Dorsal and ventral stream contributions to goal-directed actions

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CONTENTS

1 ABSTRACT

Goal-directed actions are of vital importance for our everyday life. Yet, their underlying mechanisms and neuronal correlates are still under debate. Two anatomically informed models try to integrate a variety of neurophysiological and functional descriptions of frontal, parietal and temporal areas: the idea of distinct fronto-parietal channels of reach vs. grasp motor control and the two visual stream hypothesis associating occipito-parietal processing with visuomotor control and occipito-temporal processing with visual perception. We addressed three controversial topics in the context of these two models.

We investigated the lateralization of online control of visually-guided reaching and grasping in humans using an fMRI paradigm. The two channel hypotheses would suggest that corrections in grasping should be anatomically distinguishable from corrections in reaching. Our main finding was an increased coupling between the hemispheres when fast movement corrections were required. A specific increase of functional connectivity within the ipsilateral hemisphere without corresponding contralateral activation increases during movement corrections, suggested that activations of the ipsilateral PPC are of functional importance for visually-guided actions. Furthermore, the connectivity analysis demonstrated changes in inter-regional coupling between the reaching and grasping networks during grip perturbations but no difference between reaching and grasping when those actions were matched in difficulty, arguing against an effector specificity of different cortical channels during online control.

Lesions in the posterior parietal cortex can cause optic ataxia, which is defined as a reaching deficit to visual targets in the periphery. While such modality-specificity is essential for the definition of optic ataxia, comparisons of reaching accuracy across modalities have rarely been conducted. We investigated the potential multimodality of optic ataxia in two patients who both showed the typical misreaching in the periphery for the visual modality. Reaching to auditory targets differed significantly from reaching to visual targets for both patients, arguing against an effect of optic ataxia on auditory-guided reaching. Reaching to proprioceptive targets was unimpaired in one patient, but impaired towards nonfoveated targets in line with optic ataxia. However, this misreaching for proprioceptive targets was observed for the whole hemifield but did not increase with eccentricity as observed for visually-guided

reaching. Thus, we propose that optic ataxia is unimodal but misreaching to targets in other modalities may co-occur resembling optic ataxia.

Finally, we examined the role of occipito-temporal regions in memory-guided reaching in a stroke patient suffering from lateralized visual form agnosia. In agreement with the only previous examination of memory-guided reaching in a patient suffering from visual form agnosia (David Milner, Dijkerman, & Carey, 1999), reaching to visual targets was unimpaired. In contrast, the patient showed deficits when reaching to memorized targets in the contralesional hemifield. In contrast to existing studies, we excluded working memory or short-term memory deficits that may account for the observed misreaching. A second experiment using a delayed localization task suggested that the misreaching during memory-guided reaching is associated with visuomotor processing, but not with purely perceptual deficits.

2 SYNOPSIS

2.1 SENSORIMOTOR CONTROL AND FUNCTIONAL ORGANIZATION

Reaching and grasping movements are performed seemingly effortless every day. The perceived ease stands in contrast to the complex computations the central nervous system needs to undertake to successfully reach to a goal. One key process is the processing of visual information, which is essential to gain information about the environment including the perception of possible targets, their features and location as well as of potential obstacles. Next, during the planning phase, a motor program is chosen out of several alternatives. Based on the target's features like spatial characteristics (e.g., size, shape, orientation), non-spatial characteristic (e.g., fragility), and the visual context (e.g., close vicinity to other objects), the overarching goals of an action (e.g. to cut with scissors or passing them to someone) and the appropriate movement parameters are calculated (Glover, 2004). During the following phase of online control, the movement execution is continuously monitored by the sensory system to allow for adjustments of the motor commands based on visual as well as non-visual feedback like proprioceptive information about the limb position (Desmurget et al., 2001; Sarlegna et al., 2003, 2004). Knowledge about the current position of the hand is provided by visual and proprioceptive feedback with the latter providing feedback by proprioceptive afferents and feedforward information through the efference copy of the motor command. Therefore, the availability of additional visual feedback during the execution phase increases precision (Hesse & Franz, 2010; Inoue et al., 1998). For reaches in the dark without vision of the hand, proprioceptive information is the sole source of the hand position. It is, however, sufficient to reach for a target and to correct the reaching trajectory to new target locations, even when a displacement was not consciously perceived (Goodale, Pelisson, & Prablanc, 1986; Pélisson, Prablanc, Goodale, & Jeannerod, 1986).
As has been discussed above, information from different sensory modalities are used to guide limb movements. However, the reference frame in which information is encoded depends on the sensory modality and has to be translated into a motor command that depends on the effector (Cohen & Andersen, 2002). For example, limb movements towards a visual target require additional transformations between eye-centered and hand-centered coordinates. While some studies argue in favor of eye-centered coding (e.g., Batista, Buneo, Snyder, & Andersen, 1999), others argue

for body- (Lacquaniti, Guigon, Bianchi, Ferraina, & Caminiti, 1995) or hand-centered coding (Graziano, Yap, & Gross, 1994). Recent findings point towards a role of a combination of coordinate frames (Buneo, Jarvis, Batista, & Andersen, 2002). In the latter, the contribution of each reference frame depends on the sensory modality of the target: while visual targets are encoded in gaze and body centered coordinates, reaching to proprioceptive targets is encoded in similar areas, but mainly in body-centered coordinates (Bernier & Grafton, 2010). The authors suggest that the brain is highly flexible since it does not recruit different networks for targets of different modalities but can change its reference frame in some brain regions.

The major players involved in goal directed actions are the parietal cortex, the motor cortex, the premotor cortex and the cerebellum as well as the basal ganglia. These areas are complemented by primary and secondary sensory areas for visually- and auditory-guided actions. In the following, the role of the posterior parietal cortex (PPC) will be depicted.

The functional anatomy of the PPC has been studied extensively in humans and monkeys. Animal models are of utmost importance for the understanding of the functional anatomy of the primate sensorimotor system and for the transfer of the respective findings to the human brain. Studies in monkeys (Buneo & Andersen, 2006) and humans (Culham, Cavina-Pratesi, & Singhal, 2006) depict the PPC as an interface integrating multimodal sensory and motor signals for movements to visual targets. The PPC integrates visual, proprioceptive (Beurze, de Lange, Toni, & Medendorp, 2007; Filimon, Nelson, Huang, & Sereno, 2009; Reichenbach, Thielscher, Peer, Bülthoff, & Bresciani, 2014), auditory (Alain, Arnott, Hevenor, Graham, & Grady, 2001; Weeks et al., 1999; Zatorre, Bouffard, Ahad, & Belin, 2002), and vestibular (Reichenbach, Bresciani, Bülthoff, & Thielscher, 2016) information in order to accomplish successful movements to visual, auditory or proprioceptive targets, respectively.

Moreover, the PPC is involved in the planning (Gallivan, McLean, Valyear, Pettypiece, & Culham, 2011; Glover, 2004; Glover, Wall, & Smith, 2012) and execution phase of movements. Since fMRI suffers from a poor temporal resolution, numerous fMRI studies did not disentangle the planning and control phase (Cavina-Pratesi, Monaco, et al., 2010; Fabbri, Strnad, Caramazza, & Lingnau, 2014; Filimon et al., 2009; Grefkes, Ritzl, Zilles, & Fink, 2004). To investigate these phases of a movement separately, delays between stimulus

presentation and movement initiation are often introduced. This separation of movement phases is of vital importance for the investigation of effector selectivity since the degree of effector selectivity changes over time during the evolvement of a movement (Beurze, de Lange, Toni, & Medendorp, 2009). Yet, according to the two visual stream hypothesis (Goodale & Milner, 1992; Milner & Goodale, 2008), memory-guided movements additionally recruit ventral stream areas in comparison to visually-guided movements (for more details, see section 2.4). Therefore, paradigms using a delay to separate both phases might reveal different neuronal correlates than those actually employed in visually-guided movements. One way to isolate online control from pre-movement planning without an introduction of a delay is to employ of a perturbation paradigm that specifically increases online control but leaves the planning component unaffected (e.g., Glover et al., 2005). Perturbations can be introduced e.g. by a displacement of the target (Desmurget et al., 1999), a real or virtual displacement of the effector (Reichenbach et al., 2014; Sarlegna et al., 2003), or a change in target size (Glover et al., 2005). Using such perturbation paradigms, several studies (Desmurget et al., 1999; Glover et al., 2005; Reichenbach, Bresciani, Peer, Bülthoff, & Thielscher, 2011; Rice, Tunik, & Grafton, 2006; Tunik, Frey, & Grafton, 2005) were able to demonstrate the involvement of the PPC in the execution phase separately.

2.1.1 Cortical lateralization

Regarding the functional organization across hemispheres, various motor-relevant regions are commonly assumed to be lateralized, even though most of them show only some degree of lateralization, for example the primary motor and sensory cortices. For instance, ipsilesional motor impairments as well as proprioceptive and somatosensory deficits have been reported after lesions of the primary motor and sensory cortices (Boll, 1974; Borchers, Hauser, & Himmelbach, 2011; Jones, Donaldson, & Parkin, 1989), indicating the functional importance of ipsilateral brain regions.

Contradictory findings have also been reported for the PPC. Several studies have suggested a lateralization of the PPC because increases in brain activation are reported to be either restricted to the contralateral PPC (Desmurget et al., 2001; Frey, Vinton, Norlund, & Grafton, 2005) or to be stronger contralateral (Beurze et al.,

2007). At the same time, however, bilateral activation is often observed during actions like grasping (Binkofski et al., 1998; Grefkes, Weiss, Zilles, & Fink, 2002) in the PPC. One possible explanation for bilateral activation might be cross-talk between corresponding areas of both hemispheres (Culham et al., 2006). Another explanation is that movements for both hands are prepared although the instructions clearly require the participant to use only the instructed (usually right) hand (Culham et al., 2006). Two findings, however, argue against these explanations. First, a recent study demonstrated that the effector is selected before the reach plan is formed in parietofrontal regions (Bernier, Cieslak, & Grafton, 2012) and thus argues against a parallel planning of movements for both arms. Second, TMS studies inducing virtual lesions demonstrated the causal role of the ipsilateral parieto-occipital cortex in the planning of reaching movements (Busan et al., 2009) as well as of the anterior intraparietal sulcus (aIPS) in grasping movements (Davare, Andres, Clerget, Thonnard, & Olivier, 2007). The latter study revealed that a unilateral TMS inhibition of the left aIPS affected grip force scaling in both hands while a bilateral lesion was necessary to affect hand shaping. The causal role of the ipsilateral cortex is further supported by a monkey study demonstrating that a bilateral inactivation of the PPC is required to impair online control of hand movements (Battaglia-Mayer et al., 2012). Interestingly, lesion studies have not only demonstrated the causal role of ipsilateral parietal areas in in reaching and grasping, but also indicate that the ipsilateral cortex might be able to compensate for contralateral damage. Grasping activity was observed primarily ipsilateral in a stroke patient with contralateral parietal damage (besides bilateral damage to the ventral lateral-occipital cortex) (James, Culham, Humphrey, Milner, & Goodale, 2003).

How can the findings of the causal role of the ipsilateral PPC in some studies on the one hand and only contralateral activation in other studies on the other hand (Desmurget et al., 2001; Frey et al., 2005) be reconciled? One explanation is offered by a study in monkeys showing that the inactivation of PMv affected selectively the contralesional hand when the lesion was small, but a larger lesion affected both hands (Fogassi et al., 2001a) suggesting that the lesions size affects the lateralization of the deficit. Another explanation for the seemingly contradictory findings might be that hand specificity changes during different phases of the reach movement (Beurze et al., 2007). While the intraparietal sulcus (IPS) as well as dorsal and ventral premotor cortex (PMd and PMv, respectively) besides others were clearly

lateralized for the contralateral hand during the movement preparation, the lateralization for PMv disappeared during the execution of reaching. Additionally, the degree of lateralization increases between the ipsi- and contralesional effector (Beurze et al., 2007; Beurze, de Lange, Toni, & Medendorp, 2009; Blangero, Menz, McNamara, & Binkofski, 2009; Medendorp, Goltz, Crawford, & Vilis, 2005) along an anterior-posterior gradient with, for instance, little effector-related lateralization in POJ. Finally, task complexity has been shown to modulate ipsilateral activity in the motor cortex and the time course of the ipsilateral activation suggested its relevance during movement execution (Verstynen, Diedrichsen, Albert, Aparicio, & Ivry, 2005). Thus, to draw conclusions about the lateralization of the sensorimotor network, several issues have to be addressed including the separation of the planning and execution phase as well as task difficulty. Since it is not possible to control the size of a lesion in humans, functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) studies offer good alternatives for the investigation of lateralization.

2.1.2 Effector specificity

In monkeys, the PPC has been often described as a highly modular, effector-specific brain area that is specialized for sensorimotor control (Andersen & Buneo, 2002; Snyder, Batista, & Andersen, 1997). The observed putative functional homologies between humans and monkeys (see below) so far only allow for moderate to tentative inferences about the parietal cortex and further studies are required to establish equivalencies between both species (Culham et al., 2006; Culham & Kanwisher, 2001; Grefkes & Fink, 2005). One reason is that the comparison between humans and monkeys usually relies on different techniques that differ in various aspects. For example, neurophysiological measures and imaging studies like fMRI have different spatial resolution and reflect distinct underlying processes. In contrast to single-cell recordings that depict the output of a single neuron, the blood-oxygen-level-dependent (BOLD) signal reflects the input and intracortical processing of an area containing many neurons (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). One solution is comparative mapping in humans and monkeys. This approach is promising but has its own caveats, e.g. that the human intraparietal sulcus expanded markedly and might have led to the development of new areas or to a divergence in the functional

specialization (Orban, Van Essen, & Vanduffel, 2004).

Nevertheless, studies in monkeys contribute substantially to the understanding of sensorimotor control since the investigation of visuomotor brain areas for hand and arm movements in humans is especially challenging due to several technical limitations (see section 2.1). In the following, candidate regions for effector-specific modules will be discussed for monkeys and humans.

Neurophysiological research has shown that the lateral intraparietal area (LIP) is involved in the planning of *eye movements* to memorized visual (Gnadt & Andersen, 1988) and auditory (Mazzoni, Bracewell, Barash, & Andersen, 1996; Stricanne, Andersen, & Mazzoni, 1996) targets. A fMRI study investigating monkeys and humans verified the role of LIP for saccades in monkeys and indicated the posterior SPL as a human homologue (Koyama et al., 2004).

Neurons located in the anterior part of the intraparietal sulcus (AIP) showed a high selectivity for the manipulation of specific visual (Sakata, Taira, Murata, & Mine, 1995) and memorized (Murata, Gallese, Kaseda, & Sakata, 1996) objects. The importance of this area for *grasping movements* was confirmed by deficits in hand shaping following its inactivation (Gallese, Murata, Kaseda, & Niki, 1994). A subset of AIP neurons responded either preferentially during object manipulation independent of lighting conditions (motor-dominant neurons), during object manipulation in the light and fixation in the light (visual- and motor- dominant neurons) or during fixation in the light but not in the dark (visual-dominant neurons) (Sakata et al., 1995). The ventral premotor area (PMv) that is connected to AIP (Luppino, Murata, Govoni, & Matelli, 1999; Tanné-Gariépy, Rouiller, & Boussaoud, 2002) seems to be similarly effector specific. Increased activation in neurons in the PMv is associated with grasping (Kurata & Tanji, 1986; Raos, Umiltá, Murata, Fogassi, & Gallese, 2006), and inactivation of PMv resulted in grasping deficits (Fogassi et al., 2001b).

The anterior part of the intraparietal sulcus (aIPS) has been suggested as a human homologue of the AIP (Culham et al., 2006) since it is activated during grasping with (Culham et al., 2003; Frey et al., 2005) and without visual feedback (Binkofski et al., 1999) as well as during vision without grasping (Singhal, Monaco, Kaufman, & Culham, 2013). This finding is supported by further functional similarities between monkeys and humans like crossmodal processing (Grefkes et al., 2002). To investigate the causal role of aIPS in goal directed actions, patients with parietal lesions including and excluding the aIPS were investigated in a reach-to-grasp task

(Binkofski et al., 1998). Kinematic analysis indicated a selective impairment in grasping in the patient group whose brain damage included aIPS.

Besides areas that are suggested to be specialized for saccades or grasping, further effector-specific areas have been proposed. The parietal reach region (PRR) is commonly described as comprising the medial intraparietal area (MIP) and the dorsal part of the V6A (Snyder, Batista, & Andersen, 2000), which are strongly connected (Gamberini et al., 2009), and sometimes additionally includes 7A (Andersen & Buneo, 2002). Neurons in V6A respond to visual and somatosensory stimulation (Galletti, Fattori, Battaglini, Shipp, & Zeki, 1996; Galletti, Fattori, Kutz, & Battaglini, 1997), but are also activated during the planning and execution phase of visually guided *reaching movements* without visual feedback of the hand (Fattori, Gamberini, Kutz, & Galletti, 2001). These features make area V6A a candidate region for goal-directed actions (Galletti, Kutz, Gamberini, Breveglieri, & Fattori, 2003). Indeed, misreaching can be induced by a bilateral ablation of this area (Battaglini et al., 2002). Interestingly, inactivation of other subdivision of the PRR (area MIP and/or area 5) led to selective misreaching to peripheral targets but did not impair saccades, a pattern that is typically observed in optic ataxia (OA) patients (Hwang, Hauschild, Wilke, & Andersen, 2012) suffering from a lesion in the PPC (Perenin & Vighetto, 1988) (for more details, see section 2.2 Optic ataxia). The relevant anatomical structures for OA in humans were narrowed down to the occipito-parietal junction (POJ), the junction between occipital cortex and the SPL, and the precuneus using the lesion subtraction method that compared a group of OA patients to a control group with brain damage but without OA (Karnath & Perenin, 2005). In line with this, the medial intraparietal sulcus (mIPS) was reported to show increased activation in healthy participants for reaching to central and peripheral targets while POJ was additionally activated during reaching specifically to peripheral targets (Prado et al., 2005). However, a direct comparison between reaching to visible targets in central view and peripheral view was not conducted. Recently, this direct comparison revealed a combined network of POJ, mIPS and posterior SPL spreading to POJ as key areas for reaching in the periphery (Martin, Karnath, & Himmelbach, 2015) and thus confirmed the network that was previously indicated by lesion analysis (Karnath & Perenin, 2005). A part of this network, area mIPS, has been suggested to be the human homologue of the monkey MIP. This proposal was made on the grounds of its involvement of visuomotor transformations for goal-directed actions (Grefkes & Fink,

2005; Grefkes et al., 2004). In contrast, mIPS has also been suggested to correspond to PRR (DeSouza et al., 2000). The parieto-occipital sulcus and its vicinity have been proposed as a human homologue of V6A based on retinotopic mappings and activation during memory-guided pointing movements (Pitzalis et al., 2013; Pitzalis, Fattori, & Galletti, 2015). Based on the similar consequences of lesions in monkey and human V6A, Galletti et al. (2003) have argued for a strict homology between of both species.

While these studies argue for a modular view of the parietal cortex in monkeys and humans, recent findings question the view of strong effector specificity. V6A is part of the parietal reach region, but single-cell recordings in monkeys revealed that its activity is additionally modulated by wrist orientations (Fattori et al., 2009) and different grip types (Fattori et al., 2010a), leading the authors to propose that V6A is involved in both reaching and grasping. In line with this, bilateral ablation of this area causes not only misreaching but also misgrasping and affects wrist orientation (Battaglini et al., 2002). An fMRI adaption study in humans confirmed the involvement of the parieto-occipital area in hand orientation for grasping (Monaco et al., 2011) while another fMRI study in humans using region of interest and voxel-wise analyses was not able to detect grasp-related activation in the parieto-occipital region (Cavina-Pratesi, Monaco, et al., 2010). Further evidence for an involvement of the parieto-occipital cortex also in grasping comes from a study showing that brain activation during the planning phase predicts the upcoming grasping movement (Gallivan et al., 2011).

The view of a strong effector-specificity has not only been challenged for parieto-occipital regions, but also for aIPS (Tunik et al., 2005), which was assumed to be highly specialized for grasping. It has been shown, however, that the application of TMS shortly after movement onset over aIPS, but not over V6A, led to impairments in the adjustment of forearm rotation besides the grip component, leading the authors to propose that the aIPS is responsible for goal-directed actions independent of the effector. The finding of a more general role of the aIPS in online control was strengthened by findings showing that TMS over aIPS affects reaching accuracies (Reichenbach et al., 2011). Moreover, pointing with the hand or the foot yielded similar fMRI activity during the planning phase but differed from eye movements (Heed, Beurze, Toni, Röder, & Medendorp, 2011), shifting the focus further away from an effector specific organization of the PPC.

Consequently, an alternative view of functional organization of the human PPC has emerged that argues against a strict effector specificity but rather suggest gradients of sensory and effector preference (Bernier & Grafton, 2010; Beurze et al., 2007, 2009). Beurze et al. (2009) used a paradigm in which participants sequentially received information about the target (left or right) and the effector (hand or eye). After all relevant information was provided, a delay of 1-5 seconds was introduced before participants were instructed to move their effector to the remembered target location. When only the effector information was available, no areas besides the POS showed effector specificity. As soon as information about the target location became available, the parietofrontal network displayed strong effector specificity for hand movement planning including areas aIPS, M1 and PMd besides others. In contrast, during the movement execution phase, only M1 and POS showed a preference for reaches and saccades, respectively, but no other parietal region. The authors conclude that the effector specificity is not a fixed property of a brain region, but a time-varying characteristic (Beurze et al., 2009). Importantly, while this findings indicate gradients of effector preference during memory-guided movements, they do not provide insight into the effector specificity during visually-guided reaching that is supposed to rely on different neuronal correlates (Goodale & Milner, 1992; Milner & Goodale, 2008) (for more details, see section 2.3).

To investigate specifically the effector specificity during visually-guided reaching, we separated the planning and the execution phase using a perturbation paradigm. Inside the fMRI, participants conducted reach-to-grasp movements to a target that either changed its location, size, or both (see manuscript Cornelsen, Himmelbach, Thielscher (section 3.4): ‘Material and Methods’) Further, reach perturbations and grasp perturbations were matched in the required online control to avoid a modulation of the brain activity by task difficulty and/or required amount of online control. This also allowed us to investigate the lateralization of online control in reaching and grasping. The substantial recruitment of ipsilateral structures argues for their important role during the execution phase of visually-guided movements and argues against a strict lateralization in this phase. Moreover, grip size corrections were associated with increased coupling not only across hemispheres, but also within the ipsilateral hemisphere without corresponding increases in activation in the contralateral hemisphere. This argues against a pure co-activation of the ipsilateral hemisphere but rather indicates a functional role of the ipsilateral hemisphere.

Regarding the effector specificity, connectivity analysis showed no changes in inter-regional coupling between perturbed reaching and perturbed grasping. In contrast, grip perturbations were associated with changes of inter-regional coupling between the reaching and grasping network including the coupling between aIPS and SPOC, aIPS and mIPS, and aIPS and PMd. These findings argue against a strong effector specificity during the execution phase and are in agreement with studies in monkeys (Fattori et al., 2010b) and humans (Cavina-Pratesi, Monaco, et al., 2010; Reichenbach et al., 2011).

2.2 Optic ataxia

Considering the important role of the PPC in sensorimotor control, it is not surprising that damage to the PPC compromises goal directed actions. In 1909, bilateral damage to the occipital-parietal cortex was reported to result in Balint's syndrome, consisting of simultanagnosia, ocular apraxia, and optic ataxia (OA) with the latter symptom referring to inaccuracies in visually-guided reaching (Bálint, 1909). Over time, isolated cases of OA were described after unilateral parietal damage mainly affecting the superior parietal lobule (SPL) and the intraparietal sulcus (IPS) (Perenin & Vighetto, 1988). With the advent of new imaging methods, the lesion location could be pinpointed to the occipito-parietal junction as well as the junction between occipital cortex and the SPL in both hemispheres as key regions (Karnath & Perenin, 2005). In line with the involvement of the occipito-parietal junction in reaching, grasping, and wrist orientation, behavioral deficits in OA are not limited to reaching, but also include disturbances in prehension kinematics (Jakobson, Archibald, & Carey, 1991), grip formation (Jeannerod, 1986; Jeannerod, Decety, & Michel, 1994), hand orientation (Perenin & Vighetto, 1988), and stepping with the lower limb (Evans, Milner, Humphreys, & Cavina-Pratesi, 2013). It has been argued, however, that grasping is impaired as a secondary effect of the misreaching in order to compensate for the reaching inaccuracies (Cavina-Pratesi, Ietswaart, Humphreys, Lestou, & Milner, 2010).

OA is often defined as misreaching to visual targets that cannot be attributed to primary motor or sensory deficits, but to a visuomotor deficit. This definition, however, neglects that the majority of OA patients are unimpaired when reaching to foveated targets (Jackson et al., 2009), but demonstrate a so called 'magnetic misreaching' to extrafoveal targets. This term refers to the observation that OA

patients are unable to decouple the reach direction from the gaze direction (Jackson, Newport, Mort, & Husain, 2005) as indicated by reach endpoints that seem to be 'magnetically' attracted by the gaze position (Carey, Coleman, & Della Sala, 1997). Therefore, the resulting end point deviation increases with increasing target eccentricity (Blangero et al., 2010; Carey et al., 1997; Milner, Dijkerman, McIntosh, Rossetti, & Pisella, 2003; Milner, Paulignan, Dijkerman, Michel, & Jeannerod, 1999; Revol, Rossetti, Vighetto, & Rode, 2003). In addition to the effect of eccentricity, hand and field effects are characteristic for OA. Patients display stronger misreaching in their contralesional visual field (field effect) with their contralesional hand (hand effect). In their influential study, Perenin and Vighetto (1988) proposed that patients with a lesion of the right hemisphere predominantly show a field effect whereas patients with a lesion of the left hemisphere usually demonstrate a hand effect (Perenin & Vighetto, 1988).

Besides the classic interpretation of optic ataxia as a visuomotor deficit, another theoretical approach explains the behavioral deficits with an impairment in online control (Pisella et al., 2000). This suggestion derived from observations in OA patient IG who suffered from bilateral widespread lesions in the parietato-occipital cortex. In contrast to healthy participants, IG was not able to conduct fast corrective movements in response to target jumps after movement onset while her ability for slow movement corrections remained intact, indicating that parietal damage affects the online control of movements, but not the planning phase. This idea was further supported by the observation of the same group that the same patient responded to targets jumps by first moving to the initial target position and only afterwards to the final target position instead of smoothly adapting her movement path (Gréa et al., 2002). The authors propose that a general impaired online control mechanism causing OA is able to account for the specific deficit pattern for reaches to foveated and non-foveated targets, because higher online control is required for reaches based on imprecise extrafoveal visual information compared to reaches to targets in central vision (Pisella et al., 2000). The hypothesis of a general deficit in online control as underlying mechanism of optic ataxia has been challenged by observations of impaired online control during reaching (Pisella et al., 2000) but not during grasping (Himmelbach, Karnath, Perenin, Franz, & Stockmeier, 2006) in the same patient that rather indicate the existence of distinct neuronal correlates of

online control for reaching and grasping that can be affected in isolation (see section 2.3.1).

Both theoretical approaches of OA, i.e. the visuomotor deficit theory as well as the online control deficit theory, focus on impairments in visually guided actions. It has been shown, however, that reaching errors without visual feedback of the pointing hand increased in comparison with reaching under visual feedback for the contralesional hand, but not for the ipsilesional hand (Blangero et al., 2007). This observation of a hand effect that depends on the required level of proprioceptive integration suggests according to the authors that not only visuomotor integration, but also the integration of proprioceptive information is impaired in OA patients. They investigated this in two OA patients without any primary proprioceptive deficits, who pointed with their contralesional hand to their extrafoveal ipsilesional hand and vice versa. Both patients showed stronger misreaching in the contralesional than in the ipsilesional field, thus demonstrating the field effect that is characteristic of OA in visually-guided reaching. Another typical behavioral pattern of OA, namely the dissociation between reaches to foveated and nonfoveated targets, has been demonstrated in a OA patient reaching to visual and proprioceptive targets, but was unfortunately not compared to the reaching behavior of healthy controls (Jackson et al., 2009). While these findings may be interpreted as ‘proprioceptive’ ataxia, it has to be mentioned that similar findings have been observed in stroke patients without concurrent OA. For example, misreaching to proprioceptive targets has been reported in a patient with a small lesions in the primary somatosensory cortex (Borchers et al., 2011), and the modulation of misreaching to proprioceptive targets by the amount of visual input has been observed in a patient with thalamic stroke (Newport, Hindle, & Jackson, 2001). Therefore, damage to brain areas that are not related to OA can cause proprioceptive misreaching that bears some similarities to OA. The recent observation that field effects can be reliably observed whereas hand effects occur only in some OA patients (Blangero et al., 2010) suggests that hand effects may depend on additional damage to neighboring cortical damage or damage to thalamocortical connections. This hypothesis is in agreement with selective impairments in monkeys after the removal of parts of the PRR and neighboring areas (Rushworth, Nixon, & Passingham, 1997). Bilateral removal of area 7A, 7Ab and LIP caused misreaching to visual targets but left reaching in the dark unaffected. In contrast, the removal of MIP, area 5 and 7B caused misreaching in the dark that

relies on proprioceptive feedback. Thus, in monkeys, unilateral lesions in the above mentioned areas together might result in misreaching similar to OA with a hand effect. Although other candidate regions for optic ataxia in monkeys, like V6A (Battaglini et al., 2002), are under discussion, this does not object the hypothesis that additional damage to areas beside the 'optic ataxia region' might lead to misreaching resembling a hand effect.

Even less is known about auditory guided reaching in OA. Two studies only report qualitative data (Perenin & Vighetto, 1988; Tzavaras & Masure, 1976). A third study investigated a patient suffering from Balint's syndrome due to a bilateral glioma. The patient displayed strongest misreaching to auditory targets with the contralateral hand in the contralateral hemifield that seemingly supports an 'auditory' ataxia. Importantly, in contrast to visually-guided reaching in this patient, misreaching to auditory targets was reported when the patient was allowed to foveate the targets (Guard et al., 1984), thus arguing against an 'auditory' ataxia. Taken together, the existence of a 'multimodal' ataxia so far remains an open question.

We addressed this issue by investigating reaching to visual, auditory and proprioceptive targets in two chronic OA patients (see section 3.3). In a first step, we compared the patients' reaches to foveated targets with reaching to non-foveated targets to the corresponding difference in healthy participants. This comparison was calculated separately for each modality. Next, we directly compared reaching to visual targets with reaching to auditory and proprioceptive targets, respectively. For this, we analyzed the patients' difference between foveated and non-foveated reaches to auditory and visual targets with each other. The same comparison was conducted between proprioceptive and visually guided reaching. Finally, we investigated the presence of a field effect. All comparisons focused on the most peripheral target since stronger effects of OA have been reported for higher eccentricities (Blangero et al., 2010; Carey et al., 1997; Milner et al., 2003, 1999; Revol et al., 2003). Thus, the most peripheral targets represent a critical test case. Averaging effects for these targets together with less eccentric targets would reduce the sensitivity of our experiments either because of smaller, averaged effect sizes or through necessary corrections for multiple comparisons between modalities. While other studies investigating OA with one or two patients and a rather small control sample but used either analysis of variance, chi-square tests or other nonparametric tests within single-subjects (Blangero et al., 2008; Blangero et al., 2007; Gréa et al.,

2002; Jackson et al., 2009), we calculated all comparisons using a standardized difference test for single case dissociations (Crawford & Garthwaite, 2005b). This method offers several advantages. First, it requires a significant difference between both tasks to conclude a dissociation instead of claiming a dissociation by demonstrating that a patient is significantly impaired in one task but not in the other which is insufficient (Nieuwenhuis, Forstmann, & Wagenmakers, 2011). Second, this method leads to less misclassifications of patients with equivalent deficits as showing a dissociation. Simulations showed that depending on the sample size, such misclassification can occur in up to almost 50% for conventional methods whereas the Crawford statistics cause misclassification in only up to 7% (Crawford & Garthwaite, 2005a). The standardized difference test for single case dissociations confirmed for both patients, as expected, impaired reaching to extrafoveal targets in comparison to foveated targets as well as a field effect when reaching to visual targets. For auditory guided reaching, both patients' performance clearly dissociated from reaching to visual targets. This strongly suggests that optic ataxia does not affect the auditory modality. For proprioceptive guided reaching, patient IT's performance was unimpaired. In contrast, HM accuracy decreased for nonfoveated targets in comparison to foveated targets. Importantly, the dissociation between foveated and nonfoveated targets was not strongest for the most peripheral target as would be expected in analogy to optic ataxia. Instead, HM showed a dissociation between proprioceptive guided reaching and optic ataxia for the whole hemifield. Taken together, our findings argue against a multimodality of optic ataxia but show that spatial errors in other modalities resembling optic ataxia can co-occur.

2.3 VISUAL FORM AGNOSIA

At least two forms of agnosia can be distinguished: apperceptive and associative agnosia. In both cases, patients have difficulties with the recognition of objects but for different reasons. Patients with associative agnosia can perceive the object but have difficulties during the semantic phase of object recognition. In contrast, perception is impaired in apperceptive agnosia. The most severe form of apperceptive agnosia is called Visual Form Anosia (VFA) and refers to an isolated deficit in conscious perceptual judgments after occipito-temporal damage that leaves visuomotor guidance of actions unaffected (Milner et al., 1991). This definition mainly relies on the observation of ventral stream patient DF who suffered from VFA after a carbon-

monoxide intoxication. She successfully oriented her hand according to a slot in a disc and was also able to post a card into the slot with the correct orientation while she demonstrated substantial deficits when asked to verbally indicate the position or to match the orientation of a slot in another disc accordingly (Milner et al., 1991). Her preserved visuo-motor abilities decreased, however, when the target was not visible anymore at the time of movement initiation (Goodale, Jakobson, & Keillor, 1994; Milner, Dijkerman, & Carey, 1999).

Unfortunately, DF's case did not allow a clear assignment between structure and function since the intoxication led to diffuse and widespread loss of neuronal tissue. The intoxication caused extensive lesions bilaterally that were predominantly located in ventrolateral areas with most substantial loss in the lateral occipital cortex (LOC), but also affected her dorsal stream (Bridge et al., 2013; James, Culham, Humphrey, Milner, & Goodale, 2003; Milner et al., 1991). Moreover, most reported cases of VFA were caused by intoxication and thus suffered from diffuse and widespread degeneration of grey and white matter (Karnath, Rüter, Mandler, & Himmelbach, 2009). Recently, the observation of impaired perception but largely preserved visuo-motor functions in a stroke patient with focal bilateral lesions in the fusiform and lingual gyri as well as the cingulate gyrus confirmed the pivotal role of the ventral stream in perception, but suggested that the ventromedial aspects of the ventral stream are crucial for perception (Karnath et al., 2009). Our recent group study of stroke patients with focal ventral stream lesions further specified the functional architecture of the ventral streams, revealing an isolated deficit in contralateral object processing after unilateral stroke (hemiagnosia) (Rennig, Himmelbach, Cornelsen, Wilhelm, Karnath, 2015).

While the role of the ventral stream in VFA gets more and more specified, the anatomy and exact role of the ventral stream in memory-guided actions remains to be elucidated. For instance, neither the deficits in memory-guided actions have been replicated so far with a focal ventral stream patient suffering from VFA nor with a ventral stream patient without VFA. Consequently, it is not known whether the deficits can be replicated or whether they are caused by a perceptual deficit associated with VFA (see section 2.4.2).

