:455–469.

Reichenbach A, Thielscher A, Peer A, Bülthoff HH, Bresciani JP. 2009. Seeing the hand while reaching speeds up on-line responses to a sudden change in target position. J Physiol. 587:4605–4616.

Rice NJ, Tunik E, Grafton ST. 2006. The anterior intraparietal sulcus mediates grasp execution, independent of requirement to update: new insights from transcranial magnetic stimulation. J Neurosci. 26:8176–8182.

Rizzolatti G, Matelli M. 2003. Two different streams form the dorsal visual system: anatomy and functions. Exp Brain Res. 153:146–157.

Sakata H, Taira M, Murata A, Mine S. 1995. Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. Cereb Cortex. 5:429–438.

Sarlegna F, Blouin J, Bresciani JP, Bourdin C, Vercher JL, Gauthier GM. 2003. Target and hand position information in the online control of goal-directed arm movements. Exp Brain Res. 151:524–535.

Sarlegna F, Blouin J, Vercher JL, Bresciani JP, Bourdin C, Gauthier GM. 2004. Online control of the direction of rapid reaching movements. Exp Brain Res. 157:468–471.

Simon O, Mangin JF, Cohen L, Le Bihan D, Dehaene S. 2002. Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. Neuron. 33:475–487.

Tanne-Gariepy J, Rouiller EM, Boussaoud D. 2002. Parietal inputs to dorsal versus ventral premotor areas in the macaque monkey: evidence for largely segregated visuomotor pathways. Exp Brain Res. 145:91–103.

Taubert M, Dafotakis M, Sparing R, Eickhoff S, Leuchte S, Fink GR, Nowak DA. 2010. Inhibition of the anterior intraparietal area and the dorsal premotor cortex interfere with arbitrary visuo-motor mapping. Clin Neurophysiol. 121:408–413.

Thielscher A, Reichenbach A, Ugurbil K, Uludag K. 2010. The cortical site of visual suppression by transcranial magnetic stimulation. Cereb Cortex. 20:328–338.

Tomassini V, Jbabdi S, Klein JC, Behrens TE, Pozzilli C, Matthews PM, Rushworth MF, Johansen-Berg H. 2007. Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. J Neurosci. 27:10259–10269.

Tunik E, Frey SH, Grafton ST. 2005. Virtual lesions of the anterior intraparietal area disrupt goal-dependent on-line adjustments of grasp. Nat Neurosci. 8:505–511.

Tunik E, Rice NJ, Hamilton A, Grafton ST. 2007. Beyond grasping: representation of action in human anterior intraparietal sulcus. Neuroimage. 36(Suppl 2):T77–T86.

Van Donkelaar P, Lee JH, Drew AS. 2000. Transcranial magnetic stimulation disrupts eye-hand interactions in the posterior parietal cortex. J Neurophysiol. 84:1677–1680.

Verhagen L, Dijkerman HC, Grol MJ, Toni I. 2008. Perceptuo-motor interactions during prehension movements. J Neurosci. 28:4726–4735.

Vesia M, Yan X, Henriques DY, Sergio LE, Crawford JD. 2008. Transcranial magnetic stimulation over human dorsal-lateral posterior parietal cortex disrupts integration of hand position signals into the reach plan. J Neurophysiol. 100:2005-2014.

Wilson SA, Thickbroom GW, Mastaglia FL. 1993. Transcranial magnetic stimulation mapping of the motor cortex in normal subjects. The representation of two intrinsic hand muscles. J Neurol Sci. 118:134-144.

Yang Q, Kapoula Z. 2004. TMS over the left posterior parietal cortex prolongs latency of contralateral saccades and convergence. Invest Ophthalmol Vis Sci. 45:2231-2239.

Zuber BL, Stark L. 1966. Saccadic suppression: elevation of visual threshold associated with saccadic eye movements. Exp Neurol. 16:65-79.

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Contributions of the PPC to online control of visually guided reaching movements assessed with fMRI-guided TMS

Supplementary Data

A. TMS Experiments: Setup and Exemplary Data

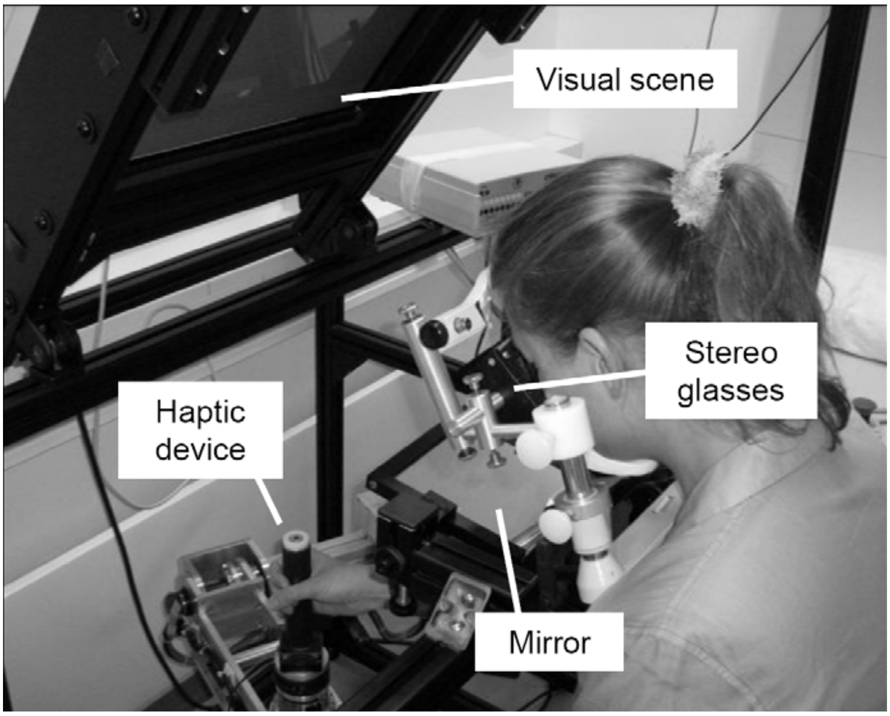

Figure S1 Experimental VR setup for the TMS experiments. During the experiments, an additional black cloth in the horizontal plane between the mirror and the robot arm prevented the subjects to get visual feedback about their real hand movement.

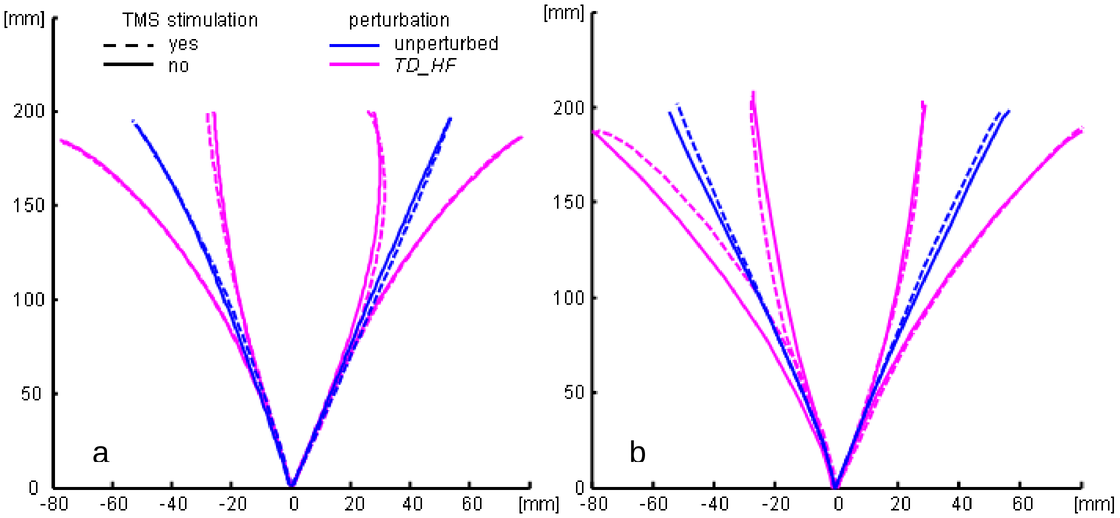

Figure S2 Additional behavioral data for TMS experiment 1. Shown are exemplary 2D trajectories for site IPS_{group} (equivalent to Fig. 1c), averaged across subjects (a) and for an exemplary single subject (b). The trajectories are aligned to the starting position and normalized over time.

B. fMRI Localizer Experiment

B.1 Stimuli and Behavioural Task

Stimuli were presented using Cogent 2000 (University College London, UK), projected on a screen located 100 cm away from the subject's eyes (LCD projector JVC DLA-SX21) and viewed through a coil-mounted mirror. The size of the visual scene was matched to the visual scene of the TMS experiments in terms of viewing angle. The subject's right index finger was fixated on the top of a MR-compatible joystick placed beside the hip (Current Designs, Inc., Philadelphia, USA), allowing a workspace of about

4x4 cm. The right wrist and arm rested comfortably on a pillow, thereby preventing motion artifacts.

