Understanding space by moving through it: Neural networks of motion- and space processing in humans

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Contents

Abstract

Humans explore the world by moving in it, whether moving their whole body as during walking or driving a car, or moving their arm to explore the immediate environment. During movement, self-motion cues arise from the sensorimotor system comprising vestibular, proprioceptive, visual and motor cues, which provide information about direction and speed of the movement. Such cues allow the body to keep track of its location while it moves through space. Sensorimotor signals providing self-motion information can therefore serve as a source for spatial processing in the brain. This thesis is an inquiry into human brain systems of movement and motion processing in a number of different sensory and motor modalities using functional magnetic resonance imaging (fMRI). By characterizing connections between these systems and the spatial representation system in the brain, this thesis investigated how humans understand space by moving through it.

In the first study of this thesis, the recollection networks of whole-body movement were explored. Brain activation was measured during the retrieval of active and passive self-motion and retrieval of observing another person performing these tasks. Primary sensorimotor areas dominated the recollection network of active movement, while higher association areas in parietal and mid-occipital cortex were recruited during the recollection of passive transport. Common to both self-motion conditions were bilateral activations in the posterior medial temporal lobe (MTL). No MTL activations were observed during recollection of movement observation. Considering that on a behavioral level, both active and passive self-motion provide sufficient information for spatial estimations, the common activation in MTL might represent the common physiological substrate for such estimations.

The second study investigated processing in the 'parahippocampal place area' (PPA), a region in the posterior MTL, during haptic exploration of spatial layout. The PPA in known to respond strongly to visuo-spatial layout. The study explored if this region is processing visuo-spatial layout specifically or spatial layout in general, independent from the encoding sensory modality. In both a cohort of sighted and blind participants, activation patterns in PPA were measured while participants haptically explored the spatial layout of model scenes or the shape of information-matched objects. Both in sighted and blind individuals, PPA activity was greater during layout exploration than during object-shape exploration. While PPA activity in the sighted could also be caused by a transformation of haptic information into a mental visual image of the layout, two points speak against this: Firstly,

no increase in connectivity between the visual cortex and the PPA were observed, which would be expected if visual imagery took place. Secondly, blind participates, who cannot resort to visual imagery, showed the same pattern of PPA activity. Together, these results suggest that the PPA processes spatial layout information independent from the encoding modality.

The third and last study addressed error accumulation in motion processing on different levels of the visual system. Using novel analysis methods of fMRI data, possible links between physiological properties in hMT+ and V1 and inter-individual differences in perceptual performance were explored. A correlation between noise characteristics and performance score was found in hMT+ but not V1. Better performance correlated with greater signal variability in hMT+. Though neurophysiological variability is traditionally seen as detrimental for behavioral accuracy, the results of this thesis contribute to the increasing evidence which suggests the opposite: that more efficient processing under certain circumstances can be related to more noise in neurophysiological signals.

In summary, the results of this doctoral thesis contribute to our current understanding of motion and movement processing in the brain and its interface with spatial processing networks. The posterior MTL appears to be a key region for both self-motion and spatial processing. The results further indicate that physiological characteristics on the level of category-specific processing but not primary encoding reflect behavioral judgments on motion. This thesis also makes methodological contributions to the field of neuroimaging: it was found that the analysis of signal variability is a good gauge for analysing inter-individual physiological differences, while superior head-movement correction techniques have to be developed before pattern classification can be used to this end.

1

General Introduction

Space is a fundamental organization principle of the world as we know it. As such, it has occupied philosophy and natural science throughout history. When talking about space, a distinction can be made between 'physical space' and 'psychological space'. The two are accurately defined in the scientific treatise "The hippocampus as a cognitive map" (O'Keefe and Nadel, 1978) which is one of the seminal works for neuroscientific research on space processing. O'Keefe and Nadel (1978)'s definition is based on Kantian theory: 'physical space' is defined as a physically measurable property of the external world which we are not necessarily aware of, and 'psychological space' as the space perceived and represented by organisms. In other words, psychological space is a result of the organism's attempt to infer the state of physical space. Psychological space is the one the organism acts in and upon which it bases its goal-directed behavior. The distinction between psychological and physical space becomes obvious when looking at the discrepancy between the two. Examples of such discrepancy are size, orientation or motion illusions, in the case of the visual system, and systematic misjudgment of walked distances, in the case of the sensorimotor system (Mittelstaedt and Mittelstaedt, 2001). Both originate from systematic errors which occur when perception fails to map the environment correctly. Another important aspect that differentiates physical and psychological space is that while the former is generally thought of being absolute, the existence of inter-individual differences in spatial competence suggests that the latter is relative and differs between individuals (Wolbers and Hegarty, 2010).

The physical space within arms or walking reach can be perceived by an organism not only as a passive observer, but also by interacting with it. In the last decades, results from both behavioral and neurophysiological research have provided evidence that interacting with the environment (physical space) plays a pivotal role in forming spatial representations (psychological space) (Newcombe, 2000). One type of interaction between an organism and the environment is its exploration by moving through it. Theories on the importance of movement for the formation of spatial representations emerged early in history. As O'Keefe and Nadel (1978) describe in their historical overview of spatial theories, already Berkeley (1685-1753) strongly advocated for a dominant role of move-

ment in the construction of spatial representations. He saw a primacy for what he called 'tactile' sensory information for forming spatial knowledge, which could serve as the basis for visual space (Berkley's definition of tactile information included proprioceptive feedback and would likely be considered haptic information by current standards (Loomis, 1986)). Poincaré (1854-1912) extended Berkeley's arguments by adding that both *real* and *represented* movements might be used in spatial processing. Poincaré thereby expanded the contributors to the formation of spatial representations beyond tactile sensing, to also include mental processing. More recently, Piaget (1896-1980) incorporated movement into his developmental theories as essential, initial access an infant has to the external world. Endowed from birth with a limited set of sensorimotor schemes an infant acts upon the world, deriving concepts about space by learning the fundamental principles it encounters. Nowadays the exact correspondence between movement and the formation of spatial representations is still poorly understood, nonetheless there are numerous empirical evidences both from behavioral and neurophysiological studies suggesting that a link between the two exists. Based on these evidences, some recently developed theories give a pivotal role to movement in the formation of spatial representations. According to those, self-motion cues arising during goal-directed movement are an important source of direction and distance information which are continuously calibrated against perceptual or memorized information on landmarks and geometry to update our own position in space (Byrne et al., 2007; Whitlock et al., 2008).

How organisms extract and represent spatial information from the environment is a key question in neuroscientific research. In particular, research on the neurophysiological foundations of spatial behavior focuses on the description of the brain areas which are involved in extracting and representing spatial information. Central questions are: Which neural networks underly spatial perception and representation? How is spatial knowledge processed, how is it integrated? Can a spatial representation system be localized in the brain? Are such neural spatial representations based on hardwired neurophysiological modules or do they develop flexibly during the encounter of the environment? In the context of this thesis, it is important to clarify the use of the term *representation*, since it has a long history and has slightly different meanings across various disciplines (biology, psychology, philosophy): *representation* can refer to both the abstract mental cognitive symbol of the external world, as well as its neurophysiological foundation. To distinguish between the two in the context of this thesis, the term *spatial representation* will be used to indicate the psychological concept, whereas the terms *neural spatial representation* and *spatial rep-*

resentation system in the brain will be used to indicate the physical location of the brain areas involved in forming, processing and storing spatial knowledge.