2.4 THE TWO VISUAL STREAM HYPOTHESES

The two visual stream hypothesis (TVSH) postulates that visual information is processed in different cortical systems depending on its purpose (Goodale & Milner, 1992; Milner & Goodale, 2008). As stated by the authors themselves, the TVSH "was inspired by, and to some extent depends on, a set of partial or complete double dissociations" between dorsal stream patients suffering from OA and ventral stream patients suffering from VFA (Milner & Goodale, 2008, p. 781). While OA affects visuomotor action but not perception after parietal damage, VFA results in the opposite pattern. Therefore, the TVSH supposes that the dorsal (occipito-parietal) stream processes visual information that is relevant for the interaction with objects while the ventral (occipito-temporal) stream processes visual information for perception.

2.4.1 THE DOUBLE DISSOCIATION BETWEEN ACTION AND PERCEPTION

According to the authors, visual information processing for action and perception needs to fulfill fundamentally different requirements. Typically, reach-to-grasp movements are not isolated events, but coincide with movements of either the target, the agent, or both, resulting in different egocentric coordinates at every instance. To successfully interact with the target, the dorsal stream computes its spatial location and shape in relation to the effector for every moment anew. These perceptual representations are not maintained for targets that are no longer visible.

In contrast, the role of the ventral stream is to represent the constant features of a target independent of the agent's position. Additionally, it processes the spatial relationships between the target and other objects in an allocentric or scene-based reference frame. The authors conclude that the representations of the ventral stream are available for an unlimited amount of time to enable their recognition based on previous experience.

According to the TVSH, the ventral stream additionally contributes to action, but its role differs substantially from that of the dorsal stream. While the ventral stream represents targets and allows to abstractly plan the interaction with it, the dorsal stream programs the distinct movements that are necessary to interact with the objects and to control the movement in real-time. The required computations are not based on the object representation form the ventral stream, but are calculated independently. Thus, both streams contribute to action and process information

about the object features and its spatial location, but differ substantially in their processing and computations (Milner & Goodale, 2008).

Initially, the TVSH's assumption of a double dissociation between perception and action were mainly based on VFA patient DF who suffered from diffuse brain damage including bilateral lesions in the ventral and dorsal stream (Bridge et al., 2013; James, Culham, Humphrey, Milner, & Goodale, 2003; Milner et al., 1991). Although her case inspired the TVSH and is undoubtedly of high value for the understanding of visual information processing, it does not allow for a clear mapping between function and brain anatomy. By now, a dissociation between action and perception was replicated in a patient with circumscribed bilateral ventral stream lesions caused by a stroke that allowed for a clear association of function and the lesion site (Karnath, Rüter, Mandler, & Himmelbach, 2009). Further evidence for the importance of the ventral stream in perception comes from imaging studies in humans (Cavina-Pratesi, Goodale, & Culham, 2007; Grill-Spector et al., 1999; Malach et al., 1995; Valyear, Culham, Sharif, Westwood, & Goodale, 2006). Additionally, there is ample evidence for the well-established role of the dorsal stream in goal directed actions from behavioral investigations in healthy and brain damaged humans (Jeannerod, 1986), from imaging studies (Culham et al., 2003; Frey et al., 2005; Rice, Tunik, Cross, & Grafton, 2007), and from studies using transcranial magnetic stimulation (TMS) (Desmurget et al., 1999; Tunik et al., 2005). Support for distinct processing preferences of both streams for perception and visually-guided action, respectively, comes from an imaging study that investigated dorsal and ventral stream areas during passive viewing, visually-guided action, and perception, using identical stimuli but different instructions. While both streams were active during passive viewing of objects, dorsal and ventral stream activation was differently modulated by the task: AIP activation was modulated by different actions while LOC activation was modulated by perceptual tasks (Cavina-Pratesi et al., 2007).

Further support for action-perception dissociation seemed to be coming from studies in healthy participants, which compared the effect of visual illusions on perception and action. A number of studies observed an influence of the illusion on perceptional estimates, but not on the associated action (Aglioti, DeSouza, & Goodale, 1995; Ganel, Tanzer, & Goodale, 2008; Ganel, Chajut, & Algom, 2008). However, it has been pointed out recently that some of the investigations suffered from crucial methodological shortcomings (Franz, 2001) and the implications for the TVSH are

still under discussion (Bruno, 2001; Carey, 2001; Franz, 2001; Schenk, Franz, & Bruno, 2011).

While numerous studies support the different functional roles of both streams, some studies indicated a less strict separation. For instance, investigating healthy participants with fMRI, the representation of object information in the dorsal stream was observed that seem to be similar to the representation in the ventral stream (Konen & Kastner, 2008). In line with this, perceptual deficits have been reported in an optic ataxia patient after a dorsal stream lesion (McIntosh, Mulroue, Blangero, Pisella, & Rossetti, 2011; Pisella et al., 2009). Further evidence for a less strict functional separation comes from the observation of slight but significant visuomotor impairments of ventral stream patients JS (Karnath et al., 2009) as well as of DF as indicated by a reanalysis of her performance with a larger control group (Himmelbach, Boehme, & Karnath, 2012).

Further doubt has been raised on the TSVH proposition that the implementation of specific kinematic parameters is largely independent of the recognition of the object (Milner & Goodale, 2008) since the familiarity of an object has been demonstrated to affect grip scaling (Borchers & Himmelbach, 2012). In this study, familiar objects that were associated with a particular size lead to a higher sensitivity to physical object size changes in comparison to meaningless cuboids with identical physical dimensions.

Going one step further, Schenk (2006) suggested that the dissociation between action and perception is not only less strict than assumed, but has to be reformulated into a dissociation between allocentric and egocentric processing. He observed that patient DF's performance in visuomotor and perceptual tasks was preserved when visual information was encoded in relationship to her own hand, but not when it was encoded in relation to an object.

Finally, the double dissociation between action and perception in OA and VFA has been also questioned since optic ataxia was mainly observed in the peripheral visual field whereas ventral stream deficits were usually investigated in central view and thus do not allow a direct comparison (Pisella, Binkofski, Lasek, Toni, & Rossetti, 2006; Rossetti, Pisella, & Vighetto, 2003).

Taken together, the double dissociation between action and perception is still under debate as is the double dissociations between OA and VFA.

2.4.2 THE DOUBLE DISSOCIATION BETWEEN VISUALLY- AND MEMORY- GUIDED ACTIONS

Besides the suggested double dissociation between action and perception, the TVSH also postulates a temporal double dissociation between both streams since it assumes that the visual information in the dorsal stream decays rapidly while the representations of the ventral stream are available for a considerable amount of time (Milner & Goodale, 2008). Therefore, the authors argue that whenever there is a delay between the visibility of the target and the initiation of the movement, the dorsal stream cannot use bottom-up visual information about the target to compute the required motor commands. In this case, information about the object will be derived from memory, thus relying on the object representation of the ventral stream. The assumption so far heavily relies on the observation of a single patient. DF's motor performance was comparable to healthy participants when the target was visible during the action execution, but her grasping was significantly impaired when she was asked to pantomime a grasp to an object in central view that was no longer visible (Goodale, Jakobson, & Keillor, 1994). Additionally, her reaching to targets in the periphery was less accurate if a delay between target presentation and movement initiation was introduced but not if the target was visible during movement execution, leading the authors to conclude that the ventral stream is crucial for memory-guided actions (Milner, Dijkerman, & Carey, 1999). In the same year, an OA patient demonstrated the opposite pattern. In contrast to healthy controls who typically show a mild decrease in performance when reaching to memorized targets compared to visible targets, the OA patient showed a relative increase in performance for memory-guided reaches in the periphery (Milner et al., 1999). The authors suggest that OA patients who are compromised in visually guided action improve after a delay since their unimpaired ventral stream is under these conditions exploited for this task and contributes allocentric information (Milner et al., 1999). This assumption is supported by a psychophysical study in healthy participants that investigating the differential threshold (JND, just noticeable difference) in a perceptual, in an immediate, and in a delayed visuomotor task. As predicted by Weber's law, the JND increased with the size of the object in the perceptual task but not in the immediate visuomotor task. The authors interpret this as a reflection of the different processing mechanisms underlying perception and action. Confirming the assumption that memory-guided actions rely on ventral stream representations, no

violation of Weber's law were observed in the memory-guided visuomotor task (Ganel, Chajut, & Algom, 2008; but see Schenk, Franz, & Bruno, 2011).
Further support for the role of the ventral stream during memory-guided actions comes from an fMRI study that revealed a re-activation of the ventral stream area LOC in the absence of visual input when contrasting memory-guided grasping with memory-guided reaching (Singhal et al., 2013). The authors suggested that LOC might become re-activated for the retrieval of detailed information about the target, especially since the grasping component was isolated. In contrast, another fMRI study investigating reach-to-grasp movements did not observe LOC re-activation, suggesting that LOC re-activation might be specific for grasping, but not reaching (Fiehler et al., 2011). Indeed, multivoxel pattern analyses revealed that activation in the occipitotemporal cortex differs between reaching and grasping, and predicts whether a contralateral grasping or a reaching movement will be initiated subsequently (Gallivan, Chapman, Mclean, Flanagan, & Culham, 2013).
Interestingly, dorsal and ventral stream activation was observed during visually-guided and memory-guided movements in healthy controls and an OA patient (Himmelbach et al., 2009). While dorsal stream activation was indistinguishable between both kinds of movements for the intact brain areas of the patient, healthy participants showed additional increases in brain activation for visually guided movements compared to memory guided movements in both streams. This led the authors to conclude a crucial role of the dorsal stream not only in visually guided, but also in memory-guided movements. To distinguish between a mere co-activation and a causal involvement of both streams, Cohen and colleagues (2009) used transcranial magnetic stimulation (TMS) to induce a virtual lesions in dorsal and ventral stream areas (Cohen, Cross, Tunik, Grafton, & Culham, 2009). They applied TMS over aIPS and LOC during visually guided and memory guided grasping. As expected, TMS over aIPS affected grasping kinematics for visual targets. Further, a disruption of LOC processing influenced grasping kinematics for memorized targets, demonstrating its causal involvement. In contrast to the predictions of the TVSH, TMS also affected grasping kinematics of memory-guided movements when pulses were delivered over aIPS, revealing a causal involvement in memory-guided actions not only of the ventral stream, but also of the dorsal stream. This observation fits well with sustained dorsal stream activation for memory-guided actions in healthy humans (Connolly, Andersen, & Goodale, 2003; Fiehler et al., 2011; Lacquaniti et al., 1997;

Singhal et al., 2013), a patient suffering from OA (Himmelbach et al., 2009), and with monkey studies (Fattori et al., 2010a; Murata et al., 1996).

Considering the strong evidence for essential contributions of the dorsal stream in memory guided reaching, it is difficult to draw conclusions about the role of the ventral stream based on observations in DF who suffered from additional lesions in the dorsal streams. This point is especially important for the temporal double dissociation between both streams. While improved performance in memory-guided action was observed consistently in several OA patients for reaching (Himmelbach & Karnath, 2005; Himmelbach et al., 2009; Milner et al., 2003), grasping (Milner et al., 2003; Milner, Dijkerman, & Pisella, 2001), and obstacle avoidance (Rice et al., 2008), the report of decreased reaching accuracy to memorized targets relies exclusively on patient DF. This is particularly problematic for two reasons. First, a recent attempt failed to demonstrate an isolated reaching deficit to memorized targets. Whereas Millner and colleagues (1999) observed that DF's reaching was selectively impaired during memory-guided reaching, but not during visually guided reaching, Hesse and colleagues (2014) reported additional deficits during visually guided reaching. Whitwell and colleagues (Whitwell, Milner, & Goodale, 2014) speculated that DF's dorsal stream damage and the surrounding atrophy increased over time. While a potential broadening of the existing brain damage could explain her recent performance resembling OA, it is not possible to reliably decide whether her brain damage increased indeed due to a lack of high-resolution images of the initial lesion. Consequently, it is unclear whether her dorsal stream lesions only gained functional relevance with increasing age or had been already affecting her performance since her intoxication. More than ten years before the recently reported atrophy (Whitwell et al., 2014), robust activation in DF's dorsal stream was observed that was, however, predominantly ipsilesional (James et al., 2003). The observation of this functional abnormality indicates that her dorsal stream damage was already relevant at this time. Second, the only study so far investigating memory-guided reaching does not meet with current standards of single-cases analyses nowadays. Single cases statistics are essential for the comparison of a single patient to a group, especially if the control group is very small as was the case for DF with three control participants. Yet, they were not available at the time of the DF's investigation in 1999. A re-analysis of some of the investigations of DF using single case statistics and a

bigger control sample already revealed that impairments had been overlooked so far (Himmelbach et al., 2012).

To obtain unambiguous evidence about the role of the ventral stream in memory-guided reaching, we investigated a patient with a lesion in the right ventromedial occipitotemporal cortex, who suffered from a unilateral VFA (see section 3.2: "Memory-guided reaching in a patient with visual hemiagnosia"). In a first step, we aimed to replicate the findings of Milner and colleagues (1999). Participants had to reach to a visual 3D target that was located at one of six possible different eccentricities while foveating a central fixation light. Reaches had to be initiated either immediately with the illumination of the target or postponed until a visual signal prompted the movement initiation after five seconds. We compared patient HWS' memory-guided reaching with visual-guided reaching to the corresponding difference in healthy participants for each target individually using a standardized difference test for single case dissociations (Crawford & Garthwaite, 2005b). As predicted by the TVSH, HWS' reaching to visual targets was comparable to controls. In contrast, his reaching accuracy to memorized targets dissociated from those to visible targets for the most peripheral goal in the contralesional hemifield in comparison to healthy participants. This finding confirms the crucial role of the contralateral ventral stream in memory-guided actions, and facilitates a comparison with optic ataxia since different eccentricities were investigated.

Next, to investigate whether potential working memory deficits might account for isolated deficits during memory-guided reaching, we tested HWS in an established clinical memory test battery that includes several visual and spatial memory subtests as well as in the corsi block tapping test. The latter demonstrated impairments of working memory in patient DF (Milner et al., 1991) that are in agreement with her parietal and prefrontal damage since the parieto-prefrontal pathway supports spatial working memory (Kravitz, Saleem, Baker, & Mishkin, 2011) and short-term memory (Aben, Stapert, & Blokland, 2012). Although our patient had no dorsal or frontal damage, the lesion in his occipito-temporal cortex might affect reaching after a delay since this area is involved in the maintenance of spatial representations (Berman & Colby, 2002). The tests did not indicate any working memory or short-term memory deficit.

Finally, we conducted a delayed localization experiment whose purpose was twofold: First, we aimed at examining HWS' visual spatial memory in a task with close

resemblance to the reaching task as the clinical memory test was substantially different from the memory-guided reaching task. Second, the delayed localization task also aimed at the investigation of the nature of the contribution (i.e. perceptual or visuomotor) of the ventral stream to memory-guided reaching. DF's lesion mainly focused on the ventrolateral occipitotemporal cortex including LOC whose involvement in object recognition and causal role in memory-guided grasping is well established (Cohen et al., 2009; Malach et al., 1995). In contrast, the lesion of HWS affected the ventromedial occipitotemporal cortex including the lingual, parahippocampal and fusiform gyrus. These regions have been associated with object and environment representation (Epstein & Kanwisher, 1998; Haxby et al., 2001), and damage to the ventromedial aspect of the ventral stream has been shown to cause VFA in other patients (Barton, Cherkasova, Press, Intriligator, & O'Connor, 2004; Karnath et al., 2009). Besides its involvement in perception, the ventromedial stream also plays a role for visually-guided actions. Gallivan and colleagues (2013) were able to decode upcoming actions from activity at the parahippocampal gyrus for the contra- and ipsilateral hand. In line with this, patient JS with ventromedial brain damage as well as patient DF showed mild visuomotor impairments (Himmelbach et al., 2012; Karnath et al., 2009). Taken together, these findings suggest an important role not only for ventromedial but also for the ventrolateral pathway in the preparation of actions, but cannot answer the question about their temporal characteristics.
We addressed both issues in an experiment that showed a close resemblance with the memory-guided condition of the first experiment. Again, participants fixated centrally while a peripheral visual target was presented, and had to respond after a delay of five seconds. The crucial difference was the mode of response. Instead of reaching to the previous target locations, participants indicated the previous target location via button presses on a keyboard. While both tasks required the subject to memorize the target location and to reproduce it, the delayed localization task did not require any processes related to visuomotor transformations. We compared HWS' performance to those of age-matched participants using a test for single case deficits (Crawford & Howell, 1998). HWS' performance was comparable to those of age-matched participants for all eccentricities. Therefore, misreaching to memorized targets in the periphery cannot be explained by memory deficits, but can be clearly attributed to the HWS' lesion in the ventral stream. To our surprise, HWS' ventral stream damage did not affect accuracy in the second experiment when no

visuomotor transformations were required. This suggests that the observed deficit in memory-guided reaching caused by ventral stream damage is a deficit that is associated with visuomotor, but not purely perceptual, processing. For visually guided movements, mild impairments have been reported before in ventral stream patients (Himmelbach et al., 2012; Karnath et al., 2009). For memory-guided reaching, the present study is the first to disentangle the contribution of perceptual and visuomotor processes.

Our findings are in agreement with recent recordings of extracellular activity in the parahippocampal gyrus during a visuomotor task (Tankus & Fried, 2012). Using a joystick, patients had to reach towards a visual target with visual feedback of the hand on a screen (visuomotor task), observe the similar action on the screen without moving their hand (vision-only task), or to move their hand without vision of the hand (motor task). The observed parahippocampal gyrus activation was correlated to kinematic measurements (speed and/or direction of hand movement) mainly during the visuomotor task. One third of the parahippocampal cells whose activity was correlated with speed encoded kinematic measurements associated with hand movements while another third seemed to encode kinematic variables associated with either eye movements or the tracked object.

2.5 SUMMARY

The presented work investigated goal-directed actions. In a first fMRI study, we investigated the effector specificity and lateralization of visuo-motor control. To investigate the execution phase in isolation, a perturbation paradigm was employed that specifically increased the amount of online control but did not affect the planning phase. Moreover, special care was taken to match the difficulty of perturbed reaching and grasping movements to avoid differences in activation between these two actions based on different required levels of online control. The role of the ipsilateral frontoparietal network during the execution phase of visually-guided movements was stressed by the recruitment of several of its key regions and argues against a strict lateralization. The observed increased coupling, especially within the ipsilateral hemisphere without corresponding contralateral activation increases, indicates that the ipsilateral activation is not just a co-activation elicited by the contralateral hemisphere. Rather, it suggests that the ipsilateral PPC has a functional role visually-

guided actions. Further, we observed no effector specificity for perturbed reaching and grasping during the execution phase, but changes in inter-regional coupling between the reaching and grasping network during grip perturbations. To clarify whether the ipsilateral aIPS plays a causal role in visually-guided grasping, lesion studies with stroke patients are not well suited since the lesions size cannot be controlled but can modulate the lateralization (Fogassi et al., 2001a). One way to investigate this question is to induce a virtual lesion with TMS using a similar paradigm.

Next, we investigated reaching to visual, auditory and proprioceptive targets in two chronic OA patients. Both showed the expected deficits for reaching to extrafoveal targets in comparison to foveated targets as well as a field effect when reaching to visual targets. Importantly, reaching to auditory targets was markedly different from reaching to visual targets, suggesting that optic ataxia does not affect the auditory modality. For reaching to proprioceptive targets, the findings seem contradictory at first glance: while patient IT's performance was unimpaired, HM accuracy decreased for nonfoveated targets in comparison to foveated targets. Crucially, this dissociation was not strongest in the periphery like for the visual targets but present for the whole hemifield. This lead us to the conclusion that optic ataxia is not multimodal in nature, but can co-occur with spatial errors in other modalities resembling optic ataxia. This finding of a modality-specific effect together with previous findings showing that misreaching to visual targets in OA patients depends on gaze-centered coordinates (Khan et al., 2005) suggests that reaches to auditory and proprioceptive targets are not predominantly encoded in a gaze-centered coordinate frames.

In contrast to the essential role of the PPC in visually-guided reaching, little is known about the role of the ventral stream in memory-guided reaches. We investigated a VFA patient with a lesion in the right ventromedial occipitotemporal cortex in a reaching paradigm. In agreement with Milner and colleagues (1999), HWS' reaching to visual targets was comparable to controls, but his reaching accuracy to memorized targets dissociated from those to visible targets for the most peripheral goal in the contralesional hemifield. A clinical memory test battery examining visual and spatial memory excluded any working memory or short-term memory deficits that might have contributed to the observed memory-guided misreaching. This was further confirmed by a delayed localization. More importantly, this task contributed to the understanding of the role of the ventral stream in memory-guided reaching. It

revealed that the observed deficit in memory-guided reaching is associated with visuomotor, but not purely perceptual, processing. However, it is still unclear whether the observed reaching deficit is a consequence of the VFA, or simply coincides with VFA but is caused by damage to different brain areas.

2.6 REFERENCES

Aben, B., Stapert, S., & Blokland, A. (2012). About the Distinction between Working Memory and Short-Term Memory. *Frontiers in Psychology*, *3*(August), 1–9. http://doi.org/10.3389/fpsyg.2012.00301

Aglioti, S., DeSouza, J. F., & Goodale, M. A. (1995). Size-contrast illusions deceive the eye but not the hand. *Current Biology*, *5*(6), 679–685. http://doi.org/10.1016/S0960-9822(95)00133-3

Alain, C., Arnott, S. R., Hevenor, S., Graham, S., & Grady, C. L. (2001). "What" and "where" in the human auditory system. *Proceedings of the National Academy of Sciences*, *98*(21), 12301–12306. http://doi.org/10.1073/pnas.211209098\r211209098 [pii]

Andersen, R. A., & Buneo, C. A. (2002). Intentional maps in posterior parietal cortex. *Annual Review of Neuroscience*, *25*, 189–220. http://doi.org/10.1146/annurev.neuro.25.112701.142922

Bálint, R. (1909). Seelenlähmung des "Schauens", optische Ataxie, räumliche Störung der Aufmerksamkeit. *Monatsschrift Für Psychiatrie Und Neurologie*, *25*, 51–81.

Barton, J. J. S., Cherkasova, M. V, Press, D. Z., Intriligator, J. M., & O'Connor, M. (2004). Perceptual functions in prosopagnosia. *Perception*, *33*(8), 939–56. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15521693

Batista, A. P., Buneo, C. A., Snyder, L. H., & Andersen, R. A. (1999). Reach plans in eye-centered coordinates. *Science*, *285*(5425), 257–260. http://doi.org/10.1126/science.285.5425.257

Battaglia-Mayer, A., Ferrari-Toniolo, S., Visco-Comandini, F., Archambault, P. S., Saberi-Moghadam, S., & Caminiti, R. (2012). Impairment of online control of hand and eye movements in a monkey model of optic ataxia. *Cerebral Cortex*, 1–13. http://doi.org/10.1093/cercor/bhs250

Battaglini, P., Muzur, A., Galletti, C., Skrap, M., Brovelli, A., & Fattori, P. (2002). Effects of lesions to area V6A in monkeys. *Experimental Brain Research*, *144*(3), 419–422. http://doi.org/10.1007/s00221-002-1099-4

Berman, R. A., & Colby, C. L. (2002). Spatial working memory in human extrastriate cortex. *Physiology & Behavior*, *77*(4–5), 621–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12527009

Bernier, P.-M., & Grafton, S. T. (2010). Human posterior parietal cortex flexibly determines reference frames for reaching based on sensory context. *Neuron*, *68*(4), 776–88. http://doi.org/10.1016/j.neuron.2010.11.002

Bernier, P., Cieslak, M., & Grafton, S. T. (2012). Effector selection precedes reach planning in the dorsal parietofrontal cortex. *Journal of Neurophysiology*, *108*(March), 57–68. http://doi.org/10.1152/jn.00011.2012

Beurze, S. M., de Lange, F. P., Toni, I., & Medendorp, W. P. (2007). Integration of target and effector information in the human brain during reach planning. *Journal*

of Neurophysiology, *97*(1), 188–99. http://doi.org/10.1152/jn.00456.2006

Beurze, S. M., de Lange, F. P., Toni, I., & Medendorp, W. P. (2009). Spatial and effector processing in the human parietofrontal network for reaches and saccades. *Journal of Neurophysiology*, *101*(6), 3053–62. http://doi.org/10.1152/jn.91194.2008

Binkofski, F., Buccino, G., Stephan, K. M., Rizzolatti, G., Seitz, R. J., & Freund, H. J. (1999). A parieto-premotor network for object manipulation: evidence from neuroimaging. *Experimental Brain Research*, *128*(1–2), 210–3. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10473761

Binkofski, F., Dohle, C., Posse, S., Stephan, K. M., Hefter, H., Seitz, R. J., & Freund, H. J. (1998). Human anterior intraparietal area subserves prehension: a combined lesion and functional MRI activation study. *Neurology*, *50*(5), 1253–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9595971

Blangero, A., Gaveau, V., Luauté, J., Rode, G., Salemme, R., Guinard, M., … Pisella, L. (2008). A hand and a field effect in on-line motor control in unilateral optic ataxia. *Cortex*, *44*(5), 560–568. http://doi.org/10.1016/j.cortex.2007.09.004

Blangero, A., Menz, M. M., McNamara, A., & Binkofski, F. (2009). Parietal modules for reaching. *Neuropsychologia*, *47*(6), 1500–7. http://doi.org/10.1016/j.neuropsychologia.2008.11.030

Blangero, A., Ota, H., Delporte, L., Revol, P., Vindras, P., Rode, G., … Pisella, L. (2007). Optic ataxia is not only “optic”: impaired spatial integration of proprioceptive information. *NeuroImage*, *36 Suppl 2*, T61-8. http://doi.org/10.1016/j.neuroimage.2007.03.039

Blangero, A., Ota, H., Rossetti, Y., Fujii, T., Ohtake, H., Tabuchi, M., … Pisella, L. (2010). Systematic retinotopic reaching error vectors in unilateral optic ataxia. *Cortex*, *46*(1), 77–93. http://doi.org/10.1016/j.cortex.2009.02.015

Boll, T. J. (1974). Right and left cerebral hemisphere damage and tactile perception: performance of the ipsilateral and contralateral sides of the body. *Neuropsychologia*, *12*(2), 235–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/4842916

Borchers, S., Hauser, T.-K., & Himmelbach, M. (2011). Bilateral hand representations in human primary proprioceptive areas. *Neuropsychologia*, *49*(12), 3383–91. http://doi.org/10.1016/j.neuropsychologia.2011.08.013

Borchers, S., & Himmelbach, M. (2012). The recognition of everyday objects changes grasp scaling. *Vision Research*, *67*, 8–13. http://doi.org/10.1016/j.visres.2012.06.019

Bridge, H., Thomas, O. M., Minini, L., Cavina-Pratesi, C., Milner, A. D., & Parker, A. J. (2013). Structural and functional changes across the visual cortex of a patient with visual form agnosia. *Journal of Neuroscience*, *33*(31), 12779–91. http://doi.org/10.1523/JNEUROSCI.4853-12.2013

Bruno, N. (2001). When does action resist visual illusions? *Trends in Cognitive Sciences*, *5*(9), 379–382. http://doi.org/10.1016/S1364-6613(00)01772-1

Buneo, C. A., & Andersen, R. A. (2006). The posterior parietal cortex: Sensorimotor interface for the planning and online control of visually guided movements. *Neuropsychologia*, *44*(13), 2594–2606. http://doi.org/10.1016/j.neuropsychologia.2005.10.011

Buneo, C. A., Jarvis, M. R., Batista, A. P., & Andersen, R. A. (2002). Direct visuomotor transformations for reaching. *Nature*, *416*(6881), 632–6. http://doi.org/10.1038/416632a

Busan, P., Jarmolowska, J., Semenic, M., Monti, F., Pelamatti, G., Pizzolato, G., & Battaglini, P. P. (2009). Involvement of ipsilateral parieto-occipital cortex in the planning of reaching movements: evidence by TMS. *Neuroscience Letters*, *460*(2), 112–6. http://doi.org/10.1016/j.neulet.2009.05.028

Carey, D. P. (2001). Do action systems resist visual illusions? *Trends in Cognitive Sciences*, *5*(3), 109–113. http://doi.org/10.1016/S1364-6613(00)01592-8

Carey, D. P., Coleman, R. J., & Della Sala, S. (1997). Magnetic misreaching. *Cortex*, *33*(4), 639–652. http://doi.org/10.1016/S0010-9452(08)70722-6

Cavina-Pratesi, C., Goodale, M. a, & Culham, J. C. (2007). FMRI reveals a dissociation between grasping and perceiving the size of real 3D objects. *PloS One*, *2*(5), e424. http://doi.org/10.1371/journal.pone.0000424

Cavina-Pratesi, C., Ietswaart, M., Humphreys, G. W., Lestou, V., & Milner, A. D. (2010). Impaired grasping in a patient with optic ataxia: primary visuomotor deficit or secondary consequence of misreaching? *Neuropsychologia*, *48*(1), 226–34. http://doi.org/10.1016/j.neuropsychologia.2009.09.008

Cavina-Pratesi, C., Monaco, S., Fattori, P., Galletti, C., McAdam, T. D., Quinlan, D. J., … Culham, J. C. (2010). Functional magnetic resonance imaging reveals the neural substrates of arm transport and grip formation in reach-to-grasp actions in humans. *Journal of Neuroscience*, *30*(31), 10306–10323. http://doi.org/10.1523/JNEUROSCI.2023-10.2010

Cohen, N. R., Cross, E. S., Tunik, E., Grafton, S. T., & Culham, J. C. (2009). Ventral and dorsal stream contributions to the online control of immediate and delayed grasping: a TMS approach. *Neuropsychologia*, *47*(6), 1553–62. http://doi.org/10.1016/j.neuropsychologia.2008.12.034

Cohen, Y. E., & Andersen, R. A. (2002). A common reference frame for movement plans in the posterior parietal cortex. *Nature Reviews. Neuroscience*, *3*(7), 553–62. http://doi.org/10.1038/nrn873

Connolly, J. D., Andersen, R. A., & Goodale, M. A. (2003). FMRI evidence for a “parietal reach region” in the human brain. *Experimental Brain Research*, *153*(2003), 140–145. http://doi.org/10.1007/s00221-003-1587-1

Crawford, J. R., & Garthwaite, P. H. (2005a). Evaluation of criteria for classical dissociations in single-case studies by Monte Carlo simulation. *Neuropsychology*, *19*(5), 664–678. http://doi.org/10.1037/0894-4105.19.5.664

Crawford, J. R., & Garthwaite, P. H. (2005b). Testing for suspected impairments and dissociations in single-case studies in neuropsychology: evaluation of

alternatives using monte carlo simulations and revised tests for dissociations. *Neuropsychology*, *19*(3), 318–31. http://doi.org/10.1037/0894-4105.19.3.318

Crawford, J. R., & Howell, D. C. (1998). Comparing an Individual's Test Score Against Norms Derived from Small Samples. *Clinical Neuropsychologist*, *12*(4), 482–486. http://doi.org/10.1076/clin.12.4.482.7241

Culham, J. C., Cavina-Pratesi, C., & Singhal, A. (2006). The role of parietal cortex in visuomotor control: what have we learned from neuroimaging? *Neuropsychologia*, *44*(13), 2668–84. http://doi.org/10.1016/j.neuropsychologia.2005.11.003

Culham, J. C., Danckert, S. L., DeSouza, J. F. X., Gati, J. S., Menon, R. S., & Goodale, M. A. (2003). Visually guided grasping produces fMRI activation in dorsal but not ventral stream brain areas. *Experimental Brain Research*, *153*(2), 180–9. http://doi.org/10.1007/s00221-003-1591-5

Culham, J. C., & Kanwisher, N. G. (2001). Neuroimaging of cognitive functions in human parietal cortex. *Current Opinion in Neurobiology*, *11*(2), 157–63. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11301234

Davare, M., Andres, M., Clerget, E., Thonnard, J.-L., & Olivier, E. (2007). Temporal dissociation between hand shaping and grip force scaling in the anterior intraparietal area. *The Journal of Neuroscience*, *27*(15), 3974–80. http://doi.org/10.1523/JNEUROSCI.0426-07.2007

Desmurget, M., Epstein, C. M., Turner, R. S., Prablanc, C., Alexander, G. E., & Grafton, S. T. (1999). Role of the posterior parietal cortex in updating reaching movements to a visual target. *Nature Neuroscience*, *2*, 563–567. http://doi.org/10.1038/9219

Desmurget, M., Gréa, H., Grethe, J. S., Prablanc, C., Alexander, G. E., & Grafton, S. T. (2001). Functional anatomy of nonvisual feedback loops during reaching: a positron emission tomography study. *Journal of Neuroscience*, *21*(8), 2919–28. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11306644

DeSouza, J. F. X., Dukelow, S. P., Gati, J. S., Menon, R. S., Andersen, R. A., & Vilis, T. (2000). Eye position signal modulates a human parietal pointing region during memory-guided movements. *Journal of Neuroscience*, *20*(15), 5835–5840. http://doi.org/20/15/5835 [pii]

Epstein, R., & Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature*, *392*(6676), 598–601. http://doi.org/10.1038/33402

Evans, C., Milner, a. D., Humphreys, G. W., & Cavina-Pratesi, C. (2013). Optic ataxia affects the lower limbs: Evidence from a single case study. *Cortex*, *49*, 1229–1240. http://doi.org/10.1016/j.cortex.2012.07.008

Fabbri, S., Strnad, L., Caramazza, A., & Lingnau, A. (2014). Overlapping representations for grip type and reach direction. *NeuroImage*, *94*, 138–146. http://doi.org/10.1016/j.neuroimage.2014.03.017

Fattori, P., Breveglieri, R., Marzocchi, N., Filippini, D., Bosco, A., & Galletti, C. (2009). Hand orientation during reach-to-grasp movements modulates neuronal

activity in the medial posterior parietal area V6A. *Journal of Neuroscience*, *29*(6), 1928–36. http://doi.org/10.1523/JNEUROSCI.4998-08.2009

Fattori, P., Gamberini, M., Kutz, D. F., & Galletti, C. (2001). “Arm-reaching” neurons in the parietal area V6A of the macaque monkey. *European Journal of Neuroscience*, *13*(12), 2309–2313. http://doi.org/10.1046/j.0953-816X.2001.01618.x

Fattori, P., Raos, V., Breveglieri, R., Bosco, A., Marzocchi, N., & Galletti, C. (2010a). The dorsomedial pathway is not just for reaching: grasping neurons in the medial parieto-occipital cortex of the macaque monkey. *The Journal of Neuroscience*, *30*(1), 342–9. http://doi.org/10.1523/JNEUROSCI.3800-09.2010

Fattori, P., Raos, V., Breveglieri, R., Bosco, A., Marzocchi, N., & Galletti, C. (2010b). The dorsomedial pathway is not just for reaching: grasping neurons in the medial parieto-occipital cortex of the macaque monkey. *Journal of Neuroscience*, *30*(1), 342–349. http://doi.org/10.1523/JNEUROSCI.3800-09.2010

Fiehler, K., Bannert, M. M., Bischoff, M., Blecker, C., Stark, R., Vaitl, D., … Rösler, F. (2011). Working memory maintenance of grasp-target information in the human posterior parietal cortex. *NeuroImage*, *54*(3), 2401–11. http://doi.org/10.1016/j.neuroimage.2010.09.080

Filimon, F., Nelson, J. D., Huang, R.-S., & Sereno, M. I. (2009). Multiple parietal reach regions in humans: cortical representations for visual and proprioceptive feedback during on-line reaching. *The Journal of Neuroscience*, *29*(9), 2961–71. http://doi.org/10.1523/JNEUROSCI.3211-08.2009

Fogassi, L., Gallese, V., Buccino, G., Craighero, L., Fadiga, L., & Rizzolatti, G. (2001a). Cortical mechanism for the visual guidance of hand grasping movements in the monkey: A reversible inactivation study. *Brain : A Journal of Neurology*, *124*(Pt 3), 571–86. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11222457

Fogassi, L., Gallese, V., Buccino, G., Craighero, L., Fadiga, L., & Rizzolatti, G. (2001b). Cortical mechanism for the visual guidance of hand grasping movements in the monkey: A reversible inactivation study. *Brain : A Journal of Neurology*, *124*(Pt 3), 571–86.