The session comprised 7 runs of about 10 min each, including an initial training run without acquisition of MR images. One run consisted of 9 blocks presented in a counter-balanced order: 4 reaching blocks (70-90 s each, dependent on subject's reaching time), and 5 fixation blocks (~30 s each). Each block was preceded by a screen informing the subject about the actual task. The reaching blocks contained 10 trials in which the subject had to move the eyes and the joystick cursor (represented by a red circle) from the starting circle to the target circle (both represented by a magenta circle) as quickly and precisely as possible. A fast event-related design was used to assess the effects of the different visual perturbations within different trials. Four trial types occurred with equal probability in a pseudo randomized order: 1) no perturbation, 2) displacement of the visual target (abbreviated *TD* indicating 'target displacement', Fig. 1a), 3) displacement of the visual feedback about the 'hand' position, i.e. the joystick cursor (abbreviated *HD* indicating 'hand displacement' according to the terminology used in the TMS main experiments, Fig. 1b), or 4) rotation of the visual feedback about the 'hand' position, i.e. the joystick cursor (included in the fMRI analysis but not used as further condition in the TMS experiments in order to limit the complexity and length of the overall study). After reaching for the target, the subjects had to wait motionless for 4 s at the end of each trial until a new starting circle appeared, resulting in an average trial duration of 4.93 (±0.55 SD) s. The displacements occurred at 10% of the way from the starting circle to the target. In the fixation blocks, the starting circle had to be continuously fixated (controlled by online monitoring on the eye-tracking screen (ASL Long Range Optic, Applied

Science Laboratories, Bedford (MA), USA)) and the hand had to be kept still. The visual scene was matched to the unperturbed reaching condition, using pre-recorded trials.

B.2 Imaging Parameters and Data Analysis

Scanning was performed on a Siemens 3T TIM Trio (Siemens, Erlangen, Germany) with a 12 channel head coil. Whole-brain functional images were recorded using gradient echo planar imaging (TR 2580 ms, TE 35 ms, 40 horizontal slices, in-plane resolution 3x3 mm^2, slice thickness 2.5 mm, gap 0.5 mm). Up to 230 volumes were acquired per experimental run, including four initial volumes which were discarded to allow for T1 equilibration. Additionally, a T1-weighted structural image was acquired (MPRAGE, TR 1900 ms, TE 2.26 ms, TI 900 ms, flip angle 9°, 192 coronal slices, 1 mm iso-voxel resolution, 2 averages). The functional data was analyzed using FSL 4.0 (FMRIB, Oxford, UK; (Smith et al. 2004; Smith et al. 2005)). The EPI volumes were motion-corrected, temporally high-pass filtered (100 s cutoff), spatially smoothed (Gaussian with 5 mm FWHM) and registered to the individual structural image using FLIRT (Jenkinson et al. 2002).

First, regions exhibiting robust reaching-related activity were determined. The BOLD activation was modeled as the convolution of the actual timings from the block design pattern with a standard hemodynamic response function (HRF), resulting in two regressors for the different block types (reaching & fixation). For each subject, separate general linear models were estimated for each experimental run and combined on the single-subject level using a fixed-effects analysis. Regions were assessed that showed higher BOLD activity during reaching than during fixation blocks (tested at $Z = 2.3$ voxel level and $p = .05$ corrected at cluster level using Gaussian random field theory (Worsley et al. 1992)). In order to create group results, the maps of the individual parameter estimates were normalized to MNI space by registering the structural image to the MNI template (Mazziotta et al. 2001) using FLIRT (Jenkinson et al. 2002) with 12 degree-of-freedom linear registration. The normalized individual maps of parameter estimates were fed into a second-level mixed-effects analysis using FLAME (Beckmann et al. 2003) with experimental conditions (reaching vs. fixation) and subjects as fixed and random factors, respectively. Again, regions exhibiting higher activity for reaching compared to fixation were determined ($Z = 2.3$ voxel level and $p = .05$ corrected at cluster level using Gaussian random field theory (Worsley et al. 1992)). For both analyses, on the single-subject and group level, the resulting statistical maps were used as masks in the subsequent analysis to ensure that the observed regions exhibited robust reaching-related activation.

As we were interested in regions involved in online control of reaching, the trials with visual perturbations were compared to unperturbed reaching as next step. The regressor representing the reaching blocks was substituted by four event-related regressors modeling the BOLD signal for the different types of reaching trials. Each of the regressors was created by convolving the time frame pattern of the corresponding reaching trials with a HRF. In two separate analyses, regions were determined that exhibited higher activity in trials with displaced visual target (*TD*) and in trials with displaced visual feedback of the hand position (*HD*), respectively, than in unperturbed trials. The same analysis sequence was applied as described above for the general reaching-related activity.

C. Control Experiments and Analyses

We conducted additional control analyses and experiments to rule out that the results presented in the main part of the paper were affected by a direct motor impairment of the TMS pulses or by an impact of TMS on saccadic- rather than reaching-related activity.

C.1 TMS impact on the initial movement period

As control, we analyzed the initial acceleration period of the reaching movements (Desmurget et al. 1999). The time needed to reach the peak acceleration at the beginning of the movement was around 180 ms, which included the time period during which the TMS stimuli were delivered. Direct TMS effects on the motor cortex (inducing, e.g. muscle twitches and silent periods) have short latencies so that, in our case, general motor impairments by TMS should also affect the initial acceleration period (Desmurget et al. 1999). Therefore, in order to rule out that the observed TMS effects over SMG and IPS were due to general motor impairments, we analyzed the peak acceleration (*PeakAcc*) and the time needed to reach it (*Time2peakAcc*) for all trials with visual perturbations of all three experiments (Table 4). There was neither an effect of the TMS pulses on the peak acceleration (main effect of TMS: $p > .3$; interaction TMS * stimulation site: $p > .2$) nor on the time to reach it (main effect of TMS: $p > .4$; interaction TMS * stimulation site: $p > .3$) for any experiment.

C.2 TMS influence on the corrective saccade

Rationale

To exclude the possibility that the observed TMS effects on reaching movements could stem from a disruption of the corrective saccade to the displaced target – for the experiment with the displaced visual hand feedback no such corrective saccade is necessary – the onset of the corrective saccades was determined using additional experimental recordings.

Experimental Procedure and Task

TMS experiment 1 (*TD_HF*) was repeated for three TMS stimulation sites: Two stimulation sites exhibiting consistent TMS effects (IPS_{group} and SMG_{indiv}), and one site where TMS had no effect on the reaching correction (SPL_{group}). Additionally, the vertical and horizontal components of the eye movements were recorded via electro-oculography (EOG). Two pairs of electrodes were placed above and below the right eye as well as adjacent to the inner and outer corner after cleaning the skin with alcohol. A ground electrode was placed on the subject’s forehead. These electrodes were connected to a BrainAmp MR plus amplifier and the signals were converted with BrainVision software (Brain Products, Germany) on a laptop. A custom-made MATLAB (The MathWorks, Natick, Massachusetts, USA) program saved the potentials from both directions (horizontal/vertical) seperately, from 300 msec before until 1000 msec after a trigger indicating the perturbation.

EOG Data Analysis

We assessed the first correction-specific changes of EOG activity after the first saccade (which triggered the perturbation). We focused on the horizontal component of the EOG signal as this component was specific to horizontal target displacements. Within the TMS trials, the window around the TMS pulses was interpolated using a spline function. As the expected onset of the corrective saccade (Becker and Fuchs 1969) was far beyond this time-window, this did not result in any bias. For each EOG trace, the AC component of the signal was then smoothed using a rectangular sliding window of 50 msec. The EOG latencies were determined using the first derivative of the signal. To define saccade onset, the first derivative of the perturbed trials had to stay for 25 msec above the threshold which was set for each subjects individually. Afterwards, each detected onset was checked manually via visualization of the EOG signal, its first derivative, and the reported onset (Fig. S3). If necessary, it was corrected manually. This procedure resulted in a detection rate of 94% and 91% for trials with and without TMS, respectively.

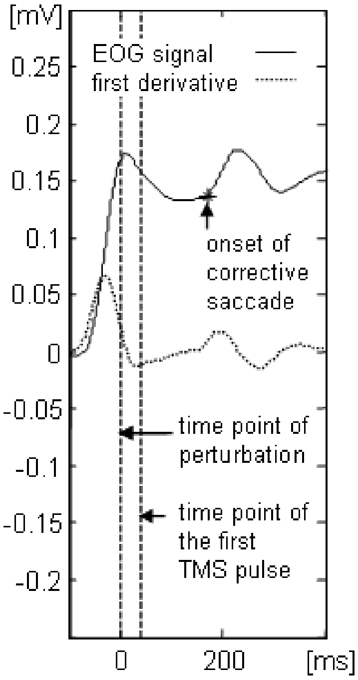

Figure S3 Visualization of the horizontal EOG signal, its first derivative, and the reported onset of the corrective saccade.