This thesis is an inquiry into the many movement and motion processing systems in the human brain, and how these systems interface with brain systems which process the space within arms or walking reach, to contribute to neural spatial representations in reference to our own body. Functional magnetic resonance imaging (fMRI) was used to investigate and characterize such brain systems. The starting point for this investigation are the identified neurophysiological correlates of spatial processing which form the 'spatial' circuitry of the brain in humans and animals: these correlates include structures of the medial temporal lobe, the 'head-direction system' along the Papez's circuit, the retrosplenial complex and the posterior parietal cortex. The interaction between these areas seems to constitute a spatial representation system in the brain (Byrne et al., 2007; Whitlock et al., 2008). What is still not determined is how motion and movement processing systems interface with this spatial circuitry. To further our understanding of this issue, the first project of this thesis explored the sensorimotor systems involved in mental simulation of active and passive whole-body motion. A modulation of the medial temporal lobe induced by different sensorimotor experiences was tested (2.1). The medial temporal lobe remained the focus also of the second project, which investigated the multimodal nature of spatial processing in the parahippocampal place area (2.2). While this region is known to process visuo-spatial layout, this study explored if it is also activated by spatial layout perceived by hand movement, i.e. haptic exploration. The focus of the final project was shifted entirely on the motion system. The study explored on which level of visual motion processing errors start to accumulate. This was investigated by comparing behavioral and physiological inter-individual differences in the visual system (2.3).

The following section will describe the neurophysiology of movement and motion processing in the locomotor and the visual system (1.1), two systems investigated during this thesis. This will be followed by an outline of the current understanding of how space is represented in the brain (1.2), and how motion information might contribute to form neural spatial representations (1.3). Finally, advances in fMRI methodology will be presented along with a description on how these were used in this thesis to address specific questions about intersubject variability and whole-body movement processing (1.4).

1.1 Processing of motion and movement in the brain

The focus of this thesis was on systems of motion and movement processing, and the following section will introduce the neural foundation of such systems. Movement is processed in parallel by multiple sensory systems: as all sensory systems encode information both in space and in time, each of them can provide motion-related information. Besides the sensory systems, also the motor system is intimately connected to motion, as activity in it precedes the perception of self-generated motion. Predictions on our self-motion can therefore be based on the motor-sequences programmed in the brain. This idea has lead to the suggestion of a general 'principle of reafference', which implies that motor circuits provide a copy (motor efference copy) of the signals they send out to the muscles, which allows the system to predict the consequential sensory feedback (see Cullen (2004) for a review). The sources of motion information are thereby more numerous during active exploration (active sensing) compared to when the environment is perceived immobile (passive sensing). In other words, while senses such as vision can provide motion information already during passive sensing (as e.g. while driving in a car, or navigating in a virtual reality environment), this information is complemented by signals of the motor systems during self-generated movement. One of the projects of this thesis characterized active sensing of motion, by comparing the neural networks processing sensorimotor information during locomotion and passive transport (see 2.1). Another project investigated activity in the visual system during passive motion perception (see 2.3). The following section will therefore introduce the current knowledge of cerebral sensorimotor processing of locomotion and the cerebral system of visual motion processing. It will further outline first connections between the processing of movement and space, which will be dealt with in greater detail in section 1.2 and 1.3.

1.1.1 Movement processing in sensorimotor systems

The system of locomotor control

To move their body towards a goal, animals use locomotion, self-generate rhythmic alternated movements such as swimming, flying or walking. The locomotor program which is most commonly executed to reach a target in humans is gait. The basic stepping pattern of gait is highly automated and is generated on relatively low levels of the nervous system. Walking towards a goal in an ever-changing environment however is controlled by a distributed neural network involving almost the entire brain.

This reflects that many computations are necessary during goal-directed walking, such as representing the goal, motor planning, motor plan selection, motor execution, and adjustment of the resulted motor act according to sensory feedback and internal motor efference copies. Due to the close interaction between motor output and sensory feedback, the functional unit which controls movement is in general considered a 'sensorimotor system' rather than a pure motor system. The following paragraphs will however focus on the motor component of this sensorimotor system, as a detailed description of the somatosensory, proprioceptive and visual feedback loops contributing to locomotor control would exceed the scope of this introduction.

To structure the cerebral system underlying locomotor control, different brain areas are in general assigned to a functional hierarchy of control levels (the following subdivision is based on Bear et al. (2001c)): 1) The lowest control level, responsible for execution, relies on neural circuits in the spinal chord and the brainstem; 2) The middle level, concerned with the control of the sequence of muscle contractions, relies on the primary motor cortex and the cerebellum; 3) The highest control level, concerned with the goal and strategy of a movement, involves association areas in the frontal and parietal cortex and the basal ganglia.

Most neurophysiological knowledge of locomotor control on the lowest and middle level stems from experiments in the cat. From these studies it is known that the basic rhythm and the initiation of walking arises from pattern-generators in the spinal cord and the brain stem (Grillner and Wallén, 1985; Mori et al., 2001; Garcia-Rill and Skinner, 1987). Brain areas such as the primary motor cortex and the cerebellum on the middle level of locomotor control are not necessary to induce this basic stepping pattern, nonetheless, they reverberated this pattern in their rhythmic neural activity (Kandel et al., 2000b). Beyond this, the middle control level comes into play when the stepping patterns get more complicated and have to be adapted to avoidance of obstacles (Armstrong, 1988; Garcia-Rill, 1986). While the basic neural circuits of the lowest and middle level of locomotor control remain preserved in humans, clinical and experimental studies show that the functional significance of the middle control level has become more pronounced in the evolutionary transition from quadrupedal to bipedal locomotion (Nielsen, 2003; Snijders et al., 2007; Fukuyama et al., 1997; Miyai et al., 2001). In particular the increasing significance of the large and monosynaptic cortico-spinal tract in comparison to the rubrospinal tract deriving from the brainstem reflects this functional reorganization.

The highest level of locomotor control consists of motor planning, representing the goal

of the movement and the developing the movement strategy to best achieve this goal. At this level, theories today envisage the formation of a mental body schema, which comprises an internal representation of the body, its current position in space and its spatial relation to the environment. The knowledge of these relations is a necessary prerequisite to plan a goal-directed movement. The highest level of locomotor control can be investigated in humans with neuroimaging by using mental imagery, the mental simulation of locomotion without actual execution (see e.g. Bakker et al. (2008); Iseki et al. (2008); Jahn et al. (2004, 2008); la Fougère et al. (2010)). Mental simulation of walking has been shown to involve areas implicated in motor planning like the premotor cortex, the supplementary motor complex, parts of the parietal cortex, the basal ganglia and the parahippocampal cortex (Iseki et al., 2008; Jahn et al., 2004, 2008; la Fougère et al., 2010).

Sensorimotor systems and spatial processing

As mentioned before, activity in the sensorimotor system reliably informs the organism of its own movement and thereby contributes to self-motion perception. Sensorimotor signals can therefore serve as a source for spatial computations based on self-motion cues. In fact, studies on rodent navigation have shown that sensorimotor cues deriving from locomotion crucially modulate neurophysiological signals involved in spatial encoding of the environment (Czurkó et al., 1999; Ekstrom et al., 2003; Save et al., 1998). It has been further shown that motor/proprioceptive signals deriving from locomotion have a stronger influence on neurophysiological signals of space encoding than other self-motion cues such as vestibular signals or optic flow (Terrazas et al., 2005).

Beyond the formation of spatial representations based on self-motion, clinical findings show that also the highest and more abstract level of motor control is linked to spatial processing. The severe effects of lesions in the parietal cortex demonstrate that this region is crucial for goal directed movement as well as for the processing of personal (concerning the own body) and extrapersonal space (space beyond the own body). Lesions of the parietal cortex lead to disturbances of the body schema, such as the confusion between different body parts in oneself and others (Bear et al., 2001b; Kandel et al., 2000a). In its most severe form a parietal lesion can lead to spatial hemineglect, a neuropsychological syndrome in which patients are unaware of the contra-lesional half of personal and extrapersonal space (Coslett, 1998; Husain and Nachev, 2007; Pavani et al., 2003). This neglect is not only perceptual but also representational, which was shown in the classical study by Bisiach and Luzzatti (1978): when patients where asked to describe imagined familiar surroundings,

they failed to describe details on the contra-lesional but not the ipsi-lesional side, depending on the imagined perspective. These neuropsychological phenomena provide evidence for the close connection between the neural sensorimotor representation of the body and the neural representation of personal and extrapersonal space.