Franz, V. H. (2001). Action does not resist visual illusions. *Trends in Cognitive Sciences*, *5*(11), 457–459.

Frey, S. H., Vinton, D., Norlund, R., & Grafton, S. T. (2005). Cortical topography of human anterior intraparietal cortex active during visually guided grasping. *Cognitive Brain Research*, *23*(2–3), 397–405. http://doi.org/10.1016/j.cogbrainres.2004.11.010

Gallese, V., Murata, A., Kaseda, M., & Niki, N. (1994). Deficit of hand preshaping after muscimol injection in monkey parietal cortex. *Neuroreport*, *5*, 1525–1529. Retrieved from http://psycnet.apa.org/psycinfo/1995-20636-001

Galletti, C., Fattori, P., Battaglini, P. P., Shipp, S., & Zeki, S. (1996). Functional demarcation of a border between areas V6 and V6A in the superior parietal gyrus of the macaque monkey. *The European Journal of Neuroscience*, *8*(1),

30–52. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8713448

Galletti, C., Fattori, P., Kutz, D. F., & Battaglini, P. P. (1997). Arm movement-related neurons in the visual area V6A of the macaque superior parietal lobule. *The European Journal of Neuroscience*, *9*(2), 410–3. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9058060

Galletti, C., Kutz, D. F., Gamberini, M., Breveglieri, R., & Fattori, P. (2003). Role of the medial parieto-occipital cortex in the control of reaching and grasping movements. *Experimental Brain Research*, *153*(2), 158–70. http://doi.org/10.1007/s00221-003-1589-z

Gallivan, J. P., Chapman, C. S., Mclean, D. A., Flanagan, J. R., & Culham, J. C. (2013). Activity patterns in the category-selective occipitotemporal cortex predict upcoming motor actions. *European Journal of Neuroscience*, *38*(3), 2408–2424. http://doi.org/10.1111/ejn.12215

Gallivan, J. P., McLean, D. A., Valyear, K. F., Pettypiece, C. E., & Culham, J. C. (2011). Decoding action intentions from preparatory brain activity in human parieto-frontal networks. *Journal of Neuroscience*, *31*(26), 9599–610. http://doi.org/10.1523/JNEUROSCI.0080-11.2011

Gamberini, M., Passarelli, L., Fattori, P., Zucchelli, M., Bakola, S., Luppino, G., & Galletti, C. (2009). Cortical connections of the visuomotor parietooccipital area V6Ad of the macaque monkey. *The Journal of Comparative Neurology*, *513*(6), 622–42. http://doi.org/10.1002/cne.21980

Ganel, T., Chajut, E., & Algom, D. (2008). Visual coding for action violates fundamental psychophysical principles. *Current Biology*, *18*, 599–601. http://doi.org/10.1016/j.cub.2008.04.052

Ganel, T., Tanzer, M., & Goodale, M. A. (2008). A double dissociation between action and perception in the context of visual illusions. *Psychological Science*, *19*(3), 221–225. http://doi.org/10.1111/j.1467-9280.2008.02071.x

Glover, S. (2004). Separate visual representations in the planning and control of action. *The Behavioral and Brain Sciences*, *27*(1), 3-24-78. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15481943

Glover, S., Miall, R. C., & Rushworth, M. F. S. (2005). Parietal rTMS disrupts the initiation but not the execution of on-line adjustments to a perturbation of object size. *Journal of Cognitive Neuroscience*, *17*(1), 124–136. http://doi.org/10.1162/0898929052880066

Glover, S., Wall, M. B., & Smith, A. T. (2012). Distinct cortical networks support the planning and online control of reaching-to-grasp in humans. *European Journal of Neuroscience*, *35*, 909–915. http://doi.org/10.1111/j.1460-9568.2012.08018.x

Gnadt, J. W., & Andersen, R. A. (1988). Memory related motor planning activity in posterior parietal cortex of macaque. *Experimental Brain Research*, *70*(1), 216–220. article. http://doi.org/10.1007/BF00271862

Goodale, M. A., Jakobson, L. S., & Keillor, J. M. (1994). Differences in the visual control of pantomimed and natural grasping movements. *Neuropsychologia*,

32(10), 1159–1178. http://doi.org/10.1016/0028-3932(94)90100-7

Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences*, *15*, 20–25. http://doi.org/10.1016/0166-2236(92)90344-8

Goodale, M. A., 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*(6064), 748–50. http://doi.org/10.1038/320748a0

Graziano, M. S., Yap, G. S., & Gross, C. G. (1994). Coding of visual space by premotor neurons. *Science (New York, N.Y.)*. http://doi.org/10.1126/science.7973661

Gréa, H., Pisella, L., Rossetti, Y., Desmurget, M., Tilikete, C., Grafton, S., … Vighetto, A. (2002). A lesion of the posterior parietal cortex disrupts on-line adjustments during aiming movements. *Neuropsychologia*, *40*(13), 2471–80. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12417474

Grefkes, C., & Fink, G. R. (2005). The functional organization of the intraparietal sulcus in humans and monkeys. *Journal of Anatomy*, *207*(1), 3–17. http://doi.org/10.1111/j.1469-7580.2005.00426.x

Grefkes, C., Ritzl, A., Zilles, K., & Fink, G. R. (2004). Human medial intraparietal cortex subserves visuomotor coordinate transformation. *NeuroImage*, *23*(4), 1494–506. http://doi.org/10.1016/j.neuroimage.2004.08.031

Grefkes, C., Weiss, P. H., Zilles, K., & Fink, G. R. (2002). Crossmodal processing of object features in human anterior intraparietal cortex: an fMRI study implies equivalencies between humans and monkeys. *Neuron*, *35*(1), 173–84. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12123617

Grill-Spector, K., Kushnir, T., Edelman, S., Avidan, G., Itzchak, Y., & Malach, R. (1999). Differential processing of objects under different viewing conditions in the human lateral occipital complex. *Neuron*, *24*(1), 187–203. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10677037

Guard, O., Perenin, M. T., Vighetto, A., Giroud, M., Tommasi, M., & Dumas, R. (1984). Syndrome pariétal bilatéral proche d'un Syndrome de Balient. *Revue Neurologique*, *140*(5), 358–367.

Haxby, J. V, Gobbini, M. I., Furey, M. L., Ishai, a, Schouten, J. L., & Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science*, *293*(5539), 2425–30. http://doi.org/10.1126/science.1063736

Heed, T., Beurze, S. M., Toni, I., Röder, B., & Medendorp, W. P. (2011). Functional rather than effector-specific organization of human posterior parietal cortex. *Journal of Neuroscience*, *31*(8), 3066–76. http://doi.org/10.1523/JNEUROSCI.4370-10.2011

Hesse, C., & Franz, V. H. (2010). Grasping remembered objects: exponential decay of the visual memory. *Vision Research*, *50*(24), 2642–50. http://doi.org/10.1016/j.visres.2010.07.026

Himmelbach, M., Boehme, R., & Karnath, H. O. (2012). 20 years later: A second look on DF's motor behaviour. *Neuropsychologia*, *50*(1), 139–144. http://doi.org/10.1016/j.neuropsychologia.2011.11.011

Himmelbach, M., & Karnath, H.-O. (2005). Dorsal and ventral stream interaction: contributions from optic ataxia. *Journal of Cognitive Neuroscience*, *17*, 632–640. http://doi.org/10.1162/0898929053467514

Himmelbach, M., Karnath, H.-O., Perenin, M.-T., Franz, V. H., & Stockmeier, K. (2006). A general deficit of the "automatic pilot" with posterior parietal cortex lesions? *Neuropsychologia*, *44*(13), 2749–56. http://doi.org/10.1016/j.neuropsychologia.2006.04.030

Himmelbach, M., Nau, M., Zündorf, I., Erb, M., Perenin, M. T., & Karnath, H. O. (2009). Brain activation during immediate and delayed reaching in optic ataxia. *Neuropsychologia*, *47*(2009), 1508–1517. http://doi.org/10.1016/j.neuropsychologia.2009.01.033

Hwang, E. J., Hauschild, M., Wilke, M., & Andersen, R. a. (2012). Inactivation of the parietal reach region causes optic ataxia, impairing reaches but not saccades. *Neuron*, *76*, 1021–1029. http://doi.org/10.1016/j.neuron.2012.10.030

Inoue, K., Kawashima, R., Satoh, K., Kinomura, S., Goto, R., Koyama, M., … Fukuda, H. (1998). PET study of pointing with visual feedback of moving hands. *Journal of Neurophysiology*, *79*(1), 117–25. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9425182

Jackson, S. R., Newport, R., Husain, M., Fowlie, J. E., O'Donoghue, M., & Bajaj, N. (2009). There may be more to reaching than meets the eye: re-thinking optic ataxia. *Neuropsychologia*, *47*(6), 1397–408. http://doi.org/10.1016/j.neuropsychologia.2009.01.035

Jackson, S. R., Newport, R., Mort, D., & Husain, M. (2005). Where the eye looks, the hand follows; limb-dependent magnetic misreaching in optic ataxia. *Current Biology*, *15*(1), 42–6. http://doi.org/10.1016/j.cub.2004.12.063

Jakobson, L. S., Archibald, Y. M., & Carey, D. P. (1991). A kinematic analysis of reaching and grasping movements in a patient recovering from optic ataxia. *Neuropsychologia*, *29*(8), 803–809. Retrieved from http://www.sciencedirect.com/science/article/pii/002839329190073H

James, T. W., Culham, J., Humphrey, G. K., Milner, A. D., & Goodale, M. A. (2003). Ventral occipital lesions impair object recognition but not object-directed grasping: An fMRI study. *Brain*, *126*, 2463–2475. http://doi.org/10.1093/brain/awg248

Jeannerod, M. (1986). Mechanisms of visuomotor coordination: a study in normal and brain-damaged subjects. *Neuropsychologia*, *24*(1), 41–78. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3517680

Jeannerod, M., Decety, J., & Michel, F. (1994). Impairment of grasping movements following a bilateral posterior parietal lesion. *Neuropsychologia*, *32*(4), 369–80. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8047246

Jones, R. D., Donaldson, I. M., & Parkin, P. J. (1989). Impairment and recovery of ipsilateral sensory-motor function following unilateral cerebral infarction. *Brain*, *112*, 113–132. http://doi.org/10.1093/brain/112.1.113

Karnath, H.-O., & Perenin, M.-T. (2005). Cortical control of visually guided reaching: evidence from patients with optic ataxia. *Cerebral Cortex*, *15*(10), 1561–1569. http://doi.org/10.1093/cercor/bhi034

Karnath, H.-O., Rüter, J., Mandler, A., & Himmelbach, M. (2009). The anatomy of object recognition--visual form agnosia caused by medial occipitotemporal stroke. *Journal of Neuroscience*, *29*(18), 5854–62. http://doi.org/10.1523/JNEUROSCI.5192-08.2009

Karnath, H. O., & Perenin, M. T. (2005). Cortical control of visually guided reaching: Evidence from patients with optic ataxia. *Cerebral Cortex*, *15*(October 2005), 1561–1569. http://doi.org/10.1093/cercor/bhi034

Khan, a Z., Pisella, L., Vighetto, a, Cotton, F., Luauté, J., Boisson, D., … Rossetti, Y. (2005). Optic ataxia errors depend on remapped, not viewed, target location. *Nature Neuroscience*, *8*(4), 418–20. http://doi.org/10.1038/nn1425

Konen, C. S., & Kastner, S. (2008). Two hierarchically organized neural systems for object information in human visual cortex. *Nature Neuroscience*, *11*(2), 224–231. http://doi.org/10.1038/nn2036

Koyama, M., Hasegawa, I., Osada, T., Adachi, Y., Nakahara, K., & Miyashita, Y. (2004). Functional Magnetic Resonance Imaging of Macaque Monkeys Performing Visually Guided Saccade Tasks. *Neuron*, *41*(5), 795–807. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15003178

Kravitz, D. J., Saleem, K. S., Baker, C. I., & Mishkin, M. (2011). A new neural framework for visuospatial processing. *Nature Reviews. Neuroscience*, *12*(4), 217–30. http://doi.org/10.1038/nrn3008

Kurata, K., & Tanji, J. (1986). Premotor cortex neurons in macaques: activity before distal and proximal forelimb movements. *The Journal of Neuroscience*, *6*(2), 403–11. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3950703

Lacquaniti, F., Guigon, E., Bianchi, L., Ferraina, S., & Caminiti, R. (1995). Representing spatial information for limb movement: role of area 5 in the monkey. *Cerebral Cortex*, *5*(5), 391–409. http://doi.org/10.1093/cercor/5.5.391

Lacquaniti, F., Perani, D., Guigon, E., Bettinardi, V., Carrozzo, M., Grassi, F., … Fazio, F. (1997). Visuomotor transformations for reaching to memorized targets: a PET study. *NeuroImage*, *5*(2), 129–46. http://doi.org/10.1006/nimg.1996.0254

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, *412*(6843), 150–7. http://doi.org/10.1038/35084005

Luppino, G., Murata, A., Govoni, P., & Matelli, M. (1999). Largely segregated parietofrontal connections linking rostral intraparietal cortex (areas AIP and VIP) and the ventral premotor cortex (areas F5 and F4). *Experimental Brain Research*, *128*(1–2), 181–7. Retrieved from

http://www.ncbi.nlm.nih.gov/pubmed/10473756

Malach, R., Reppas, J. B., Benson, R. R., Kwong, K. K., Jiang, H., Kennedy, W. a, … Tootell, R. B. (1995). Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. *Proceedings of the National Academy of Sciences*, *92*(18), 8135–8139. http://doi.org/10.1073/pnas.92.18.8135

Martin, J. A., Karnath, H.-O., & Himmelbach, M. (2015). Revisiting the cortical system for peripheral reaching at the parieto-occipital junction. *Cortex*, *64*, 363–379. http://doi.org/10.1016/j.cortex.2014.11.012

Mazzoni, P., Bracewell, R. M., Barash, S., & Andersen, R. A. (1996). Spatially tuned auditory responses in area LIP of macaques performing delayed memory saccades to acoustic targets. *Journal of Neurophysiology*, *75*(3), 1233–1241.

McIntosh, R. D., Mulroue, A., Blangero, A., Pisella, L., & Rossetti, Y. (2011). Correlated deficits of perception and action in optic ataxia. *Neuropsychologia*, *49*(1), 131–7. http://doi.org/10.1016/j.neuropsychologia.2010.11.017

Medendorp, W. P., Goltz, H. C., Crawford, J. D., & Vilis, T. (2005). Integration of target and effector information in human posterior parietal cortex for the planning of action. *Journal of Neurophysiology*, *93*(2), 954–962. http://doi.org/10.1152/jn.00725.2004

Milner, A. D., Dijkerman, H. C., & Carey, D. P. (1999). Visuospatial processing in a pure case of visual-form agnosia. In N. Burgess, K. J. Jeffery, & J. O'Keefe (Eds.), *The hippocampal and parietal foundations of spatial cognition* (pp. 443–466). Oxford: Oxford University Press.

Milner, A. D., Dijkerman, H. C., McIntosh, R. D., Rossetti, Y., & Pisella, L. (2003). Delayed reaching and grasping in patients with optic ataxia. *Progress in Brain Research*, *142*, 225–42. http://doi.org/10.1016/S0079-6123(03)42016-5

Milner, A. D., Dijkerman, H., & Pisella, L. (2001). Grasping the past: Delay can improve visuomotor performance. *Current Biology*, 1896–1901. Retrieved from http://www.sciencedirect.com/science/article/pii/S0960982201005917

Milner, A. D., & Goodale, M. A. (2008). Two visual systems re-viewed. *Neuropsychologia*, *46*(2008), 774–785. http://doi.org/10.1016/j.neuropsychologia.2007.10.005

Milner, A. D., Paulignan, Y., Dijkerman, H. C., Michel, F., & Jeannerod, M. (1999). A paradoxical improvement of misreaching in optic ataxia: new evidence for two separate neural systems for visual localization. *Proceedings of the Royal Society B: Biological Sciences*, *266*(1434), 2225–2229.

Milner, A. D., Perrett, D. I., Johnston, R. S., Benson, P. J., Jordan, T. R., Heeley, D. W., … Davidson, D. L. W. (1991). Perception and Action in "Visual Form Agnosia." *Brain*, *114*(1), 405–428. http://doi.org/10.1093/brain/114.1.405

Monaco, S., Cavina-Pratesi, C., Sedda, A., Fattori, P., Galletti, C., & Culham, J. C. (2011). Functional magnetic resonance adaptation reveals the involvement of the dorsomedial stream in hand orientation for grasping. *Journal of*

Neurophysiology, *106*(5), 2248–63. http://doi.org/10.1152/jn.01069.2010

Murata, A., Gallese, V., Kaseda, M., & Sakata, H. (1996). Parietal neurons related to memory-guided hand manipulation. *Journal of Neurophysiology*, *75*(5), 2180–2186. JOUR. Retrieved from http://jn.physiology.org/content/75/5/2180.abstract

Newport, R., Hindle, J. V., & Jackson, S. R. (2001). Links between vision and somatosensation: Vision can improve the felt position of the unseen hand. *Current Biology*, *11*, 975–980. http://doi.org/10.1016/S0960-9822(01)00266-4

Nieuwenhuis, S., Forstmann, B. U., & Wagenmakers, E.-J. (2011). Erroneous analyses of interactions in neuroscience: a problem of significance. *Nature Neuroscience*, *14*(9), 1105–1109. http://doi.org/10.1038/nn.2886

Orban, G. A., Van Essen, D., & Vanduffel, W. (2004). Comparative mapping of higher visual areas in monkeys and humans. *Trends in Cognitive Sciences*, *8*(7), 315–324. http://doi.org/10.1016/j.tics.2004.05.009

Pélisson, D., Prablanc, C., Goodale, M. A., & 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. *Experimental Brain Research*, *62*(2), 303–11. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3709715

Perenin, M.-T., & Vighetto, A. (1988). Optic Ataxia : A specific disuption in visuomotor mechanisms I. Different aspects of the deficit in Reaching for objects. *Brain*, *111*(3), 643–674. http://doi.org/doi: 10.1093/brain/111.3.643

Pisella, L., Binkofski, F., Lasek, K., Toni, I., & Rossetti, Y. (2006). No double-dissociation between optic ataxia and visual agnosia: multiple sub-streams for multiple visuo-manual integrations. *Neuropsychologia*, *44*(13), 2734–48. http://doi.org/10.1016/j.neuropsychologia.2006.03.027

Pisella, L., Gréa, H., Tilikete, C., Vighetto, A., Desmurget, M., Rode, G., … Rossetti, Y. (2000). An “automatic pilot” for the hand in human posterior parietal cortex: toward reinterpreting optic ataxia. *Nature Neuroscience*, *3*(7), 729–36. http://doi.org/10.1038/76694

Pisella, L., Sergio, L., Blangero, A., Torchin, H., Vighetto, A., & Rossetti, Y. (2009). Optic ataxia and the function of the dorsal stream: Contributions to perception and action. *Neuropsychologia*, *47*(14), 3033–3044. http://doi.org/10.1016/j.neuropsychologia.2009.06.020

Pitzalis, S., Fattori, P., & Galletti, C. (2015). The human cortical areas V6 and V6A. *Visual Neuroscience*, *32*, E007. http://doi.org/10.1017/S0952523815000048

Pitzalis, S., Sereno, M. I., Committeri, G., Fattori, P., Galati, G., Tosoni, A., & Galletti, C. (2013). The human homologue of macaque area V6A. *NeuroImage*, *82*, 517–530. http://doi.org/10.1016/j.neuroimage.2013.06.026

Prado, J., Clavagnier, S., Otzenberger, H., Scheiber, C., Kennedy, H., & Perenin, M.-T. (2005). Two cortical systems for reaching in central and peripheral vision. *Neuron*, *48*(5), 849–58. http://doi.org/10.1016/j.neuron.2005.10.010

Raos, V., Umiltá, M.-A., Murata, A., Fogassi, L., & Gallese, V. (2006). Functional properties of grasping-related neurons in the ventral premotor area F5 of the macaque monkey. *Journal of Neurophysiology*, *95*(2), 709–29. http://doi.org/10.1152/jn.00463.2005

Reichenbach, A., Bresciani, J.-P., Peer, A., Bülthoff, H. H., & Thielscher, A. (2011). Contributions of the PPC to online control of visually guided reaching movements assessed with fMRI-guided TMS. *Cerebral Cortex*, *21*(7), 1602–12. http://doi.org/10.1093/cercor/bhq225

Reichenbach, A., Bresciani, J. P., Bülthoff, H. H., & Thielscher, A. (2016). Reaching with the sixth sense: Vestibular contributions to voluntary motor control in the human right parietal cortex. *NeuroImage*, *124*(2016), 869–875. http://doi.org/10.1016/j.neuroimage.2015.09.043

Reichenbach, A., Thielscher, A., Peer, A., Bülthoff, H. H., & Bresciani, J.-P. (2014). A key region in the human parietal cortex for processing proprioceptive hand feedback during reaching movements. *NeuroImage*, *84*(2013), 615–25. http://doi.org/10.1016/j.neuroimage.2013.09.024

Revol, P., Rossetti, Y., Vighetto, A., & Rode, G. (2003). Pointing errors in immediate and delayed conditions in unilateral optic ataxia. *Spatial Vision*, *16*(3), 347–364. http://doi.org/10.1163/156856803322467572

Rice, N. J., Edwards, M. G., Schindler, I., Punt, T. D., Mcintosh, R. D., Humphreys, G. W., … Milner, A. D. (2008). Delay abolishes the obstacle avoidance deficit in unilateral optic ataxia, *46*, 1549–1557. http://doi.org/10.1016/j.neuropsychologia.2008.01.012

Rice, N. J., Tunik, E., Cross, E. S., & Grafton, S. T. (2007). On-line grasp control is mediated by the contralateral hemisphere. *Brain Research*, *1175*, 76–84. http://doi.org/10.1016/j.brainres.2007.08.009

Rice, N. J., Tunik, E., & Grafton, S. T. (2006). The anterior intraparietal sulcus mediates grasp execution, independent of requirement to update: new insights from transcranial magnetic stimulation. *Journal of Neurophysiology*, *26*(31), 8176–82. http://doi.org/10.1523/JNEUROSCI.1641-06.2006

Rossetti, Y., Pisella, L., & Vighetto, A. (2003). Optic ataxia revisited: Visually guided action versus immediate visuomotor control. *Experimental Brain Research*, *153*(2003), 171–179. http://doi.org/10.1007/s00221-003-1590-6

Rushworth, M. F. S., Nixon, P. D., & Passingham, R. E. (1997). Parietal cortex and movement. *Experimental Brain Research*, *117*(2), 311–323. http://doi.org/10.1007/s002210050225

Sakata, H., Taira, M., Murata, A., & Mine, S. (1995). Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. *Cerebral Cortex*, *5*(5), 429–38. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8547789

Sarlegna, F., Blouin, J., Bresciani, J. P., Bourdin, C., Vercher, J. L., & Gauthier, G. M. (2003). Target and hand position information in the online control of goal-directed arm movements. *Experimental Brain Research*, *151*(4), 524–535. http://doi.org/10.1007/s00221-003-1504-7

Sarlegna, F., Blouin, J., Vercher, J.-L., Bresciani, J.-P., Bourdin, C., & Gauthier, G. M. (2004). Online control of the direction of rapid reaching movements. *Experimental Brain Research*, *157*(4), 468–71. http://doi.org/10.1007/s00221-004-1860-y

Schenk, T. (2006). An allocentric rather than perceptual deficit in patient D.F. *Nature Neuroscience*, *9*(11), 1369–70. http://doi.org/10.1038/nn1784

Schenk, T., Franz, V., & Bruno, N. (2011). Vision-for-perception and vision-for-action: Which model is compatible with the available psychophysical and neuropsychological data? *Vision Research*, *51*(8), 812–818. http://doi.org/10.1016/j.visres.2011.02.003

Singhal, A., Monaco, S., Kaufman, L. D., & Culham, J. C. (2013). Human fMRI reveals that delayed action re-recruits visual perception. *PloS One*, *8*(9), e73629. http://doi.org/10.1371/journal.pone.0073629

Snyder, L. H., Batista, A. P., & Andersen, R. A. (1997). Coding of intention in the posterior parietal cortex. *Nature*, *386*(6621), 167–170. http://doi.org/10.1038/386167a0

Snyder, L. H., Batista, A. P., & Andersen, R. A. (2000). Intention-related activity in the posterior parietal cortex: A review. *Vision Research*, *40*(10–12), 1433–1441. http://doi.org/10.1016/S0042-6989(00)00052-3

Stricanne, B., Andersen, R. A., & Mazzoni, P. (1996). Eye-centered, head-centered, and intermediate coding of remembered sound locations in area LIP. *Journal of Neurophysiology*, *76*(3), 2071–2076. http://doi.org/10.1021/je9001366

Tankus, A., & Fried, I. (2012). Visuomotor Coordination and Motor Representation by Human Temporal Lobe Neurons. *Journal of Cognitive Neuroscience*, *24*, 600–610. http://doi.org/10.1162/jocn_a_00160

Tanné-Gariépy, J., Rouiller, E. M., & Boussaoud, D. (2002). Parietal inputs to dorsal versus ventral premotor areas in the macaque monkey: evidence for largely segregated visuomotor pathways. *Experimental Brain Research*, *145*(1), 91–103. http://doi.org/10.1007/s00221-002-1078-9

Tunik, E., Frey, S. H., & Grafton, S. T. (2005). Virtual lesions of the anterior intraparietal area disrupt goal-dependent on-line adjustments of grasp. *Nature Neuroscience*, *8*(APRIL), 505–511. http://doi.org/10.1038/nn1430

Tzavaras, A., & Masure, M. C. (1976). Aspects différents de l'ataxie optique selon la latéralisation hémisphérique de la lésion. *Lyon Médical*, *236*, 673–683.

Valyear, K. F., Culham, J. C., Sharif, N., Westwood, D., & Goodale, M. A. (2006). A double dissociation between sensitivity to changes in object identity and object orientation in the ventral and dorsal visual streams: A human fMRI study. *Neuropsychologia*, *44*(2), 218–228. http://doi.org/10.1016/j.neuropsychologia.2005.05.004

Verstynen, T., Diedrichsen, J., Albert, N., Aparicio, P., & Ivry, R. B. (2005). Ipsilateral motor cortex activity during unimanual hand movements relates to task complexity. *Journal of Neurophysiologyeurophysiology*, *93*(3), 1209–22.

http://doi.org/10.1152/jn.00720.2004

Weeks, R. a, Aziz-Sultan, a, Bushara, K. O., Tian, B., Wessinger, C. M., Dang, N., … Hallett, M. (1999). A PET study of human auditory spatial processing. *Neuroscience Letters*, *262*(3), 155–158. http://doi.org/10.1016/S0304-3940(99)00062-2

Whitwell, R. L., Milner, A. D., & Goodale, M. A. (2014). The Two Visual Systems Hypothesis: New Challenges and Insights from Visual form Agnosic Patient DF. *Frontiers in Neurology*, *5*(255), 1–8. http://doi.org/10.3389/fneur.2014.00255

Zatorre, R. J., Bouffard, M., Ahad, P., & Belin, P. (2002). Where is “where” in the human auditory cortex? *Nature Neuroscience*, *5*(9), 905–909. http://doi.org/10.1038/nn904

3 PEER-REVIEWED PUBLICATIONS AND MANUSCRIPTS

3.1 DELINEATION OF CONTRIBUTION TO COLLECTIVE WORK

The thesis includes three peer-reviewed papers or manuscripts.
In the following I specify the contribution of each of the co-authors and myself.

Cornelsen, S., Rennig, J, Himmelbach, M. (2016). Memory-guided reaching in a patient with visual hemiagnosia. *Cortex*, 79, 32-41.

Sonja Cornelsen	designed the experiment, acquired and analyzed the data and wrote the manuscript.
Johannes Rennig	conducted the lesion analysis.
Marc Himmelbach	contributed to the analysis, the design the experiment and the writing of the manuscript as supervising author.

Cornelsen, S., Karnath, H.-O., Himmelbach, M. (2016). Optic ataxia is only 'optic': a comparison of visual, auditory and proprioceptive reaching. *Cortex*, submitted.

Sonja Cornelsen	contributed to the design of the experiment, acquired and analyzed the data and wrote the manuscript.
Hans-Otto Karnath	contributed to the design of the experiment.
Marc Himmelbach	contributed to the design of the experiment and the writing of the manuscript as supervising author.

Cornelsen, S., Thielscher, A., Himmelbach, M. (2016). Functional specificity and lateralization of fronto-parietal pathways for online-correction.

Sonja Cornelsen	acquired and analyzed the data and wrote the manuscript.
Axel Thielscher	contributed to the design of the experiment and to the writing of the manuscript as supervising author.
Marc Himmelbach	contributed to the design of the experiment and to the writing of the manuscript as supervising author.

3.2 PEER-REVIEWED PUBLICATION AND MANUSCRIPTS

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Research report

Memory-guided reaching in a patient with visual hemiagnosia

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ABSTRACT

The two-visual-systems hypothesis (TVSH) postulates that memory-guided movements rely on intact functions of the ventral stream. Its particular importance for memory-guided actions was initially inferred from behavioral dissociations in the well-known patient DF. Despite of rather accurate reaching and grasping movements to visible targets, she demonstrated grossly impaired memory-guided grasping as much as impaired memory-guided reaching. These dissociations were later complemented by apparently reversed dissociations in patients with dorsal damage and optic ataxia. However, grasping studies in DF and optic ataxia patients differed with respect to the retinotopic position of target objects, questioning the interpretation of the respective findings as a double dissociation. In contrast, the findings for reaching errors in both types of patients came from similar peripheral target presentations. However, new data on brain structural changes and visuomotor deficits in DF also questioned the validity of a double dissociation in reaching. A severe visuospatial short-term memory deficit in DF further questioned the specificity of her memory-guided reaching deficit. Therefore, we compared movement accuracy in visually-guided and memory-guided reaching in a new patient who suffered a confined unilateral damage to the ventral visual system due to stroke. Our results indeed support previous descriptions of memory-guided movements' inaccuracies in DF. Furthermore, our data suggest that recently discovered optic-ataxia like misreaching in DF is most likely caused by her parieto-occipital and not by her ventral stream damage. Finally, multiple visuospatial memory measurements in HWS suggest that inaccuracies in memory-guided reaching tasks in patients with ventral damage cannot be explained by visuospatial short-term memory or perceptual deficits, but by a specific deficit in visuomotor processing.

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1. Introduction

The two-visual-systems hypothesis (TVSH) of Goodale and Milner (Goodale & Milner, 1992; Milner & Goodale, 2008) formulates two key postulations regarding the control of actions. First, planning and control of visually-guided reaching to visible targets essentially rely on the dorsal stream. Second, for memory-guided movements towards the remembered position of a target that is no longer visible, the dorsal stream alone is not sufficient and requires contributions from the ventral stream.

The TVSH assumes a crucial involvement of the ventral stream in memory-guided actions based on the famous and extensively investigated case of patient DF. DF suffered from a carbon monoxide intoxication in 1988 that caused a dramatic bilateral damage to her brain, especially to her ventral streams, and left her with a severe visual agnosia. Experimental studies showed that her reaching and grasping performance was mostly similar to that of healthy controls when she acted on visible target. However, acting on memorized targets she revealed significant movement impairments in comparison to healthy controls (Goodale, Jakobson, & Keillor, 1994; Milner, Dijkerman, & Carey, 1999). Important evidence on this behavioral dissociation in DF came from an analysis of maximum grip aperture with target objects presented in central vision (Goodale et al., 1994). Grip aperture scaling was pretty normal in DF when she immediately grasped actually visible objects in front of her. Her performance deteriorated considerably when she was asked to withhold her grasping movement for delays of respectively 2 and 30 sec after the target object had been removed. Later, Milner, Dijkerman, et al. (1999) reported that also in a reaching task with memorized point-like targets in her visual periphery, DF's spatial errors (i.e., misreaching) substantially exceeded those of age-matched healthy controls (Milner, Dijkerman, et al., 1999).

In contrast to the behavioral dissociation in DF, with rather normal visually-guided movement execution and poor memory-guided execution in the abovementioned reports, some optic ataxia patients with dorsal lesions paradoxically improved their terminal accuracy when they reached for remembered targets relative to their typical significant misreaching errors when movements were executed immediately upon target presentation (Himmelbach & Karnath, 2005; Himmelbach et al., 2009; Milner, Dijkerman, McIntosh, Rossetti, & Pisella, 2003; Milner, Paulignan, Dijkerman, Michel, & Jeannerod, 1999). A similar effect was observed for maximum grip aperture in grasping (Milner & Dijkerman, 2001; Milner, Dijkerman, & Pisella, 2001).

These results on visually-guided and memory-guided reaching and grasping in few optic ataxia and one visual agnosia patient have been summarized as evidence for a double dissociation of visually-guided and memory-guided movement control in these patients (Milner & Goodale, 2008).

However, looking closely at the available experiments and data, their interpretation in support of a double dissociation in optic ataxia and visual agnosia needs to be further qualified. A straightforward double dissociation was found only for reaching. Here, optic ataxia patients as well as DF aimed their movements at targets in the visual periphery with reversed results in comparison to healthy controls (Himmelbach & Karnath, 2005; Himmelbach et al., 2009; Milner et al., 2003; Milner, Paulignan, et al., 1999). For grasping, however, target objects were presented in the central visual field for DF but in the visual periphery for optic ataxia patients (Milner & Dijkerman, 2001; Milner et al., 2001).

Recently, Bridge et al. (2013) reported a bilateral atrophy in DF's posterior parietal regions beyond the ventral stream system. In agreement with this anatomical finding, Hesse, Ball, and Schenk (2012, 2014) reported a misreaching for visible peripheral targets in DF that resembled the typical pattern in optic ataxia patients for both hands in both visual hemifields. This recent report is inconsistent with rather normal absolute errors in visually-guided reaching for peripheral targets reported almost two decades earlier (Milner, Dijkerman et al., 1999; Milner, Paulignan et al., 1999; Milner & Goodale, 2008). In a recent comprehensive review Whitwell, Milner, and Goodale (2014) implied that parieto-occipital atrophy in DF increased since the first anatomical descriptions in the early 90's. Such an anatomical change could explain the apparent change in behavioral measurements. Summarizing the available data on visually-guided and memory-guided reaching in optic ataxia patients and DF, we conclude that the new reports of a bilateral parieto-occipital damage in DF and significant impairments also in visually-guided reaching for peripheral targets call for additional evidence to support the assumption that a damage of the ventral visual system alone can indeed cause a specific impairment of memory-guided reaching with essentially spared visually-guided reaching to targets in the peripheral visual field.

The first detailed report of patient DF included detailed neuropsychological test results (Milner et al., 1991). Among these was a short report of a very substantial visuospatial short term memory deficit as measured with a corsi block-tapping task (Corsi, 1972). The observation of this visuospatial short term memory deficit in a test with a behavioral response modality that is substantially different from visuomotor reaching poses the question whether her impairment in memory-guided visuomotor reaching represented a specific visuomotor memory deficit or whether it could be interpreted as one behavioral consequence among others of a more general visuospatial memory deficit.

In this study, we investigated whether a confined ventral stream lesion due to stroke causes specific impairments in memory-guided actions in the presence of intact visually-guided reaching. We measured and analyzed the patient's reaching accuracy at different eccentricities. Further, we examined the performance of this patient in an established clinical memory test battery that includes several visual and spatial memory subtests. Finally, we conducted an experimental measurement of visual spatial memory with a task that resembled the reaching experiment as closely as possible. Based on the existing data from DF and optic ataxia patients, we expected a dissociation between visually-guided and memory-guided reaching compared to age-matched healthy controls for targets in the contralesional visual hemifield with better performance of the patient in visually-guided and worse performance in memory-guided reaching. With respect

to the presence of a visual spatial short-term memory deficit we had no specific expectation.