As a prior TMS study (Yang and Kapoula 2004) showed effects only on saccades to the right when TMS was administered to the left PPC (with stimulation sites more posterior than the ones tested here), we analyzed the data for all target positions and perturbation directions independently.

Results

Five of the subjects who took part in the main experiment were tested and none of them showed any TMS-evoked disruption of the corrective saccade. The onset of the corrective saccade without TMS stimulation varied between subjects and was in the range between 160 and 205 ms. Neither condition-specific (target location * perturbation direction) nor pooled data analysis revealed any intra-subject effects in favor of a disruption of the corrective saccade by TMS at any stimulation site. Also on the group level (figure S4), no indication for a disruption of the corrective saccade by TMS can be found.

Conclusion

The TMS stimulation did not delay the onset of the corrective saccade for any of the stimulation sites tested. Therefore, the possibility that the observed TMS effect on reaching movements resulted from a disruption of corrective saccades seems very unlikely.

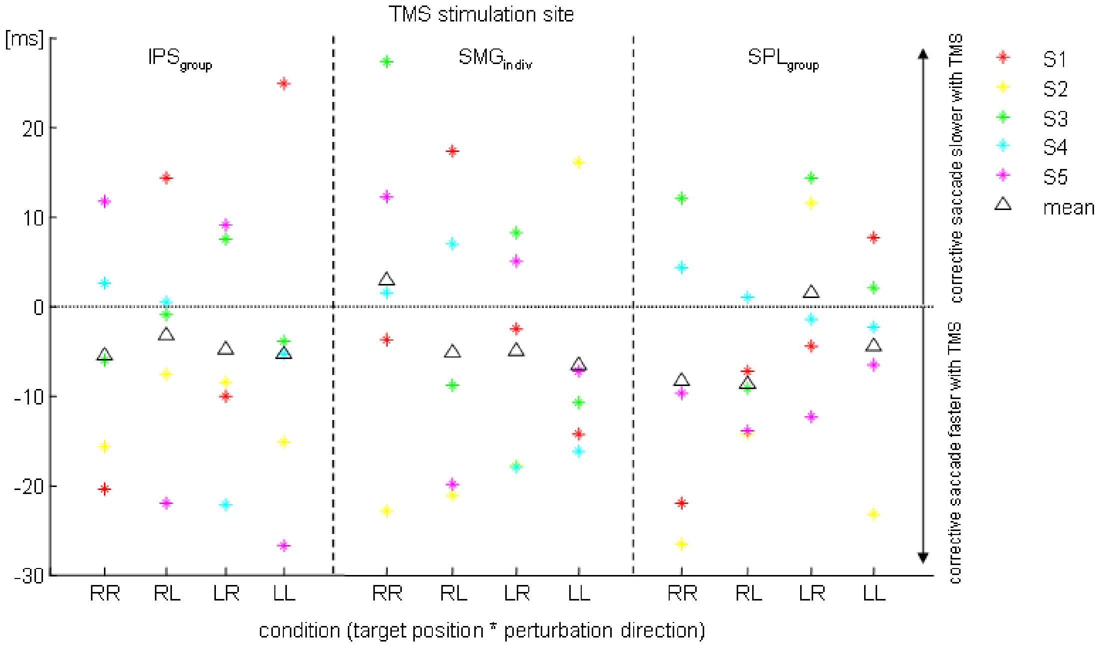

Figure S4 Differences in onset of the corrective saccade (onset with TMS – onset without TMS) for all subjects (S1 – S5, differently colored asterisks) and their mean (black triangle). The three panels depict the data for the three TMS stimulation sites. The data is shown separately for all conditions (target position * perturbation direction) – RR: target to the right, perturbation to the right; RL: target to the right, perturbation to the left; LR: target to the left, perturbation to the right; LL: target to the left, perturbation to the left.

C.3 FMRI activity for reaching + saccades vs. saccades only

Rationale

To exclude the possibility that the enhanced BOLD activity for the perturbed trials was mainly driven by (corrective) saccades, we conducted a control fMRI experiment contrasting BOLD activity during reaching + saccades vs. saccades only, both for perturbed and unperturbed trials.

Experimental Procedure and Task

The fMRI localizer task was repeated with 5 subjects and the following modifications: In the reaching blocks only unperturbed and target displacement trials were used, randomly intermixed. Instead of fixation blocks, we used the visual stimulation of the previous reaching blocks and instructed the subjects to make a saccade to the target, i.e. the very same task as in the reaching block only without the reaching movement.

fMRI Data Analysis

Regions exhibiting larger reaching-related activity (incl. saccades) than only saccade-related activity were determined. The BOLD activation was modeled as the convolution of the block design pattern with a standard hemodynamic response function (HRF), resulting in two regressors for the different block types (reaching & saccades). For each subject, separate general linear models were estimated for each experimental run and combined on the single-subject level using a fixed-effects analysis. Regions were assessed that showed higher BOLD activity during reaching than during saccade blocks (tested at $Z = 2.3$ voxel level and $p = .05$ corrected at cluster level). In order to create group results, the maps of the individual parameter estimates were normalized to MNI space by registering the structural image to the MNI template (Mazziotta et al. 2001). The normalized individual maps of parameter estimates were fed into a second-level mixed-effects analysis with experimental conditions (reaching vs. saccades) and subjects as fixed and random factors, respectively. Again, regions exhibiting higher activity for reaching compared to saccades were determined ($Z = 2.3$ voxel level and $p = .05$ corrected at cluster level).

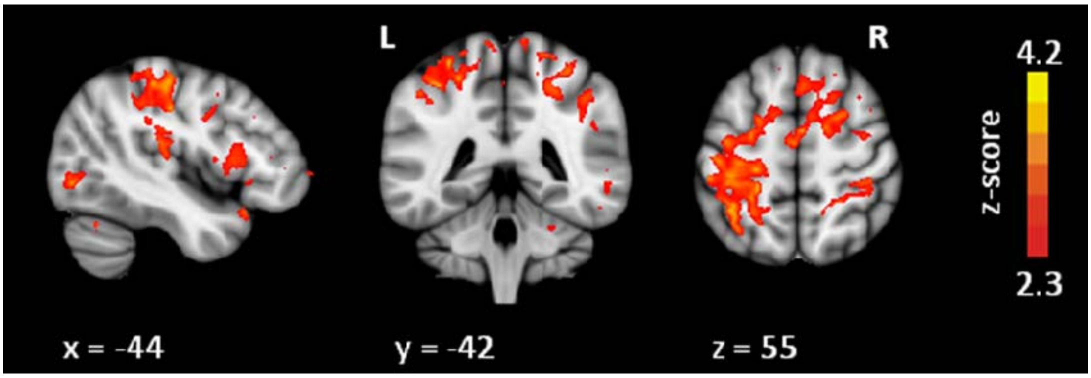

Figure S5 fMRI activation pattern for reaching + saccades vs. saccades only for the group analyses (thresholded at $Z = 2.3$ voxel level and $p = .05$ cluster level). The depicted position corresponds to the MNI coordinates of IPS_{group}.

Results

Larger BOLD activity for reaching + saccades vs. saccades only mainly clustered in the left hemisphere (Fig. S5), spanning from motor cortex over somatosensory cortex to the posterior parietal cortex (PPC). Additional activations occurred bilaterally in the frontal lobes (including premotor areas) and the right cerebellum. A smaller cluster was present in the right PPC. All MNI coordinates on which TMS stimulation sites were planned upon had a Z-value > 1.6, i.e. robust larger activation for reaching+saccades vs. saccades only. Site IPS_{group} (depicted in Fig. S5) had a Z-value of 2.7.

Conclusion

The brain sites serving as basis for the stimulation sites robustly exhibited stronger BOLD activity for reaching incl. saccades than for saccades alone. Therefore, the possibility that the observed effects of perturbed vs. unperturbed reaching in the original fMRI localizer stemmed predominantly from additional saccadic activity seems very unlikely.

References

Becker W, Fuchs AF. 1969. Further properties of the human saccadic system: eye movements and correction saccades with and without visual fixation points. Vision Res. 9: 1247-1258.

Beckmann CF, Jenkinson M, Smith SM. 2003. General multilevel linear modeling for group analysis in FMRI. Neuroimage. 20: 1052-1063.

Desmurget M, Epstein CM, Turner RS, Prablanc C, Alexander GE, Grafton ST. 1999. Role of the posterior parietal cortex in updating reaching movements to a visual target. Nat Neurosci. 2: 563-567.