Besides these physiological evidences, also results from behavioral studies suggest that the sensorimotor system contributes to the encoding of space. Several studies in sighted and blind humans have shown that accurate direction and distance estimations can be based exclusively on sensorimotor cues (Frissen et al., 2011; Klatzky et al., 2008; Loomis et al., 2001; Mittelstaedt and Mittelstaedt, 2001; Siegle et al., 2009). Surprisingly, such estimations remain in large part accurate even during passive transport to a target, during which only vestibular and somatosensory information are available (Israël et al., 1997; Frissen et al., 2011; Mittelstaedt and Mittelstaedt, 2001). It remains a subject of debate, on which mental processes spatial estimation ability during active and passive movement is based. Some argue that such spatial estimations can be based on the extraction of self-motion information from the sensorimotor system, suggesting a perceptual foundation (Israël et al., 1997; Frissen et al., 2011). Others stress the importance of an inner simulation of the body moving through space based on prior experience, suggesting an (additional) cognitive foundation (Seidman, 2008; Wertheim et al., 2001; Yong et al., 2007).

Neurophysiological data might help to clarify the relative contribution of the perceptual and cognitive processes to this spatial estimation ability. To contribute to the scarce body of neurophysiological data on the topic, the first project of this thesis investigated neural networks representing active and passive self-motion experience through space (see 2.1).

1.1.2 Visual motion processing

The visual system processes many aspects of the world around us, and one of these aspects is motion. While basic attributes of visual stimuli are analyzed already in the thalamus and the primary visual cortex (V1 or striate cortex), aspects like shape or motion are specifically processed in areas of the 'extrastriate cortex', a term summarizing visual areas beyond the striate cortex, along the temporal and parietal lobe. Extrastriatal areas are organized in two anatomically and functionally separate streams. While the ventral stream extends towards the inferior temporal lobe, the dorsal stream projects towards the posterior parietal cortex (PPC). Areas along these streams exhibit different functional properties: while areas along the ventral stream process object informations like shape and color, areas along the dorsal stream are predominantly involved in location and motion processing (Bear

et al., 2001a).

Particularly important for motion processing in the dorsal stream is a functionally well-defined region first described in non-human primates as area MT [1] (Allman and Kaas (1971) in owl monkey, Dubner and Zeki (1971) in macaque). While most of what we know about this region has been first described in primate animal models, neuroimaging studies in humans meanwhile suggest that its organization resembles closely the organization in the human brain. MT receives its major input from V1, and is thought to do essential integration, segmentation and structure computations based on visual motion (see Born and Bradley (2005) for a review). It then projects these computations further to several other motion sensitive areas in the posterior parietal cortex (PPC) such as the medial superior temporal area (MST) and the ventral intraparietal area (VIP). These PPC areas have been shown to extract heading information from optic flow (Bremmer et al., 2002; Britten, 2008; Logan and Duffy, 2006) and have been suggested to integrate visual motion information with motion cues from other sensory modalities (Duhamel et al., 1998). Further prominent MT projections go to areas processing eye-movement. On the cellular level, it has been found that the majority of neurons in MT are selective for direction and speed of visual motion (see Born and Bradley (2005) for a review). Single cell recordings have also shown a direct link between neural activity and perception, as neurometric functions reliably predict psychometric functions for direction sensitivity within individual monkeys (Britten et al., 1992).

A functionally equivalent region to MT in the human cortex was first identified based on a clinical finding: a patient who suffered brain damage was unable to perceive visual motion, while other aspects of vision were preserved. The lesions were located in the lateral temporo-occipital cortex (Zihl et al., 1983). The sensitivity of this region to motion specifically was later confirmed by a neuroimaging study, which compared cortical blood-flow patterns to a motion stimulus in PET and fMRI (Watson et al., 1993). Following this first study, hMT+ can meanwhile be reliably identified with functional neuroimaging at the intersection of the ascending limb of the inferior temporal sulcus and the lateral occipital sulcus (Dumoulin et al., 2000). In parallel with the primate nomenclature, this motion-sensitive region has been named human MT (hMT), and as this region is difficult to separate from human MST with neuroimaging methods, most studies refer to the combination of hMT and hMST as hMT+ (the human motion complex). hMT+ properties from basic sensory encoding up to perceptual decision making have meanwhile been characterized

[1] MT stands for 'middle temporal' gyrus: in owl monkeys, the region has been found on the posterior bank of the middle temporal gyrus; in macaque, the functionally equivalent region has been called V5

by neuroimaging studies (see e.g. Huk et al. (2002); Morrone et al. (2000); Muckli et al. (2002); Rees et al. (2000); Smith et al. (2006)). In parallel to primate data, some recent neuroimaging studies provide evidence for direction-selective neuronal subpopulations in hMT+ (Kamitani and Tong, 2005, 2006).

The perception of visual motion is the basis for the detection of optic flow during self-motion. While optic flow is only one among many self-motion cues, behavioral findings in humans however show that spatial estimations of distance and direction can be base solely on this visual information (Warren et al., 1989; Wolbers et al., 2007). fMRI studies in humans have shown that hMT+ is activated during the perception of optic flow (Diekmann et al., 2009; Kovács et al., 2008; Wolbers et al., 2007). This region could therefore contribute essential visual motion information to brain areas involved in self-motion integration. In non-human primates, strong connections between MT and VIP in the PPC suggest that visual motion information is forwarded to this region. A human equivalent of area VIP has been described (Bremmer et al., 2001), which makes this pathway also plausible in humans. Another candidate for the integration of self-motion cues is the medial temporal lobe (MTL). Areas in the MTL have been implicated in the extraction of spatial information from the environment, based on the integration of self-motion cues from different sensory modalities in rodents (Moser et al., 2008) (see also 1.3). These areas might have a similar function in humans, as recent neuroimaging studies in humans show that MTL areas are active during navigation in virtual reality environments, during which the only source of self-motion information is optic flow (Caplan et al., 2003; Cornwell et al., 2008; Ekstrom et al., 2005; Wolbers et al., 2007). In particular the study by Wolbers et al. (2007) suggests that self-motion information from optic flow is sufficient to trigger MTL activity: using an impoverished virtual environment in which distance and direcion information could only be inferred from optic flow, this study shows that the hippocampus was coactivated with hMT+ and the medial frontal cortex during a spatial estimation task.

This short overview shows that hMT+/MT has been studied extensively in humans and monkeys on different levels. The fact that its response properties are well understood in primates, and that it has been shown to be closely linked to perception and behavior makes hMT+ an ideal candidate to explore new questions on motion perception. Because of this, we focused on this region to explore physiological correlates of inter-individual difference in visual motion perception (2.3).

1.2 Processing of space in the brain

During exploration, our body acquires information about the world via our senses, which provide information on the external state of the world, as well as feedback on our interaction with it. In the brain, all these informations converge and based on present and past sensorimotor informations, representations of the world are formed which can be used to control behavior pro- and reactively. Spatial representation for example serve to control planning and execution of goal-directed movement.

All senses map the same 3-dimensional world and spatial representations are thought to form drawing on multiple sensory modalities (Klatzky et al., 2003; Loomis et al., 1998; Loomis, 2007). Visual and auditory information can provide information about environmental features such as geometry or position of landmarks. In addition, spatial knowledge can be extracted from self-motion cues arising during bodily movement. Self-motion cues comprise optic flow processed in the visual system, acceleration and rotation signals processed in the vestibular system, proprioceptive cues from muscles, joints and tendons and motor efference copies deriving from the motor system (Cullen, 2004). During whole-body movement, integration of self-motion cues over time can serve to track the own position in reference to a starting point or a goal, a computation called path integration (Etienne and Jeffery, 2004). Movement of the upper extremities can provide spatial information within arms reach: haptic exploration can be used to understand spatial layout of the immediate environment (Giudice, 2009; Giudice et al., 2011; Loomis, 1986).

These examples show that experiencing space does not fit into the classical action-perception scheme, which describes gaining knowledge of the environment as perception and moving in the environment as action (Hurley, 1998). Rather, acquiring spatial knowledge about the environment is based on both action- and perception-systems. Indeed, matches between spatial estimations based on visual or sensorimotor cues provide evidence that spatial information highly overlaps between these systems. It has for example been shown that learning spatial layouts haptically or visually resulted in similar spatial updating performance during intra- and inter-modal trials (Giudice, 2009). And the finding that humans can blindfoldedly walk to a previously seen target with high accuracy shows that visual distance cues can be converted into a spatially equivalent motor output (Klatzky et al., 2008; Mittelstaedt and Mittelstaedt, 2001).