2. Methods

2.1. Participants

The 56 years old, right-handed patient HWS suffered a posterior cerebral artery stroke 6 days before the experimental measurements reported here. Magnetic resonance FLAIR images acquired six days post-stroke on a 3T Siemens TIM Trio Scanner (12-channel receive head coil, 40 axial slices, TE = 75 msec, TR = 9000 msec, 2 mm slice thickness, gap of 2 mm, flip angle 150°, FoV 176 × 256 mm^2, matrix size 176 × 256) revealed an acute unilateral lesion in the right ventromedial occipito-temporal cortex and white matter (Fig. 1). The scan also showed a small acute lesion in the right hemisphere at the boundary of the posterior part of the capsula interna and the lateral part of the thalamus with an in-plane diameter of ~11 mm, detectable in 12 slices. According to the John Hopkins University (JHU) white-matter tractography atlas and the ICBM-DTI-81 white matter labels atlas (Mori, Wakana, Nagae-Poetscher, & van Zijl, 2005), corticospinal tract and the posterior limb of the internal capsula are likely to be affected by the lesion. A comparison with the human thalamus connectivity atlas (Behrens et al., 2003) suggests that the lesion predominantly affects the lateral sensorimotor nuclear group and might stretch into the ventral anterior nucleus, the lateral posterior and the mediodorsal (MD) nuclei. The lesion can account for the reported disturbances of sensory function in HWS' left fingertips.

The occipito-temporal lesion mainly affected the inferior cuneus, the lingual, fusiform, and parahippocampal gyri. After normalization of the patient's brain (SPM8, unified segmentation and normalization), a direct comparison between his lesion and a probabilistic histological atlas (Eickhoff et al., 2005) suggested that his lesion affected parts of V1, the lingual gyrus, occipital sections of the fusiform gyrus, and the posterior hippocampus. In agreement with the lesion location, a perimetry demonstrated a visual field defect in the upper left quadrant beyond an eccentricity of −30°. At the horizontal meridian, where the targets were presented, HWS' vision was completely intact in both hemifields up to an eccentricity of ±70°. HWS demonstrated a unilateral visual agnosia (Mazzucchi, Posteraro, Nuzzi, & Parma, 1985) with impairments of object recognition and discrimination upon tachistoscopic presentations in his intact contralesional visual hemifield. HWS demonstrated no signs of visual neglect, visual, auditory, or tactile extinction. His memory performance was examined with the German revised version of the Wechsler Memory Scale (WMS-R, Härting et al., 2000) including the Corsi Block Tapping Test (Corsi, 1972), which investigates spatial short term memory. For an evaluation of the patient's performance in our experimental visuomotor tasks we also examined 19 healthy, age-matched adults (12 female, age range = 52–62 y; mean age = 57.6 y) without any history of neurological disorders. We tested HWS and 8 controls from the same group (5 female, age range = 56–60 y; mean age = 57.8 y) in a control experiment investigating visuospatial short term memory. All participants were right-handed, had normal or corrected to normal vision and gave their informed consent to participate in the study, which was performed in accordance with the Declaration of Helsinki and approved by the local Ethic Committee of the Medical Faculty Tuebingen.

2.2. Procedure and apparatus

2.2.1. Visually-guided and memory-guided reaching

Participants sat at a table with a black vertical panel fixed on the tabletop. Their head rested on a chinrest and their left index finger rested on a start button at the midsagittal body plane. The vertical panel was at a distance of 36 cm from the chin rest and of 30 cm from the start button. LEDs (light emitting diodes) were mounted at the panel at a height of 47 cm from the tabletop. A permanent red-white marker at the midsagittal body plane located 1 cm above the height of the target LEDs served as fixation point and all participants fixated this position throughout all trials. The room light was dimmed so participants could easily perceive the illuminated LEDs, but it was bright enough to allow for visual feedback of the hand and the perception of the surrounding. The experimenter started each trial manually. After a variable interval (ranging from 1 sec to 1.5 sec) one of the red target LEDs lighted up and became visible for 2 sec at three different eccentricities (±9°, ±17° or ± 28° degree of visual angle). In the visually-guided reaching condition, participants reached instantly to the red

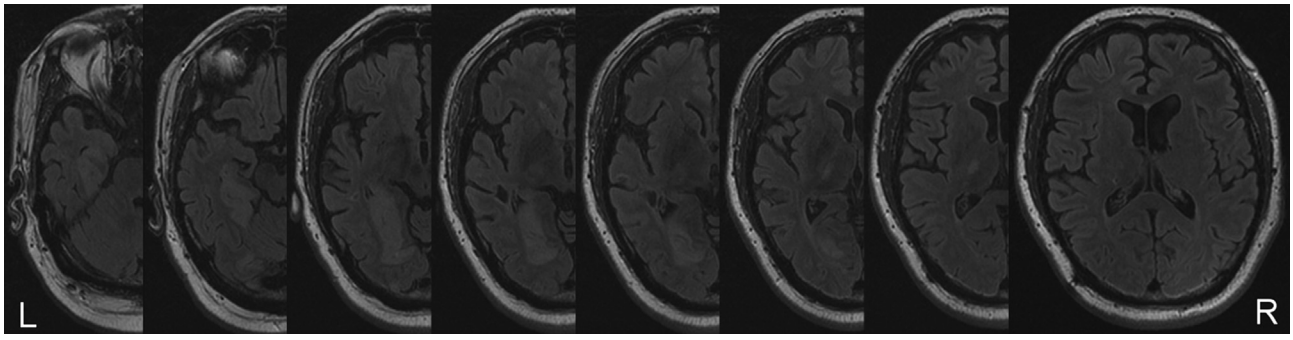

Fig. 1 – Individual FLAIR scan of patient HWS six days post-stroke. To avoid distortions of the lesion, the image is not normalized and thus no z-scores are indicated.

LED. In the memory-guided reaching condition, participants postponed their response for 5 sec until a green LED occurred underneath the fixation that instructed the start of the movement. Participants were instructed to reach the target with an uninterrupted and fluent movement and as accurately as possible. The order of target positions was randomized. The visually-guided and memory-guided reaching conditions were presented in blocks of 18 trials (3 trials per target) in a counterbalanced sequence (Immediate-Delayed-Delayed-Immediate). Following the practice trials, the performance of patient HWS was measured in 8 experimental blocks, i.e., two repetitions of the balanced sequence. For each control, 16 experimental blocks were recorded per participant in two sessions with practice trials at the beginning of both sessions. Reaching trajectories were recorded with a magnetic sensor attached to the participants' left index finger (miniBird Motion Tracking system, .5 mm resolution, Ascension Technology Cooperation, Vermont, USA) at a rate of 100 Hz. Correct fixation throughout the measurements was verified using a digital video camera for the patient and a SMI iView™ X HED system (SensoMotoric Instruments GmbH, Teltow, Germany) for all controls.

2.2.2. *Visuospatial short-term memory*

To investigate HWS' short-term memory in a task with comparable spatial and temporal characteristics as the reaching task, we conducted a control experiment. Participants were seated 36 cm away from a computer screen on which a green fixation point was presented centrally. After a variable time interval, a red target dot appeared for 2 sec in the same positions that were used in the reaching task (i.e., at eccentricities of ±9°, ±17° or ±28° degree of visual angle). After a delay of 5 sec, a new red dot appeared in a position either 100 pixels to the left or to the right of the previous target dot. Participants indicated the previously presented target position by an adjustment of the red dot to the left or right via keys on a keyboard in front of them (W for leftward movement of the response dot, P for rightward adjustment). There was no time limit for the adjustment of the response stimulus, the participants gave a verbal feedback to the experimenter when they finished their response. Correct fixation throughout the measurements was verified using a digital video camera.

2.3. *Analysis*

2.3.1. *Visually-guided and memory-guided reaching*

All data were analyzed using custom software based on MATLAB (MathWorks Inc., Sherborn, MA, USA) and R (r-project.org). First, raw data was filtered using a forth-order zero-phase shift Butterworth filter. Movement onset was defined as the time at which the velocity exceeded a threshold of 5 cm/sec in four consecutive frames. If no onset could be detected at this rate, the threshold was changed to 10 cm/sec. Reaction time (RT) was defined as the time between the onset of the target presentation in the visually-guided reaching condition (or the Go-Signal in the memory-guided reaching condition) and movement onset. The end of the movement towards the target was defined (i) as lying within the interval between the highest velocity of the movement towards the target and the highest velocity of the movement back to the start button; (ii) by the point at which the absolute deceleration was 0 mm/sec^2; and (iii) velocity was below 10 cm/sec at the same time. Movement time (MT) was defined as the time between the movement onset and the end of the movement.

Trials were excluded from further analysis if no movement end point could be identified or if saccades were detected. We analyzed the absolute horizontal deviation of the movement end point from the respective target position. We chose this measure because a number of previous reports on visually-guided and memory-guided reaching accuracy used absolute errors to quantify the respective patients' performance, with significant findings (e.g. Milner, Dijkerman et al., 1999). We compared patient HWS' pointing errors between visually-guided and memory-guided trials for each of the six targets to the respective differences in healthy subjects using a test for single case dissociations (Crawford & Garthwaite, 2005). For these comparisons we adopted a global type-1 error probability threshold of .05, which corresponds to a threshold of .0083 for each individual target after Bonferroni correction.

We also conducted a complementary analysis of the variable terminal error, i.e., standard deviations of horizontal errors. As this analysis was conducted only after the successful analysis of the absolute errors, again a correction for multiple comparisons took into account the six target positions and provided a critical threshold of .0083.

For an illustration of the movement paths (cf. Fig. 2), we normalized the trajectories from HWS and one healthy control to 100 equally timed intervals between movement onset and movement offset to facilitate the comparisons of individual reaching trajectories independent of the movement duration.

2.3.2. *Visuospatial short-term memory*

In correspondence to the visuomotor tasks, we analyzed the absolute horizontal deviation of the adjusted response positions from the respective target position. We compared patient HWS' averaged absolute horizontal deviations in this experiment to those of healthy subjects using a test for single deficits (Crawford & Garthwaite, 2005; Crawford & Howell, 1998).

3. Results

3.1. *Visually-guided and memory-guided reaching*

HWS conducted fluent and smooth reaching movements. His RT and MT were comparable to healthy controls in visually-guided and memory-guided reaches (Table 1). As expected, movement accuracy decreased from visually-guided to memory-guided trials for all participants including HWS. Importantly, even though HWS was as accurate as the healthy control group, even better than some of them, in visually-guided reaching, his reaches were much less precise in the memory-guided condition (see Figs. 2 and 3).

Single case dissociation tests (Crawford & Garthwaite, 2005) for each target indicated a significant dissociation between HWS' and the healthy subjects' performance for the contralesional target at −28° [$t(18) = 3.09$, $p = .003$, correlation

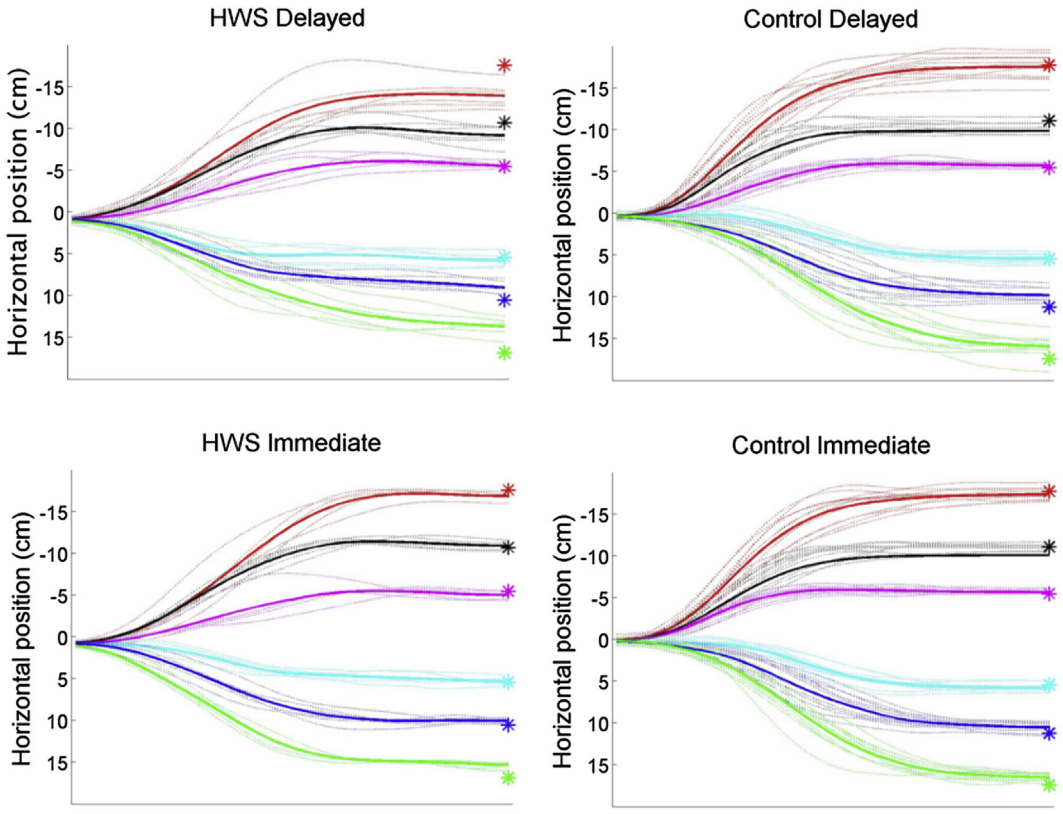

Fig. 2 – Trajectories for patient HWS and a representative control subject. The six targets are each depicted as an asterisk; dotted lines depict single trajectories, bold lines averaged trajectories. Negative values represent the left site, positive the right site.

Table 1 – Reaction times (RT) and movement times (MT) for patient HWS and age-matched controls separately for the peripheral target on the contralesional side (−28°) and averaged across all other targets.

	Mean RT (SD) in ms		Mean MT (SD) in ms	
	Contralesional peripheral target	Across remaining targets	Contralesional peripheral target	Across remaining targets
HWS visually-guided	885	738	661	746
Controls visually-guided	807 (152)	788 (162)	878 (131)	899 (131)
HWS memory-guided	518	524	724	787
Controls memory-guided	627 (265)	661 (278)	911 (129)	914 (103)

coefficient for controls r_{con} = .752] between visually-guided and memory-guided reaching. The outcome was neither significant for the target at −17° [$t(18) = .68$, $p = .25$, $r_{con} = .002$] nor for the target at −9°[$t(18) = 1.07$, $p = .14$, $r_{con} = .758$]. Movements towards ipsilesional targets showed no detectable dissociation for any target position [+28°: $t(18) = .61$, $p = .54$, $r_{con} = .326$; +17°: $t(18) = .08$, $p = .46$, $r_{con} = .656$; +9°: $t(18) = .96$, $p = .17$, $r_{con} = .391$].

Analyzing the variable error, we found no evidence for a significant behavioral dissociation in HWS relative to the healthy subjects' performance for the contralesional target at any target [target at −28°: $t(18) = .98$, $p = .16$, $r_{con} = .359$; −17°: $t(18) = .164$, $p = .43$, $r_{con} = .453$; −9°: $t(18) = 1.14$, $p = .13$, $r_{con} = .603$; +28°: $t(18) = .79$, $p = .21$, $r_{con} = -.016$; +17°: $t(18) = 1.14$, $p = .13$, $r_{con} = .585$; +9°: $t(18) = .61$, $p = .27$, $r_{con} = .365$]. For descriptive data on this measure, please see Table 2.

3.2. *Clinical memory tests*

The patient's WMS-R sum scores for general attention, verbal memory, and visual memory were in the normal range (Table 3). Also, the outcome for general memory, a combination of sub-tests already summarized under verbal and visual memory, was just below the 25th percentile (Table 3). In contrast to these observations, HWS' outcome for delayed memory was clearly worse, with only 8% of the normal population showing an equivalent or worse performance. Note that those sub-tests that contributed to the delayed memory score tested the performance of the patient after a delay of about 30 min. Among those sub-tests that are individually standardized with communicated percentile ranks only his results in the digit span forward and visual reproduction II were clearly below the average. His result for the digit span forward was puzzling as he performed normally for the digit span

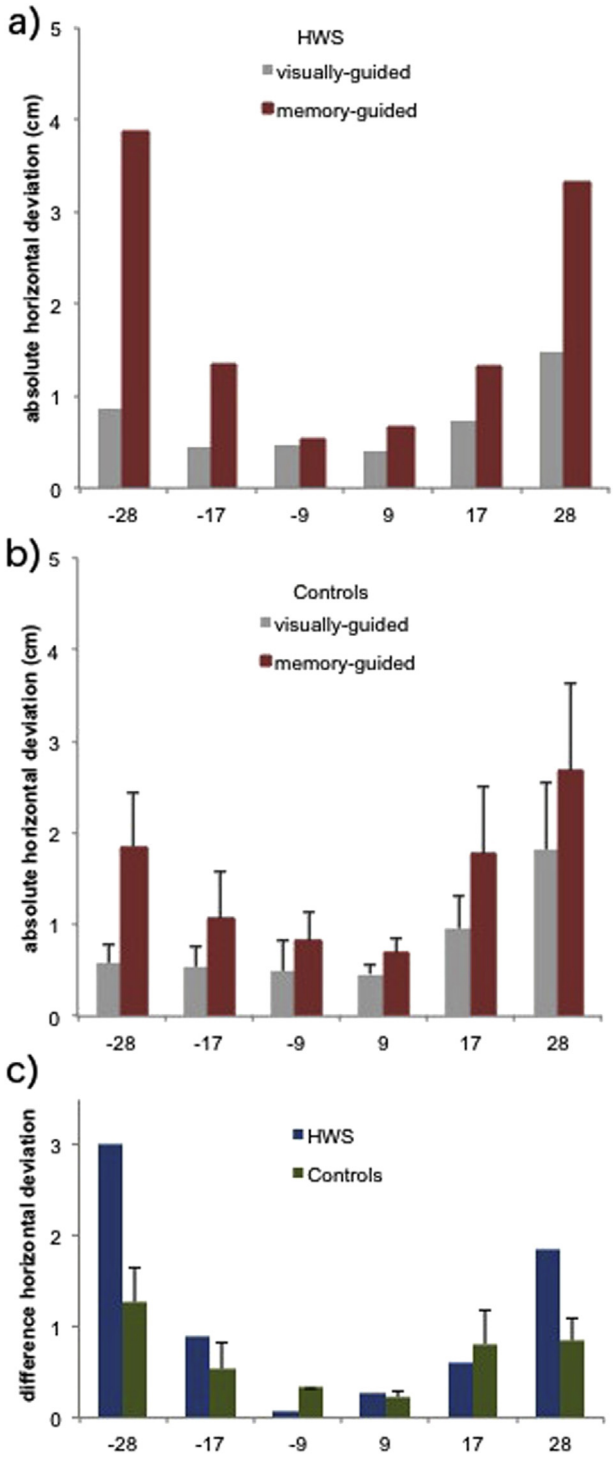

Fig. 3 – Mean absolute horizontal error in cm for a) patient HWS and b) age-matched control subjects for all six target positions. c) depicts the difference between visually-guided and memory-guided reaches for HWS (blue) and controls (green). Black lines indicate the standard deviation for the controls.

backwards. Visual reproduction II requires the patient to draw four figures that were presented about 30 min ago. For this task, HWS performed particularly poorly. We cannot attribute this impairment to an inability to recognize these drawings (i.e., a possible consequence of his unilateral agnosia) because his short-term memory for the same items (i.e., a reproduction immediately after the presentation of the figures) was within the normal range. In the Corsi Block Tapping Test, requiring the patient to remember a sequence of spatial targets for a few seconds and commonly interpreted as a test of visuospatial short term memory, HWS performed within the normal range in contrast to patient DF who showed a severe impairment at the time of her first experimental measurements with a span of only two blocks (Milner et al., 1991).

3.3. *Visuospatial short-term memory experiment*

HWS accuracy in a non-visuomotor memory task that used the same spatial configuration and presentation and delay timing as the reaching experiment, quantified by the mean absolute error of his responses, was comparable to healthy controls at all eccentricities [$-28°$: $t(7) = .24$, $p = .40$; $-17°$: $t(7) = .29$, $p = .39$; $-9°$: $t(7) = -.20$, $p = .42$; $+9°$: $t(7) = -.29$, $p = .38$; $+17°$: $t(7) = -.36$, $p = .36$; $+28°$: $t(7) = .28$, $p = .39$]. For descriptive data on this measure, please see Table 4.

4. Discussion

So far only one study investigated memory-guided reaching for peripheral targets in a ventral stream patient and reported an impairment for memory-guided reaching with normal performance in visually-guided reaching (Milner, Dijkerman, et al., 1999). These data represent an important part of an apparently straightforward double dissociation of memory-guided and visually-guided actions in a comparison of patients with damage to the dorsal visual system and a patient with damage to the ventral visual system. However, the recent observation of a considerable impairment of visually-guided peripheral reaching in DF questions the validity of the original report. Therefore, the present study aimed at a validation of the previously reported dissociation between misreaching to memorized peripheral targets and normal accuracy in reaching to visible targets after a damage to the ventral visual system.

Patient HWS, who suffered from a unilateral stroke with a selective damage to his right ventromedial occipito-temporal cortex and white matter, as well as a small thalamus lesion, showed a terminal accuracy of his visually-guided reaching towards visible peripheral targets that was comparable with the accuracy of age-matched healthy controls across all target positions. In contrast, HWS' performance for the most peripheral contralesional target was considerably worse in comparison to controls when the target was no longer visible and movements were memory-guided.

Albeit a significant dissociation was observed for only one target position, the topography of the dissociation seemed intuitively reasonable. We detected it for the contralesional hand in the most peripheral contralesional target position. The dissociation in HWS at this target position was significant after stringent control of inflated false positive probabilities caused by the independent analysis of multiple target positions. Nevertheless, without a strong retinotopy being reported for the ventromedial structures affected in HWS, the

Table 2 – Mean variable error and standard deviation for patient HWS and age-matched controls.

Target position	HWS memory-guided	Controls memory-guided	HWS visually-guided	Controls visually-guided
−28°	1.48	1.49 (.44)	.83	.44 (.15)
−17°	1.00	1.04 (.27)	.52	.52 (.45)
−9°	.64	.76 (.23)	.49	.42 (.11)
+9°	.86	.75 (.17)	.44	.51 (.21)
+17°	1.01	1.06 (.20)	.44	.74 (.21)
+28°	.96	1.42 (.34)	.86	.91 (.31)

Table 3 – Scores of patient HWS in subtests of the Wechsler Memory Scale (Härting et al., 2000). Please note that memory domains printed in bold are composite scores that partially include the following scores for individual subtests. The WMS domain scores are usually standardized as IQ-equivalent indices, which we have converted to percentiles.

Subtest	(Weighted) Raw value	Percentile
Verbal memory	64	27
Visual memory	48	42
General memory	105	21
Attention	60	37
Delayed memory	52	8
Digit span forwards	5	2
Digit span backwards	6	38
Block span forwards	8	58
Block span backwards	8	70
Logical memory I	22	27
Logical memory II	19	30
Visual reproduction I	34	62
Visual reproduction II	15	2

strong impact of the targets eccentricity on the behavioral dissociation could not easily be explained based on HWS' performance alone. Unfortunately, movement errors of DF in the memory-guided reaching experiment published in 1999 (Milner, Dijkerman, et al., 1999) were only reported as an average across eight peripheral target locations in her left and right visual hemifield. No presentation of the respective datapoints for individual target eccentricities was available for a comparison to HWS′ data. The substantial change of DF's visually-guided reaching accuracy from Milner, Dijkerman, and Carey (1999) to the recent measurements reported by Hesse et al. (2012, 2014) even prevents conclusive new measurements in DF on this particular issue.

Keeping in mind the limitations of our study, we interpret our observation as one piece of evidence for the suggested dissociation. Beyond the widely known original study on memory-guided grasping and grip aperture scaling in DF (Goodale et al., 1994), the supposed dissociation between visually-guided and memory-guided movement execution has been addressed with quite a number of different experimental paradigms. A psychophysical experiment demonstrated that the differential threshold (JND, just noticeable difference) in a perceptual task increased with the size of the object as predicted by Weber's law. In contrast, the results of a visuomotor task violated this law since the JND did not increase with object size. The authors concluded a fundamental difference in the visual coding between action and perception. Interestingly, Weber's law was not violated in a memory-based visuomotor task, indicating that memory-guided reaching relies on stored perceptual information (Ganel, Chajut, & Algom, 2008; but see Schenk, Franz, & Bruno, 2011). This interpretation is in line with the observation that DF's anticipatory hand shaping is comparable to controls when the target is visible, but the introduction of a delay between vision and pantomimed grasping led to inappropriate scaling of her hand that was suggested to be caused by her perceptual deficits (Goodale et al., 1994). The suggested dissociation between perception and action was also investigated using visual illusions. Participants had to either grasp an object placed within a Poncho illusion or give a manual estimation of its size by opening their index finger and thumb a matching amount. Whereas grasping was unaffected by the illusion, participants erroneously perceived the larger object as the shorter one as indicated by the finger opening (Ganel, Tanzer, & Goodale, 2008; but see again Schenk et al., 2011).

While DF and HWS both suffered from damage to the ventral visual system, the nature, the extent, and the location of their respective damage is substantially different. Whereas the damage in DF is a combination of rather confined severe structural damage with more diffuse subtle degenerative changes, HWS showed a clearly confined damage due to a first-ever stroke. Despite the nature of the respective damage, also its location apparently differs. The main damage to the ventral stream in DF has been localized in the bilateral LOC, or

Table 4 – Mean horizontal absolute error in the memory task and confidence intervals on the patient's abnormality score. Standard deviations for controls in brackets.

Target position	−28	−17	−9	+9	+17	+28
HWS	51.36	43.75	15.63	20.83	21.08	46.50
Controls	41.22 (38.66)	34.53 (29.86)	18.63 (14.00)	27.11 (19.98)	34.02 (33.03)	37.88 (28.99)
Estimated % of normal population falling below HWS′ score	59.41	61.02	42.29	38.78	36.14	60.63
95% Lower CI	32.54	33.99	18.18	15.50	13.55	33.64
95% Upper CI	83.13	84.35	68.96	65.83	63.40	84.06

ventrolateral occipito-temporal cortex in contrast to the ventromedial damage in HWS. In their detailed anatomical measurement and analysis of DF's brain, Bridge et al. (2013) further emphasized the ventrolateral localization of DF's main structural damage by two independent single case statistical analyses of cortical thickness measures in the ventromedial and ventrolateral cortex respectively. These analyses revealed a significantly lower thickness value in comparison to five controls for the ventrolateral cortex in DF and no significant difference for the ventromedial cortex. However, a direct comparison, i.e. a dissociation test of thickness estimations between the two cortical masks relative to the controls has not been calculated. As the combination of a significant finding on the one hand and a non-significant finding on the other hand cannot easily be interpreted as a significant difference between the two findings (Nieuwenhuis, Forstmann, & Wagenmakers, 2011) we cannot preclude that a descriptively smaller thickness value also in DF's ventromedial cortex relative to controls might have a functional impact.

Most available data on the ventrolateral cortex that is significantly compromised in DF, more specifically the lateral occipital cortex, would not let us expect a particular deficit in memory-guided reaching. LOC is an important area for visual recognition of objects (Cavina-Pratesi, Goodale, & Culham, 2007; Malach et al., 1995) that indeed has been shown to be reactivated during memory-guided actions (Singhal, Monaco, Kaufman, & Culham, 2013), likely providing information about spatial object properties for memory-guided grasping. Further support came from a TMS study demonstrating LOC's causal involvement in memory-guided actions (Cohen, Cross, Tunik, Grafton, & Culham, 2009). However, LOC might be less important for memory-guided reaching. An fMRI study investigating memory-guided reaching and grasping did not observe an LOC reactivation after memory delay (Fiehler et al., 2011). The authors argued that LOC reactivation can only be detected if grasping signals are isolated from the reach component (Singhal et al., 2013), because object features like shape or size are of high importance to adjust hand aperture, whereas such features are less important for reaching movements.

Rejecting the idea that a non-significant thinning of the ventromedial cortex in DF has a functional, network effects of anatomical damage in different locations of the ventral stream might better explain the consistent findings in HWS and DF. A possible role of the ventral stream in memory-guided actions is that its structures represent spatial object information in allocentric coordinates. Whereas targets of visually-guided movements are supposed to be encoded egocentrically (Milner & Goodale, 2008), allocentric coded information (i.e., with respect to external objects or visual landmarks) gains more importance in memory-guided movements, grasping as much as reaching, as uncertainty about the position of a target increases with increasing delays. This assumption was supported by the observation that DF's allocentric coding was impaired (Dijkerman, Milner, & Carey, 1998; Schenk, 2006). The present study as well as Milner, Dijkerman, et al. (1999) were conducted in the presence of landmarks in the visual environment beyond the experimental setup that allowed for an allocentric coding of target positions. If it is not the temporal delay between target presentation and movement execution by itself but the allocentric coding of target positions in the memory-guided condition, this more general feature of the ventral visual system might explain common deficits in both patients with only small, if any, anatomical overlap.

With respect to our patient HWS, possible candidate regions for impaired allocentric coding of visual targets are the retrosplenial cortex (RSC) and the lingual gyrus, the latter being clearly affected in HWS. The RSC receives indirect projections from the parieto-medial temporal pathway connecting dorsal regions with the medial temporal lobe (for a comprehensive review, see Kravitz, Saleem, Baker, & Mishkin, 2011). It is associated with the allocentric representations of the surroundings and with the processing of visual landmarks (Committeri et al., 2004). It is even speculated that the RSC codes objects in relation to landmarks (Galati, Pelle, Berthoz, & Committeri, 2010). The cuneus and the lingual gyrus are specifically involved in allocentric coding during memory-guided reaching (Chen et al., 2014). Both were damaged in HWS, but not in DF. However, even if there would be no dysfunction in DF's ventromedial cortex, impaired functional connectivity between structurally impaired ventrolateral area and usually densely connected components of the abovementioned allocentric coding system might have been sufficient to cause her memory-guided reaching deficits back in 1999 (Milner, Dijkerman, et al., 1999).

Acknowledging the apparent anatomical and behavioral changes in DF since the early 90's, our data from HWS also provides conclusive information on the recently described optic-ataxia like misreaching in DF. In two studies Hesse et al. (2012, 2014) reported deficits in visually-guided reaching for peripheral targets relative to foveated targets in DF. The authors discussed whether this unexpected behavioral observation could be associated with the well-known bilateral ventral stream damage in DF (Hesse et al., 2012, 2014). However, Bridge et al. (2013) reported considerable bilateral parieto-occipital atrophy, which was presumably more extensive than the structural changes already reported in DF's parietal cortex in the first report by Milner et al. (1991). In the light of our knowledge about optic ataxia patients, this bilateral parieto-occipital degeneration would suffice to explain DF's peripheral misreaching. Nevertheless, with damage to the ventral and the dorsal stream in DF and only dorsal damage in some optic ataxia patients we can only conclude that ventral stream damage is not necessary for peripheral misreaching, but it might be sufficient to cause such an impairment. Two empirical observations argue against such an assumption. Although we did not directly compare movements to foveated targets with movements to extra-foveal targets in HWS, his accuracy in the visually-guided condition for all peripheral targets up to the maximum eccentricity of 30° is in the normal range. Thus, a potential dissociation between peripheral and central reaching in HWS could only rely on a considerably better performance of HWS for foveated targets in comparison to healthy controls. Although such a pattern is possible and would be informative, it would not easily qualify as a classical or strong behavioral dissociation. Furthermore, a clinical screening for optic ataxia in the visual agnosia patient JS with bilateral damage of the ventromedial system due to stroke reported by Karnath, Rüter, Mandler, and Himmelbach (2009) revealed no peripheral misreaching. Thus,

we support the speculation by Hesse et al. (2012, 2014) (see also Whitwell et al., 2014) that the atrophy in DF's dorsal stream may be responsible for the dramatic misreaching described in Hesse et al. (2012, 2014).

Our data further characterizes the impairments in memory-guided reaching in DF and HWS as a rather specific visuomotor deficit. Beyond her severe perceptual deficits and her impairment in memory-guided movement tasks, DF also demonstrated a severe impairment in a visuospatial short term memory task, namely the corsi block tapping test (Milner et al. (1991). To exclude the possibility that impairments in memory-guided reaching might be only one consequence of a more general visuospatial memory deficit, we also tested HWS with the corsi block tapping test, but found no deficit. As this clinical test was substantially different from a memory-guided reaching task, we further explored HWS' visuospatial memory performance with a memory task designed to be as similar to our reaching task as possible. Both tasks were almost identical except for the mode of response by the participant: The target stimulus first had to be perceived and to be maintained during the delay period until the participant indicated the previous target location. In the memory task, participants indicated the previous target position via button presses on a keyboard. In contrast, the reaching task required participants not only to indicate the target position, but additionally required a visuomotor transformation and action. In other words, both tasks had identical requirement on perception, but only the memory-guided reaching required additional processes related to visuomotor transformations. Importantly, HWS showed a specific deficit only in the memory-guided reaching task but not in the memory task. Therefore, we conclude that an impairment of memory-guided reaching as observed in HWS and DF represents a rather specific deficit of the visuomotor system based on necessary contribution from ventral areas for memory-guided actions.

Finally, beyond the interpretation of our current data and the original finding in DF (Milner, Dijkerman, et al., 1999), an alternative interpretation of behavioral differences between visually-guided and memory-guided reaching is based on the availability of concurrent visual feedback about the movements accuracy relative to the presented target. Our study implemented closed-loop movement conditions. The scarce reports about the original experiment in DF (Milner, Dijkerman, et al., 1999; Milner & Goodale, 2008) provide no information on this point. However, without explicitly mentioning total darkness or other means to efficiently prevent any visual feedback, we assumed that also the data from DF was based on closed-loop movement execution. Thus, it might be that whenever DF or HWS are forced to execute their movements without direct visual feedback their respective movements accuracy would be reduced. This interpretation could also easily explain why HWS reveals specific deficits in a memory-guided movement task but not in an extremely similar perceptual visuospatial short-term memory tasks. However, although this alternative interpretation would clearly change the structure-function associations of the ventral stream in the context of visuomotor control, it does not invalidate the mere observation and successful replication of a behavioral dissociation in the first place. With an extremely small number of patients available for these studies we first strived for a successful replication of a known, important, but scarcely described finding and look forward to further investigations on the open questions mentioned above.

5. Conclusion

We demonstrated that a unilateral damage of the ventral stream resulted in a dissociation between visually-guided and memory-guided reaching compared to age-matched healthy controls for a peripheral target in the contralesional visual hemifield. Deficits in memory-guided reaching in HWS cannot be explained by perceptual or a general visuospatial short-term memory deficit but seem to be represent a specific deficit in visuomotor processing. Since patient HWS does not display any dorsal stream lesions, the behavioral deficit can be clearly attributed to the unilateral ventral stream lesion. The absence of a significant misreaching in the visually-guided movement condition provides a straightforward interpretation for a recently described optic-ataxia like misreaching in the well known patient DF based on a recently described extensive, bilateral damage of her parieto-occipital cortex.

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REFERENCES

Behrens, T. E. J., Johansen-Berg, H., Woolrich, M. W., Smith, S. M., Wheeler-Kingshott, C. A. M., Boulby, P. A., et al. (2003). Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nature Neuroscience, 6*(7), 750–757. http://dx.doi.org/10.1227/01.NEU.0000309595.77090.89.