Jenkinson M, Bannister P, Brady M, Smith S. 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage. 17: 825-841.

Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, Woods R, Paus T, Simpson G, Pike B, Holmes C, Collins L, Thompson P, MacDonald D, Iacoboni M, Schormann T, Amunts K, Palomero-Gallagher N, Geyer S, Parsons L, Narr K, Kabani N, Le Goualher G, Boomsma D, Cannon T, Kawashima R, Mazoyer B. 2001. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philos Trans R Soc Lond B Biol Sci. 356: 1293-1322.

Smith SM, Beckmann CF, Ramnani N, Woolrich MW, Bannister PR, Jenkinson M, Matthews PM, McGonigle DJ. 2005. Variability in fMRI: a re-examination of inter-session differences. Hum Brain Mapp. 24: 248-257.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM. 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 23 Suppl 1: S208-219.

Worsley KJ, Evans AC, Marrett S, Neelin P. 1992. A three-dimensional statistical analysis for CBF activation studies in human brain. J Cereb Blood Flow Metab. 12: 900-918.

Yang Q, Kapoula Z. 2004. TMS over the left posterior parietal cortex prolongs latency of contralateral saccades and convergence. Invest Ophthalmol Vis Sci. 45: 2231-2239.

2.4 Reichenbach et al. (in review): Different neural substrates for proprioceptively vs. visually guided movements in the human parietal cortex

Different neural substrates for proprioceptively vs. visually guided movements in the human parietal cortex

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Running head: Proprioceptive online control of reaching

Summary

In everyday life, we adjust our movements to ever changing environments. These adjustments rely on fast and automatic control loops continuously processing sensory information [1]. In humans, the posterior parietal cortex (PPC) has been highlighted as crucial neural substrate of these control mechanisms. To date, most neuroimaging studies focused on visual feedback loops [2]. We used event-related transcranial magnetic stimulation (TMS) to test whether proprioceptive signals are processed by the same sub-regions of the left PPC as visual signals or whether different areas are recruited. Reaching movements were executed either with or without visual feedback of the reaching hand, so that the control relied either predominantly on visual information [3, 4] or only on proprioception. TMS affected the online corrections for a force impulse over distinct sites differently, depending on the condition. Without visual feedback, stimulating the medial superior parietal lobe (SPL) compromised reaching accuracy. With visual feedback, stimulating the anterior intraparietal sulcus prolonged reaching time. Our results highlight the importance of the medial SPL in the continuous integration of proprioception for executing movements and suggest that it is a key node for processing proprioception in motor control. Furthermore, this area is clearly separable from sub-regions involved in visuo-motor processing.

Highlights

- Medial SPL is a key node for processing of proprioceptive cues in motor control.
- This area is a likely functional equivalent to the macaque's area PEc.
- It is clearly separable from PPC sub-regions involved in visuo-motor processing.

Results and Discussion

For ordinary reaching movements to a visual target, both visual and proprioceptive sensory information is utilized to control the movement [4]. Depending on the situation and the demand, the one or the other sensory channel gains higher importance [3]. When the reaching hand cannot be seen (visual open-loop), proprioception is the only sensory information available to monitor the position of the hand and to control the movement. On the other hand, when the reaching hand can be seen (visual closed-loop) and the task demands high spatial accuracy [5-9], vision is the leading sensory information to monitor the position of the hand [3, 10] and to control the movement [4, 11, 12]. In this study, participants performed reaching movements to visual targets in a virtual reality environment (Fig. 1). The visual scene was observed through stereo glasses in spatial congruence with the haptic scene which was rendered with a robot arm operated by the participant [13]. During closed-loop reaching movements, participants received visual feedback about their hand position whereas open-loop reaching movements were performed without this feedback. During some trials, a force impulse was administered to the reaching arm perpendicular to the reaching direction, perturbing movement execution. The participants had to counteract this force online in order to preserve reaching accuracy. As shown in Table 1, the compensations for the perturbation were mostly incomplete: The end position of the hand (*EndAcc*) was on average deviated in the direction in which the force impulse had pushed the arm. Moreover, reaching accuracy was higher for closed- than for open-loop reaching, confirming previous findings [7, 8].

We assessed the causal contributions of eight selected brain areas in the anterior-to-medial left posterior parietal cortex (PPC, plus one contralateral control site, Fig. 2, Table 2) to the online control of the different types of reaching movements by intermittently administering event-related transcranial magnetic stimulation (TMS) over one of these stimulation sites. The TMS pulses were applied either shortly after perturbation onset or during the matched time window for unperturbed trials. The effect of TMS on the online responses to the force perturbation depended on the availability of visual feedback about the hand position. When visual feedback was not available, TMS over $SPL_{posterior}$ selectively reduced participants' ability to correct online for the force perturbation. This resulted in a further deviation of the movement end position in the direction in which the arm had been pushed ($p < .05$, corrected, Fig. 3a). When visual feedback was available, TMS over $IPS_{anterior}$ prolonged overall reaching time for the force perturbed trials ($p < .05$, corrected, Fig. 3b). A closer look at the acceleration-deceleration profiles of those trials revealed that the acceleration phase remained in fact unaltered by the TMS pulses (223.1 ± 10 ms vs. 223.8 ± 10 ms for TMS and no TMS trials, respectively) and that only the deceleration phase was prolonged significantly (472.5 ± 28 ms vs. 445.8 ± 25 ms for TMS and no TMS trials, respectively, $p < .03$, corrected). No other significant TMS-evoked effects were observed for any of the stimulation sites (data collapsed in Table 1).

Using individually adjusted stimulation intensities, we carefully ruled out that TMS caused direct motor impairments which could have biased our results. This was confirmed by the specificity of the effects during either open- or closed-loop reaching: General motor impairments or any other unspecific effect would have influenced both types of reaching movements to a similar extent. Also the absence of TMS effects when stimulating adjacent sites with equal or closer proximity to the primary motor cortex and the unaltered reaching times for the unperturbed movements render the possibility of any unspecific TMS effects unlikely. The analysis of the acceleration-deceleration profiles served as additional control. The acceleration phase, which included the time period during which the TMS stimuli were delivered, was not altered by TMS stimulation over any site. Direct TMS effects on the motor cortex (inducing, e.g. muscle twitches and silent periods) have short latencies so that, in our case, general motor impairments by TMS should have in particular affected the initial acceleration period [14]. In general, the close proximity of adjacent stimulation sites and the specificity of TMS effects on either open- or closed-loop reaching render the possibility of any other side effect, e.g. disruption of eye movements, very unlikely. To summarize, the observed TMS effects above $SPL_{posterior}$ and $IPS_{anterior}$ demonstrate a specific disturbance of sensory integration during online control of the reaching movement, and cannot stem from unspecific TMS effects.

Our results strongly suggest that two distinct but neighboring parietal regions are crucial for the integration of proprioceptive and visual afferents during online control of reaching movements. This study clearly demonstrates that the medial superior parital lobe (SPL, $SPL_{posterior}$) plays an essential role in controlling proprioceptively guided reaching movements. In contrast, the anterior intraparietal sulcus (IPS, $IPS_{anterior}$) seems to be a crucial structure for the integration of visual information during an ongoing reaching movement. Controlling closed-loop reaching movements relies predominantly on visual information [4, 11, 12] but in this study, proprioception was also useable during these movements. However, the present results complement a previous study [15] where TMS over the anterior IPS interfered unambiguously with the integration of various visual cues into an ongoing reaching movement. Taken together, these two studies provide robust evidence that the anterior IPS constitutes a crucial structure for the integration of visual information during online movement control. Regarding the segregation between these two adjacent regions, the data show clearly that they are actually separate and not simply a large area comprising a visual-proprioceptive gradient. Specifically, stimulating the three sites located in between these two regions resulted in unaltered reaching movements.

Recent fMRI studies in humans investigated the contribution of proprioception to the control of reaching movements by using unperturbed reaching paradigms. Both open- and closed-loop reaching movements [16] have been shown to equally activate the anterior precuneus and medial IPS, whereas the superior parito-occipital sulcus was more active for closed-loop reaching. Contrasting reaching movements executed with the right or left arm [17] has revealed a posterior-anterior gradient in the PPC for the processing of visual-to-somatosensory information during reaching. Moreover, the medial aspect of the SPL extending into the precuneus has been proposed as a candidate region for the integration of proproceptive information into a reaching movement using an experimental paradigm with a proprioceptive target [16]. All these studies suggested the involvement of the medial SPL in the integration of proprioceptive information for motor control. However, they neither differentiated planning and online control processes nor demonstrated the necessity of this area for online control. Our results demonstrate for the first time that a specific area in the medial SPL is essential for the integration of proprioceptive information during online control of reaching movements. Furthermore, we clearly separated this area from an area more anterior which is crucial for visuo-motor processing during an ongoing movement. Regarding more posterior sites which have been identified by the abovementioned studies for visual-driven motor control, we can neither confirm nor rebut their specificity as these areas are located outside of the region we tested in this study.