This flexibility in conversion is remarkable if one considers that all sensory and motor cues are initially processed in different peripheral sensory receptors or motor effectors. Depending on the receptor and the way of encoding, spatial information can differ in

resolution and accuracy: some studies show modality specific distortion of spatial information if only one modality is available, like distance compression for auditory or haptic perception (Loomis et al., 1998; Abravanel, 1971). Additionally, all senses encode spatial information in different coordinate systems: visual information enters the system in retinal coordinates, vestibular information is organized in reference to the head and motor efference copies are organized in reference to the respective effector (i.e eye-centered if coming from eye-movements, body-centered if coming from limb-movements). Finally, spatial information arriving in these different coordinate systems has to be re-transformed into the coordinates of the specific effectors for goal-directed motor output.

To explain how spatial information of different resolution and encoded in different coordinates can produce a unitary space for perception and action, it has been suggested that the brain integrates input from multiple sensory modalities into an universal, amodal spatial representation. This integration might comprise a conversion from the respective body-centered coordinate systems (egocentric representations) to an abstract coding of space relative to the environment (allocentric representation). Such a representation could serve as an unbiased way to store incoming spatial information before it is re-transformed into the respective motor-coordinate system for goal-directed action (Byrne et al., 2007; Whitlock et al., 2008). Such a spatial representation might also serve to maintain stable spatial behavior when only insufficient or ambiguous sensory information is available, such as during navigation to an unseen target. It has been suggested that spatial behavior in this case relies on spatial memory, on which mental simulations of spatial relationships can be based (Byrne et al., 2007).

Therefore a spatial representation system in the brain is expected to comprise 1) neural systems which extract spatial information from sensory and motor cues and integrate them, 2) systems which convert spatial information from different coordinate systems to an allocentric spatial representation, 3) memory systems which store and retrieve such information and can simulate spatial relations, and finally, 4) systems which transform spatial information into egocentric coordinates for goal-directed motor output. Consistent with this multitude of functions, empirical findings suggest a distributed neural network underlying spatial representation (see Figure 1.1). A central role in this network is assigned to structures of the medial temporal lobe (MTL), which are assumed to construct a neural allocentric representation of space by integrating information on environmental and self-motion cues (Byrne et al., 2007; Moser et al., 2008; Whitlock et al., 2008). A prominent role is also assigned to the parietal cortex which has been found to process spatial information

in multiple egocentric coordinate systems (Byrne et al., 2007; Sack, 2009; Whitlock et al., 2008). Furthermore, it has been suggested that a transformation circuit comprising the retrosplenial complex, the posterior parietal cortex (PPC) and the head-direction system distributed along the Papez's circuit translates between neural egocentric and allocentric representations (Byrne et al., 2007; Whitlock et al., 2008). The following section will introduce one of these brain areas, the medial temporal lobe, in greater detail.

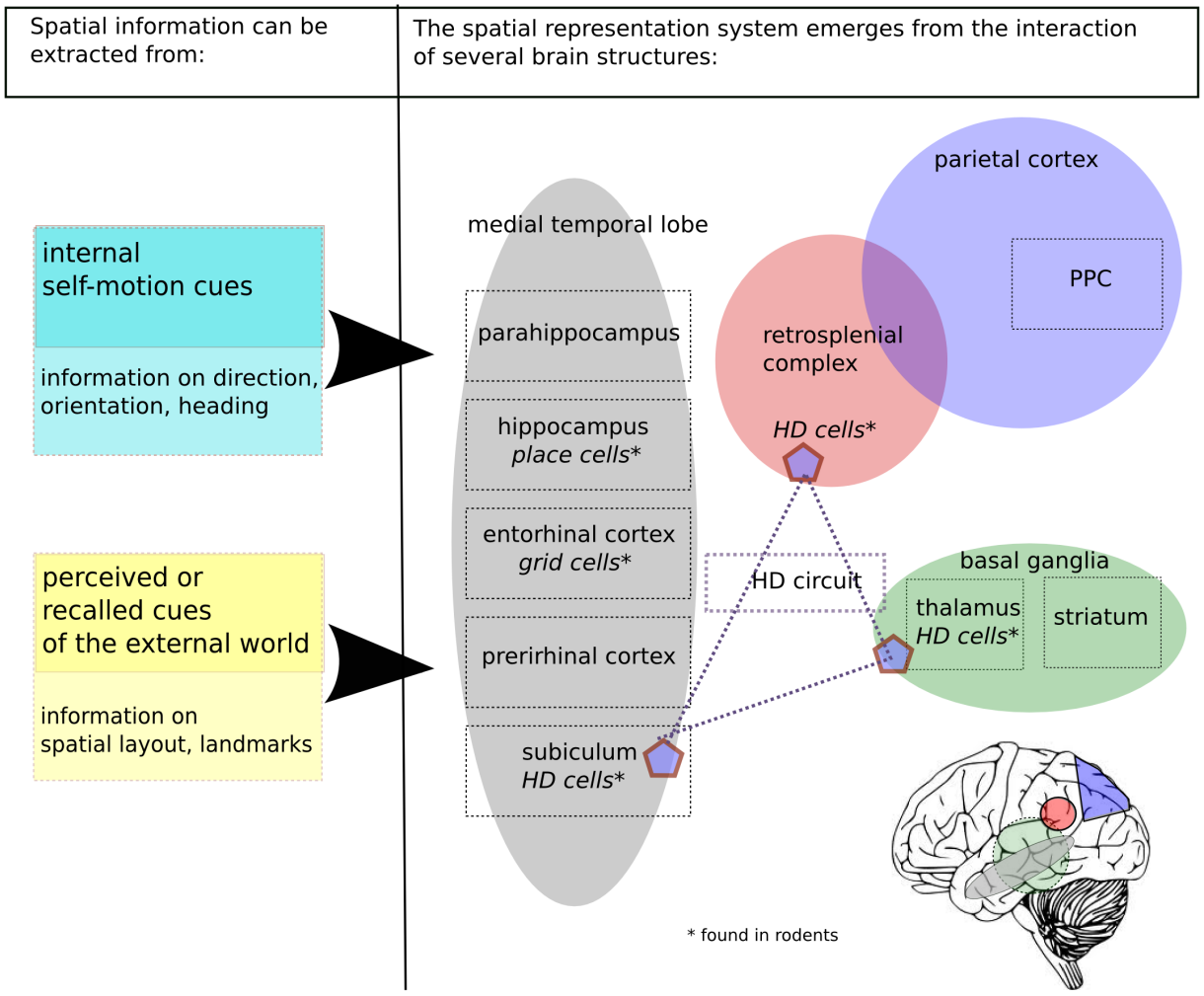

Figure 1.1: A spatial representation system in the brain. A schematic overview of the brain circuits which are currently thought to compose the neural spatial representation system, taking into account converging data from studies in humans, primates and rodents. In humans and animals, spatial information is extracted from self-motion cues and external cues on spatial layout and landmarks. Neurophysiological studies in primates (including humans) point to important roles of medial temporal lobe structures, the retrosplenial complex and the parietal lobe, in particular the posterior parietal cortex in spatial processing. The rodent literature further assigns an important role to basal ganglia structures like the striatum and the thalamus. A further discovery in rodents was crucial for the description of neural circuits processing space: cells showing specific space coding have been found, like place cells in the hippocampus, grid cells in the entorhinal cortex and head direction cells in the subiculum, the retrosplenial complex and the thalamus (properties of these cells will be described in section 1.3.2). HD cells: head direction cells, PPC: posterior parietal cortex. Schematic based on Byrne et al. (2007), Moser et al. (2008), Poucet et al. (2003), Taube (2007), Whitlock et al. (2008).