Bridge, H., Thomas, O. M., Minini, L., Cavina-Pratesi, C., Milner, A. D., & Parker, A. J. (2013). Structural and functional changes across the visual cortex of a patient with visual form agnosia. *The Journal of Neuroscience, 33*(31), 12779–12791. http://dx.doi.org/10.1523/JNEUROSCI.4853-12.2013.

Cavina-Pratesi, C., Goodale, M. A., & Culham, J. C. (2007). FMRI reveals a dissociation between grasping and perceiving the size of real 3D objects. *PLoS One, 2*(5), e424. http://dx.doi.org/10.1371/journal.pone.0000424.

Chen, Y., Monaco, S., Byrne, P., Yan, X., Henriques, D. Y. P., & Crawford, J. D. (2014). Allocentric versus egocentric representation of remembered reach targets in human cortex. *Journal of Neuroscience, 34*(37), 12515–12526. http://dx.doi.org/10.1523/JNEUROSCI.1445-14.2014.

Cohen, N. R., Cross, E. S., Tunik, E., Grafton, S. T., & Culham, J. C. (2009). Ventral and dorsal stream contributions to the online control of immediate and delayed grasping: a TMS approach. *Neuropsychologia, 47*(6), 1553–1562. http://dx.doi.org/10.1016/j.neuropsychologia.2008.12.034.

Committeri, G., Galati, G., Paradis, A.-L., Pizzamiglio, L., Berthoz, A., & LeBihan, D. (2004). Reference frames for spatial

cognition: different brain areas are involved in viewer-, object-, and landmark-centered judgments about object location. *Journal of Cognitive Neuroscience, 16*(9), 1517–1535. http://dx.doi.org/10.1162/0898929042568550.

Corsi, P. M. (1972). Human memory and the medial temporal region of the brain. *Dissertation Abstracts International, 34*, 891.

Crawford, J. R., & Garthwaite, P. H. (2005). Testing for suspected impairments and dissociations in single-case studies in neuropsychology: evaluation of alternatives using monte carlo simulations and revised tests for dissociations. *Neuropsychology, 19*(3), 318–331. http://dx.doi.org/10.1037/0894-4105.19.3.318.

Crawford, J. R., & Howell, D. C. (1998). Comparing an individual's test score against norms derived from small samples. *Clinical Neuropsychologist, 12*(4), 482–486. http://dx.doi.org/10.1076/clin.12.4.482.7241.

Dijkerman, H. C., Milner, A. D., & Carey, D. P. (1998). Grasping spatial relationships: failure to demonstrate allocentric visual coding in a patient with visual form agnosia. *Consciousness and Cognition, 7*(3), 424–437. http://dx.doi.org/10.1006/ccog.1998.0365.

Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., et al. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage, 25*(4), 1325–1335. http://dx.doi.org/10.1016/j.neuroimage.2004.12.034.

Fiehler, K., Bannert, M. M., Bischoff, M., Blecker, C., Stark, R., Vaitl, D., et al. (2011). Working memory maintenance of grasp-target information in the human posterior parietal cortex. *NeuroImage,* 54(3), 2401–2411. http://dx.doi.org/10.1016/j.neuroimage.2010.09.080.

Galati, G., Pelle, G., Berthoz, A., & Committeri, G. (2010). Multiple reference frames used by the human brain for spatial perception and memory. *Experimental Brain Research, 206*(2), 109–120. http://dx.doi.org/10.1007/s00221-010-2168-8.

Ganel, T., Chajut, E., & Algom, D. (2008). Visual coding for action violates fundamental psychophysical principles. *Current Biology, 18*, 599–601. http://dx.doi.org/10.1016/j.cub.2008.04.052.

Ganel, T., Tanzer, M., & Goodale, M. A. (2008). A double dissociation between action and perception in the context of visual illusions. *Psychological Science, 19*(3), 221–225. http://dx.doi.org/10.1111/j.1467-9280.2008.02071.x.

Goodale, M. A., Jakobson, L. S., & Keillor, J. M. (1994). Differences in the visual control of pantomimed and natural grasping movements. *Neuropsychologia, 32*(10), 1159–1178. http://dx.doi.org/10.1016/0028-3932(94)90100-7.

Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences, 15*, 20–25. http://dx.doi.org/10.1016/0166-2236(92)90344-8.

Härting, C., Markowitsch, H.-J., Neufeld, H., Calabrese, P., Deisinger, K., & Kessler, J. (2000). *Wechsler memory scale – Revised Edition, German Edition. Manual.* Bern: Huber.

Hesse, C., Ball, K., & Schenk, T. (2012). Visuomotor performance based on peripheral vision is impaired in the visual form agnostic patient DF. *Neuropsychologia, 50*(2012), 90–97. http://dx.doi.org/10.1016/j.neuropsychologia.2011.11.002.

Hesse, C., Ball, K., & Schenk, T. (2014). Pointing in visual periphery: is DF's dorsal stream intact? *PLoS One,* 9(3), e91420. http://dx.doi.org/10.1371/journal.pone.0091420.

Himmelbach, M., & Karnath, H.-O. (2005). Dorsal and ventral stream interaction: contributions from optic ataxia. *Journal of Cognitive Neuroscience,* 17, 632–640. http://dx.doi.org/10.1162/0898929053467514.

Himmelbach, M., Nau, M., Zündorf, I., Erb, M., Perenin, M. T., & Karnath, H. O. (2009). Brain activation during immediate and delayed reaching in optic ataxia. *Neuropsychologia,* 47(2009), 1508–1517. http://dx.doi.org/10.1016/j.neuropsychologia.2009.01.033.

Karnath, H.-O., Rüter, J., Mandler, A., & Himmelbach, M. (2009). The anatomy of object recognition–visual form agnosia caused by medial occipitotemporal stroke. *The Journal of Neuroscience, 29*(18), 5854–5862. http://dx.doi.org/10.1523/JNEUROSCI.5192-08.2009.

Kravitz, D. J., Saleem, K. S., Baker, C. I., & Mishkin, M. (2011). A new neural framework for visuospatial processing. *Nature Reviews. Neuroscience, 12*(4), 217–230. http://dx.doi.org/10.1038/nrn3008.

Malach, R., Reppas, J. B., Benson, R. R., Kwong, K. K., Jiang, H., Kennedy, W. A., et al. (1995). Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. *Proceedings of the National Academy of Sciences, 92*(18), 8135–8139. http://dx.doi.org/10.1073/pnas.92.18.8135.

Mazzucchi, A., Posteraro, L., Nuzzi, G., & Parma, M. (1985). Unilateral visual agnosia. *Cortex, 21*, 309–316. http://dx.doi.org/10.1016/S0010-9452(85)80036-8.

Milner, A. D., & Dijkerman, H. C. (2001). Direct and indirect visual routes to action. In B. de Gelder, E. H. F. de Haan, & C. A. Heywood (Eds.), *Out of mind: Varieties of unconscious processes* (pp. 241–264). Oxford: Oxford University Press.

Milner, A. D., Dijkerman, H. C., & Carey, D. P. (1999). Visuospatial processing in a pure case of visual-form agnosia. In N. Burgess, K. J. Jeffery, & J. O'Keefe (Eds.), *The hippocampal and parietal foundations of spatial cognition* (pp. 443–466). Oxford: Oxford University Press.

Milner, A. D., Dijkerman, H. C., McIntosh, R. D., Rossetti, Y., & Pisella, L. (2003). Delayed reaching and grasping in patients with optic ataxia. *Progress in Brain Research, 142*, 225–242. http://dx.doi.org/10.1016/S0079-6123(03)42016-5.

Milner, A. D., Dijkerman, H., & Pisella, L. (2001). Grasping the past: delay can improve visuomotor performance. *Current Biology*, 1896–1901. Retrieved from http://www.sciencedirect.com/science/article/pii/S0960982201005917.

Milner, A. D., & Goodale, M. A. (2008). Two visual systems re-viewed. *Neuropsychologia, 46*(2008), 774–785. http://dx.doi.org/10.1016/j.neuropsychologia.2007.10.005.

Milner, A. D., Paulignan, Y., Dijkerman, H. C., Michel, F., & Jeannerod, M. (1999). A paradoxical improvement of misreaching in optic ataxia: new evidence for two separate neural systems for visual localization. *Proceedings of the Royal Society B: Biological Sciences, 266*(1434), 2225–2229.

Milner, A. D., Perrett, D. I., Johnston, R. S., Benson, P. J., Jordan, T. R., Heeley, D. W., et al. (1991). Perception and action in "visual form agnosia". *Brain,* 114(1), 405–428. http://dx.doi.org/10.1093/brain/114.1.405.

Mori, S., Wakana, S., Nagae-Poetscher, L. M., & van Zijl, P. C. (2005). *MRI atlas of human white matter.* Amsterdam, Netherlands: Elsevier.

Nieuwenhuis, S., Forstmann, B. U., & Wagenmakers, E.-J. (2011). Erroneous analyses of interactions in neuroscience: a problem of significance. *Nature Neuroscience,* 14(9), 1105–1109. http://dx.doi.org/10.1038/nn.2886.

Schenk, T. (2006). An allocentric rather than perceptual deficit in patient D.F. *Nature Neuroscience,* 9(11), 1369–1370. http://dx.doi.org/10.1038/nn1784.

Schenk, T., Franz, V., & Bruno, N. (2011). Vision-for-perception and vision-for-action: which model is compatible with the available psychophysical and neuropsychological data? *Vision Research,* 51(8), 812–818. http://dx.doi.org/10.1016/j.visres.2011.02.003.

Singhal, A., Monaco, S., Kaufman, L. D., & Culham, J. C. (2013). Human fMRI reveals that delayed action re-recruits visual perception. *PLoS One, 8*(9), e73629. http://dx.doi.org/10.1371/journal.pone.0073629.

Whitwell, R. L., Milner, A. D., & Goodale, M. A. (2014). The two visual systems hypothesis: new challenges and insights from visual form agnosic patient DF. *Frontiers in Neurology,* 5(255), 1–8. http://dx.doi.org/10.3389/fneur.2014.00255.

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Abstract: Patients with optic ataxia show deficits in reaching movements to visual targets in the peripheral visual field. Even though the very name optic ataxia suggests an isolated deficit in visuomotor coordination, there is some evidence that the disorder is not restricted to visual targets, but might also affect other modalities. We examined two chronic optic ataxia patients in reaching tasks with visual, auditory and proprioceptive targets, directly comparing all three modalities. Both patients showed the characteristic pattern of visual misreaching in optic ataxia patients. This disorder clearly dissociated from reaching towards auditory or proprioceptive targets. Both patients were unimpaired in auditory reaching and the errors in proprioceptive reaching – observed in one of the two patients – were substantially different from errors in reaching to visual targets. We conclude that optic ataxia is not multimodal in nature. This argues against a common neuronal correlate for visual, proprioceptive and auditory reference frames, but does not exclude an independent co-occurrence of spatial errors in other modalities with optic ataxia.

Cover Letter

Dear Editors,

This submission is intended for the Special Issue entitled: "Where to go now with the 'What & Where' pathway model" edited by Mel Goodale, Steve Jackson, Thomas Schenk and Edward de Haan.

Sincerely yours,

Hans-Otto Karnath

*Title page

Optic ataxia is only 'optic': a comparison of visual, auditory and proprioceptive reaching

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Highlights:

- We investigated possible dissociations or commonalities between modalities in optic ataxia.
- We examined two optic ataxia patients with peripheral visual, auditory and proprioceptive targets.
- Both patients were unimpaired in auditory reaching.
- Proprioceptive reaching errors in one patient were substantially different from visual reaching errors.
- We conclude that optic ataxia is a visual not a multimodal deficit.

Optic ataxia is only 'optic': a comparison of visual, auditory and proprioceptive reaching

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Abstract

Patients with optic ataxia show deficits in reaching movements to visual targets in the peripheral visual field. Even though the very name *optic* ataxia suggests an isolated deficit in visuomotor coordination, there is some evidence that the disorder is not restricted to visual targets, but might also affect other modalities. We examined two chronic optic ataxia patients in reaching tasks with visual, auditory and proprioceptive targets, directly comparing all three modalities. Both patients showed the characteristic pattern of visual misreaching in optic ataxia patients. This disorder clearly dissociated from reaching towards auditory or proprioceptive targets. Both patients were unimpaired in auditory reaching and the errors in proprioceptive reaching − observed in one of the two patients − were substantially different from errors in reaching to visual targets. We conclude that optic ataxia is not multimodal in nature. This argues against a common neuronal correlate for visual, proprioceptive and auditory reference frames, but does not exclude an independent co-occurrence of spatial errors in other modalities with optic ataxia.

Key Words:

Optic ataxia; Proprioceptive ataxia; Auditory ataxia; Dissociation; Dorsal; Ventral; Stroke; Human

Introduction

Lesions to the posterior parietal cortex (PPC) may cause a visuomotor deficit towards visual targets in the periphery termed ‘optic ataxia’. Under central fixation, reaching errors increase with increasing eccentricity of target location (Blangero et al., 2010; Carey, Coleman, & Della Sala, 1997; Milner, Dijkerman, McIntosh, Rossetti, & Pisella, 2003; Milner, Paulignan, Dijkerman, Michel, & Jeannerod, 1999; Revol, Rossetti, Vighetto, & Rode, 2003). In their seminal group study, Perenin and Vighetto (1988) reported that while right brain-damaged patients showed pronounced misreaching with both hands in the contralesional visual field (field effect), left brain-damaged patients displayed additional misreaching with the contralesional hand even in the ipsilesional visual field (hand effect). This apparent lateralization of field- and hand-effect was not supported by a more recent group study. Blangero et al. (2010) found a field effect in each of their 4 left brain damaged and 3 right brain damaged patients. However, they found a hand effect only in 2 left and 2 right brain damaged patients. The authors proposed that hand and field effects are not specific for either hemisphere and are independent deficits that can occur in combination.

The purpose of the present study was to investigate whether or not ‘optic ataxia’ is visual (or visuomotor) in nature, i.e. whether or not the misreaching particularly affects reaches towards visual targets, but not targets of other modalities. Perenin and Vighetto (1988) described optic ataxia as a purely visuomotor deficit that is independent of primary visual, motoric or proprioceptive deficits. The exclusion of a proprioceptive disturbance was based on the observation of unimpaired seizing of either thumb with opened or closed eyes in their patients. Blangero and colleagues (2007) directly investigated proprioceptive guided reaching in two optic ataxia patients without primary proprioceptive deficits. Both patients showed gross

misreaching when reaching in the dark with their contralesional (ataxic) hand to their ipsilesional hand and vice versa (Blangero et al., 2007). The latter argued for disturbed proprioceptive reaching and the authors therefore suggested that optic ataxia is multimodal in nature. Unfortunately, this study did not investigate whether or not a difference in performance existed between reaches to foveated proprioceptive targets and non-foveated proprioceptive targets, as it typically is observed for optic ataxia patients' reaches toward visual targets. Importantly, it is possible that the observed misreaching is independent of a concomitant optic ataxia and caused by anatomically different substrates. In fact, misreaching to proprioceptive targets as a function of visual input has been demonstrated before in the absence of optic ataxia in a patient with thalamic stroke (Newport, Hindle, & Jackson, 2001).

What about reaching to auditory targets in optic ataxia patients? Considering the involvement of the PPC in the localization of sound sources (Alain, Arnott, Hevenor, Graham, & Grady, 2001; Zündorf, Lewald, & Karnath, 2013) and reaching movements towards sounds with a joystick (Weeks et al., 1999; Zatorre, Bouffard, Ahad, & Belin, 2002), one can speculate whether reaches to auditory targets are affected by optic ataxia. Cell recordings in monkeys demonstrated the encoding of auditory targets in an eye centered reference frame (Cohen & Andersen, 2000; Mazzoni, Bracewell, Barash, & Andersen, 1996; Stricanne, Andersen, & Mazzoni, 1996) and supported the hypothesis of multimodal retinotopic target encoding as well as behavioral studies in humans (Pouget, Ducom, Torri, & Bavelier, 2002). In contrast to this line of research, research on optic ataxia in neurological patients assumed a clear-cut dissociation between misreaching to visual targets and intact reaching to auditory targets. But there are surprisingly few studies substantiating this widely accepted dissociation with empirical data. Perenin and Vighetto (1988) reported that they observed misreaching to auditory targets in only one out of 10

patients who showed optic ataxia. Nine of their patients “behaved as normals or nearly so when required to reach for or to point towards an auditory target (a small loudspeaker) located at various places in front of them, while keeping their eyes closed” (Perenin & Vighetto, 1988; p. 661). Only one of their patients showed reaching errors for auditory targets. However, beyond this anecdotal report the authors presented no data. It was also unknown how many of the patients who behaved “nearly” normal were in fact impaired. Moreover, it is interesting to note that Perenin and Vighetto (1988) instructed the patients to close their eyes for the auditory reaching task. Thence, by definition there were no extrafoveal targets as there was no determined fixation position. Tzavaras and Masure (1976) examined an optic ataxia patient who was hearing impaired. They reported auditory misreaching that was, however, not consistent with an ‘auditory ataxia’. A third study examined reaching to visual and auditory targets in a patient suffering from Balint’s syndrome due to a bilateral glioma (Guard et al., 1984). The authors reported misreaching for peripheral visual targets under free gaze condition and misreaching to auditory targets when the patient was allowed to foveate the targets. Taken together, misreaching to auditory targets was so far not systematically investigated and compared to reaching to visual targets in optic ataxia patients.

Summarizing the existing body of evidence, we conclude that the available data on behavioral dissociations between target modalities in optic ataxia patients is still equivocal. We thus examined two patients with optic ataxia after stroke and compared visual, proprioceptive, and auditory reaching tasks. We focused on three typical characteristics of optic ataxia to decide whether reaching accuracy in the non-visual modalities was similar to the individual pattern of misreaching in the visual modality. First, we compared reaching to non-foveated targets with reaching to foveated targets since optic ataxia patients are impaired when reaching to an extra

foveal target, but unimpaired when the target is fixated (Jackson et al., 2009). Second, we analyzed field effects, which have been reliably observed for reaching to visual targets in optic ataxia patients (Perenin & Vighetto, 1988; Blangero et al., 2010) and have already been demonstrated for proprioceptive reaching in one optic ataxia patient (Blangero et al. 2007), in all modalities. Finally, because of the typical eccentricity dependence of misreaching in optic ataxia we focused on the most eccentric target positions. If visual, proprioceptive, and/or auditory misreaching represent common components of a 'multimodal ataxia', differences between foveated and non-foveated reaching should be maximal at the most peripheral contralesional target location across modalities.

Methods

Patients

The 42-year-old, left-handed patient IT had an occlusion of the middle cerebral artery leading to a left hemispheric stroke 8 years before the experimental measurements reported here. Magnetic resonance FLAIR images acquired at the time of testing on a 3T Siemens TIM Trio Scanner (12-channel receive head coil, 40 axial slices, TE 75 ms, TR=9000 ms, 2 mm slice thickness, gap of 2 mm, flip angle 150°, FoV 176 x 256 mm^2, matrix size 176 x 256) revealed a widespread chronic temporo-parietal lesion that also spread into frontal as well as occipital regions (Figure 1a). Subcortically, parts of the thalamus and basal ganglia were affected. In agreement with the damage to the left postcentral sulcus, clinical examination showed a hypoesthesia in her right hand and arm. After an initial hemiplegia after her stroke, she displayed a dystonia of fingers III-IV on the right hand, but no latent or manifested paresis. This deficit is in accord with damage to the inferior aspects of her precentral gyrus. A clinical perimetry using the confrontation technique indicated no primary visual field defect. A detailed test in the experimental setup confirmed this finding: IT was asked to give a verbal response as soon as a target was illuminated and performed this detection task correctly under fixation. A computerized threshold-based perimetry examination (Octopus 101, Haag-Streit International, Köniz, Switzerland) indicated visual deficits beyond 30° of visual angle. IT demonstrated a unilateral visual agnosia (Mazzucchi, Posteraro, Nuzzi, & Parma, 1985) with impairments of object recognition and discrimination upon tachistoscopic presentations in her contralesional visual hemifield. She demonstrated no signs of visual, auditory, or tactile extinction in a clinical screening with 10 left, 10 right and 10 bilateral stimuli (visual: simultaneous confrontation testing, detection of the examiner's left and/or right index finger

movement in the left and right visual field; auditory: clicking ballpoint pens near the patient's left and/or right ear; tactile: twitching the left and/or right shoulder). An audiometry indicated comparable hearing thresholds for both ears (interaural difference did not exceed 10 dB).

The 63-year-old right-handed patient HM had an internal carotid artery stenosis that caused a right hemispheric media stroke about 4 years before the experimental measurements reported here. A CT was acquired about 4 weeks post-stroke. It revealed a right hemispheric temporo-parietal lesion that spread to the rostral part of the postcentral sulcus (Figure 1b). Anterior, the temporal operculum as well as the dorsal part of the insula were affected. He initially showed a latent paresis of his left arm (pronation) that was recovered at the time of testing. Patient HM demonstrated no signs of visual neglect, visual, auditory, or tactile extinction. An audiometry indicated comparable hearing thresholds for both ears (interaural difference did not exceed 10 dB) except for a frequency of 8 kHz. Repeated visual field testing with the confrontation technique at the time of his first hospital admission and before each experimental measurement reported here did not reveal any visual field defects.

For the recruitment for this study, both patients were clinically examined for the presence of optic ataxia (Borchers, Müller, Synofzik, & Himmelbach, 2013). In both patients the results of the initial examinations demonstrated the presence of optic ataxia. For detailed results, please see table 1 (initial screening).

- Figure 1 about here -

- Table 1 about here –

General procedure

Both patients participated in multiple measurements that took place on multiple days. In the following, we will first give an overview of the series of experiments for each patient.

Patient IT first participated in a measurement of her visually and auditory guided reaching accuracy with her right, contralesional hand in Experiment 1. Two months later, we re-examined visually and auditory guided reaching in IT with her right, contralesional hand, followed by an examination of her left, ipsilesional hand (Experiment 2). On the same day, we also examined her proprioceptive reaching accuracy (Experiment 3).

Patient HM conducted one session of Experiment 1 (visual and auditory targets) and Experiment 3 (proprioceptive targets) on the same day. Later, he was invited again to conduct a second session of experiment 1. In both experiments we examined his performance with his left, contralesional hand.

Healthy controls first conducted visually and auditory guided reaching, with each hand tested at a different day. The proprioceptive measurements in healthy controls were always conducted after the visual-auditory measurements on a separate day.

All participants gave their informed consent to participate in the study, which was performed in accordance with the Declaration of Helsinki and approved by the local Ethic Committee.

Clinical screening for optic ataxia

On each respective testing day, the patients were re-examined for the presence of optic ataxia with the procedure and scoring system reported in Borchers et al. (2013). Thus, patient IT was tested four times; during initial recruitment, on the day of experiment 1, on the day of experiments 2 and 3, and finally again when she was recruited for another experiment (please see table 1). Patient HM was tested three times; during initial recruitment, on the day of the acquisition of the first session of experiment 1 and full experiment 3, and finally on the day of the acquisition of session 2 of experiment 1.

All examinations confirmed the presence of optic ataxia in both patients. Their error scores for the contralesional hand in the contralesional field always exceeded the healthy controls' threshold (Crawford and Garthwaite (2005), threshold of $p < 0.05$).

Experiment 1: Reaching to visual and auditory targets with the contralesional hand.

Participants

We examined IT, HM and 13 healthy, age-matched adults (11 females, age range = 37- 64 y; mean age = 56 y) without any history of neurological or psychiatric disorder. All controls were right-handed and had normal or corrected to normal vision. Monaural auditory thresholds showed no differences between the ears exceeding 10dB across a frequency range between 0.125 and 3kHz.

Procedure and apparatus

The participants sat in a darkened room at a table with a black vertical panel fixed on the tabletop. Their head rested on a chinrest and the index finger of their reaching hand rested on a start button at the midsagittal body plane. The vertical panel was at a distance of 36 cm from the chin rest and of 30 cm from the start button. Light emitting diodes (LEDs, diameter 3mm, light intensity 20 mcd) were mounted at the panel at a height of 47 cm from the tabletop. Behind each LED, a tube (length 14 cm) was fixated with a speaker (3.3 x 2.3 cm) at its end. The tube served to avoid distortions of the magnetic field of the motion tracking system and additionally channeled the sound so it appeared at the same location as the visual targets. A green LED at the midsagittal body plane and at the same height as the targets served as fixation target. The experimenter started each trial manually. After a variable interval (ranging from 1 s to 1.5 s in steps of 100 ms) one of the targets - red LEDs in the visual-guided reaching or white noise stimuli with an average sound pressure level of 78 dB(A) in the auditory-guided reaching - was presented for 2 seconds at one of three possible eccentricities (± 9°, ± 17° or ± 28° degree of visual angle, Figure 2 a, b).

Participants were tested in two conditions: They were either instructed to keep their gaze on the fixation LED and only reach with their hand for the respective target (H, hand) or to look at the respective target in their peripheral visual field and reach for it with their hand (EH, eye-hand). The participants were instructed to execute movements as quick and precise as possible. The order of target positions was randomized. The visual and auditory targets were presented in blocks of 18 trials for each condition (3 trials per target) within an ABBA design (visual H, visual EH, acoustic H, acoustic EH, acoustic EH, acoustic H, visual EH, visual H). In total, 16 experimental blocks, 8 visual and 8 auditory blocks, were recorded per participant in two sessions with a minimum of 10 practice trials at the beginning of either session. Please note that patient IT conducted the full experiment 1 on one day, whereas patient HM conducted one session with all conditions on one day and later conducted a full second session.

Healthy controls conducted the measurements twice, once with their right and once with their left hand. Patients HM used only his contralesional hand, patient IT also used her ipsilesional hand in experiment 2. Reaching trajectories were recorded with a magnetic sensor attached to the participants' index finger (miniBird Motion Tracking system, 0.5 mm resolution, Ascension Technology Cooperation, Vermont, USA) at a rate of 100 Hz. Correct fixation during fixation trials was verified online and recorded for later offline control with a digital IR video system.

- Figure 2 about here -

Analysis

All data were analyzed using custom software based on MATLAB (MathWorks Inc., Sherborn, MA, USA) and R (r-project.org, version 3.0.1). First, raw data was filtered

using a fourth-order zero-phase shift lowpass Butterworth filter with a cutoff frequency of 20 Hz. Movement onset was defined as the time at which the velocity of the marker at the index finger exceeded a threshold of 5 cm/s in four consecutive frames. If no onset could be detected with this threshold, we analyzed the same trial with a threshold of 10 cm/s. Reaction time (RT) was defined as the time between target presentation and detected movement onset. The end of the movement towards the target was defined (i) as lying within the interval between the highest velocity of the movement towards the target, and the highest velocity of the movement back to the start button and (ii) by the point at which the absolute deceleration was 0 mm/s^2 and (iii) velocity was below 10 cm/s at the same time. Movement time (MT) was defined as the time between the movement onset and the end of the movement.

Trials were excluded from further analysis if no movement end point could be identified. We analyzed the absolute horizontal deviation of the movement end point from the respective target position. Because of a strong effect of target eccentricity with largest errors always for the most eccentric targets in optic ataxia (Blangero et al., 2010; Carey et al., 1997; Milner et al., 2003, 1999; Revol et al., 2003) and to avoid multiple independent single case analyses for multiple target locations, we focused our analysis on the most eccentric contralesional target (i.e. +28° for IT, -28° for HM) if not stated otherwise.

We compared the difference of the patients' reaching errors between both viewing conditions (H vs. EH) with the corresponding difference in reaching errors of healthy subjects using single case dissociation tests (Crawford & Garthwaite, 2005) for both modalities individually, i.e. for visual and auditory targets (Vis[H-EH], Audit[H-EH]). Then, we compared the patients' difference values (H - EH) between modalities (Vis[H-EH] – Audit[H-EH]), again using a standardized difference test for single case

dissociations (Crawford & Garthwaite, 2005). Finally, we compared the differences between both viewing conditions (H – EH) for the contralesional and the ipsilesional target in the visual and the auditory conditions respectively (Vis: contra[H-EH]-ipsi[H-EH]; Audit: contra[H-EH]-ipsi[H-EH]) to verify visual field effects of movement errors that would be typical for optic ataxia.

The reported p-values correspond to one-tailed tests, because of directional hypotheses for all comparisons (always H worse than EH; visual worse than auditory; contralesional field worse than ipsilesional field).

Results

The experimental measurement confirmed the screening results: both patients revealed a dissociation between movement conditions (H vs. EH) in visually-guided reaching. They showed larger misreaching errors under central fixation relative to coordinated Eye-Hand movements in comparison to controls as evidenced by the results of the dissociation tests for the respective most peripheral contralesional target (vis[H – EH]; IT at +28°: $t(12)= 7.97$; $p<0.001$; HM at -28°: $t(12)= 3.37$; $p= 0.003$; see table 2 and 3). Furthermore, we found a significant field effect for visually guided reaching in both patients (contra[H-EH]-ipsi[H-EH]; IT: $t(12)= 8.90$; $p<0.001$; HM: $t(12)= 2.21$; $p=0.02$).

No significant dissociation between viewing conditions (H vs. EH) was observed for auditory guided reaching (aud[H-EH]; IT: $t(12)= 0.68$; $p= 0.25$; HM: $t(12)= 1.10$; $p= 0.15$; see table 2 and 3). Neither patient showed a field effect when reaching to auditory targets (contra[H-EH]-ipsi[H-EH]; IT: $t(12)= 0.03$; $p= 0.49$; HM: $t(12)= 0.75$; $p= 0.23$). Finally, we directly compared the differences between both viewing conditions in auditory and visually guided reaching (vis[H-EH] – aud[H-EH]) for the most eccentric contralesional target at +28° for IT, respectively -28° for HM. Visually-

guided reaching dissociated from auditory-guided reaching in comparison to controls in IT ($t(12)= 6.18$, $p<0.001$) and HM ($t(12)= 3.16$, $p= 0.004$).

- Figure 3 about here -

Discussion Experiment 1

As expected based on the clinical screening, IT and HM demonstrated the characteristic signs of optic ataxia in the experimental setup including stronger misreaching to peripheral visual targets in comparison to foveated visual targets. Both patients showed typical field effects for visual targets.

As can be seen in figure 3, the interpretation of the statistical test outcomes in IT suggest a straightforward interpretation. Optic ataxia deficits in visually guided reaching were contrasted with reaching errors in the normal range for auditory guided reaching.

The outcome was apparently less clear for patient HM. He also showed the typical error pattern for visually guided reaching. However, the difference between movement conditions (H-EH) was larger in the auditory than in the visual condition. This descriptive result pattern was completely reversed once the normal performance of healthy controls was taken into account. Reaching for auditory targets with their left hand, healthy controls showed larger errors than for visual targets and a much larger inter-individual variability. As a result, the standardization of HM's movement errors in both target modalities (visually-guided reaching $z = 6.21$, auditory-guided reaching $z = 1.51$) revealed behavioral dissociations in the same direction as in patient IT. While the outcome for the comparison between hand and eye-hand conditions for auditory targets was rather inconclusive with $p = 0.15$ (aud[H-EH]), the outcome of the dissociation test between target modalities (vis[H-EH] – aud[H-EH]) was clear also for patient HM, with $p = 0.004$ in the expected direction, i.e. a

significantly larger standardized difference in visual reaching than in auditory reaching relative to controls.

The apparently contradictory outcome in patient HM is a consequence of the standardization of a patient's performance relative to a control sample. If two tasks are considerably different from each other in healthy controls, this must be taken into account for between task comparisons in patients. If two tasks are sufficiently different from each other in a control sample, standardization can indeed result in a substantially different results pattern relative to unstandardized performance scores of the respective patient.

Because patient IT revealed visual field defects close to, although not overlapping with the eccentricity of the most peripheral contralesional target, we additionally examined her performance with her ipsilesional hand to exclude that the dissociation between the auditory and visual modality were evoked by impaired visual processing. The presence of a hand-effect would argue against the objection that the results of IT in experiment 1 were primarily caused by visual field defects.

Experiment 2: Hand effect of reaching to visual and auditory targets in patient IT.

Participants

Only patient IT participated in this experiment together with the same controls who participated in experiment 1. We tested both hands in IT, thereby a replication of the measurements with the contralesional hand already conducted in experiment 1 was included in experiment 2.

Procedure and apparatus

Procedure and apparatus were identical to experiment 1 with the following exceptions. For IT, only 12 trials per block were recorded respectively for reaches with the ipsilesional left hand and for the re-test of the contralesional right hand. As in experiment 1, all participants conducted 16 experimental blocks (8 visual blocks and 8 auditory blocks) in two sessions and controls conducted 18 trials per block.

Analysis

We compared IT's difference between eye-hand conditions (E-EH) between both hands for the most eccentric target at +28° in the contralateral hemifield (contraHand[H-EH] – ipsiHand[H-EH]) to the respective difference in controls using a standardized single case dissociation test (Crawford & Garthwaite, 2005). Again, p-values are reported for directional hypotheses.

Results

In the experimental measurements, twelve weeks after experiment 1, IT again demonstrated a significant dissociation between the hand only and eye-hand conditions in visually guided reaching with her contralesional, right hand ($t(12)= 5.67$; $p<0.001$). As before, no dissociation was observed in auditory-guided reaching ($t(12)= 0.09$, $p=0.46$; see table 2). The performance difference between both viewing

conditions in the visually-guided reaching compared to the difference in auditory-guided reaching was again significant (vis[H-EH] – aud[H-EH]: t(12)= 3.82, *p*=0.001). Reaching to visual targets, the difference between eye-hand conditions was significantly larger with her contralesional than with her ipsilesional hand in comparison to controls (t(12)= 2.02, *p*=0.03). No significant dissociation between hands was observed when reaching to the auditory target (t(12)=0.62, *p*=0.27).

Discussion Experiment 2

A significant dissociation between IT's hands supported the interpretation that her reaching deficits to a peripheral target in the contralesional hemifield were not primarily caused by visual deficits that would have affected both hands. This experimental finding was supported by the clinical optic ataxia screening, which in the contralesional visual field always showed worse outcomes for the contralesional hand than for the ipsilesional hand (table 1). In the following third experiment we examined both patients' accuracy in proprioceptive guided reaching.

Experiment 3: Reaching to proprioceptive targets

Participants

Patient IT and patient HM participated in this experiment together with 12 controls who already participated in experiments 1 and 2.

Procedure and apparatus

Experiment 3 was conducted right after experiment 2 in patient IT and right after the first session of experiment 1 in patient HM. The data from this proprioceptive experiment were compared to the data from the visual conditions of experiment 1. The participants were seated at a table with a miniature table on top of it (70 cm x 39.5 cm). Three rows with six horizontal targets each were arranged vertically on the miniature table, resulting in 18 targets in total with horizontal eccentricities of ±8°, ±22°, and ±33° from fixation (Figure 2 c). Target positions were marked underneath the table and were invisible on the top of the miniature table (Figure 4 b).

One hand of the participant was placed below the miniature table with the palm of the hand oriented upwards and only the index finger extended (Figure 4 a). The experimenter instructed the participant to close her/his eyes and positioned the tip of the index finger of the participant's passive hand at one of the target positions underneath the table. Subsequently, the participant was instructed to open her/his eyes again. In the EH condition, participants were instructed to saccade to the felt target position and to reach with the index finger of the active hand to the felt position of the opposite index finger of the passive hand (Figure 4 b). In the H condition, participants fixated a marker at the midsagittal body plane at a distance of 8 cm to the closest horizontal line of targets (Figure 2 c and Figure 4 b). In both conditions, participants were encouraged to execute an uninterrupted smooth movement at comfortable speed. Participants were not permitted to correct presumably inaccurate

reaches after they made contact with the table surface. Every condition comprised 36 trials, 2 trials per target position. 7 control participants conducted the H condition before the EH condition whereas 5 controls first conducted the EH condition. Arm reaches were recorded with a video camera. The experimenter was situated opposite to the participant and monitored correct fixation during the H condition. Trials with incorrect fixation were repeated at the end of the experiment.