Administering TMS over the medial SPL severely affected the ability to fully correct for the force perturbation during open-loop reaching. In this case, only proprioception could be used to detect and correct for the perturbation. This suggests that the proprioceptive representation of the hand position was temporarily disturbed by the TMS pulses. Re-calibration of proprioception with the spatial more precise visual representation was impossible during the movement so that the internal update of the actual hand position became increasingly imprecise. Along this line, is has been shown that TMS applied over this area also interferes with the learning of novel dynamics induced by a force field [17]. Although this study is not utterly conclusive about whether the adaptation or the online correction has been disturbed by the TMS pulses, it strongly argues for an interference with the adaptation process. Furthermore, it has been demonstrated that this area is important to adjust the contact forces for object manipulation [18]. Both studies have used the same stereotactic coordinates as we have to plan the TMS coil position and have applied a similar coil placement procedure. However, these studies have not tested nearby control sites and therefore could not conclude on the spatial specificity of the TMS effects. Taken together, these results indicate that this area is generally important for the integration of proprioceptive information in motor control, for adaptation as well as online processing. This specific functionality taken together with this area’s anatomical localization render the medial SPL a likely candidate for the human homologue to the macaque PEc, where mainly somatosensory information for movement organization is processed [19]. Furthermore, the medial SPL is anatomically a part of the dorso-dorsal stream [20-22] and highly interconnected with the dorsal premotor cortex [23]. This fronto-parietal circuit is supposed to be involved in non-standard stimulus response mappings, control of actions online, and the processing of visuospatial parameters for grasping. The position of the medial SPL within this network of regions supporting sensory motor integration is perfectly suited to supply motor control processes with proprioceptive information.

Administering TMS over the anterior IPS, the junction between the postcentral and intraparietal sulcus, significantly prolonged the end phase of closed-loop reaching movements when they were perturbed by a force impulse. In this case, predominantly vision was used to detect and correct for the perturbation, as demonstrated by previous studies [4, 11, 12]. Providing visual feedback about the hand position yields in rather good reaching accuracy [7, 8] and given the transient effects of online TMS, the reaching accuracy was not compromised by the TMS pulses. Our results suggest that the integration of visual information about the current hand position into the reaching movement was temporarily disturbed so that the fine-adjustment phase at the end was prolonged. This further strengthens the hypothesis that the anterior IPS is more generally involved in visuo-motor transformations for online movement control beyond grasping [15, 24]. Furthermore, the anterior IPS is anatomically a part of the ventro-dorsal stream [20-22] and highly interconnected with the ventral premotor cortex [23]. This fronto-parietal circuit is supposed to subserve transforming spatial object locations for motor commands and adapting motor behavior on the basis of information from the ventral visual stream. The position of the anterior IPS within this network of regions supporting visuo-motor processes is perfectly suited to supply these processes with spatial accurate visual information about the current hand position.

To summarize, using a densely spaced grid of TMS coil positions over the anterior to medial part of the left PPC, we demonstrated for the first time a causal contribution of the medial SPL to proprioceptively guided online control of reaching movements. We hypothesize that this area is a key structure for the processing of proprioception during movement control and a putative functional equivalent to macaque area PEc. Additionally, we demonstrated a causal contribution of the anterior IPS to visually guided online control of reaching movements. This strengthens its role as a key structure in visuo-motor processing. Finally, we showed a clear functional and anatomical separation between the medial SPL and the anterior IPS. In the future, this approach can be used to further disentangle PPC sub-regions which integrate different sensory modalities within different behavioral contexts for reaching, grasping, and other motor interactions with the environment.

Materials and Methods

General Procedure

Nine healthy, right-handed volunteers (age 21-32 years, four females) including one of the authors participated in the study. Besides the author, all participants were naïve about the purpose of the study. They had normal or corrected-to-normal vision and no history of neurological disorders. Written informed consent was obtained from each participant prior to the first experiment. The study was approved by the local ethics committee of the Medical Faculty of the University of Tübingen. Each participant attended several experimental sessions in which he/she was first familiarized with the overall procedure, then the pre-experiments were conducted, and finally the TMS experiment was performed in three sessions. Successive TMS sessions were separated by one week or more. During the MRI scan and the TMS experiments participants wore ear plugs to prevent hearing damage and auditory influence on task performance.

Pre-experiments

A T1-weighted structural image (MPRAGE, TR 1900 ms, TE 2.26 ms, TI 900 ms, flip angle 9°, 192 coronal slices, 1 mm iso-voxel resolution, 2 averages) was acquired on a Siemens 3T TIM Trio (Siemens, Erlangen, Germany) for each participant. For the TMS experiments, the strength of the force impulse was determined for each participant individually. The goal was to match the resulting reaching trajectories between participants by matching the maximal trajectory deviation between the actual trajectory and the direct connection between starting position and target (*MaxDev*), which results from the force perturbation. Participants performed the same task as in the main experiment (see below) without TMS stimulation, but with force impulses of different strengths intermixed, ranging from 0 to 25 N in steps of 5 N. The force level resulting in a maximal trajectory deviation closest to 25 mm was used as individual force strength. This procedure led to force impulses of 10 N in two participants and 15 N in the remaining seven. The results of the main experiment (*MaxDev* in Table 1) confirmed that this manipulation was successful.

TMS Stimulation

Biphasic TMS stimuli were applied using a Medtronic MagPro X100 stimulator (MagVenture, Farum, Denmark) with a MC-B70 butterfly coil. The coil position was monitored using a neuronavigation system (BrainView, Fraunhofer IPA, Germany; see [25] for a description of the system). The spatial accuracy of the registration between the participant's real head and his anatomical MR image in the neuronavigation system was established at the beginning and checked again at the end of each session using positions of clearly visible landmarks (e.g., the nasion and inion). The coil was held manually by a trained investigator, keeping the coil position in a range of 2 mm to the pre-planned stimulation sites. Blocks were repeated whenever the distance of the coil to the stimulation site exceeded 2 mm. The stimulation intensity was chosen to meet two competing goals: It should be as high as possible to maximize the impact on the stimulation site without eliciting direct effects on the primary motor cortex. For this purpose, the coil was placed at the most anterior stimulation site at the beginning of each session and the motor threshold was determined (tested by recording surface EMG from the relaxed first dorsal interosseus). Finger muscles were used for this purpose as it is known that these muscles exhibit the lowest TMS thresholds. 80% of the individual motor threshold was used as stimulation intensity throughout the experiment. The coil was initially oriented parallel to the central sulcus and adjusted when necessary. This procedure resulted in stimulation intensities of 32-61% of maximum stimulator output.

Procedure and Behavioural Task

A session proceeded in complete darkness and consisted of several blocks, including an initial training block at the beginning of each session. The training block was executed in order to familiarize the participant with the task and to minimize training effects throughout the experiment. One block lasted 10-15 min and contained 72 trials, covering uniformly distributed all possible combinations of the independent variables: Position of the target (15° to the left / 15° to the right), force perturbation (to the right / to the left / none), visual feedback about the hand position (present / absent), and TMS (yes / no). The order of presentation was fully randomized to prevent any predictability or anticipation of the force perturbation or the TMS pulses. Altogether, 12 repetitions were recorded for each combination of variables, resulting in four blocks per TMS stimulation site. The order of stimulation sites was randomized to prevent putative training or fatigue effects from biasing the results. It is important to note that the stimulation sites over the left PPC were not distinguishable for the participants, i.e. also the participating author was not able to tell apart the sites during stimulation.

A trial started with the presentation of the starting position with visual feedback about the hand position present. The starting position was randomly jittered in a 2*2 cm area located 10 cm in front of the participant about the body midline. After the hand had been maintained in the starting position for about one second, the target appeared and the starting position disappeared. The target was displayed at a distance of 20 cm from the starting position and its location was 15° on either side of the body midline. The participant's task was to look at and reach for the target as quickly and precisely as possible. In open-loop reaching trials, the representation of the hand disappeared as soon as the target appeared. The time at which the velocity of the hand dropped below 1 cm/s again was defined as the end of the trial. In between trials, the visual scene disappeared for two seconds.

In the perturbation trials, the force impulse began randomly between 1 and 4 cm away from the starting position and lasted 5 cm. In TMS trials, four magnetic pulses were applied at a frequency of 60 Hz. The first pulse was delivered 30 ms after the onset of the force impulse [13, 15].