1.3 The medial temporal lobe: linking movement to space

The most likely candidates to mediate between neural movement processing and neural space processing are brain structures which exhibit both space- and movement-sensitive responses. Several such structures can be found in the medial temporal lobe (MTL), which it therefore the prime region of interest for research on goal-directed movement through space, also known as navigation. The medial lobe has as a folded structure: located along this fold from dorso-medial to ventro-lateral are the hippocampus, the subiculum, the rhinal sulcus with the entorhinal and the perirhinal cortex, and the parahippocampal cortex (see Figure 1.2). In rodents, the same structures have been identified, as the basic circuitry of the MTL is highly conserved in mammals (Manns and Eichenbaum, 2006). This conservation allows to revert to the vast literature on MTL properties in rodents

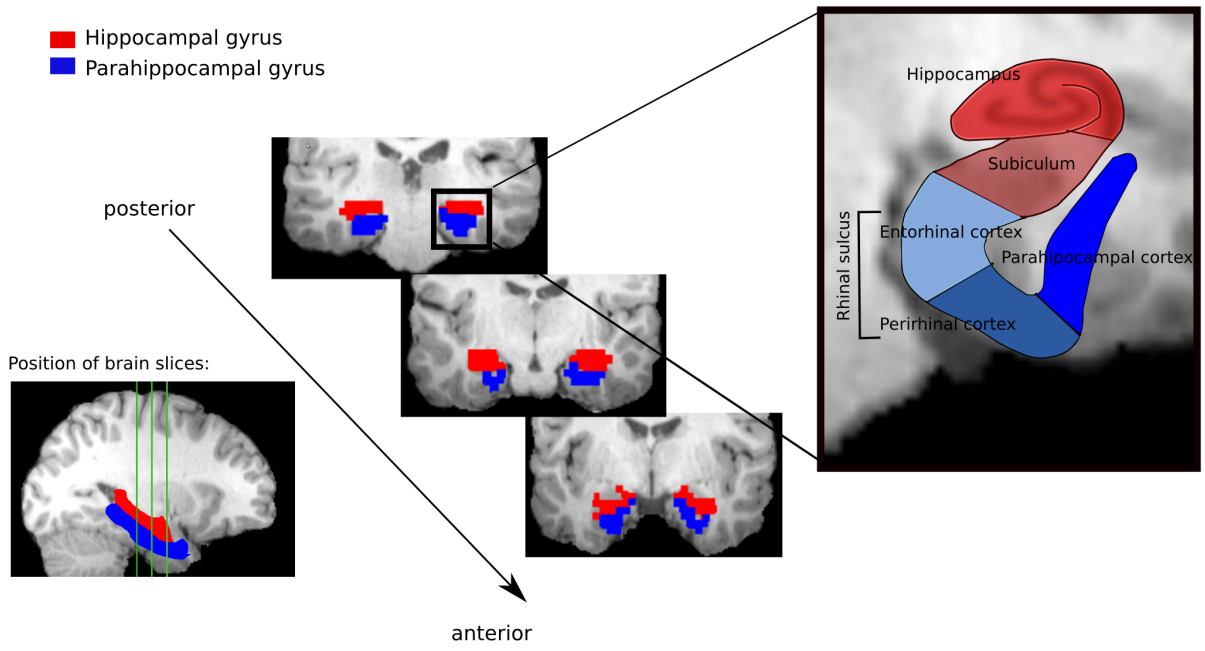

Figure 1.2: The medial temporal lobe. Shown are sagittal and coronal views of the hippocampal (red) and the parahippocampal gyrus (blue), as defined by the Wake Forest University PickAtlas (aal atlas) (Tzourio-Mazoyer et al., 2002; Maldjian et al., 2003), overlayed on a brain image normalized to MNI space. Upper panel: at higher resolution, one can differentiate the subdivisions of the medial temporal lobe in the hippocampus, the subiculum, the rhinal sulcus comprising entorhinal and perirhinal cortex, and the parahippocampal cortex.

when forming physiological hypothesis in humans.

1.3.1 Activity during locomotion

Since the seventies it is known that self-movement modulates MTL structures in mammals. The first evidence for a relation between the hippocampus and movement stems from electroencephalographic studies in rats showing that hippocampal theta rhythm (6-10 Hz rhythmical activity) accompanies locomotion, but not behavior such as body grooming or face washing (Vanderwolf, 1969; Coenen, 1975). It has also been shown that hippocampal lesions result in movement deficits in rodents (Bast and Feldon, 2003). Closer analysis of neurophysiological signals has further revealed that the spectral power of the theta rhythm (Czurkó et al., 1999) and hippocampal population firing rate (McNaughton et al., 1983; Czurkó et al., 1999; Ekstrom et al., 2001) depend on running speed. Recently, it has also been shown that the theta rhythm is parametrically modulated by the amount of self-motion cues available (Terrazas et al., 2005). On the cellular level, it has been shown that inhibitory interneurons in the hippocampus are sensitive to properties of the movement signal like acceleration or velocity (Buzsáki, 2002). It has been further found that firing characteristics of pyramidal neurons in the hippocampus are modulated by the amount of self-motion cues available (Terrazas et al., 2005).

Also in humans the MTL is activated during locomotion. Neuroimaging studies have shown that MTL structures are active during walking on a treadmill (la Fougère et al., 2010; Fukuyama et al., 1997) and during mental simulation of locomotion (la Fougère et al., 2010; Jahn et al., 2004, 2008; Malouin et al., 2003; Sacco et al., 2006; Iseki et al., 2008).

These results suggest that a relation exists between MTL activity and locomotion. Regarding the nature of this relation, most empirical evidence nowadays support the view that activity in MTL structures during movement does not primarily reflect locomotor control, but rather reflects spatial processing due to navigational demand. Processes in the hippocampus and the parahippocampus might contribute to solve questions such as: Where am I going? Where am I coming from? Where am I now?

1.3.2 The medial temporal lobe and goal-directed movement

The understanding of spatial processing in the MTL began with the crucial discovery of 'place cells' in the rodent hippocampus, neurons which show modulation by the absolute location an animal occupies in space. The discovery of these cells was the first sign that

a neurophysiological foundation of a 'cognitive map' (i.e. neural allocentric representation of space) exists in mammals (O'Keefe and Dostrovsky, 1971). Over the following 40 years of research, further 'spatial' cells were found in rodent MTL structures. One example are 'grid-cells' in the medial entorhinal cortex: these cells exhibit multiple firing fields which tessellate the environment in a grid-like pattern (Hafting et al., 2005). Another example are 'head-direction-cells', distributed along the Papez's circuit[2], which code the heading direction of the animal (see Taube (2007) for a review). It has been suggested that a neural representation of navigable space could result from the interaction between populations of these three cell types (McNaughton et al., 2006; Moser et al., 2008).

Far less is known about navigation processing in the human brain, however more and more results point to MTL structures also in humans. Activity in MTL structures is frequently observed in neuroimaging studies during mental navigation (Ghaem et al., 1997; Rosenbaum et al., 2004) or navigation with a joystick through virtual environments (Caplan et al., 2003; Cornwell et al., 2008). And further paralleling results obtained in rodents, recent electrophysiological and neuroimaging studies report evidence for place cells and grid cells in the human hippocampus and the entorhinal cortex (Ekstrom et al., 2003; Doeller et al., 2010). Furthermore, structural and functional properties of MTL areas have been shown to correlate with navigational skill. On a structural level, significantly larger posterior hippocampi have been described in London taxi drivers, a profession with high navigational demand, compared to a group of control subjects (Maguire et al., 2000). On a functional level, neuroimaging studies showed that hippocampal and parahippocampal activation patterns correlate with individual performance on navigation tasks (Janzen et al., 2008; Wolbers et al., 2007). Also clinical reports of patients with hippocampal or parahippocampal lesions support the view that these regions are involved in spatial processing. Patients with such lesions show impaired performance on spatial tasks such as route learning and navigation (Barrash et al., 2000; Glikmann-Johnston et al., 2008).