- Figure 4 about here -

Analysis

All data were analyzed using custom software based on MATLAB (MathWorks Inc., Sherborn, MA, USA) and R (r-project.org). We first removed spatial distortions in the video recordings, which were due to the viewing angle of the camera using custom written Matlab-scripts. The end positions of the index finger of the active (reaching) hand were marked manually and compared to the actual target position. Results were averaged across the three vertically distributed targets at the same horizontal eccentricity in each participant (cp. Figure 2 c).

As in the previous experiments, we compared the patients' absolute horizontal reaching errors between both viewing conditions (H vs. EH) with the contralesional hand towards peripheral targets in the contralesional hemifield to those of healthy controls (proprio[H-EH]). Afterwards, we directly compared the differences between H and EH for visually-guided reaching, taken from experiment 1, and for proprioceptive-guided reaching (vis[H-EH] – proprio[E-EH]). Since data from one control participant was missing in the proprioceptive task, we also excluded her data

from the visually-guided reaching dataset. All comparisons were calculated using a standardized test for single case dissociations (Crawford & Garthwaite, 2005).

Results

IT's proprioceptive-guided reaching with her contralesional hand showed no dissociation between viewing conditions for the most peripheral contralesional targets at +28° (proprio[H – EH]; t(11)= 0.37, *p*=0.36, see table 4 and figure 5). She demonstrated a significant dissociation between the visual movement condition difference and the proprioceptive difference (vis[H-EH] – proprio[H-EH]; t(11)= 4.26, *p*< 0.001) with a larger difference for visual targets and virtually no difference between movement conditions for proprioceptive targets.

The outcome was different in patient HM. When reaching with the contralesional hand to the unseen ipsilesional hand, he showed a significant dissociation for the most peripheral target of the contralesional hemifield between both movement conditions (proprio[H - EH]) (t(11)= 3.33, *p*= 0.003, see table 4 and figure 5) with larger errors in the central fixation condition. Moreover, HM showed no dissociation between his performance in the visually-guided reaching and proprioceptive-guided reaching for the most peripheral target alone (vis[H – EH] – proprio[H – EH]; t(11)= 0.31, *p*= 0.38). However, in clear contrast to HM's performance in visually guided reaching and the typical pattern in optic ataxia (increasing errors with increasing eccentricities), the differences between proprioceptive movement conditions increased with decreasing target eccentricities (Figure 5).

In a complementary dissociation analysis, we included HM's movement errors across all target positions in the whole contralesional (left) hemifield – three targets in the visual conditions of experiment 1, nine targets in the proprioceptive experiment 3. Here we report the p-value for a two-tailed test, as we did not expect worse performance in the proprioceptive condition before the measurement. Based on the

data from the whole contralesional field, we now found a dissociation between the visual and proprioceptive modality (vis[H – EH] – proprio[H – EH]; t(11)= 2.88, *p*= 0.015). However, the difference was larger for the proprioceptive measurements (Figure 5 b).

- Figure 5 about here -

Discussion Experiment 3

Even though both patients showed the typical behavioral patterns associated with optic ataxia, their performance in proprioceptive guided reaching differed considerably. IT's difference between movement conditions for proprioceptive targets was comparable to controls. In line with this, her reaching errors for the most peripheral contralesional target clearly dissociated between visual and proprioceptive conditions, arguing against a proprioceptive ataxia that would resemble the pattern of optic ataxia.

In contrast, HM's proprioceptive guided reaching dissociated between hand only and eye-hand movements to peripheral targets with larger errors for movements under central fixation, indeed comparable to optic ataxia. This finding was further supported by the lack of evidence for a dissociation between reaching to visual and proprioceptive targets. In summary, these findings indicate the presence of a proprioceptive 'optic' ataxia. However, a closer look at the data from the whole contralesional field revealed a misreaching pattern that was inconsistent with the typical pattern of optic ataxia, i.e. stronger misreaching with decreasing eccentricity of the target position. This topography of HM's reaching errors argues against a proprioceptive 'optic' ataxia.

General Discussion

Both patients demonstrated the characteristic misreaching to visual targets in the contralesional peripheral visual field under central fixation, i.e. the typical pattern of optic ataxia, not only in repeated clinical screenings but also in our experimental measurements. In both patient, we found a significant dissociation between these errors in visually guided reaching and auditory guided reaching. Since general deficits in auditory guided reaching and sound localization have been observed after right hemispheric lesions (Bisiach, Cornacchia, Sterzi, & Vallar, 1984). We thus suggest that optic ataxia can coincide with reaching deficits to auditory targets as indicated by a verbal report that suggested that some optic ataxia patients may show signs of an auditory ataxia (Perenin & Vighetto, 1988). This suggests that misreaching to auditory targets and misreaching to visual targets occur independently and thus may be caused by different neuronal modules.

Also our results from the proprioceptive reaching task support the idea of optic ataxia as a purely visuomotor deficit. In IT, visually guided reaching clearly dissociated from proprioceptive guided reaching with impaired performance only for reaching to visual targets. This finding clearly argued against a ‘proprioceptive’ ataxia. Patient HM indeed showed optic ataxia-like misreaching for proprioceptive targets in the contralateral visual hemifield. Additionally, visual and proprioceptive guided reaching did not dissociate for the most peripheral targets. These findings in HM were in line with previous observations in another two patients (Blangero et al., 2007). On closer examination, however, the proprioceptive misreaching pattern in HM across all contralesional target positions was not in agreement with a ‘proprioceptive ataxia’. HM’s misreaching increased with decreasing eccentricity, thus showing a pattern that is opposite to the one typically observed for optic ataxia (Carey et al., 1997; Milner et

al., 2003, 1999; Revol et al., 2003). This latter observation indicated that HM's misreaching to proprioceptive targets is unrelated to optic ataxia and reflects a more general deficit. Indeed, a hand effect as well as an increased misreaching with decreasing visual input has been reported before after a hematoma in the lateral pulvinar and the internal capsule (Newport et al., 2001). Moreover, proprioceptive guided misreaching for both hands has been observed after a lesion (mainly) to the primary somatosensory cortex (Borchers, Hauser, & Himmelbach, 2011). Taken together, these observations indicate that damage to several regions can result in proprioceptive misreaching. Consequently, as for the auditory modality, we conclude that misreaching to proprioceptive targets and misreaching to visual targets occur independently and thus may be caused by different neuronal modules.

Interestingly, not only general difficulties in proprioceptive-guided reaching can be observed after a stroke in the absence of optic ataxia, but also specific misreaching patterns like the hand effect. For example, mildly affected mirror ataxia patients may demonstrate an isolated hand effect (Pisella, Binkofski, Lasek, Toni, & Rossetti, 2006). Taking into consideration that hand effects were not observed consistently in all optic ataxia patients (Blangero et al., 2010), but can be observed independent of optic ataxia, it can be argued that the hand effect itself is actually not caused by optic ataxia and depends on different anatomical modules, but co-occurs frequently. This idea is supported by the observation that field and hand effects are additive (see also Blangero et al., 2010).

The existence of 'proprioceptive ataxia' was proposed based on misreaching to proprioceptive targets in two optic ataxia patients (Blangero et al., 2007). However, we believe that these results require a different interpretation for several reasons. First, patients only reached for extrafoveal targets. Thus, the typical dissociation between reaching to foveated and non-foveated could not be investigated. Second, a

hand effect was reported for one patient. It referred to the observation that misreaching to visual targets decreased when visual feedback of the hand was available, but only for the contralesional hand. Importantly, no direct comparison between the ipsi- and contralateral hand was calculated. The combination of a significant finding for the contralesional hand but a non-significant finding for the ipsilesional hand, however, cannot easily be interpreted as a significant difference between both hands (Nieuwenhuis, Forstmann, & Wagenmakers, 2011) Third, the field effect was postulated based on the observation that the both patients perform worse in their contralesional field than in their ipsilesional field, but their performance was not compared to control participants. Finally, reaching to visual and proprioceptive targets was not directly compared. Taken together, also these results cannot unequivocally be interpreted as evidence for 'proprioceptive ataxia'.

Comparison to studies in macaques

Inactivation of the parietal reach region (PRR) in monkeys caused misreaching to extrafoveal visual targets similar to optic ataxia (OA) in neurological patients (Hwang, Hauschild, Wilke, & Andersen, 2012). Indeed, anatomical studies showed that regions that are putative homologues of the monkey PRR are typically damaged in OA patients (Karnath & Perenin, 2005; Martin, Karnath, & Himmelbach, 2015). Besides encoding of visual target location, the macaque PRR also encodes reaches to auditory targets (Cohen, Batista, & Andersen, 2002) in eye-centered coordinates (Cohen & Andersen, 2000). Moreover, a lesion of the PRR caused deficits in proprioceptive reaching (Rushworth, Nixon, & Passingham, 1997). If the homologue of the monkey PRR has a comparable functional architecture in humans and optic ataxia is due to damage of the PRR, optic ataxia patients should demonstrate misreaching also to auditory and proprioceptive targets.

At first glance, impaired proprioceptive guided reaching in only one of our two patients seems contradictory to the findings of the monkey studies, and argues against a comparable coding mechanism between humans and monkeys for proprioceptive reaching. These apparently conflicting observations can be reconciled taking into account a subdivision of the monkey PRR into two areas (area 7a and MIP). Area 7a is crucial for spatial coordination of visual motor transformations and its removal causes misreaching to visual targets but does not impair reaching in the dark that relies strongly on proprioceptive input (Rushworth et al., 1997). Area MIP is involved in the spatial coordination of reaches based on its role in proprioceptive and efference copy information processing. Its removal mainly affects misreaching in the dark but has little effect on reaching to visual targets (Rushworth et al., 1997). This suggests that for monkeys, damage to area 7a can cause misreaching resembling optic ataxia, and additional damage to the neighboring area MIP might impair proprioceptive guided reaching and cause hand effects. Consequently, we propose that whether or not misreaching to proprioceptive targets can be observed in human optic ataxia patients depends on the precise lesion location and extent. The existence of other candidate regions for optic ataxia in monkeys, like V6A (Battaglini et al., 2002) does not object our conclusion. The assumption of an additional lesion site causing misreaching to proprioceptive targets is in line with our observations. Whereas IT's reaching to proprioceptive targets was unimpaired, HM's reaching was impaired, but not in line with the typical misreaching observed towards visual targets, indicating different underlying mechanisms.

The lack of a deficit in the auditory modality in both patients was surprising given that auditory targets are encoded in eye centered reference frame in the PRR in monkeys (Cohen & Andersen, 2000) and behavioral studies in humans suggested that the location of visual, auditory and proprioceptive targets are coded in eye-centered

coordinates across modalities (Pouget et al., 2002). Yet, other parietal areas like LIP (Mazzoni et al., 1996; Stricanne et al., 1996) and VIP (Schlack, Sterbing-D'Angelo, Hartung, Hoffmann, & Bremmer, 2005) are additionally involved in the encoding of auditory targets and might be sufficient for auditory guided reaching.

Conclusion

The demonstration that reaching to auditory targets was unimpaired in two optic ataxia patients and dissociated from reaching to visual targets strongly argues against an ‘auditory ataxia’. The present results further demonstrated that even though misreaching to proprioceptive targets can co-occur with optic ataxia, this does not necessarily imply a ‘proprioceptive ataxia’; the spatial topography of reaching errors differed from those to visual targets. Our results thus suggest that optic ataxia is not a multimodal deficit. It is restricted to the visual modality but can coincide with deficits in proprioceptive guided reaching (or in reaching to auditory targets) caused by impaired mechanisms that are unrelated to optic ataxia.

References

Alain, C., Arnott, S. R., Hevenor, S., Graham, S., & Grady, C. L. (2001). “What” and “where” in the human auditory system. *Proceedings of the National Academy of Sciences*, *98*(21), 12301–12306. http://doi.org/10.1073/pnas.211209098\r211209098 [pii]

Battaglini, P., Muzur, A., Galletti, C., Skrap, M., Brovelli, A., & Fattori, P. (2002). Effects of lesions to area V6A in monkeys. *Experimental Brain Research*, *144*(3), 419–422. http://doi.org/10.1007/s00221-002-1099-4

Bisiach, E., Cornacchia, L., Sterzi, R., & Vallar, G. (1984). Disorders of perceived auditory lateralization after lesions of the right hemisphere. *Brain*, *107 (Pt 1*(1984), 37–52.

Blangero, A., Ota, H., Delporte, L., Revol, P., Vindras, P., Rode, G., … Pisella, L. (2007). Optic ataxia is not only “optic”: impaired spatial integration of proprioceptive information. *NeuroImage*, *36 Suppl 2*, T61–8. http://doi.org/10.1016/j.neuroimage.2007.03.039

Blangero, A., Ota, H., Rossetti, Y., Fujii, T., Ohtake, H., Tabuchi, M., … Pisella, L. (2010). Systematic retinotopic reaching error vectors in unilateral optic ataxia. *Cortex*, *46*(1), 77–93. http://doi.org/10.1016/j.cortex.2009.02.015

Borchers, S., Hauser, T.-K., & Himmelbach, M. (2011). Bilateral hand representations in human primary proprioceptive areas. *Neuropsychologia*, *49*(12), 3383–91. http://doi.org/10.1016/j.neuropsychologia.2011.08.013

Borchers, S., Müller, L., Synofzik, M., & Himmelbach, M. (2013). Guidelines and quality measures for the diagnosis of optic ataxia. *Frontiers in Human Neuroscience*, *7*(July), 324. http://doi.org/10.3389/fnhum.2013.00324

Carey, D. P., Coleman, R. J., & Della Sala, S. (1997). Magnetic misreaching. *Cortex*, *33*(4), 639–652. http://doi.org/10.1016/S0010-9452(08)70722-6

Cohen, Y. E., & Andersen, R. a. (2000). Reaches to sounds encoded in an eye-centered reference frame. *Neuron*, *27*(3), 647–652. http://doi.org/10.1016/S0896-6273(00)00073-8

Cohen, Y. E., Batista, A. P., & Andersen, R. a. (2002). Comparison of neural activity preceding reaches to auditory and visual stimuli in the parietal reach region. *Neuroreport*, *13*(6), 891–4. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11997708

Crawford, J. R., & Garthwaite, P. H. (2005). Testing for suspected impairments and dissociations in single-case studies in neuropsychology: evaluation of alternatives using monte carlo simulations and revised tests for dissociations. *Neuropsychology*, *19*(3), 318–31. http://doi.org/10.1037/0894-4105.19.3.318

Hwang, E. J., Hauschild, M., Wilke, M., & Andersen, R. a. (2012). Inactivation of the Parietal Reach Region Causes Optic Ataxia, Impairing Reaches but Not Saccades. *Neuron*, *76*, 1021–1029. http://doi.org/10.1016/j.neuron.2012.10.030

Jackson, S. R., Newport, R., Husain, M., Fowlie, J. E., O'Donoghue, M., & Bajaj, N. (2009). There may be more to reaching than meets the eye: re-thinking optic ataxia. *Neuropsychologia*, *47*(6), 1397–408. http://doi.org/10.1016/j.neuropsychologia.2009.01.035

Jackson, S. R., Newport, R., Mort, D., & Husain, M. (2005). Where the eye looks, the hand follows; limb-dependent magnetic misreaching in optic ataxia. *Current Biology*, *15*(1), 42–6. http://doi.org/10.1016/j.cub.2004.12.063

Karnath, H. O., & Perenin, M. T. (2005). Cortical control of visually guided reaching: Evidence from patients with optic ataxia. *Cerebral Cortex*, *15*(October 2005), 1561–1569. http://doi.org/10.1093/cercor/bhi034

Khan, a Z., Pisella, L., Vighetto, a, Cotton, F., Luauté, J., Boisson, D., … Rossetti, Y. (2005). Optic ataxia errors depend on remapped, not viewed, target location. *Nature Neuroscience*, *8*(4), 418–20. http://doi.org/10.1038/nn1425

Martin, J. a., Karnath, H.-O., & Himmelbach, M. (2015). Revisiting the cortical system for peripheral reaching at the parieto-occipital junction. *Cortex*, *64*, 363–379. http://doi.org/10.1016/j.cortex.2014.11.012

Mazzoni, P., Bracewell, R. M., Barash, S., & Andersen, R. a. (1996). Spatially tuned auditory responses in area LIP of macaques performing delayed memory saccades to acoustic targets. *Journal of Neurophysiology*, *75*(3), 1233–1241.

Mazzucchi, A., Posteraro, L., Nuzzi, G., & Parma, M. (1985). Unilateral visual agnosia. *Cortex*, *21*, 309–316. http://doi.org/10.1016/S0010-9452(85)80036-8

Milner, A. D., Dijkerman, H. C., McIntosh, R. D., Rossetti, Y., & Pisella, L. (2003). Delayed reaching and grasping in patients with optic ataxia. *Progress in Brain Research*, *142*, 225–42. http://doi.org/10.1016/S0079-6123(03)42016-5

Milner, A. D., Paulignan, Y., Dijkerman, H. C., Michel, F., & Jeannerod, M. (1999). A paradoxical improvement of misreaching in optic ataxia: new evidence for two separate neural systems for visual localization. *Proceedings of the Royal Society*

B: Biological Sciences, *266*(1434), 2225–2229.

Newport, R., Hindle, J. V., & Jackson, S. R. (2001). Links between vision and somatosensation: Vision can improve the felt position of the unseen hand. *Current Biology*, *11*, 975–980. http://doi.org/10.1016/S0960-9822(01)00266-4

Nieuwenhuis, S., Forstmann, B. U., & Wagenmakers, E.-J. (2011). Erroneous analyses of interactions in neuroscience: a problem of significance. *Nature Neuroscience*, *14*(9), 1105–1109. http://doi.org/10.1038/nn.2886

Perenin, M.-T., & Vighetto, A. (1983). Optic ataxia: A specific disorder in visuomotor coordination. In A. Hein & M. Jeannerod (Eds.), *Spatially oriented behavior* (pp. 305–326). New York: Springer.

Perenin, M.-T., & Vighetto, A. (1988). Optic Ataxia : A specific disuption in cisuomotor mechanisms I. Different aspects of the deficit in Reaching for objects. *Brain*, *111*(3), 643–674. http://doi.org/doi: 10.1093/brain/111.3.643

Pisella, L., Binkofski, F., Lasek, K., Toni, I., & Rossetti, Y. (2006). No double-dissociation between optic ataxia and visual agnosia: multiple sub-streams for multiple visuo-manual integrations. *Neuropsychologia*, *44*(13), 2734–48. http://doi.org/10.1016/j.neuropsychologia.2006.03.027

Pouget, A., Ducom, J. C., Torri, J., & Bavelier, D. (2002). Multisensory spatial representations in eye-centered coordinates for reaching. *Cognition*, *83*(1), 1–11. http://doi.org/10.1016/S0010-0277(01)00163-9

Revol, P., Rossetti, Y., Vighetto, A., & Rode, G. (2003). Pointing errors in immediate and delayed conditions in unilateral optic ataxia. *Spatial Vision*, *16*(3), 347–364. http://doi.org/10.1163/156856803322467572

Rushworth, M. F. S., Nixon, P. D., & Passingham, R. E. (1997). Parietal cortex and movement. *Experimental Brain Research*, *117*(2), 311–323. http://doi.org/10.1007/s002210050225

Schlack, A., Sterbing-D'Angelo, S. J., Hartung, K., Hoffmann, K.-P., & Bremmer, F. (2005). Multisensory space representations in the macaque ventral intraparietal area. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *25*(18), 4616–25. http://doi.org/10.1523/JNEUROSCI.0455-05.2005

Stricanne, B., Andersen, R. a, & Mazzoni, P. (1996). Eye-centered, head-centered, and intermediate coding of remembered sound locations in area LIP. *Journal of Neurophysiology*, *76*(3), 2071–2076. http://doi.org/10.1021/je9001366

Tzavaras, A., Masure, M.C. (1976). Aspects differents de l'ataxie optique selon la lateralisation hemispherique de la lesion. *Lyon Medical, 236*, 673-683.

Weeks, R. a, Aziz-Sultan, a, Bushara, K. O., Tian, B., Wessinger, C. M., Dang, N., … Hallett, M. (1999). A PET study of human auditory spatial processing. *Neuroscience Letters*, *262*(3), 155–158. http://doi.org/10.1016/S0304-3940(99)00062-2

Zatorre, R. J., Bouffard, M., Ahad, P., & Belin, P. (2002). Where is “where” in the human auditory cortex? *Nature Neuroscience*, *5*(9), 905–909. http://doi.org/10.1038/nn904

Zündorf IC, Lewald J, Karnath H-O (2013). Neural correlates of sound localization in complex acoustic environments. PLoS ONE 8: e64259.

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Tables

Table 1: Percentage error scores of the optic ataxia screenings (Borchers et al. 2013) based on the difference between foveated and non-foveated reaching at different time points for a) patient IT and for b) patient HM. Cut-off scores for healthy controls are given for comparison. Please note that in IT contra = right and ipsi = left, in HM contra = left and ipsi = right.

IT	Con Hand Ipsi Field	Con Hand Con Field	Ipsi Hand Con Field	Ipsi Hand Ipsi Field
Initial screening (t=0)	-3.3	43.0	6.6	10.0
Experiment 1 (t=1)	13.8	52.5	23.3	12.1
Experiment 2 Experiment 3 (t=3)	13.3	26.7	20.7	3.3
Final Screening (t=5)	0.0	36.6	3.3	0.0
Cut-off scores	9.1	11.8	5.1	15.0

HM	Con Hand Ipsi Field	Con Hand Con Field	Ipsi Hand Con Field	Ipsi Hand Ipsi Field
Initial screening (t=0)	0.5	33.3	18.9	-1.2
Experiment 1/Sess 1 Experiment 3 (t=40)	6.6	26.6	16.6	9.2
Experiment 1/Sess 2 (t=42)	10.0	40.0	16.6	8.7
Cut-off scores	5.1	15.0	9.1	11.8

t: time after initial screening in months; Con: contralesional; Ipsi: ipsilesional. Cut-off scores are taken from Borchers et al. (2013) and are based on single-case statistics by Crawford and Garthwaite (2005) for a threshold of $p < 0.05$.

Table 2: Mean absolute horizontal error for visual and auditory reaching to the contralesional target at +28° in patient IT and controls in experiments 1 and 2. Standard deviations for the control group are presented in brackets. Correlation coefficients between H and EH errors are reported for controls.

	Visually-guided reaching					**Auditory-guided reaching**				
	IT		**Controls**			**IT**		**Controls**		
	H	**EH**	**H**	**EH**	**r**	**H**	**EH**	**H**	**EH**	**r**
Con Hand Exp 1	5.82	1.18	1.06 (0.34)	0.79 (0.28)	0.081	2.00	2.32	3.12 (1.23)	2.50 (1.33)	0.484
Con Hand Exp 2	3.66	0.49	-	-		4.03	3.33	-	-	
Ipsi Hand Exp 2	3.01	1.32	1.68 (0.58)	1.56 (0.57)	0.752	3.32	3.91	2.61 (1.22)	2.11 (0.81)	0.191

H: Hand; EH: Eye-Hand; Con: contralesional (right); Ipsi: ipsilesional (left); r: Pearson correlation coefficient.

Table 3: Mean absolute horizontal error for visual and auditory reaching to the contralesional target at -28° in patient HM and controls in experiment 1. Standard deviations for the control group are presented in brackets. Correlation coefficients between H and EH errors are reported for controls.

	Visually-guided reaching					**Auditory-guided reaching**				
	HM		**Controls**			**HM**		**Controls**		
	H	**EH**	**H**	**EH**	**r**	**H**	**EH**	**H**	**EH**	**r**
Con Hand	3.30	0.78	0.92 (0.33)	0.40 (0.14)	0.270	7.24	4.30	3.40 (1.55)	2.38 (1.38)	0.609

H: Hand; EH: Eye-Hand; Con: contralesional (left); Ipsi: ipsilesional (right); r: Pearson correlation coefficient.

Table 4: Mean absolute horizontal error for proprioceptive-guided reaching with the contralesional hand (IT: right hand; HM: left hand) to contralesional target positions defined by the index fingertip of the respective ipsilesional hand at a horizontal eccentricity of + 28° for IT and – 28° for HM. Standard deviations for the control group are presented in brackets. Correlation coefficients between H and EH errors are reported for controls.

	IT		**HM**		**Controls**		
	H	**EH**	**H**	**EH**	**H**	**EH**	**r**
LH	-	-	4.07	1.64	1.29 (0.43)	1.09 (0.47)	0.030
RH	1.27	1.12	-	-	2.34 (1.34)	1.86 (1.77)	0.597

H: Hand; EH: Eye-Hand; LH: left hand; RH: right hand; r: Pearson correlation coefficient.

Figure Legends

Figure 1: a) FLAIR scan of patient IT. b) CT of patient HM. The red line indicates the central sulcus.

Figure 2: Schematic drawing of the setup for a) visual, b) auditory and c) proprioceptive guided reaching. The green circle depicts the fixation point. The red circles, loudspeaker symbols and hand symbols indicate the location of the visual, auditory or proprioceptive targets. Please note that visual and auditory targets were presented in a vertical plane whereas proprioceptive targets were presented on a horizontal table. For the analysis of proprioceptive data, targets of the same eccentricity were combined as indicated by the blue rectangle for the most peripheral left eccentricity.

Figure 3: Mean absolute horizontal deviation differences for reaches to visual and auditory targets of both patients and controls. a) differences between hand only and eye-hand movement conditions (vis[H-EH]; aud[H-EH]) for patient IT and the according controls' data. b) differences for patient HM and the according controls' data.

Figure 4: Depiction of the setup for proprioceptive guided reaching. a) depicts a participant pointing with her left hand to her right hand underneath the miniature table, b) depicts the miniature table with the fixation point (red).

Figure 5: Mean absolute horizontal deviation differences for reaches to visual and proprioceptive targets of both patients and controls. a) differences between hand only and eye-hand movement conditions (vis[H-EH]; proprio[H-EH]) for patient IT and the according controls' data. b) differences for patient HM and the according controls' data. Please note that targets for the proprioceptive guided reaching were presented at slightly different eccentricities. For the sake of readability, we labelled the target positions in the figure according to the visual target presentation.

Figure1

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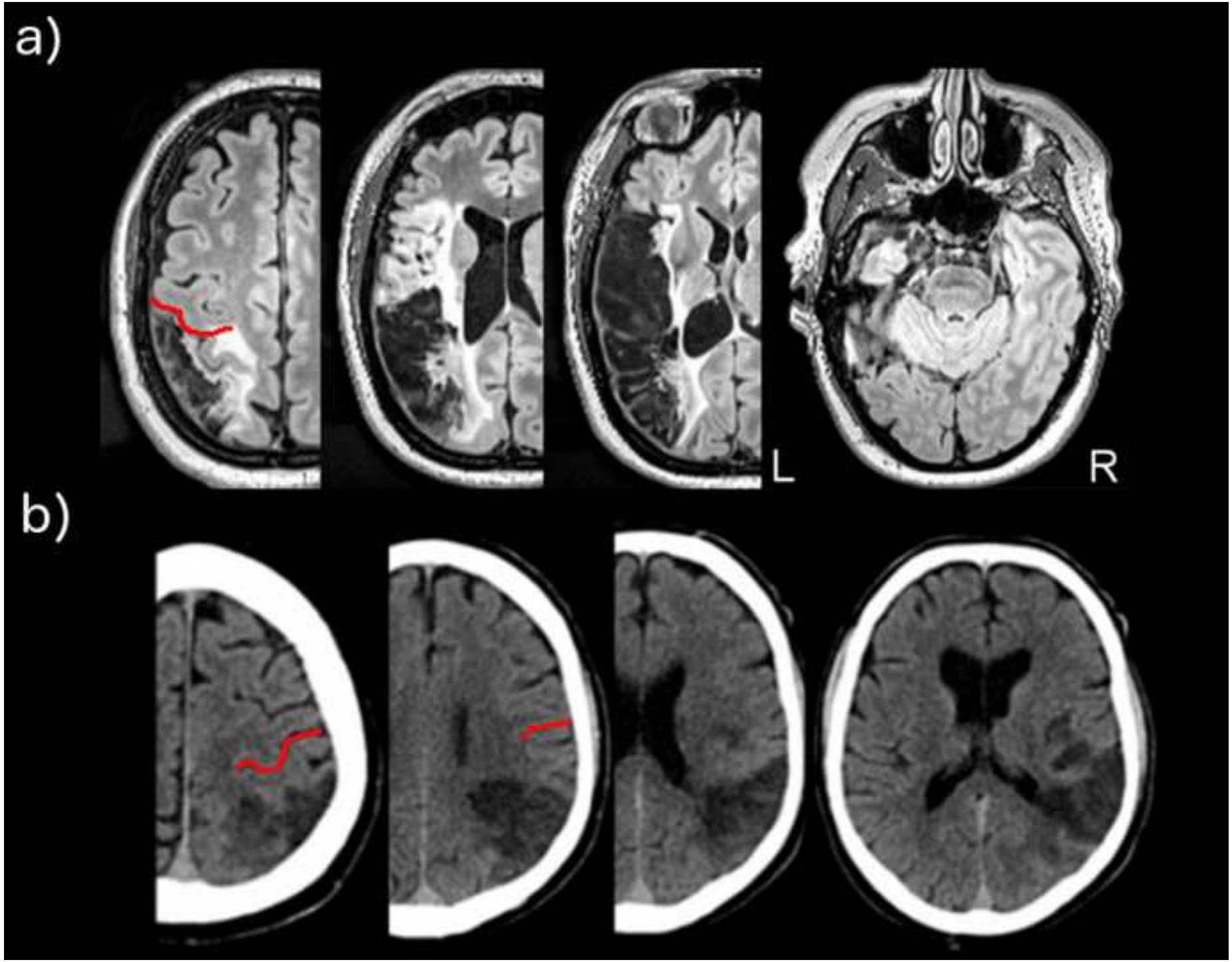

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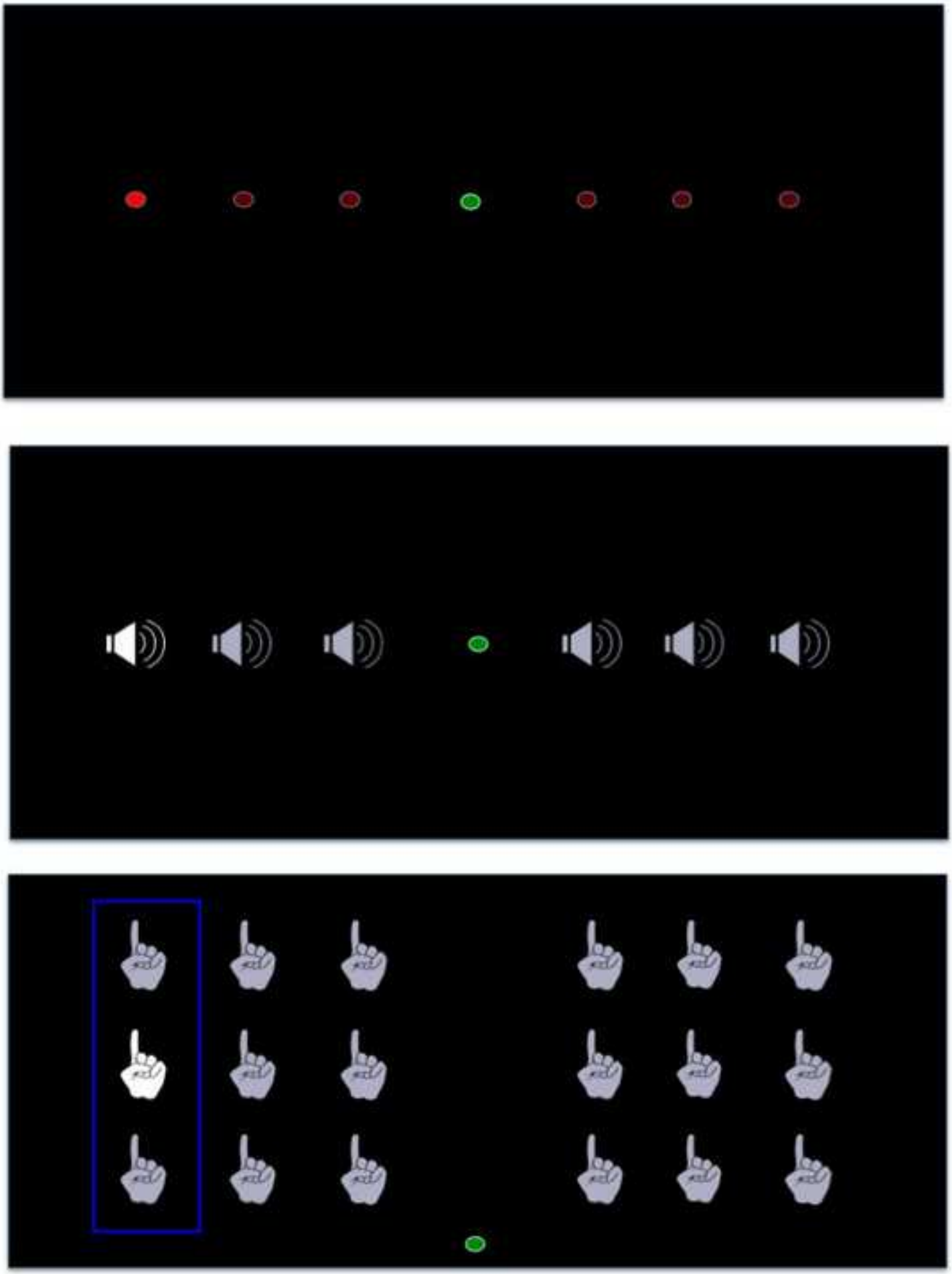

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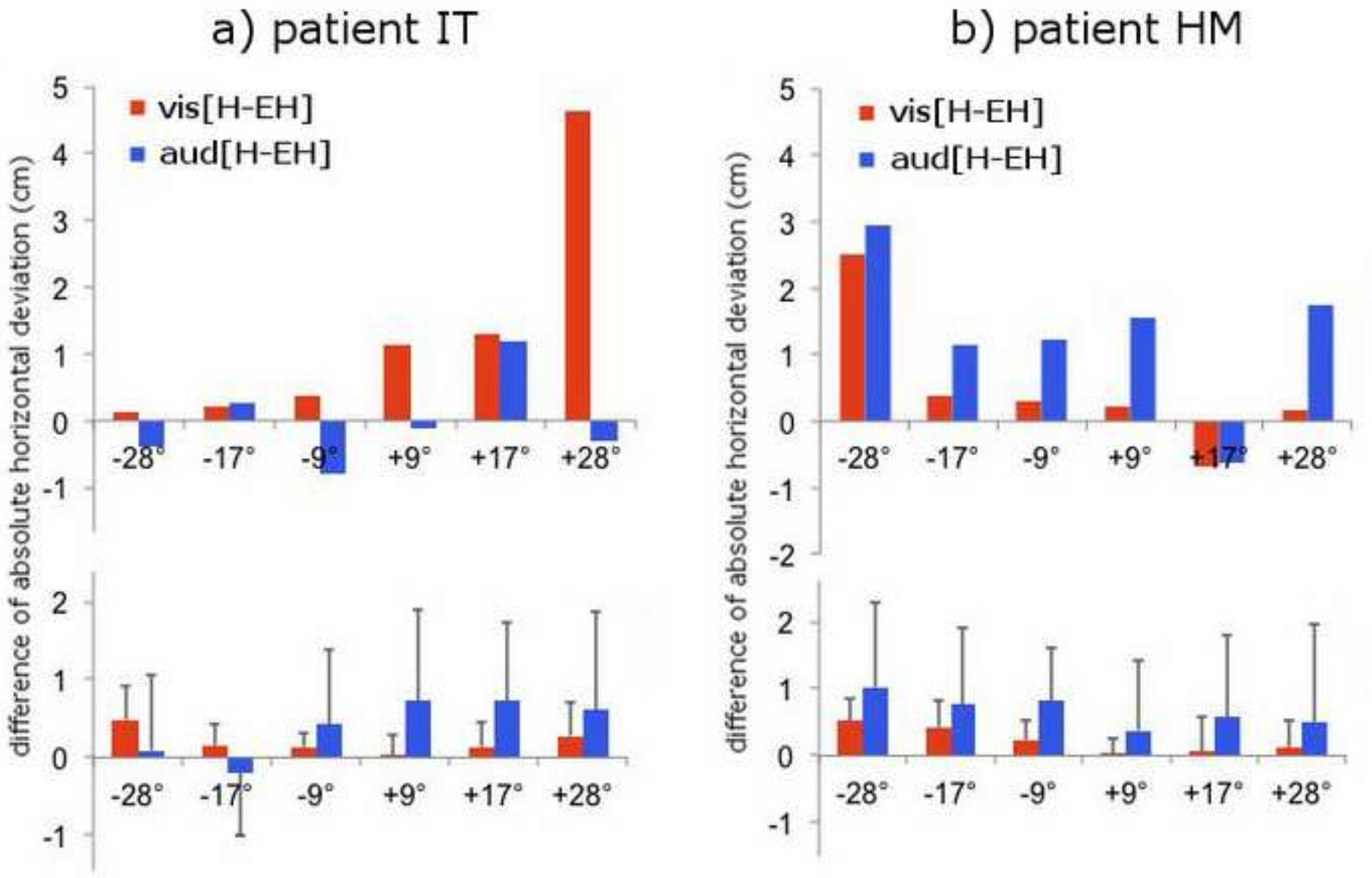