Behavioural Measures & Data Analysis

The on- and offset of the movement were defined as the time at which the velocity of the robot arm exceeded and fell below 2 cm/s, respectively. Less than 2% of trials were excluded from further analysis because total time, total path length, or peak velocity were outside the range of the participant's mean±3*SD. The impact of TMS on the online corrections to the force impulse was assessed by applying different measures to the kinematic data. Endpoint accuracy (*EndAcc*) was defined as the distance of the final hand position to the final target, whereby the evaluation was restricted to the component perpendicular to the original reaching direction (the direction in which the correction for the perturbation was necessary). Incomplete compensations for the force perturbation were coded as positive values. Additionally to the overall reaching time (*ReachTime*), we assessed the time point when the maximal velocity was reached (*TPMaxVel*) in order to obtain the acceleration-deceleration periods. For each TMS stimulation site and reaching condition (perturbed / unperturbed, open- / closed-loop), group analyses were conducted comparing trials with versus without TMS using paired t-tests. Bonferroni corrections for the number of stimulation sites were used for multiple comparisons correction. Reported values are mean ± SE across participants, unless stated otherwise. Re-analysis of the data without the participating author did not change any of the effects.

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References

1. Desmurget, M., and Grafton, S. (2000). Forward modeling allows feedback control for fast reaching movements. Trends Cogn. Sci. *4*, 423-431.

2. Culham, J.C., Cavina-Pratesi, C., and Singhal, A. (2006). The role of parietal cortex in visuomotor control: what have we learned from neuroimaging? Neuropsychologia *44*, 2668-2684.

3. Ernst, M.O., and Banks, M.S. (2002). Humans integrate visual and haptic information in a statistically optimal fashion. Nature *415*, 429-433.

4. Sarlegna, F., Blouin, J., Vercher, J.L., Bresciani, J.P., Bourdin, C., and Gauthier, G.M. (2004). Online control of the direction of rapid reaching movements. Exp. Brain Res. *157*, 468-471.

5. Bard, C., Hay, L., and Fleury, M. (1985). Role of peripheral vision in the directional control of rapid aiming movements. Can. J. Psychol. *39*, 151-161.

6. Proteau, L., Boivin, K., Linossier, S., and Abahnini, K. (2000). Exploring the limits of peripheral vision for the control of movement. J. Mot. Behav. *32*, 277-286.

7. Spijkers, W., and Spellerberg, S. (1995). On-line visual control of aiming movements? Acta Psychol. (Amst.) *90*, 333-348.

8. Spijkers, W.A., and Lochner, P. (1994). Partial visual feedback and spatial end-point accuracy of discrete aiming movements. J. Mot. Behav. *26*, 283-295.

9. Woodworth, R.S. (1899). The accuracy of voluntary movement. Psychol. Rev. *3*, 1-114.

10. Pavani, F., Spence, C., and Driver, J. (2000). Visual capture of touch: out-of-the-body experiences with rubber gloves. Psychol. Sci. *11*, 353-359.

11. Holmes, N.P., Crozier, G., and Spence, C. (2004). When mirrors lie: "visual capture" of arm position impairs reaching performance. Cogn. Affect. Behav. Neurosci. *4*, 193-200.

12. Touzalin-Chretien, P., Ehrler, S., and Dufour, A. (2010). Dominance of vision over proprioception on motor programming: evidence from ERP. Cereb. Cortex *20*, 2007-2016.

13. Reichenbach, A., Thielscher, A., Peer, A., Bulthoff, H.H., and Bresciani, J.P. (2009). Seeing the hand while reaching speeds up on-line responses to a sudden change in target position. J. Physiol. *587*, 4605-4616.

14. Desmurget, M., Epstein, C.M., Turner, R.S., Prablanc, C., Alexander, G.E., and Grafton, S.T. (1999). Role of the posterior parietal cortex in updating reaching movements to a visual target. Nat. Neurosci. *2*, 563-567.

15. Reichenbach, A., Bresciani, J.P., Peer, A., Bülthoff, H.H., and Thielscher, A. (2010). Contributions of the PPC to online control of visually guided reaching movements assessed with TMS and fMRI. in revision.

16. Pellijeff, A., Bonilha, L., Morgan, P.S., McKenzie, K., and Jackson, S.R. (2006). Parietal updating of limb posture: an event-related fMRI study. Neuropsychologia *44*, 2685-2690.

17. Della-Maggiore, V., Malfait, N., Ostry, D.J., and Paus, T. (2004). Stimulation of the posterior parietal cortex interferes with arm trajectory adjustments during the learning of new dynamics. J. Neurosci. *24*, 9971-9976.

18. Chib, V.S., Krutky, M.A., Lynch, K.M., and Mussa-Ivaldi, F.A. (2009). The separate neural control of hand movements and contact forces. J. Neurosci. *29*, 3939-3947.

19. Colby, C.L., and Duhamel, J.R. (1991). Heterogeneity of extrastriate visual areas and multiple parietal areas in the macaque monkey. Neuropsychologia *29*, 517-537.

20. Rizzolatti, G., and Matelli, M. (2003). Two different streams form the dorsal visual system: anatomy and functions. Exp. Brain Res. *153*, 146-157.

21. Tanne-Gariepy, J., Rouiller, E.M., and Boussaoud, D. (2002). Parietal inputs to dorsal versus ventral premotor areas in the macaque monkey: evidence for largely segregated visuomotor pathways. Exp. Brain Res. *145*, 91-103.

22. Verhagen, L., Dijkerman, H.C., Grol, M.J., and Toni, I. (2008). Perceptuo-motor interactions during prehension movements. J. Neurosci. *28*, 4726-4735.

23. Tomassini, V., Jbabdi, S., Klein, J.C., Behrens, T.E., Pozzilli, C., Matthews, P.M., Rushworth, M.F., and Johansen-Berg, H. (2007). Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. J. Neurosci. *27*, 10259-10269.

24. Tunik, E., Rice, N.J., Hamilton, A., and Grafton, S.T. (2007). Beyond grasping: representation of action in human anterior intraparietal sulcus. Neuroimage *36 Suppl 2*, T77-86.

25. Kammer, T., Vorwerg, M., and Herrnberger, B. (2007). Anisotropy in the visual cortex investigated by neuronavigated transcranial magnetic stimulation. Neuroimage *36*, 313-321.

26. Buss, M., and Schmidt, G. (1999). Control problems in multimodal telepresence systems. In Advances in Control, Highlights of ECC '99. (London: Springer-Verlag), pp. 65-101.

27. Mazziotta, J., Toga, A., Evans, A., Fox, P., Lancaster, J., Zilles, K., Woods, R., Paus, T., Simpson, G., Pike, B., et al. (2001). A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philos. Trans. R. Soc. Lond. B. Biol. Sci. *356*, 1293-1322.

28. Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage *23 Suppl 1*, S208-219.

29. Smith, S.M., Beckmann, C.F., Ramnani, N., Woolrich, M.W., Bannister, P.R., Jenkinson, M., Matthews, P.M., and McGonigle, D.J. (2005). Variability in fMRI: a re-examination of inter-session differences. Hum. Brain Mapp. *24*, 248-257.