Most knowledge on spatial processing in the human brain however comes from research using static spatial stimuli. A region in the posterior parahippocampus has been identified as being specifically sensitive to information about the 3D structure of space. This region was originally discovered in a neuroimaging study comparing brain activation while viewing photographs of landscapes to brain activation while viewing photographs of objects (Epstein and Kanwisher, 1998). Due to its higher response to 'place' rather than 'object' photographs, it was given the name 'parahippocampal place area' (PPA). Further

[2]more precisely, they have been described so far in the subiculum, the thalamus and the retrosplenial cortex

characterization of this region revealed that it responds to outdoor and indoor scenes, to familiar and unfamiliar scenes, to real and artificial scenes, that it responds to far-scenes as well as desktop environments, that it is viewpoint invariant and that it depends on the background elements defining the geometry of a landscape rather than on discrete objects contained in the scene (Epstein et al., 1999; Epstein, 2005; Epstein et al., 2007). Common to all stimuli was the spatial layout which could be extracted, which lead to the suggestion that the PPA is selectively processing the visuo-spatial structure of a scene (the 'spatial layout hypothesis') (Epstein, 2008).

Despite the thorough characterization of the PPA with a multitude of static visuo-spatial stimuli, it remains unclear if it is the spatial content of the stimulus or its visuo-spatial structure which drives PPA activity. If this region is selective for spatial computations in general, the source of the spatial information might not depend on visual stimulation, but could also arise from the integration of self-motion cues. To clarify this question, the second project of this thesis compared PPA activity during haptic exploration of spatial layout (see 2.2).

1.4 Designs for fMRI: Studying brain processing of movement and space in immobile participants

In the last twenty years, the use of magnetic resonance imaging (MRI) in behavioral and cognitive research has increased exponentially. This is mainly due to the discovery that hemodynamic changes which accompany neural activity can be captured with MRI (first described by Ogawa et al. (1990) in rats; Ogawa et al. (1992) in humans). This technique allowed for the first time to study functional changes in the human brain non-invasively. The most used imaging method within this *functional* form of MRI (fMRI) is based on the 'blood-oxygen-level-dependent' (BOLD) signal. By making MR images sensitive to disruptions in the magnetic field, bloodflow in the brain, which has magnetic properties itself, can be used to track neurophysiological activity (Amaro and Barker, 2006; Nair, 2005). The BOLD signal originates from neurovascular coupling: when synaptic activity rises in a particular brain region, energy is needed for transmitter release and re-uptake, which leads to a rise of metabolic rate and oxygen consumption. Oxygen-rich blood streaming into the activated region changes the local gradient of oxygenated and deoxygenated hemoglobin, which changes the magnetic properties in a confined region (oxyhemoglobin has paramagnetic, deoxyhemoglobin has diamagnetic properties). This local magnetic changes can be picked up by specific scanning sequences used in fMRI (Nair, 2005). While the exact mechanisms linking neuronal activity to hemodynamics remain to be explored, it has been shown that the BOLD signal correlates with neural population signals like the local field potential in primates (Logothetis et al., 2001). Another study using optogenetics in rodents shows that it is excitatory circuits specifically which evoke a positive BOLD signal (Lee et al., 2010).

A major challenge when using fMRI to describe neural correlates of a behavior or a cognitive function is the translation of behavioral experiments into a design appropriate for the scanner, or as the neuroscientist Melvyn Goodale puts it: 'fMRI is like trying to assemble a ship in a bottle - every which way you try to move you encounter a constraint'[3]. Such constraints are obvious for research on movement and spatial abilities: how to design experiments addressing brain processing of movement through space, during which participants lie stock-still in a 60 cm diameter tube? This thesis therefore explored different study designs with the aim to choose the right design and analytical tools to address the

[3]Culham, Jody. Tutorial: Basic Experimental Design, [Online] Available htttp://psychology.uwo.ca/fmri4newbies/Tutorials.html, June 5, 2011

specific scientific question at hand. In the following I will lay out three scientific questions of this thesis and the selected study designs and analytical tools used to answer them. Those scientific questions were: 1) Which are the brain networks involved in active and passive whole-body movements? We used an approach of mental movement simulation. 2) Is the parahippocampal place area a visuo-spatial region, or does it respond to spatial layout independently of input-modality? We used an approach of comparing subject groups with different spatial experiences (blind and sighted people). 3) Do inter-individual differences in performance on visual motion tasks have a physiological correlate in hMT+? In the course of addressing this question, we explored novel analytic tools which answer physiological questions beyond mere localization.

1.4.1 Mental simulation as a tool to study action and perception

The first project of this thesis aimed to investigate the overlap between brain networks activated during locomotion and passive transport through space. As actual movement is not possible during fMRI, a study design which addressed the brain networks activated during recall of movement was chosen. Subjects experienced specific whole-body motion sequences and recalled these experiences in a subsequent fMRI session. How can this tell us something about the actual networks during perceiving whole-body motion under natural conditions? Multiple lines of evidence suggest that mental simulation of experiences activates brain areas involved in execution and perception of those experiences. Evidence comes from comparisons of real and mentally simulated perceptions (Goldberg et al., 2006; Kosslyn et al., 1999; Slotnick, 2004; Weinberger, 2004), from real and simulated limb- and whole-body movements (Deiber et al., 1998; Filimon et al., 2007; Hanakawa et al., 2008; Lacourse et al., 2005; la Fougère et al., 2010; Miyai et al., 2001; Porro et al., 1996; Stippich et al., 2002), and simulations of complex actions such as playing piano (Meister et al., 2004), peeling a banana, using a razor (Ruby and Decety, 2001) or navigating through a town (Ghaem et al., 1997; Rosenbaum et al., 2004). Another line of evidence comes from the successful use of mental simulation in brain computer interfaces, which has promising outlooks for the field of neuroprosthetics (Pfurtscheller et al., 2006). More evidence comes from the success of imagery in motor rehabilitation (Langhorne et al., 2009). Building on this notion, more and more studies investigate whole-body movements like gait with mental simulation protocols in fMRI (Bakker et al., 2008; Jahn et al., 2004, 2008, 2009; Iseki et al., 2008; Sacco et al., 2006; Wang et al., 2008).

That mental simulation draws on the same neural foundation as action and percep-

tion challenges a basic theme with prevailed in experimental and cognitive psychology for decades: that mental processes can be divided into perception, cognition and action (also referred to as 'the sandwich view', see (Hurley, 1998)). To the contrary, more and more theories develop which try to unify action, perception and, in part, cognition. One such theory is the 'mental simulation theory of motor cognition', brought forward by Jeannerod (2001). He arguments that action consists not only of an overt stage, observable on the outside when we grasp something or walk somewhere, but includes also the covert stage of intending actions, imagining actions, recognizing tools, learning by observation and understanding the behavior of other people (Jeannerod, 2001). He hypothesizes that the motor system is part of a simulation network which is activated during these covert actions. Another theory, which still goes a step further and tries to unify action, perception AND cognitive processes like memory and planning, is the 'perceptual symbol theory' brought forward by Barsalou (1999). This theory describes mental simulation of information stored in the neural sensorimotor units as the underlying process for both imagery and memory (Barsalou, 1999, 2003, 2008). Barsalou calls his point of view 'grounded cognition' and asserts that mental simulation, drawing on the same brain areas used for perception and action, provides an essential form of computation in the brain and is the basis for many cognitive processes such as memory, spatial cognition, perception-action coordination and interpreting action intentions of other agents (Barsalou, 2008).

The use of mental simulations of action thereby makes it possible to investigate the neural foundation of spatial and movement processing during whole-body motion with fMRI.

1.4.2 Multimodality in the PPA: comparing different subject groups

The next scientific question concerned a specific physiological hypothesis about the properties of the 'parahippocampal place area' (PPA), which has been described in the fMRI literature as a category-specific region for visuo-spatial layout (Epstein et al., 1999). In neuroimaging, the term 'category-specific region' has been used for brain regions which are described to respond specifically to a complex stimulus such as the fusiform-face area (FFA) to photographs of faces (Kanwisher et al., 1997), the hMT+ to visual motion or the lateral occipital complex (LOC) to object-shape (Malach et al., 1995). Recently, neuroimaging studies in blind people found that many of these regions process multimodal information: the FFA for example has been shown to be activated by tactile perception of

faces (Goyal et al., 2006), the hMT+ has been shown to respond to tactile and auditory information (Poirier et al., 2006; Ricciardi et al., 2007; Wolbers et al., 2011a), and the LOC to process object information learned by haptic exploration (Mahon et al., 2009). If these findings capture a general property of category specific regions, the PPA is also likely to respond to spatial layout independent of the modality of the input.