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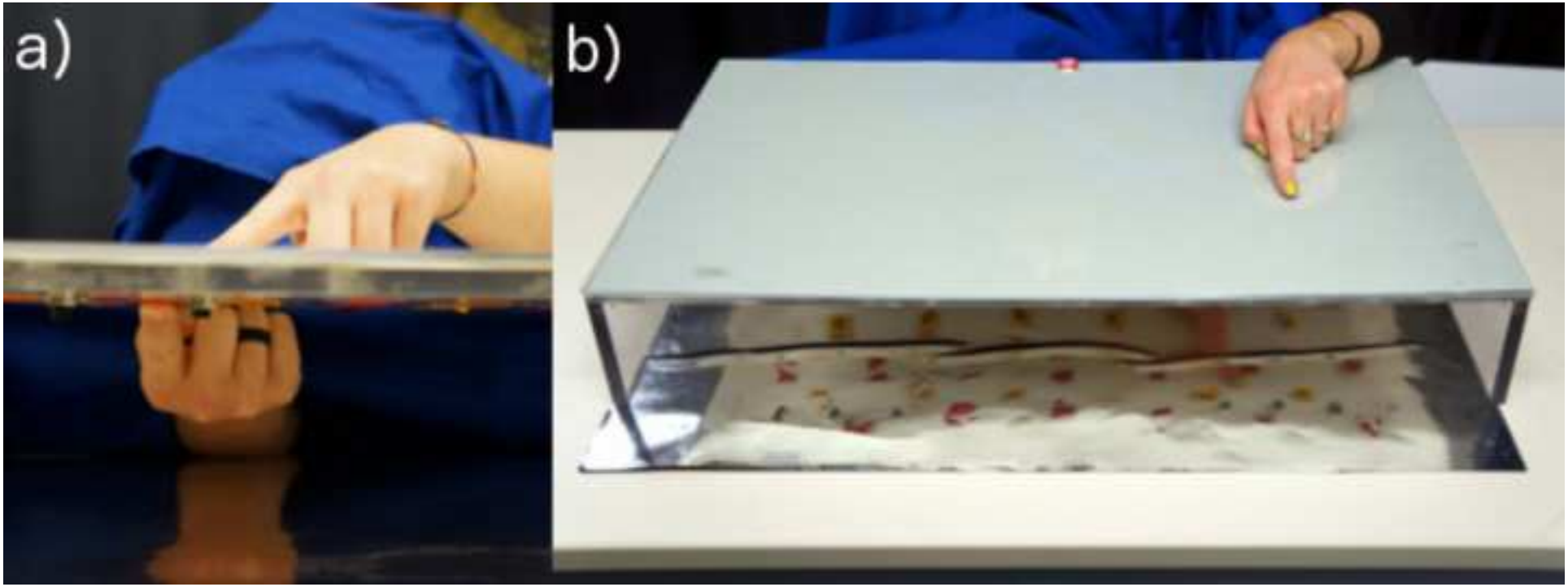

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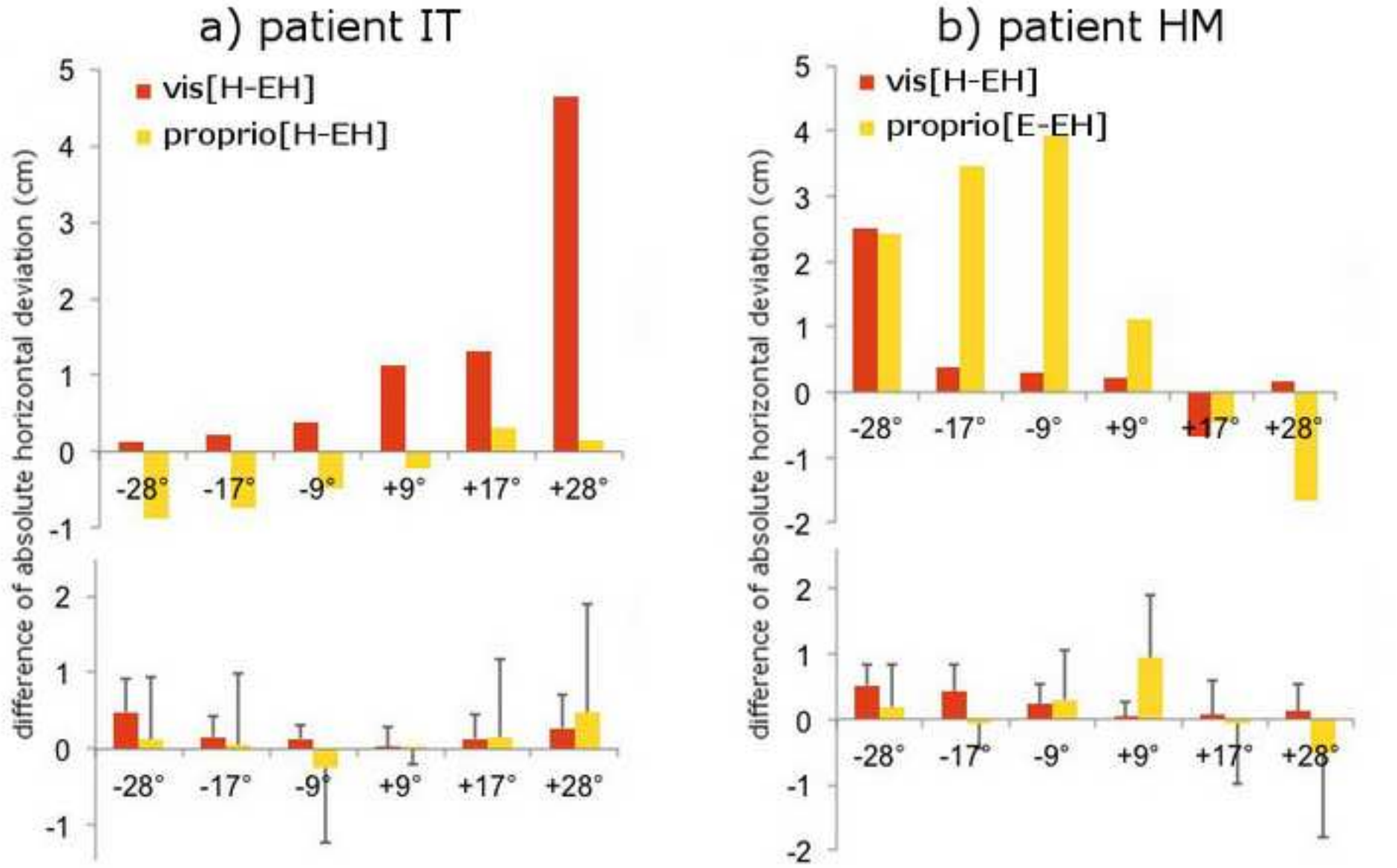

Functional specificity and lateralization of fronto-parietal pathways for online-correction

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Abstract

The dorsomedial circuit is traditionally associated with reaching, whereas the dorsolateral circuit is associated with grasping. Previous fMRI studies investigated this segregation without separating planning and execution phases of movements or by isolating the phases using delayed movements. We focused on the functional organization of the two anatomical circuits using a perturbation paradigm to specifically investigate online control. Participants reached-to-grasp objects that could change their location (reach perturbation) or size (grasp perturbation). None of the core regions of either circuit exhibited signal differences when directly contrasting perturbed reaching and perturbed grasping. Specific contrasts and connectivity analyses for grip size corrections confirmed previously observed signal differences in the medial intraparietal sulcus and changes of the inter-regional coupling between both circuits. In contrast, no change in inter-regional coupling occurred when comparing perturbed reaching versus perturbed grasping across different grip size corrections. Our findings argue against a strict functional separation of both circuits during the execution phase and instead suggest two congruent systems with varying functional overlap depending on the required degree of online control. A considerable recruitment of ipsilateral structures in our data suggests an important role of the ipsilateral reach-to-grasp networks in online control of visually-guided reach-to-grasp movements.

Introduction

Previous neuroimaging and neurostimulation studies showed that different regions in the human posterior parietal and premotor cortices contribute differently to reaching and grasping movements (Andersen and Buneo, 2002; Castiello, 2005; Culham et

al., 2006; Grefkes & Fink, 2005). Based on structural connectivity, the parieto-frontal motor network is divided into a dorsolateral and a dorsomedial circuit (Geyer et al., 2000; Tanné-Gariépy et al., 2002; Tomassini et al., 2007). The dorsolateral circuit includes the anterior intraparietal sulcus (aIPS), which is interconnected with the ventral premotor cortex (PMv). Consistent with their putative homologues in macaques, these areas have been suggested to be functionally specific for controlling grasping (Cavina-Pratesi, et al., 2010b; Culham et al., 2003; Murata et al., 2000). The dorsomedial circuit includes the parieto-occipital regions and the medial intraparietal sulcus (mIPS) and connects them with the dorsal premotor cortex (PMd). This circuit has been associated with the control of arm movements (Andersen and Buneo, 2002; Buneo et al., 2002; Cavina-Pratesi et al., 2010a).

Several studies already challenged the idea of strict effector specificity. Tunik et al. (2005) showed in an elegant TMS study that the aIPS contributed to the control of finger configuration *and* wrist orientation during reach-to-grasp movements. Reichenbach et al. (2011) extended this finding to this region's involvement in the control of arm movements. Furthermore, planning of hand and foot movements yielded similar fMRI activity (Heed et al., 2011). Similarly, fMRI studies in humans (Cavina-Pratesi et al., 2010b) and electrophysiological recordings in macaques (Fattori et al., 2010; Galletti et al., 2003) demonstrated an involvement of the dorsomedial pathway in reaching *and* grasping.

These inconsistencies regarding the functional specificity of fronto-parietal motor areas might be partly explained by the finding that the functional specificity is not stable throughout movement planning and execution but varies across these phases (Beurze et al., 2009). Introducing a delay between the object presentation and movement execution in an fMRI study reliably isolates the activation of the planning phase (Heed et al., 2011). Applying this approach for the isolated investigation of the

execution is, however, problematic. Depending on the duration of the delay, functional circuits beyond the fronto-parietal motor systems might be recruited instead or additionally (Goodale et al., 2003; Singhal et al. 2013).

Grol et al. (2007) investigated the hypothesis that the functional difference between the dorsomedial and dorsolateral stream consists of a different involvement in the online control of movements. They examined cortical signal changes and connectivity patterns during grasping small objects, with a presumed high demand on online control, and grasping large objects, with a presumed lower demand on online control. They found increased inter-regional couplings within the dorsomedial circuit for large objects and increased inter-regional couplings within the dorsolateral circuit for small objects (Grol et al. 2007). They concluded that the dorsolateral circuit is particularly involved in situations that demand high precision and online control of movements.

Both aspects, the distinction between movement planning and movement execution and the required amount of online control might partly account for the inconsistency of previous studies regarding the functional anatomy of reaching and grasping.

In our current study we focused on the functional anatomy of online movement control. We examined whether a functional separation between the dorsolateral and the dorsomedial circuits with regard to the effector, i.e. reaching versus grasping, can be found for inflight movement corrections. We employed a perturbation paradigm (see Prablanc and Martin, 1992; Tunik et al. (2005), Reichenbach et al. 2011; Glover et al., 2005) to manipulate the online-control independently of the planning phase of reach-to-grasp movements. By changing either the location or the size of the targets after movement onset, we selectively perturbed the reaching or grasping component. In a behavioural pilot experiment we matched kinematic parameters between all grasp and reach perturbations like response times and movement times to equalize the demand of online movement control as good as possible. Different activation and

functional coupling patterns along the two circuits for perturbed grasping movements versus perturbed reaching movements would clearly argue in favor of two separate, functionally specific networks during movement execution. In contrast, a failure to find different patterns across both movement conditions would argue against a strict functional dissociation between the circuits.

Beyond this analysis of general differences between reach and grasp perturbations we further inspected a specific effect predicted by the results and interpretation of Grol et al. (2007). These authors assumed that a higher degree of online control particularly recruits the dorsolateral pathway irrespective of the movement effector. We assumed that the unexpected change from small to large objects places higher demands on a grasp online control than changes from large to small. The latter can be solved by simply proceeding to close the finger aperture whereas the former requires a complete new movement component. Thus, during small-to-large object changes, signal levels in dorsolateral areas should increase and the coupling between the dorsolateral and dorsomedial system should change. Please note that across both possible grasp perturbations difficulty levels were roughly matched between grasp and reach perturbations as mentioned above.

Materials and Methods

Participants

Eighteen neurologically healthy participants (mean 26.2 ± 3.8 years, 11 females) with normal or corrected-to-normal vision were tested. Data of two subjects were excluded from further analyses due to excessive motion during scanning. All participants were right-handed (laterality quotient mean = 89.96, +68 to +100) according to the Edinburgh Inventory (Oldfield, 1971). Thirteen additional participants (mean 26.1 ± 3.6 years, 7 females) were tested in a behavioral control experiment in order to

match movement times between trials with perturbed grasping and perturbed reaching. All participants received payment and gave their informed consent before taking part in the experiment. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical Faculty of Tuebingen.

Experimental Setup and Stimuli

The participant lay supine in the scanner. The head was tilted by about 30° to allow for a direct line of sight of the targets (see Fig. 1). Foam wedges and memory foam pillows were placed around and underneath the participant's head for stabilization. The upper right arm was fixated tightly in an elevated position in order to minimize movements of the upper arm and related shoulder and head movements. A start button was fixed on the participant's chest and two target objects were mounted on an arc-shaped target-holder above the participant's right hip and left groin. The starting position of the hand and the orientation and distance of the target-holder were adjusted individually to allow natural reaching to both target objects. Each target object consisted of five acrylic glass panels that could be illuminated individually with red LEDs. For the small target, only the horizontal panel in the middle was illuminated (height 0.5 cm). For the large target, two additional horizontal panels above and below (distance 2.7 cm) were illuminated as well as an interconnecting vertical panel between each of them (height 6.9 cm; see inset of Fig. 1). The distance between the horizontal panels of each target (2.7cm) allowed for an unrestricted grasping of the middle panel. Furthermore, we manipulated the direction of the reach-to-grasp movements through the illumination of either the left or the right target object. The horizontal distance between the two targets was 11.0 cm. The distance between the start button and the targets varied depending on the arm length

of every participant but was approximately 45 cm. The experiment was conducted in complete darkness. The only visual input consisted of the illuminated target and a red light emitting diode (LED) serving as fixation light. The latter was attached to the ceiling of the scanner bore at the midline of the scanner. Eye and hand movements were recorded using MR-compatible cameras while fiber optics mounted on top of the head coil connected with an infrared light source outside the MR cabin provided invisible IR illumination of the movement space.

--- Please insert figure 1 around here ---

Experimental Procedure and Design

The participant had to maintain fixation on the LED throughout the measurement. The right hand rested on the start button. As soon as one of the targets was illuminated the participant's task was to move their hand to the (left or right) target, grasp the illuminated horizontal panel(s) (one or five) using a precision grip with the index and middle fingers opposing the thumb, and lightly press them into the apparatus. This extinguished the illumination of the target. After that, the participant returned the hand to the start button. A brief green flash of the fixation LED confirmed the return to the start button. The complete trial lasted 17.04 s.

In perturbed trials, the illuminated target changed with the release of the start button. When reaching was perturbed (ReachP), the target location changed by switching the illumination from the left to the right object (or vice versa). When grasping was perturbed (GraspP), the target size changed by switching the number of illuminated target panels from one to five (SmallLarge) or vice versa (LargeSmall). When both reaching and grasping were perturbed (BothP), the target location and size switched simultaneously. Thus, participants had to perform online corrections of either arm

trajectory (ReachP), hand aperture (GraspP), or both (BothP) during movement execution.

We implemented a 2 x 2 factorial design with the within-subject factors reaching perturbation (unperturbed vs. perturbed) and grasping perturbation (unperturbed vs. perturbed). The experiment consisted of two initial training sessions without MR scanning and eight sessions with scanning. Each session consisted of 32 trials of which 18 were perturbed. A preceding behavioral experiment (n = 13) in a mock scanner setup that was built similar to the real scanner demonstrated that this proportion of perturbed trials did not change behavioral performance in unperturbed trials in comparison to a session without any perturbed trials. The MR-experiment lasted approximately 2 hours including setup time (e.g. padding, adjustments for arm length) and recording of 320 trials (training and experimental sessions).

Image acquisition

Magnetic resonance images were acquired on a 3T Scanner (Siemens, TIM Trio, Erlangen, Germany) using a 12-channel receive head coil. Functional images with whole-brain coverage were collected using an echo planar T2* gradient echo pulse sequence (GRE-EPI, 33 axial slices, 3.0 x 3.0 mm in-plane resolution, 3.5 mm slice thickness, slice gap of 0.5 mm, flip angle 76°, 64 x 64 matrix, TR/ TE = 2130/ 35 ms). Each experimental session lasted 9 min 6 s and consisted of 32 trials. We recorded eight volumes per trial. Time-locking the presentation of the target objects to the volume acquisition ensured that the overall movements were completed during the acquisition of a single volume (please see results for Overall_MT below). The standard Siemens GRE field map covering the same volume as the EPIs was acquired for correcting static image distortions due to B0 inhomogeneities. In addition, a structural T1-weighted image (MPRAGE, 192 sagittal slices, matrix size =

256 × 256, voxel size = 1mm^3, flip angle 9°, TR/ TE/ TI = 2300/ 2.98/ 1100 ms) was collected.

Eye movement Analysis

Eye position was recorded with ViewPoint (Arrington Research, Scottsdale, AZ) to control for continuous fixation of the LED during movement execution. Data from one participant was excluded from this analysis due to technical problems. The remaining data was analyzed using in-house MATLAB scripts (The MathWorks, Natick, MA). The position data was high-pass filtered (zero-phase shift filtering with 4th order Butterworth filter; 1 Hz cut-off frequency), followed by median filtering to remove spurious noise data points (window length was 180 ms). The position data was divided into time windows from 0.5 s before until 2 s after target presentation and baseline corrected using the periods before target presentation as references. For each trial, saccades were detected semi-automatically by applying a threshold criterion (derived from previous example data) and then by visual inspection. Finally, we analyzed the occurrence of saccades using a two-way repeated measures ANOVA with 2 factors: reaching (perturbed vs. unperturbed) and grasping (perturbed vs. unperturbed).

Behavioral Analysis of Reach-to-Grasp Movements

We assessed the following measures: reaction time (RT), defined as the time between onset of target illumination and release of the start button; movement time (MT), defined as the time between the release of the start button and a successful precision grasp of the target; and the overall time (Overall_MT), defined as the time between the release of the start button and the return to the start button.

Data analysis started with the visual inspection of the video recordings of the hand movements. This allowed us to exclude erroneous trials (e. g., the participant grasped the wrong target) and to assure that the participant performed a smooth online correction of the movement in reaction to the perturbations. There must be no recognizable hesitation of the movement trajectory in the video recordings that would separate a first movement to the initial target and a second, new and temporally separated movement with a new start position and the final target after the perturbation. A second naïve rater re-examined over 1,000 trials based on the same criteria that were used for the original rating of the full dataset by one of the authors (S.C). The correlation of the number of error trials was $\rho = 0.93$. Additionally, to examine whether the discarded trials were identical, we calculated an inter-rater agreement of $\kappa = 0.67$, which can be regarded as good or substantial agreement. Rejection of trials based on this visual inspection was followed by the exclusion of trials exceeding quantitative *a priori* cutoff criteria. Movements with an RT of less than 200 or more than 700ms, an MT of less than 200 or more than 1200ms, or an RT or MT outside of the respective participant's mean ± 3 S.D. were excluded. These combined criteria resulted in an average of 15% of the trials rejected per participant (*SD* = 10.19, range: 3 - 24%).

Two-way repeated measures ANOVAs with the factors reaching perturbation (perturbed vs. unperturbed) and grasping perturbation (perturbed vs. unperturbed) was conducted for MT, RT and Overall_MT. Planned comparisons of MT, RT and Overall_MT between perturbed reaching and perturbed grasping movements, as well as between grip size corrections from small to large and from large to small, were conducted using two-sided paired t-tests. In addition, the effect of target size perturbations (small-large vs. large-small) was examined to investigate the influence

of difficulty on the functional organization of the dorsolateral and dorsomedial circuits. Only trials with an exclusive perturbation of grasping (i.e. without change in target location) were used for the latter analysis.

Imaging Data Analysis

Preprocessing. The preprocessing and analysis of the data were carried out using FSL 4.1 (FMRIB, Oxford University, UK). The first four volumes of each session were discarded to eliminate nonequilibrium effects of magnetization. The remaining volumes were motion corrected using six degrees-of-freedom (DoF) registrations to the reference volume. The EPI volume that was acquired immediately before the anatomical images was chosen as reference volume. This was followed by a brain extraction step and by the correction of static image distortions due to B0 inhomogeneties, as measured by the acquired field map. The EPI images were transformed into MNI space in a two step approach: First, the distortion-corrected EPI images were linearly registered to the individual T1-weighted anatomical image using 6 DoF. The T1-weighted image was then non-linearly registered to the structural MNI template using FSL FNIRT. Finally, the transformations for distortion-correction, for registration to the T1-weighted image, and further to MNI space were combined in a single transformation step and applied to the EPI images. The co-registered functional images were spatially smoothed using an isotropic Gaussian kernel with 5 mm full-width at half-maximum and temporally high-pass filtered with a cutoff of 100 s.

Whole-brain analysis. A general linear model was used to compare the brain activity between the different movement conditions. Four regressors-of-interest modeled the unperturbed trials and the trials with perturbed reaching, perturbed grasping, or both.

Only correct trials were included in these regressors. In a second, independent analysis, we investigated the difference in brain activity for small-to-large and large-to-small adjustments of the grasping component. In the latter analysis, two corresponding regressors-of-interest replaced the regressor for the perturbed grasping component. All regressors were modeled using stick functions that indicated the EPI volumes of movement execution for the respective conditions. Several additional regressors-of-no-interest were used to control for unspecific brain activations. The values for RT, MT and Overall_MT were first centered and standardized across all sessions and then used to weight stick functions representing the volumes of movement execution. This procedure served to account for the varying duration of neuronal signals associated with the varying length of RT, MT or Overall_MT (e.g. longer M1 activation during higher MTs). The error trials were modeled using stick functions indicating the incorrect movements. All aforementioned regressors were subsequently convolved with a gamma-shaped hemodynamic response function. To account for shifts in the onset of the hemodynamic response, temporal derivatives of the resulting time courses were included in the model as regressors-of-no-interest (Friston et al., 1997; Smith et al., 2004).

Specific care was taken to control for artifacts and distortions of the magnetic field caused by hand movements. These artifacts do not possess the standard hemodynamic lag of about 5 seconds and were restricted to the single EPI volume during which the movement was executed. The successive volumes covered the hemodynamic response of the reach-to-grasp related neuronal processes (see Culham et al. 2008 for a similar procedure). We included a stick function as regressor-of-no-interest indicating the single volume per trial in which the movement was conducted (see Image Acquisition) to account for the variance induced by the artifacts. In addition, the six motion parameters obtained during preprocessing and

the average time courses of the cerebrospinal fluid (CSF), white matter (WM) and non-brain areas were included as regressors-of-no-interest (Verhagen et al., 2008). The latter three regressors were obtained using FSL FAST to create mask images based on the segmentation of the T1-weighted anatomical image. The masks were transformed into the individual EPI-space and applied to the volumes before taking the average time course of the remaining voxels. We decided to implement this rather high number of nuisance regressors to reduce the risk of false-positive findings.

Even though other studies successfully implemented similar numbers of nuisance regressors (e.g. Grol et al., 2007) we considered that the high number of nuisance regressors might also diminish the statistical power of our study. Please note that we repeated our analyses using only two nuisance regressors to rule out that relevant activation differences between the conditions of interest were not detected due to a lack of sensitivity caused by the high number of regressors. The same regressors-of-interest for the 4 different movement conditions and their temporal derivatives were included in the control analyses, but only two stick functions were used to model incorrect trials and the volume corresponding to movement execution, respectively.

In each of the above analyses, separate general linear models were estimated for the experimental sessions in each participant. The results of the single sessions were then combined in each participant using a fixed-effects analysis. Finally, the results of the single-subject analyses were subjected to a mixed-effects group analysis with experimental conditions and participants as fixed and random factors, respectively. If not indicated otherwise, group Z-statistical images were derived using a corrected statistical threshold of $p < .05$ at the cluster level based on Gaussian random field theory (Worsley et al., 1996). The threshold applied on the voxel level was $Z > 2.3$ (corresponding to an uncorrected $p < 0.01$).

Region of Interest analysis (ROI)

The goal of the ROI analysis was to maximize the sensitivity of our approach towards finding specific reaching and specific grasping activation patterns associated with movement execution (i.e. ReachP vs. GraspP, respectively) within the regions of the fronto-parietal motor networks (Culham et al., 2008). The definition of the ROIs was based on previously reported anatomical landmarks and MNI coordinates in combination with the positions of the activation peaks observed for ReachP or GraspP on the group level in our study. This resulted in ROIs optimally placed to capture effector-related activations for the arm and hand, respectively. For example, when aiming to test whether a ROI showed a reaching-specific activation pattern, its position was first based on the activation pattern for ReachP versus unperturbed movements. The subsequent ROI-based analysis then assessed the contrast ReachP vs. Grasp. Obviously, these ROI analyses are not statistically sound in case of positive signal difference detection because they were based on group level contrasts that at least partially predicted a signal increase within the respective ROI. However, if we do not see any differences even in these tests, albeit being strongly biased towards positive findings, we might conclude that there are indeed no differences detectable between both perturbation conditions.

MNI coordinates and anatomical landmarks were chosen bilaterally for PMd, PMv, aIPS, medial IPS (mIPS), and superior parieto-occipital cortices (SPOC), as follows. The PMd locations were determined using the junction of the superior precentral sulcus with the superior frontal sulcus (Tomassini et al., 2007). The aIPS was localized using the junction of the IPS with the postcentral sulci (Frey et al., 2005). mIPS was defined as being halfway up the length of the IPS and close to the coordinates reported in Grefkes et al. (2004). The SPOC was defined as the medial

areas close to the brain surface directly anterior to the posterior endings of the parieto-occipital fissures (Gallivan et al., 2011) including parietal aspects but not part of the cuneus. These positions were further confirmed using the anatomy toolbox of SPM (Eickhoff et al., 2005). Subsequently we used group level contrasts of perturbed trials versus unperturbed trials to identify the nearest local signal peaks to the aforementioned anatomical landmarks. Centered on these peak signal locations we created spheres with a diameter that depended on the variability of the individual activation peak MNI coordinates between participants on the single-subject level. Two different radii were tested in order to demonstrate the robustness of the results, corresponding to 2 and 3 S.D.'s of the positions of individual peaks.

Preferably, as outlined above, we used the specific contrasts ReachP > Unperturbed and GraspP > Unperturbed to determine ROI locations to push the probability of a signal difference detection between ReachP and GraspP in the absence of any significant differences between these conditions in the whole brain analysis. As only exception, the bilateral PMv exhibited no significant differences for these contrasts. For this reason, the PMv ROIs were based on the comparison of all perturbed trials (reaching, grasping and both perturbed) versus unperturbed trials. The ROI centers were chosen according to the peak activations close to the PMv coordinates reported by Tomassini et al. (2007) and lying within Brodman 6 as indicated by the probability maps of the SPM anatomy toolbox. All ROIs are presented in table 1 together with the respective group level contrast that was used for their definition, mean MNI coordinates and SDs and atlas labels and probabilities taken from the anatomy toolbox of SPM (Eickhoff et al., 2005).

--- Please insert table 1 around here ---

In the ROI analyses, the average of the parameter estimates (PE) obtained in the single-subject analyses was determined across the voxels in each ROI for each participant. We used t-tests to detect average signal differences in these ROIs for the contrast ReachP vs. GraspP. Additional t-tests were conducted to compare signal levels between large to small and small to large grip size corrections. The results are reported corrected for multiple comparisons across the number of ROIs (n = 11) using a Bonferroni correction (indicated as p_B) for a global error probability threshold of p = 0.05.

Connectivity Analysis. The aim of the connectivity analysis was to assess whether the functional coupling pattern within the fronto-parietal network exhibited effector-specific differences. That is, whether the correlations between signal time courses of the aforementioned ROIs differed between perturbed reaching and perturbed grasping movements. The time course in a “seed” ROI (averaged across voxels; ROI size: 2 S.D.) was subdivided into four condition-specific time courses by multiplying it with box functions that indicated the trials for ReachP, GraspP, BothP and Unpert, respectively. These condition-specific time courses were centered and standardized before subjecting them to a GLM analysis as regressors-of-interest, thereby replacing the normal boxcar/hrf regressors for the four conditions. The other regressors were identical to those used in the GLM for the whole-brain analysis with two nuisance regressors for incorrect trials and volumes corresponding to movement executions (please see section on whole-brain analysis above). In each participant, estimation results of the single sessions were combined using a fixed-effects analysis, and the average parameter estimates (PE) for each regressor-of-interest were extracted from each ROI. The average PE for a single regressor-of-interest indicates the degree of correlation between the signal time courses of the respective seed and target ROIs

only for the time periods of a given condition such as ReachP or GraspP. In combination with the mean centering and standardization of the seed time courses within each condition this approach ensures that general task-related differences do not influence the observed correlations. Finally, we compared the average PEs for the ReachP and GraspP conditions for each ROI using paired t-tests across participants. This direct comparison between conditions excluded an impact of spontaneous purely physiological correlations across regions that would be independent of the particular conditions. Thus, we tested if the time course of the "seed" ROI explained different amounts of variance in one of the other ROIs depending on the condition (GraspP vs. ReachP), as would be expected if the condition modulates the functional coupling, corresponding to a psychophysiological interaction analysis (Friston et al. 1997). This procedure was repeated for each ROI serving as the "seed" region. Again, results are reported with a correction for multiple comparisons (n = 11) using a Bonferroni correction (indicated as p_B) for uncorrected p-values < 0.05.

In a second ROI analysis, the differences in connectivity between grasp corrections from large to small and from small to large were tested by creating condition-specific time courses for grasping perturbed large to small and grasping perturbed small to large and testing for average PE differences between these two conditions.

Results

Behavioral data: Saccades

Saccades occurred in 5.76% (*SD* = 7.2) of all trials. Saccade frequency did not differ between conditions (reaching perturbation: $F(1,14) = 0.35$, $p = 0.558$, $M = 6.66\%$, *SD*

= 8.2; grasping perturbation: $F(1,14) = 2.12$, $p = 0.167$, $M = 7.13\%$, $SD = 9.6$; interaction reaching x grasping: $F(1,14) = 2.63$, $p = 0.127$).

Behavioral data: Reaching and grasping

Reaction time was not influenced by any condition (reaching perturbation, $F(1, 15) = 0.42$, $p = 0.52$; grasping perturbation, $F(1, 15) = 1.62$, $p = 0.22$, interaction reaching x grasping, $F(1, 15) = 1.59$, $p = 0.22$) indicating that the required amount of movement planning was similar. Moreover, comparing RT in perturbed grasping trials directly with perturbed reaching trials revealed no difference ($t(15) = 1.17$, $p = 0.25$). As expected, analysis of MT revealed highly significant main effects for the factors reaching perturbation ($F(1,15) = 89.59$, $p < .001$) and grasping perturbation ($F(1,15) = 138.98$, $p < .001$), and the interaction between the factors ($F(1, 15) = 151.01$, $p < .001$). These findings reflect the fact that movements in completely unperturbed trials were shorter compared to perturbed trials (see table 2). More importantly, the comparison of trials in which only grasping was perturbed (but not reaching) and trials in which only reaching was perturbed (but not grasping) revealed no difference ($t(15) = 0.98$, $p = 0.33$), indicating that the additional behavioral effort was similar for both types of perturbation. The analysis of Overall_MT followed the pattern found for MT and showed highly significant main effects for reaching perturbation ($F(1,15) = 48.74$, $p < .001$) and grasping perturbation ($F(1, 15) = 54.57$, $p < .001$) as well as a significant interaction ($F(1, 15) = 45.06$, $p < .001$). Unperturbed trials had a shorter overall movement duration compared to perturbed trials. Within perturbed trials, however, Overall_MT was not different between perturbed reaching and perturbed grasping trials ($t(15) = 0.35$, $p = 0.72$).

--- Please insert table 2 around here ---

When subdividing the trials with perturbed grasping into SmallLarge and LargeSmall corrections, we found an effect of the direction of grip size perturbations ($t(15)= 5.10$, $p < .001$; $p_B < .001$) on RT. Participants started the movement on average 18 ms later if initially preparing to grasp a small (in SmallLarge trials) compared to large target (in LargeSmall trials). The analysis of unperturbed trials confirmed that RT was 23 ms longer for small targets. Furthermore, the direction of the grip size perturbation had a highly significant effect on MT ($t(15) = 6.30$, $p < .001$; $p_B < 0.001$). Correcting the grip size from a small target to a large target led to 80 ± 76 ms shorter movement times as compared to adapting the grip size from a large target to a small target. Overall_MT followed the same pattern, in that, grip size corrections from a small to a large target required less total movement time than corrections from large to small targets; however, the difference did not reach significance ($t(15) = -1.9$, $p = .075$).

To summarize, the behavioral findings demonstrate an expected general increase in MT for perturbed versus unperturbed movements. Notably, no behavioral difference occurs when comparing perturbed reaching versus perturbed grasping movements. In contrast, grip size is demonstrated to affect both RT and MT specifically for perturbed grasping movements.