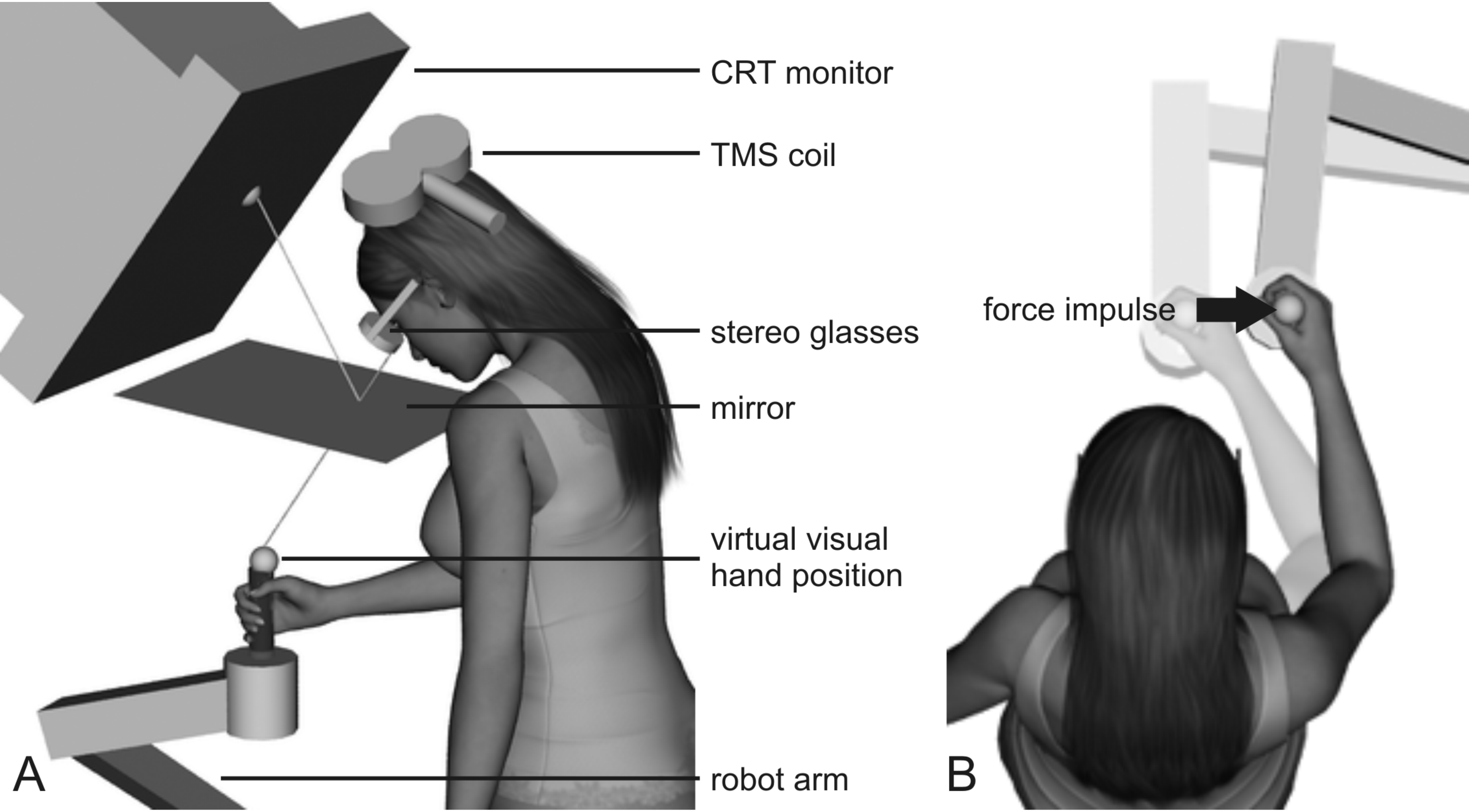
Figure Legends

Figure 1 Virtual reality environment for the TMS experiments. A) Side view on the complete setup. B) Top view on the robot arm for illustration of the force perturbation. A mirror-setup with a top-mounted CRT monitor and shutter glasses (StereoGraphics / REAL D, Beverly Hills, California, USA) was used to render the 3D visual scene in spatial congruence to the haptic scene. The latter was controlled by a robot arm (DekiFeD, Technische Universität München, Germany; [26]) used as manipulandum that restricted the hand movements to a horizontal plane. The participants kept the handle which was mounted on the robot arm grasped with their dominant right hand throughout the experimental blocks. An additional black cloth located in the horizontal plane between the mirror and the robot arm prevented the participants from seeing their real hand. The visual feedback about the hand position (represented by a red sphere), whenever given, corresponded spatially to the top of the handle. The robot arm actively followed the hand movements to minimize its inertia as felt by the participant. A head and chin rest limited head movements. Visual scene presentation and acquisition of the kinematic data was performed at 120 Hz. For additional details please refer to [13]. The figure was created with DAZ Studio 3.1 (DAZ Productions Inc., Draper, UT, USA).

Figure 2 TMS stimulation sites, rendered on the reconstructed left hemisphere of an exemplarily participant. A grid of eight TMS coil positions ranging from the anterior SMG to the medial SPL in the left hemisphere and one position on the contralateral hemisphere (not depicted) were derived from previous studies investigating online control or force perturbations during reaching [15, 17, 18] (Table 2). The distance between adjacent stimulation sites ranged between 1 and 1.5 cm, dependent on the sites and the participants' head size. The proximity of stimulation sites enabled us to separate different sub-regions of the PPC which served as mutual control sites. The MNI coordinates of the grid were transformed back from MNI space [27] to the space of the individual structural images using the linear registration (FLIRT) of FSL 4.0 (FMRIB, Oxford, UK; [28, 29]. The closest coil position on the skull was determined for each MNI coordinate using custom-written MATLAB routines (The MathWorks, Natick, MA, USA). The routines used the surface reconstruction of the skull as obtained with BrainVoyager 2000 (Brain Innovation, Maastricht, The Netherlands). CS: central sulcus; PCS: postcentral sulcus; IPS: intraparietal sulcus; SPL: superior parietal lobe; SMG: supramarginal gyrus. The notations anterior, posterior etc. in the names of the stimulation sites are used in respect to the relative locations for this study.

Figure 3 Mean differences of end accuracy (upper panel) and overall reaching time (lower panel) for trials with TMS – trials without TMS for perturbed trials. Whiskers denote standard errors between participants.