The experiment we designed to address this question compared activity in PPA during visual and haptic perception of spatial layout, contrasted with the perception of objects. To test if the PPA is a true multimodal region, we had to clarify if a possible activation of PPA by haptic input was due to haptic information per se, or due to visual recoding. As expanded on in section 1.4.1, mental simulation plays an important role in perception and cognition, and haptic perception of spatial layout could have lead to visual mental imagery of the spatial layout, which is known to activate PPA (O'Craven and Kanwisher, 2000). We approached this possible confound by including a subject group which is not able to do recoding based on visual experience: blind people. Special subject groups provide behavioral and brain research with invaluable new insights into behavioral capabilities and brain functions. The study of specific sensory deprivations like the loss of the visual sense have taught us for example the multimodal nature of spatial perception and representation: while space is mostly considered through our visual access to it, spatial capabilities in blind people clearly show that spatial understanding and representation can be built up through auditory, haptic and self-motion input (Thinus-Blanc and Gaunet, 1997; Loomis et al., 2001; Loomis, 2007).

By comparing PPA activity during haptic exploration of spatial layout in both sighted and blind people, we could address the question of multimodality in the parahippocampus and, at the same time, could distinguish between its activation due to haptic perception or visual recoding.

1.4.3 Analytical tools for exploring neural inter-individual differences

The last project of this thesis explored physiological correlates of inter-individual differences in visual motion perception using a psychophysical direction discrimination task. Specifically, the study investigated on which stage of visual processing individual differences in psychophysical threshold would be reflected in the neural activation pattern by comparing the early stage of visual processing in V1 and the more complex processing level in hMT+.

Based on results obtained in electrophysiological studies in monkeys, we hypothesized that activity in hMT+ correlates with individual direction discrimination thresholds. Such monkey studies have found evidence that psychophysical thresholds correlate with sharpness of direction coding in MT. Specifically, it was found that a broadening in tuning curves of direction-selective neurons accompanies worsening of directional judgment during aging (Liang et al., 2010).

Based on such findings, we tested whether individual direction discrimination thresholds were correlated to the specific pattern of direction-selective neuronal sub-populations in hMT+. As such differences between individuals would not be detectable in our datasets using the conventional voxel-based fMRI analysis, we used a multivariate approach (pattern classification). While the conventional voxel-based approach based on the general linear model cannot separate different direction-selective populations at the current limit of fMRI resolution, the method of pattern classification can detect signal biases within voxels. As such, this method can tell us if a set of voxels contains more or less information about motion direction. Differences in the amount of information about direction contained in hMT+ between individuals might indicate differences in the underlying functional physiology. Such differences might in turn be related to inter-individual variability in discrimination acuity.

Another analysis we performed was to characterize the variability of the hMT+ BOLD signal during perception of motion. It was tested whether such variability correlates with individual discrimination thresholds.

The principles of pattern classification and the analysis of BOLD signal variability will be introduced shortly in the following sections.

Multivariate analysis

In contrast to the wide-spread use of univariate analytical methods based on the general linear model, multivariate methods which use machine learning algorithms to train classifiers have been introduced to the field of fMRI only recently (see O'Toole et al. (2007) for a historical review). Instead of dealing with each voxel independently, such methods treat the dataset as a whole (therefore the term multivariate). Pereira et al. (2009) describes in his methodological review on machine learning classifiers and fMRI the principles and single steps of the methodology as follows: classifiers can be understood as functions, which relate the features in an example dataset to a class which this dataset belongs to. As features in the case of fMRI one chooses voxels, and the classes they can be related to are the

types of stimuli presented to the subject. A classifier has to be first trained on a subsample of the dataset, to learn the relationship between features and classes. Subsequently, its ability to classify an unknown dataset is tested. If the classifier succeeds in classifying this unknown dataset correctly, this means that this dataset contains information about the variable of interest. How well a classifier performs is usually measured as its accuracy (percent correct classification).

In our experiment, we tested whether a classifier could distinguish the activation in hMT+ or V1 as a result of seeing visual motion in four different directions. The possibility of decoding direction information from the visual system has been shown before (Kamitani and Tong, 2006). By determining the classification accuracy of motion direction based on V1 or hMT+ signals we aimed to identify on which level of visual processing behavioral performance is reflected in brain physiology.

Measuring neural noise: BOLD signal variability

The second analysis we used to characterize inter-individual differences in hMT+ processing considered the 'noise' of the BOLD signal. The term 'noise' traditionally derives from the field of engineering and has been used to describe undesirable fluctuations, obscuring meaningful information in communication technology (McDonnell and Abbott, 2009). Following the general trend of considering the brain as a communication system, with neurons and brain regions communicating with each other, variability in nervous signals has also here be termed 'neural noise'. In parallel to its use in engineering, neural noise has been considered to disturb potentially smooth information transfer in the brain, and has been described to be increased in mental diseases such as schizophrenia (Winterer et al., 2006). However, some new ideas on neural noise have been recently expressed which assert that variability of nervous signals could under some circumstances have a functional significance. The brain is a variable physiological system, processing variable environmental information, and some phenomena in the brain have meanwhile be described in which signal variability can serve to amplify the signal in a thresholded system (McDonnell and Abbott, 2009). These phenomena have been summarized under the term 'stochastic resonance' (McDonnell and Abbott, 2009).

Which impact would neural noise have on hemodynamics, in other words, how can noise be detected with fMRI? Several studies now exist which use the measure of variability of the BOLD signal to estimate such neural noise (Garrett et al., 2010, 2011; Ghosh et al., 2008; McIntosh et al., 2008; Samanez-Larkin et al., 2010). The variability of the BOLD signal can

be estimated by calculating the standard-deviation (SD) over blocks, after accounting for global sources of noise like scanner drifts, head-movement or fluctuations due to heart-beat and breathing (Garrett et al., 2010, 2011). Others calculate the mean squared successive difference (MSSD) rather than the SD, to account for different means of the expected signals (Samanez-Larkin et al., 2010). If the mean varies between different task conditions, the SD overestimates the variability and therefore the MSSD is a more appropriate measure (Mohr and Nagel, 2010). Furthermore, care must be taken to explain stimulus-induced fluctuations of the signal, such as switching the stimulus on and off during a block, to not confuse such variability with endogenous BOLD signal fluctuations. The current study used the approach of modeling the expected BOLD signal by a generative model and then estimating the variability based on this model (see 2.3).

1.5 Aim of this thesis

The general goal of this thesis was to explore brain networks of motion and movement processing in a number of different sensory and motor modalities in order to understand how these are combined to create an internal representation of space. To this end, two projects explored brain processing of motion during active sensing, on the one hand while moving the whole-body through space, on the other hand while exploring spatial layout with the hand. The third project explored visual motion processing during passive sensing.

The first project investigated neural networks underlying self-motion processing during active and passive whole-body motion (2.1). It was tested whether sensorimotor brain networks during mental simulation of self-motion experience overlap for locomotion and passive transport. Retrieval of previously experienced locomotion and passive transport during fMRI scanning was used to address this question.

The second project investigated processing in the parahippocampal place area (PPA), which is known to process visuo-spatial layout in humans (2.2). This study explored, whether PPA is selective only for visuo-spatial layout, or processes spatial layout in general, independent of the encoding modality. To this end, a group of sighted and blind participants haptically explored the spatial layout of model-scenes during fMRI. Activations in PPA during the haptic condition were compared to activations during a matched visual task in the sighted participants.

The final project focused on motion processing in the visual system. It explored on which level of visual processing inter-individual physiological differences reflect behavioral

performance (2.3). This study focused on the motion sensitive area hMT+, based on results from neurophysiological studies in monkeys, which show that neuronal population codes in its monkey equivalent MT relate to direction discrimination thresholds. Brain activity during the perception of visual motion in different directions was characterized with multivariate pattern classification and a measure for variability of the BOLD signal. It was tested whether such measures correlate with individual thresholds on a direction discrimination task.