Whole-Brain Analysis

All conditions revealed typical activation patterns for visually guided reaching and grasping movements with the right dominant hand (green maps in Fig. 2), spreading bilaterally from the primary visual cortex (V1: left: x= -4, y= -82, z= 10; right: 6, -80, 8) and V5 (or MT+, left: -40, -76, 6; right: 50, -64, 8) to parietal areas, including the SPOC (left: -8, -84, 48; right: 22, -74, 50), IPS (right: 36, -48, 42; left: -40, -42, 40) and clusters located in the SPL (left: -36, -38, 44; right: 38,-36, 44) and extending into

the SMG (left: -40, -38, 42; right: 54, -32, 50). On both hemispheres, the activation pattern further extends medially into the supplementary motor area (SMA, left: -4, 4, 48; right: 6, 4, 56) and the cingulate motor area (CMA, left: -6,-4, 46; right: 6, 4, 44). Laterally, it spreads into the dorsal and ventral premotor cortex, thereby including the primary motor cortex (M1, left: -34, -16, 54) and the primary somatosensory cortex (S1, left: -30, -38, 56) on the left hemisphere.

The contrasts for ReachP > Unpert, GraspP > Unpert and BothP > Unpert (red and yellow maps in Fig. 2) revealed areas that are associated with online control of reach-to-grasp movements. For all three contrasts, we observed bilateral activation increases for perturbed movements in the SPOC (left: -10, -78, 48; right: 24, -76, 48), whereas only right hemisphere activation increases were observed in the PMd (right: 28, -4, 56) and the supramarginal gyrus (SMG, right: 56, -32, 50). With cluster-level correction, aIPS was significantly activated bilaterally for the contrast GraspP > Unpert and BothP > Unpert, but only in the right hemisphere for the contrast ReachP > Unpert. Without cluster-level correction, the left aIPS showed similar activation peaks for ReachP > Unpert (z-value = 2.62; -44, -40, 42) and GraspP > Unpert (z-value = 2.91; -42, -40, 42). Compared to the implicit baseline, the activation patterns for ReachP and GraspP were very similar (green activation patterns in Figure 2), particularly at the left aIPS (ReachP: z= 3.60, GraspP: z= 3.76). Thus, the absence of a significant difference in the left aIPS in the contrast ReachP > Unpert seems to be caused by differences in cluster size, not in effect strength.

Directly comparing GraspP and ReachP did not reveal any significant differences in the whole brain analysis. Even without cluster-level correction, only a small cluster occurred in the Precunus for ReachP > GraspP (left: z-value = 2.49; coordinates: -2, -54, 46; right: z-value = 3.28; coordinates: 4, -54-, 54).

The complementary analysis with a reduced number of nuisance regressors did not show any differences to our main analysis. In summary, all three types of perturbation (reach, grasp, and combined) resulted in similar signal increases relative to the unperturbed trials.

Focusing on the predictions based on the results of Grol et al. (2007), the comparison of trials with grasping perturbations from small to large versus large to small (or vice versa) with a cluster-level correction did not reveal any significant activation differences in the whole brain analysis. On an uncorrected level, several clusters in the right medial IPS and right SPL exhibited tendencies towards higher activations for perturbations from small to large compared to large to small (z-value = 2.63; 38, -48, 58; z-value = 2.69; 14, -48, 62; z-value = 2.63; 28, -58, 54).

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Region of Interest Analyses

All ROIs are listed in table 1. Confirming the results of the whole brain analysis, we found no significant differences when comparing ReachP versus GraspP for any of the ROIs, even when *not* correcting for multiple comparisons (Table 3, t-test ReachP vs GraspP). Please note that we failed to find any effector-specific differences despite the fact that the ROIs were optimally positioned to capture either grasping- or reaching-related activity using the contrasts GraspP>Unpert and ReachP>Unpert, respectively, and therefore strongly biased towards a potential signal difference. A control analysis using the GLM with the reduced number of nuisance regressors (see paragraph on whole-brain analysis in the Methods section) to calculate the average PEs in the ROIs confirmed the above results, ruling out that the absence of signal

differences was caused by a reduced sensitivity of the model. Similarly, increasing the ROI sizes to 3 SD's did not affect the results.

--- Please insert table 3 around here ---

In contrast, comparing the corrections between the two possible perturbations in grip size revealed differences in the average PEs in a specific subset of ROIs. Corrected for multiple comparisons, the right mIPS robustly exhibited a higher signal for target size changes from small-to-large versus large-to-small (Fig. 3 & Table 3). Furthermore, right PMd and left PMv showed a similar trend on the uncorrected level (Table 3). Neither aIPS nor SPOC showed higher signals in response to the required change of grip size. Conducting the ROI analysis with the GLM results for the reduced number of nuisance regressors or using a ROI size of 3 SD's did not affect the results. Our finding not only supports the previous report and interpretation of Grol et al. (2007) but also indicates that the failure to detect a general difference between perturbed grasping and perturbed reaching cannot be simply attributed to a ceiling effect or insufficient sensitivity of our approach.

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Connectivity Analysis

The analysis of connectivity strength revealed no differences between any of the perturbed reaching vs. perturbed grasping contrasts after correcting for multiple comparisons.

Focusing on the predictions based on the results of Grol et al. (2007), the connectivity analysis contrasting small-to-large and large-to-small grasp corrections

resulted in 5 modulations of inter-regional connectivity after correcting for multiple comparisons. We found an increased coupling across the dorsolateral and dorsomedial circuit within the ipsilateral hemisphere, specifically between the right SPOC and the right aIPS, for grip size corrections from small to large (figure 4). Also, within the ipsilateral hemisphere, the same modulation pattern occurred between the mIPS (associated with the dorsomedial circuit) and aIPS (associated with the dorsolateral circuit) regardless of whether mIPS was defined by the contrast GraspP > Unpert or ReachP > Unpert. We also observed increased coupling across hemispheres, namely between the ipsilateral (right) mIPS (defined by the contrast GraspP > Unpert) and contralateral (left) aIPS (table 4). Finally, we found an increased ipsilateral coupling between the right PMd (defined by the contrast ReachP > Unpert) and the right aIPS.

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Discussion

Specificity of fronto-parietal pathways

We investigated the functional organization of the dorsomedial and dorsolateral fronto-parietal pathways during movement execution. Employing a perturbation paradigm allowed us to measure BOLD signal changes that were specifically associated with the manipulation of the execution phase without the need to introduce time delays between target presentation and movement execution. The results revealed that almost the entire parieto-frontal motor network exhibited

increased activity during increased demands of online control. We found no signal differences between the execution of grasp corrections and reach corrections, neither in the dorsomedial nor in the dorsolateral circuit. Even in ROI analyses of individual regions of these circuits which were on purpose biased to capture either reaching or grasping specific activation we found no signal difference between perturbed grasping and perturbed reaching trials. Importantly, in contrast to the absence of general differences between grasp perturbations and reach perturbations we observed a robust and specific signal difference in the mIPS for grasping perturbations from small-to-large versus large-to-small that was consistent with interpretations and predictions of previous reports (Grol et al., 2007; Verhagen et al., 2013). Beyond this confirmation the detection of a difference between small-to-large and large-to-small corrections showed that null-findings in the general comparisons between types of perturbations were not simply due to a general lack of sensitivity. A connectivity analysis addressing changes in the pair-wise functional coupling patterns between the regions of interest provided consistent results. The comparison between different online changes in grip aperture resulted in a robust modulation in coupling strength between parietal and premotor regions. Consistent with prior results (Grol et al., 2007) this suggests an increased coupling between the dorsomedial and dorsolateral pathways for grip aperture corrections from small to large. This again included the mIPS as one of the network nodes that exhibited changes in the coupling strength with other ROIs. In contrast, comparing perturbed grasping and perturbed reaching trials in general, no differences in coupling were observed during the execution phase.

Studies in non-human primates served as major support for the hypothesis of an effector-specific organization of the PPC, with the dorsomedial network contributing predominantly to the control of reaching movements (Galletti et al., 1996; Galletti et

al., 1997) and the dorsolateral network being mainly involved in the control of grasping (Gallese et al., 1994; Murata et al., 2000). However, more recent studies challenged these early studies and generated a more complex view. Neurons in area V6A apparently not only encode the direction of arm reaching (Fattori et al., 2001; Fattori et al., 2005; Monaco et al., 2011) but also encode hand orientation (Fattori et al., 2009) during planning and movement execution as well as hand preshaping and grip formation (Fattori et al., 2010; Gamberini et al., 2009). A similar complex picture has emerged on the role of the human PPC for reaching and grasping. Although some previous work has indicated that the aIPS (dorsolateral stream) shows preferences for grasping and the mIPS and SPOC regions (dorsomedial stream) show preferences for reaching, using both fMRI (Cavina-Pratesi et al., 2010b; Culham et al., 2003; Culham et al., 2008) and TMS paradigms (Tunik et al., 2005; Vesia et al., 2010), other studies employing the same methods could not confirm clear-cut functional preferences in these regions (Gallivan et al., 2011; Glover et al., 2005; Heed et al., 2011; Reichenbach et al., 2011).

Some of these discrepancies might stem from methodological factors such as the available sensory information, its way of manipulation, the target object's affordances, and whether planning and execution phase were analyzed jointly (Gallivan et al., 2009; Gibson, 1979, Beurze et al., 2009). For example, Tunik et al. (2005) reported that TMS applied to the aIPS disturbed grasping but not reaching in a reach-to-grasp task. However, in their paradigm, only the grasping component had to be adjusted by the participants during movement execution, initiated by a change of the object size, but not the reaching component. In other words, TMS disrupted only the component that required an increased amount of online control. In line with the latter interpretation, a subsequent study demonstrated that TMS over aIPS also affected the transport component by explicitly testing the participants' ability to

correct for target and cursor displacements (Reichenbach et al., 2011). This observation is difficult to reconcile with the view that aIPS is functionally specific for grasping but not for reaching, but is in accordance with the previous interpretation that this region plays a crucial role for the online correction of movements to accomplish goal-directed movements. Similarly, besides the involvement of the mIPS in visually guided reaching movements (Prado et al., 2005), that area was also shown to contribute to online adjustment of the grasping component in response to grasping perturbations (Glover et al., 2005) and the control of hand aperture (Grol et al., 2007).

One important reason for the conflicting findings might be that either the planning phase or the execution phase was investigated, or both phases were not disentangled at all. A separate investigation is crucial since the effector-specificity of PPC areas seems to differ across the temporal phases of reach-to-grasp movements with more clear-cut findings for the planning compared to the execution phase (Beurze et al., 2007; Beurze et al., 2009). It could be argued that during movement execution the PPC is continuously flooded by sensory (in particular visual) input, making it more difficult to detect any functional specificity during that phase. However, the observed differences between large-small and small-large aperture corrections in our study and the work of Grol et al. (2007) argue against this interpretation as well as the observed deficits in reaching and grasping after TMS stimulation of aIPS (Tunik et al. 2005; Reichenbach et al., 2011). Our findings indicate that demands on online control, but not effector specificity, determine the coupling and the separation between dorsomedial and dorsolateral cortical areas during movement execution.

Lateralization of online corrections

We observed a general effect of online-corrections on the lateralization in the reach-to-grasp network with stronger involvement of the ipsilateral hemisphere for both types of perturbations. This finding is in agreement with other studies that investigated movements of higher complexity. For example, demanding sequencing tasks are correlated with ipsilateral activation (e.g. Haaland et al., 2004; Solodkin et al., 2001) and the extent of ipsilateral activity changes with task complexity (Verstynen et al., 2005). TMS experiments supported these observations by demonstrating an interaction effect of inhibitory ipsilateral TMS and movement complexity on motor deficits (Chen et al., 1997; Avanzino et al., 2008).

The recruitment of ipsilateral regions is a general finding for reach-to-grasp movements; for instance, of the mIPS, PMd and parieto-occipital regions during reaching (Prado et al., 2005) and of the aIPS during precision grasping (Binkofski et al., 1999; Culham et al., 2003). A single unit recording study by Battaglia-Mayer et al. (2012) also demonstrated the pivotal role of ipsilateral motor regions in monkeys. It showed that neither ipsi- nor contralateral inactivations of SPL alone are sufficient to induce deficits in pointing, but bilateral transient lesions lead to increased movement times, suggesting that the ipsilateral SPL is able to compensate contralateral dysfunctions. Similar processes seem to take place in humans as indicated by a study showing primarily ipsilateral activation during grasping movements with the right hand in Patient D.F. who suffered a substantial loss of grey matter at the left PPC (James et al., 2003). The behavioral significance of these ipsilateral activations was further demonstrated in healthy participants by the demonstration that only bilateral TMS-induced lesions are sufficient to affect hand shaping, but not an unilateral lesion (Davare et al., 2007) and that TMS stimulation of the ipsilateral

parieto-occipital cortex affected the planning of reaching movements (Busan et al., 2009).

Conclusions

The demand of online control during movement execution seems to be a major factor that determines the amount of separation and functional coupling between the dorsomedial and dorsolateral stream. In contrast, we found no evidence for an effector-specificity in areas of the dorsomedial and dorsolateral fronto-parietal pathways for movement control and correction processes during movement execution. However, we only investigated the execution phase. Notably, this finding likely does not transfer to the planning phase as previous studies showed that there might be differences in effector-specificity between planning and execution (Beurze et al., 2007; Beurze et al., 2009). The successive recruitment of ipsilateral homologue areas of the fronto-parietal reach-to-grasp network with increasing task demands seems to be a general mechanism independent of the type of movement correction. Again, in agreement with previous studies our data suggests that the demand of online control, rather than effector-specificity, determines the amount of ipsilateral recruitment in the online-correction of reach-to-grasp movements.

Our findings thus pave the way for future research tackling the question of how the contributions of the areas documented here are coherently integrated to coordinate the overall reach-to-grasp movement. For example, using TMS on premotor areas, this has been successfully done for grip-lift movements, showing that the left PMd contributes to the temporal coordination of the grasping and lifting phases while PMv being solely involved in grasping control (Davare et al., 2006). A similar approach might prove fruitful for deciphering the roles of the mainly parietal brain areas targeted here.

References

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

Avanzino L, Bove M, Trompetto C, Tacchino A, Ogliastro C, Abbruzzese G. 2008. 1-Hz repetitive TMS over ipsilateral motor cortex influences the performance of sequential finger movements of different complexity. Eur J Neurosci 27:1285–1291.

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: 188–99.

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.

Binkofski F, Buccino G, Stephan KM, Rizzolatti G, Seitz RJ, Freund HJ. 1999. A parieto-premotor network for object manipulation: evidence from neuroimaging. Exp Brain Res 128:210–213.

Borra E, Belmalih A, Calzavara R, Gerbella M, Murata A, Rozzi S, Luppino G. 2008. Cortical connections of the macaque anterior intraparietal (AIP) area. Cereb Cortex 18:1094–1111.

Buneo CA, Jarvis MR, Batista AP, Andersen RA. 2002. Direct visuomotor transformations for reaching. Nature 416:632–636.

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.

Castiello U. 2005. The neuroscience of grasping. Nat Rev Neurosci 6:726–736.

Cavina-Pratesi C, Ietswaart M, Humphreys GW, Lestou V, Milner AD. 2010a. Impaired grasping in a patient with optic ataxia: primary visuomotor deficit or secondary consequence of misreaching? Neuropsychologia 48:226–234.

Cavina-Pratesi C, Monaco S, Fattori P, Galletti C, McAdam TD, Quinlan DJ, Goodale MA, Culham JC. 2010b. 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.

Chen R, Gerloff C, Hallett M, Cohen LG. 1997. Involvement of the ipsilateral motor cortex in finger movements of different complexities. Ann Neurol 41:247–254.

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, Danckert SL, DeSouza JFX, 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.

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.), pp247–274. New York: Psychology Press.

Davare M, Andres M, Clerget E, Thonnard JL, Olivier E. 2007. Temporal dissociation between hand shaping and grip force scaling in the anterior intraparietal area. J Neurosci 27:3974–3980.

Davare M, Andres M, Cosnard G, Thonnard JL, Olivier E. 2006. Dissociating the role of ventral and dorsal premotor cortex in precision grasping. J Neurosci 26:2260–2268.

Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, Zilles K. 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. NeuroImage 25:1325–1335.

Fattori P, Breveglieri R, Marzocchi N, Filippini D, Bosco A, Galletti C. 2009. Hand orientation during reach-to-grasp movements modulates neuronal activity in the medial posterior parietal area V6A. J Neurosci 29:1928–1936.

Fattori P, Gamberini M, Kutz DF, Galletti C, Bologna Á, Donato PS. 2001. Arm-reaching neurons in the parietal area V6A of the macaque monkey. Eur J Neurosci, 13:2309–2313.

Fattori P, Kutz DF, Breveglieri R, Marzocchi N, Galletti C. 2005. Spatial tuning of reaching activity in the medial parieto-occipital cortex (area V6A) of macaque monkey. Eur J Neurosci, 22:956–972.

Fattori P, Raos V, Breveglieri R, Bosco A, Marzocchi N, Galletti C. 2010. The dorsomedial pathway is not just for reaching: grasping neurons in the medial parieto-occipital cortex of the macaque monkey. J Neurosci 30:342–349.

Frey SH, Vinton D, Norlund R, Grafton ST. 2005. Cortical topography of human anterior intraparietal cortex active during visually guided grasping. Brain Res Cogn Brain Res 23:397–405.

Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. 1997. Psychophysiological and modulatory interactions in neuroimaging. NeuroImage 6:218–229.

Gallese V, Murata A, Kaseda M, Niki N. 1994. Deficit of hand preshaping after muscimol injection in monkey parietal cortex. Neuroreport 5:1525–1529.

Galletti C, Fattori P, Battaglini PP, Shipp S, Zeki S. 1996. Functional demarcation of a border between areas V6 and V6A in the superior parietal gyrus of the macaque monkey. Eur J Neurosci 8:30–52.

Galletti C, Fattori P, Kutz DF, Battaglini PP. 1997. Arm movement-related neurons in the visual area V6A of the macaque superior parietal lobule. Eur J Neurosci 9:410–413.

Galletti C, Kutz DF, Gamberini M, Breveglieri R, Fattori P. 2003. Role of the medial parieto-occipital cortex in the control of reaching and grasping movements. Exp Brain Res 153:158–170.

Gallivan JP, Cavina-Pratesi C, Culham JC. 2009. Is that within reach? fMRI reveals that the human superior parieto-occipital cortex encodes objects reachable by the hand. J Neurosci 29:4381–4391.

Gallivan JP, McLean DA, Valyear KF, Pettypiece CE, Culham JC. 2011. Decoding action intentions from preparatory brain activity in human parieto-frontal networks. J Neurosci 31:9599–9610.

Gamberini M, Passarelli L, Fattori P, Zucchelli M, Bakola S, Luppino G, Galletti C. 2009. Cortical connections of the visuomotor parietooccipital area V6Ad of the macaque monkey. J Comp Neurol 513:622–642.

Geyer S, Matelli M, Luppino G, Zilles K. 2000. Functional neuroanatomy of the primate isocortical motor system. Anat Embryol (Berl) 202: 443–474.

Gibson JJ. 1979. The ecological approach to visual perception. Boston: Houghton Mifflin.

Glover, S, Miall, RC, Rushworth, MFS. 2005. Parietal rTMS disrupts the initiation but not the execution of on-line adjustments to a perturbation of object size. J Cog Neurosci 17:124–136.

Goodale MA, Westwood DA, Milner AD. 2003. Two distinct modes of control for object-directed action. Prog Brain Res 144:131–144.

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

Grol MJ, Majdandzić J, Stephan KE, Verhagen L, Dijkerman HC, Bekkering H, Verstraten FA, Toni I. 2007. Parieto-frontal connectivity during visually guided grasping. J Neurosci 27:11877–11887.

Haaland KY, Elsinger CL, Mayer AR, Durgerian S, Rao SM. 2004. Motor sequence complexity and performing hand produce differential patterns of hemispheric lateralization. J Cog Neurosci 16:621–636.

Heed T, Beurze SM, Toni I, Röder B, Medendorp WP. 2011. Functional rather than effector-specific organization of human posterior parietal cortex. J Neurosci 31:3066–3076.

James TW, Culham JC, Humphrey GK, Milner AD, Goodale MA. 2003. Ventral occipital lesions impair object recognition but not object-directed grasping: an fMRI study. Brain 126:2463-2475.

Monaco S, Cavina-Pratesi C, Sedda A, Fattori P, Galletti C, Culham JC. 2011. Functional magnetic resonance adaptation reveals the involvement of the dorsomedial stream in hand orientation for grasping. J Neurophysiol 106:2248–2263.

Murata A, Gallese V, Luppino G, Kaseda M, Sakata H. 2000. Selectivity for the Shape, Size, and Orientation of Objects for Grasping in Neurons of Monkey Parietal Area AIP. J Neurophysiol 83:2580–2601.

Oldfield RC. 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113.

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

Prado J, Clavagnier S, Otzenberger H, Scheiber C, Kennedy H, Perenin MT. 2005. Two cortical systems for reaching in central and peripheral vision. Neuron 48:849–858.

Reichenbach A, Bresciani JP, Peer A, Bülthoff HH, Thielscher A. 2011. Contributions of the PPC to online control of visually guided reaching movements assessed with fMRI-guided TMS. Cereb Cortex 21:1602–1612.

Singhal A, Monaco S, Kaufman LD, Culham JC. 2013. Human FMRI reveals that delayed action re-recruits visual perception. PLoS One, 8:e73629.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnnak I, Flitney DE, Nianzy R, Saunders 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.

Solodkin A, Hlustik P, Noll DC, Small SL. 2001. Lateralization of motor circuits and handedness during finger movements. Eur J Neurol 8:425–434.

Tanné-Gariépy 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 TEJ, 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.

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

Verhagen L, Dijkerman HC, Medendorp WP, Toni I. 2013. Hierarchical organization of parietofrontal circuits during goal-directed action. J Neurosci 33:6492–6503.

Verstynen T, Diedrichsen J, Albert N, Aparicio P, Ivry RB. 2005. Ipsilateral motor cortex activity during unimanual hand movements relates to task complexity. J Neurophysiol 93:1209–1222.

Vesia M, Prime SL, Yan X, Sergio LE, Crawford JD. 2010. Specificity of human parietal saccade and reach regions during transcranial magnetic stimulation. J Neurosci 30:13053–13065.

Tables

Table 1: Regions of interest and their defining contrast, the average MNI coordinates of the ROI centers across participants and the standard deviations of the center coordinates (SD; characterizing the positional jitter of the individual centers) and the volume size. The Z-scores refer to the peak activations for the defining contrasts at the ROI centers. The anatomical locations are reported as percentage overlap with the regions reported in the anatomy toolbox for SPM (Eickhoff et al., 2005). Abbreviations see Figure 2.

ROI	hemis-phere	contrast	x (SD)	y (SD)	z (SD)	volume (mm^3)	z score	anatomical location
aIPS	left	GraspP > Unpert	-46 (4.9)	-42 (4.9)	48 (5.4)	4280	2.87	left Area 2 (30.8%) left hIP2 (28.2%) left IPC (PF) (17.4%) right IPC (PFm) (7.2%)
aIPS	right	GraspP > Unpert	46 (5.3)	-38 (4.1)	48 (4.9)	3576	3.68	right Area 2 (33.4%) right hIP2 (18.7%) right IPC (PF) (17.2%) right IPC (PFt) (11.8%)
mIPS	left	GraspP > Unpert	-38 (3.9)	-52 (4.9)	46 (3.6)	2312	3.37	left hIP1 (54.0%) left hIP3 (21.1%) left hIP2 (6.7%) left IPC (PFm) (6.6%)
mIPS	right	GraspP > Unpert	32 (6.8)	-62 (3.4)	46 (3.7)	2888	3.75	right hIP3 (24.4%) right IPC (PGa) (10.7%) right SPL 7A (8.1%) right hIP1 (3.2%)
mIPS	right	Reach > Unpert	36 (4.2)	-46 (3.7)	52 (5.7)	2920	3.25	right Area 2 (40.2%) right hIP3 (23.3%) right SPL (7PC) (22.1%) right hIP2 (11.0%)
SPOC	left	ReachP > Unpert	-12 (5)	-76 (4.1)	52 (4.6)	3040	3.57	left SPL (7P) (70.7%) left SPL (7A) (9.7%)
SPOC	right	ReachP > Unpert	26 (4.8)	-78 (2.6)	45 (4.1)	1704	3.82	right SPL (7P) (25.9%) right IPC (PGp) (5.6%)
PMd	right	GraspP > Unpert	24 (5.0)	-10 (4.4)	56 (2.8)	2136	2.97	right Area 6 (38.3%)
PMd	right	ReachP > Unpert	30 (4.7)	-4 (4.7)	56 (4.8)	3688	2.85	right Area 6 (13.7%)
PMv	left	Perturbation > Unpert	-56 (4.0)	6 (4.0)	26 (4.0)	2056	5.94	left Area 44 (57.5%) left Area 6 (22.9%) left Area 4p (1.1%)
PMv	right	Perturbation > Unpert	58 (4.0)	8 (4.0)	16 (4.0)	2056	6.42	right Area 44 (19.2%)

Table 2: Behavioral Data. Mean ± standard deviation for reaction time (RT) and movement time (MT) for all conditions (Unpert= unperturbed movements, ReachP= perturbed reaching; GraspP= perturbed grasping, LargeSmall= grasp corrections from large to small, SmallLarge= grasp corrections from small to large).

	RT (ms)	MT (ms)	Overall_MT (ms)
Unpert	414 ± 45	625 ± 74	1529 ± 272
ReachP	413 ± 47	721 ± 86	1642 ± 280
GraspP	410 ± 49	713 ± 64	1638 ± 283
LargeSmall	402 ± 47	747 ± 76	1663 ± 267
SmallLarge	420 ± 47	667 ± 76	1615 ± 330
Small	426 ± 47	643 ± 77	1527 ± 266
Large	403 ± 45	607 ± 80	1532 ± 282

Table 3: Results of the main analysis for ROIs with a size of two standard deviations. The column 'Contrast' indicates where the respective peak location had been taken from. Results corrected for multiple comparisons using Bonferroni are indicated by p_B.

ROI	Contrast	t-test ReachP vs GraspP		t-test small_large vs large_small		
		t	p	t	p	p_B
left SPOC	ReachP > Unpert	1.119	0.280	0.813	0.429	
right SPOC	ReachP > Unpert	0.501	0.623	0.483	0.636	
left aIPS	GraspP > Unpert	0.626	0.540	0.382	0.708	
right aIPS	GraspP > Unpert	0.282	0.780	1.188	0.080	
right mIPS	ReachP > Unpert	0.683	0.505	4.313	**0.001**	**0.007**
left mIPS	GraspP > Unpert	1.204	0.247	0.518	0.612	
right mIPS	GraspP > Unpert	0.275	0.787	0.575	0.574	
right PMd	ReachP > Unpert	0.940	0.362	2.279	**0.038**	0.415
right PMd	GraspP > Unpert	2.092	0.054	2.646	**0.018**	0.201
left PMv	Perturbation > Unpert	0.377	0.697	2.178	**0.046**	0.508
right PMv	Perturbation > Unpert	-0.396	0.360	0.094	0.93	

Table 4: Results of the connectivity analysis for ROIs with a size of two standard deviations. The column 'Whole brain contrast' indicates where the respective peak location had been taken from. Results corrected for multiple comparisons using Bonferroni are indicated by p_B.

ROI 1 ("seed")	Contrast	ROI 2	Contrast	t-test: small_large vs large_small		
				t	p	p_B
right SPOC	ReachP > Unpert	right aIPS	GraspP > Unpert	4.382	**0.001**	**0.005**
right mIPS	ReachP > Unpert	right aIPS	GraspP > Unpert	3.914	**0.008**	**0.015**
right mIPS	GraspP > Unpert	left aIPS	GraspP > Unpert	3.147	**0.001**	**0.006**
right mIPS	GraspP > Unpert	right aIPS	GraspP > Unpert	4.378	**0.001**	**0.002**
right PMd	ReachP > Unpert	right aIPS	GraspP > Unpert	3.640	**0.002**	**0.026**

Figure captions

Figure 1: Experimental setup. Targets were fixed on the arc-shaped target-holder above the participant's hip and groin. The right arm was fixed in an elevated position. The head was elevated and additionally tilted to allow a direct line of sight on the targets. MR-compatible cameras were used to record hand (camera 1) and eye (camera 2) movements. Fiber optics mounted on the head coil illuminated the whole setup with invisible infra red light. A fixation LED was attached to the scanner bore right above the target area. **Inset**: The two targets and the fixation LED seen from camera 1. The targets could vary in size by changing the illumination of the individual object panels (here: full illumination of the left target and illumination of the central panel of right target). During the experiment, only one target was visible at a time.

Figure 2: Group activation patterns of the whole brain analysis. The green overlays indicate activation for ReachP, GraspP and BothP relative to the implicit baseline (mixed effects analysis, voxel level of $Z > 2.3$). Red to yellow heat maps show difference signals based on the following contrasts: perturbed grasping > unperturbed movements (GraspP > Unpert), perturbed reaching > unperturbed movements (ReachP > Unpert), and both movements perturbed > unperturbed movements (BothP > Unpert) (mixed effects analysis, voxel level of $z > 2.3$, cluster level $p < 0.05$ corrected for multiple comparisons). Functional maps are overlayed on the mean of sixteen participants T1-weighted anatomical scans.

Figure 3: Bar graphs display the average magnitude of the BOLD signal from the right mIPS (defining contrast ReachP > Unpert), right aIPS (defining contrast GraspP > Unpert) and right SPOC (defining contrast ReachP > Unpert) at the group level. Abbreviations see Table 2 and Figure 2. Red lines indicate standard errors.

Figure 4: The modulation of coupling as a function of condition is indicated by differences in the average parameter estimates in the right aIPS (left: "seed" right SPOC; right: "seed" right mIPS). The four bars on the left show the results of the analysis focusing on perturbed reaching and perturbed grasping. The two rightmost bars show the results of the comparison of grip size changes. Abbreviations see Table 2 and Figure 2.

Figures

Figure 1:

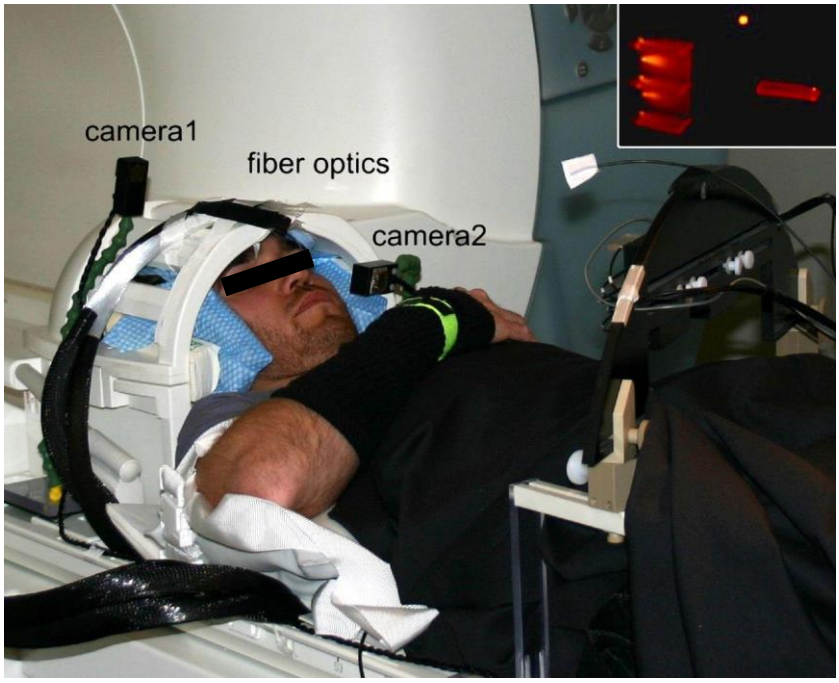


Figure 2:

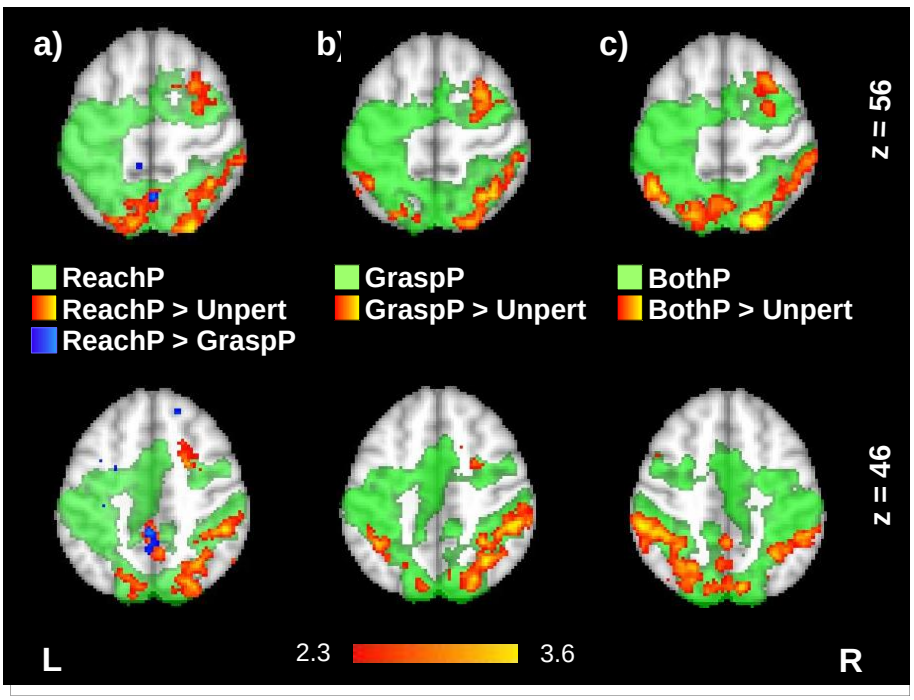


Figure 3:

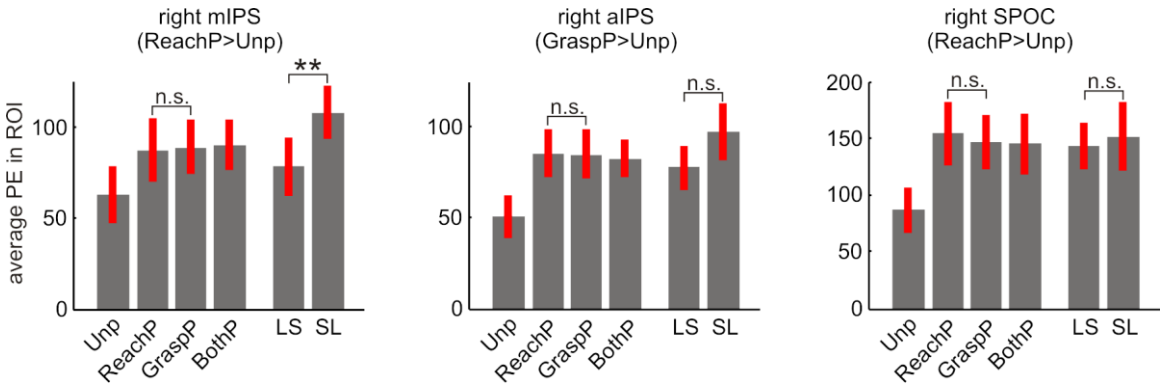
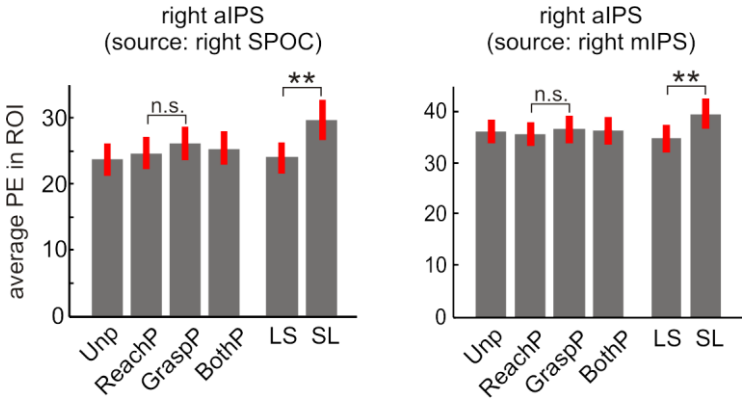


Figure 4:



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