* differences significant at $p < .05$ Bonferroni corrected for the number of stimulation sites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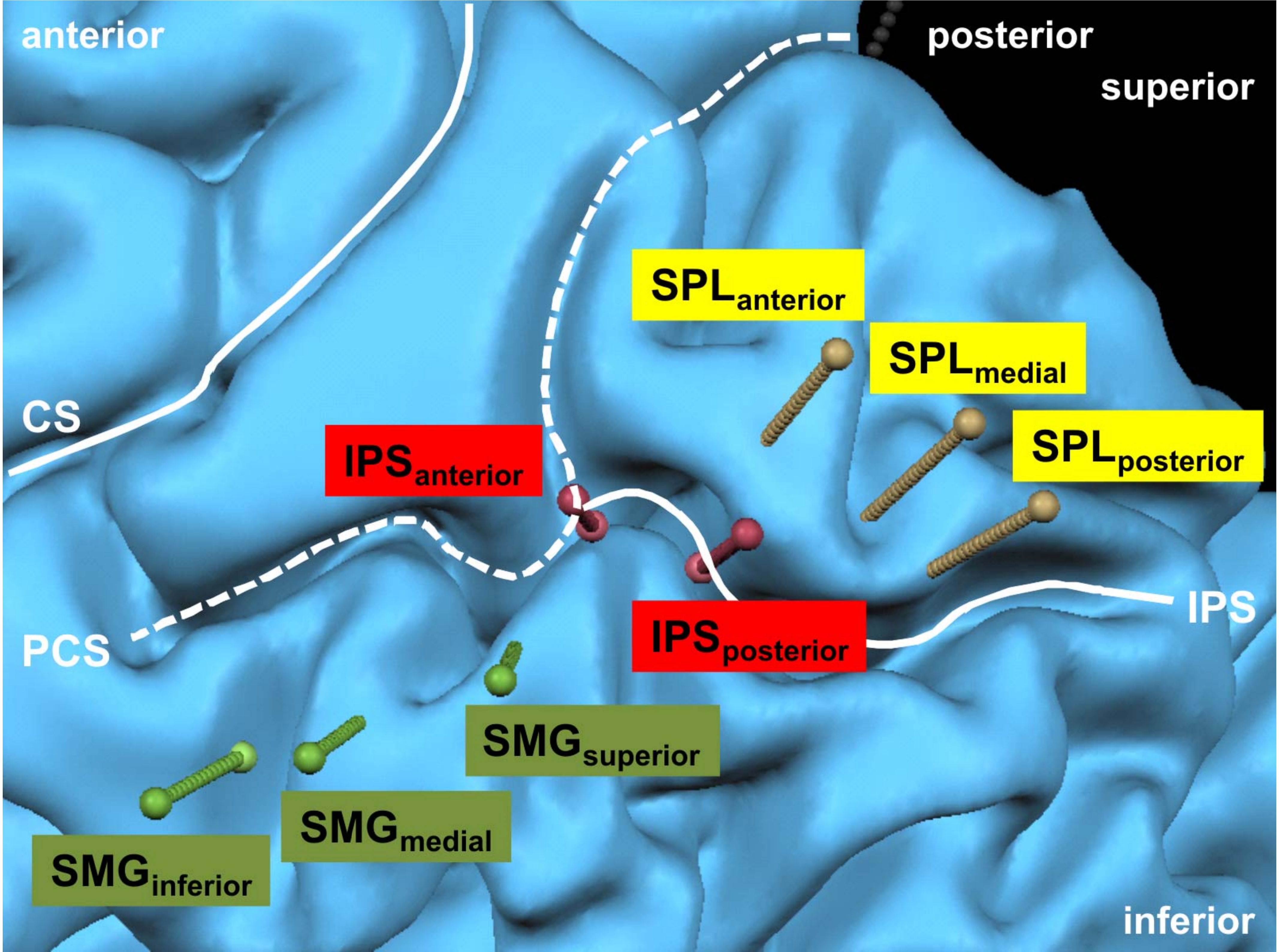
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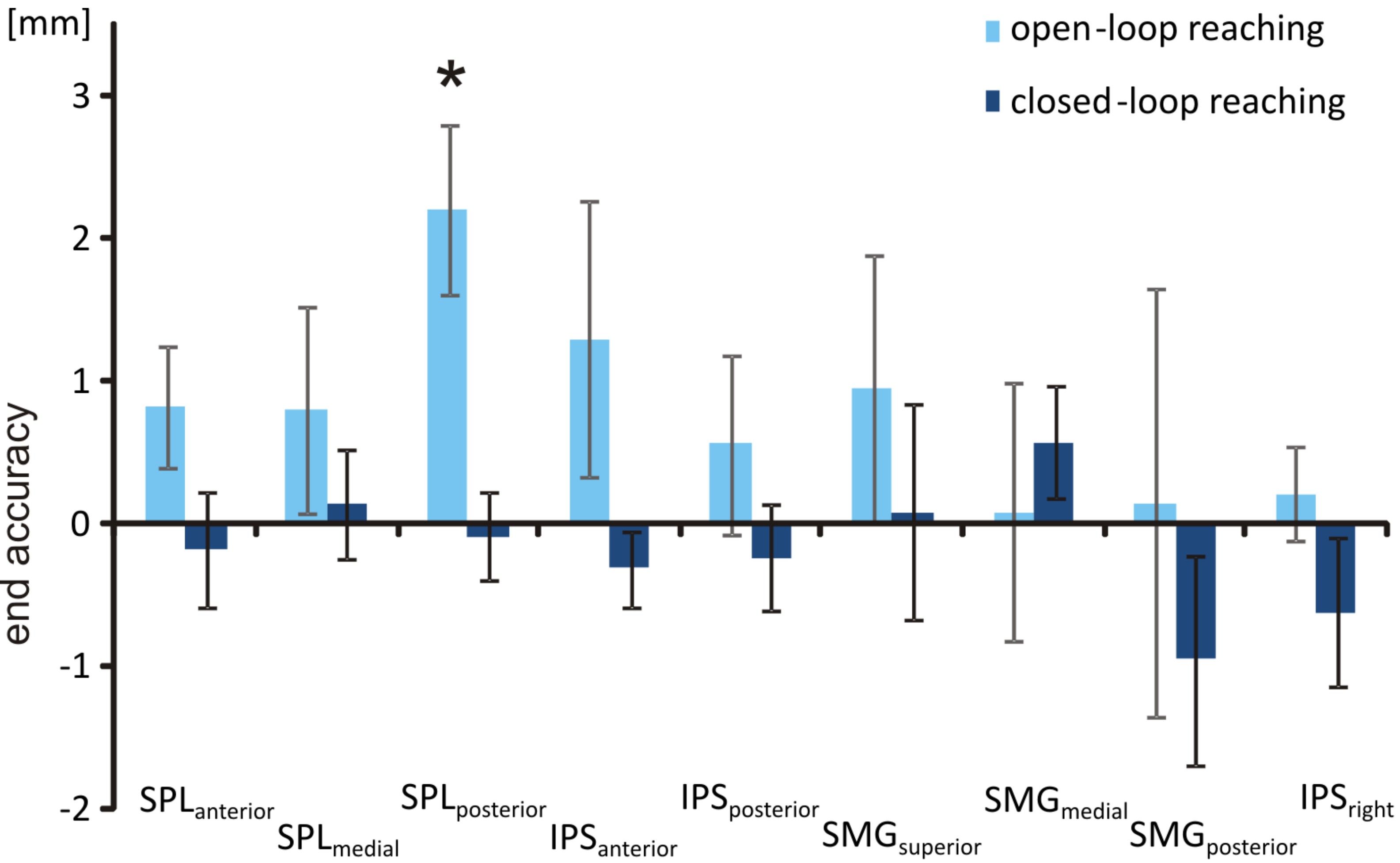
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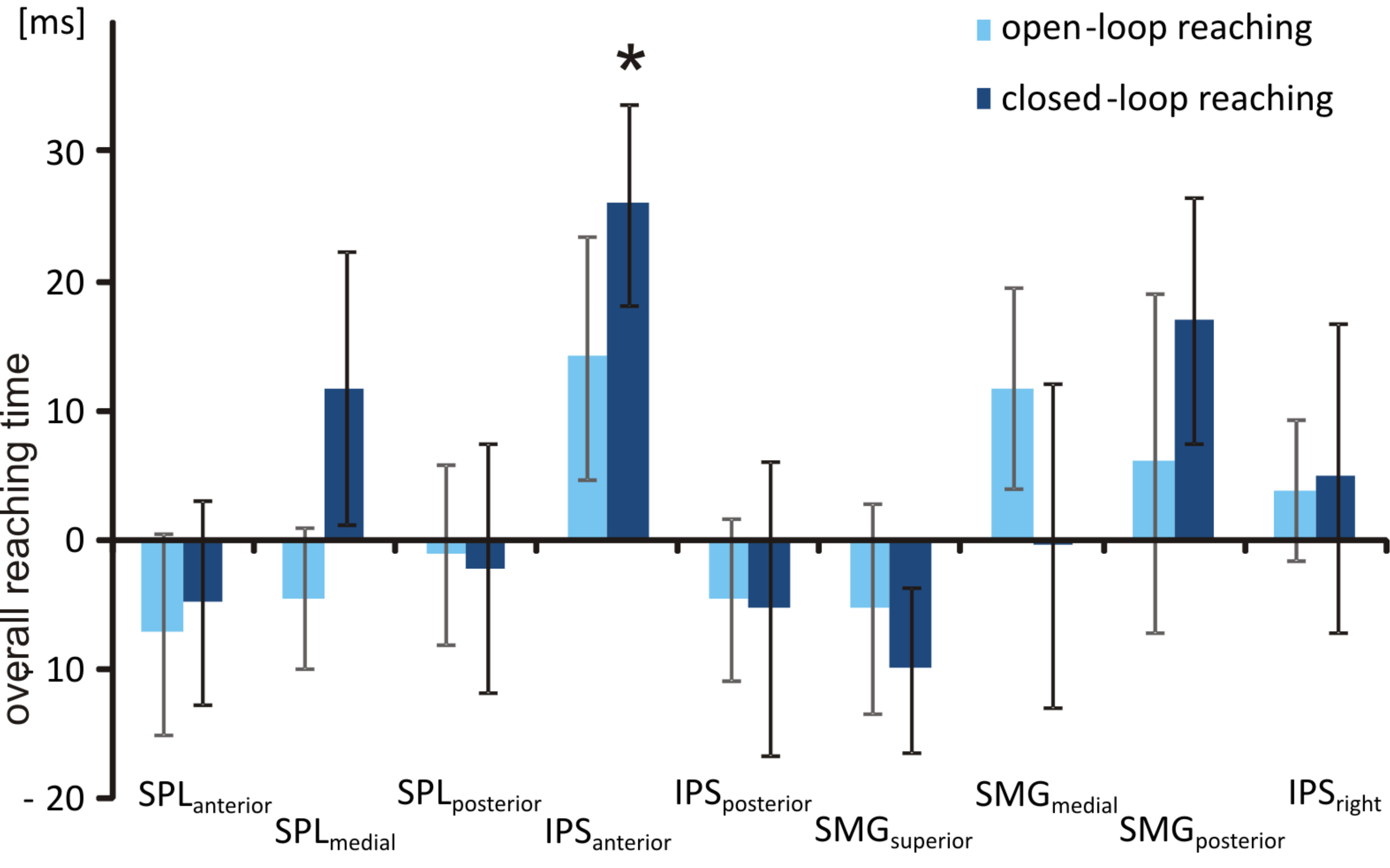
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IPS$_{anterior}$
IPS$_{posterior}$
SMG$_{superior}$
SMG$_{medial}$
SMG$_{posterior}$
IPS$_{right}$

3 Author's publications

- Reichenbach, A., Thielscher, A., Peer, A., Bülthoff H.H., and Bresciani, J.-P. (in review) Different neural substrates for proprioceptively vs. visually guided movements in the human parietal cortex.
- Reichenbach, A., Bresciani, J.-P., Peer, A., Bülthoff, H.H., and Thielscher, A. (2011) Contributions of the PPC to online control of visually guided reaching movements assessed with fMRI-guided TMS. Cerebral Cortex 21(7), 1601-1612.
- Reichenbach, A., Whittingstall K., and Thielscher, A. (2010) Effects of Transcranial Magnetic Stimulation on visual evoked potentials in a visual suppression task. NeuroImage (in press).
- Thielscher, A., Reichenbach, A., Ugurbil, K., and Uludag, K. (2010) The Cortical Site of Visual Suppression by Transcranial Magnetic Stimulation. Cerebral Cortex 20(2), 328-338.
- Reichenbach, A., Thielscher, A., Peer, A., Bülthoff, H.H., and Bresciani, J.-P. (2009) Seeing the hand while reaching speeds up on-line responses to a sudden change in target position. The Journal of Physiology 587(19), 4605-4616.

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