As a contribution to the field of brain research on movement through space, the study designs of this thesis show different ways how to address motion and movement processing in the brain with fMRI. A central physiological result obtained within this thesis is that the medial temporal lobe plays a central role both in motion processing and the formation of internal spatial representations.

2 Research Articles

The research conducted in the realm of this thesis is presented in the form of four research articles. Full papers are included and are preceded with a short description about the extent of my contribution to the respective project.

2.1 Networks of self-motion

The following section consists of two research articles:

- Flanagin, V.L., **Wutte, M.**, Glasauer, S., Jahn, K., 2009. Driving Dreams: Cortical Activations during Imagined Passive and Active Whole Body Movement. *Annual New York Academy of Science* 1164, 372375.

  The author of this thesis helped with the data collection, scanning and did the pre-processing analysis of the data. The design of the paradigm, the final analysis and the writing of the article was done by Virginia Flanagin.

- **Wutte, M.G.**, Glasauer, S., Jahn, K., Flanagin, V.L., 2011. Moving and being moved: Differences in cerebral activation during recollection of whole-body motion, *Behavioural Brain Research*. [Epub ahead of print, doi: 10.1016/j.bbr.2011.09.042]

  The author of this thesis designed the experiment based on the prior work of Virginia Flanagin, collected the data, analyzed the data and wrote the research article.

Driving Dreams

Cortical Activations during Imagined Passive and Active Whole Body Movement

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It is unclear how subjects perceive and process self-motion cues in virtual reality environments. Movement could be perceived as passive, akin to riding in a car, or active, such as walking down the street. These two very different types of self-motion were studied here using motor imagery in fMRI. In addition, the relative importance of visual and proprioceptive training cues was examined. Stronger activations were found during proprioceptive motor imagery compared with visual motor imagery, suggesting that proprioceptive signals are important for successful imagined movement. No significant activations were found during active movement with proprioceptive training. Passive locomotion, however, was correlated with activity in an occipital-parietal and parahippocampal cortical network, which are the same regions found during navigation with virtual reality stimuli.

Key words: **motor imagery; passive locomotion; active locomotion; fMRI; factorial design**

Introduction

In humans, virtual reality environments are often used to study navigation, particularly in functional MRI. It is unclear what type of movement subjects engage in when navigating through virtual reality environments. Subjects could perceive passive motion, where the subject does not move himself but is moved by another person or object, or the subject could imagine that he is actively walking through the environment. These two types of movement may influence distinct cortical networks, due to differences in sensory input. Passive movement, for instance, lacks a motor efference copy[1] and has reduced proprioceptive input.[2] Passive head movements lead to spiking in the vestibular nuclei in primates, which is suppressed during active head movement.[3] Active whole body motion has been studied in fMRI revealing cortical and subcortical centers responsible for locomotion.[4,5] However, there are to date no functional MRI studies on passive whole body movement. We therefore tested the difference between passive and active whole body movement with human fMRI.

The scanner configuration and image acquisition methods strongly limit the types of stimulation that can be tested with functional MRI. The problem of immobility can be partially overcome by using motor imagery instead of real movement. Path length estimation during motor imagery corresponds to path length estimation during real locomotion, suggesting a

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doi: 10.1111/j.1749-6632.2009.03844.x

common neurophysiological basis for both.[6] A variety of sensory information, such as visual, vestibular, or proprioceptive input, can be used to influence the performance and brain activity patterns of motor imagery. The difference between visual and proprioceptive input during motor imagery of whole body movement was also tested here.

Methods

Three movement conditions were tested: walk, stand, and ride, with either visual or proprioceptive imagery training. For proprioceptive training, subjects were asked to walk at a comfortable pace, or stand in one place, with their eyes closed to exclude visual input. Subjects were passively moved on a cart traveling at 4 m/sec to train for ride, or the passive movement task. In order to completely separate proprioceptive and visual input, a third person was used as the target for visual-based motor imagery, such that subjects watched someone else perform all three movement conditions during visual training. Tasks were trained until subjects felt confident in their ability to imagine the condition; then imagery was also trained. Nine right-handed subjects were imaged immediately after training on a GE 3T Signa HDx MR-Scanner using an EPI sequence with 34 slice volumes. One scanning session consisted of three time series containing 215 volumes and lasting 8.06 minutes each. Subjects' eyes were closed throughout the experiment, and stimulus commands were given acoustically at the beginning of each block. Proficient motor imagery requires a substantial amount of concentration; therefore, simple cognitive brain teasers were given between each time series acquisition to ensure subject alertness.

Analysis was done in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Volumes were realigned to the mean and normalized to the standard Motreal Neurological Institute (MNI) template. Data were smoothed with a 10 mm Gaussian kernel and entered into the general linear model. Each condition in the 2×3 factorial design (visual/proprioceptive and walk/stand/ride) was modeled as a step function convolved with the hemodynamic response function. The appropriate F- and t-contrasts were created at the single-subject level. T-contrasts were then used to test for population level effects. Activations are reported with a voxel-based height threshold of $P < 0.001$ uncorrected for multiple comparisons and an extent threshold of 10 contiguous voxels.

Results and Discussion

All subjects reported a beneficial effect of the concentration task on the ability to perform imagined locomotion. Activations were found in plausible regions despite a high probability of type 1 error (false positives); suggesting that a higher sample size would lead to significantly corrected activation in congruent locations. The proprioceptive motor imagery tasks lead to more activation than the complimentary visual-based imagery tasks. The visual input was separated from proprioceptive input by using a third party as the target for visual-based motor imagery, which has been shown to decrease path length estimation accuracy compared to self-motion imagery,[6] suggesting that third-person-based motor imagery is less effective than motor imagery in the first person. Therefore, only first-person proprioceptive motor imagery contrasts were examined further. Significant interactions were found in all conditions except walk–ride and stand–ride (Table 1). Hence, simple contrasts are reported here.

Imagined walking, the active movement task, did not show significant brain activity (Table 1). Previous studies on locomotion have found cortical activations during walking; however, those experiments were done using a combination of visual- and proprioceptive-based motor imagery, which could lead to higher activations.[4,5] Passive self-movement, such as the

TABLE 1. Stereotactic MNI-coordinates and Anatomical Locations of Peak Activations from the Group Analysis

Contrast	Area	BA	Cluster	*t*-value	*x*	*y*	*z*
Interactions:							
proprioceptive-visual							
Walk–ride	NONE						
Ride–walk	Cuneus R.	19	458	13.79	6	−86	34
Ride–stand	Mid. Occipital L. (V3)	19	32	11.43	−24	−78	18
	Mid. Occipital R. (V3)	19	103	10.20	22	−80	18
	Lingual R.	19	38	5.68	−20	−60	0
	Dorsolateral Prefrontal L.	46	11	5.61	−46	46	−2
	Mid. Orbitofrontal L.	11	12	4.91	−24	40	−10
Stand–ride	Mid. Orbitofrontal R.	11	11	5.34	14	60	−6
Walk–stand	Sup. Occipital L. (V3)	19	15	5.14	−18	−76	42
Stand–walk	NONE						
Simple effects:							
visual							
Walk–ride	Supplementary Motor Area L.	6	19	5.32	−2	−10	56
	Precentral R.	6	50	6.60	58	2	40
	Precentral L.	6	10	5.07	−44	−10	54
Ride–walk	Cerebellum Crus2 L.		10	9.66	−26	−80	−38
	Thalamus R.		128	8.69	20	−14	14
	Supramarginal R.	41	42	6.81	48	−42	22
Ride–stand	Medial Prefrontal R.	11	10	5.55	18	62	−4
Stand–ride	Lingual L.	37	10	5.43	−20	−44	−2
Walk–stand	NONE						
Stand–walk	Mid. Temporal L.	21	22	6.19	−50	4	−22
	Cerebellum R.		47	7.36	6	−66	−50
	Parahippocampus L.	36	49	6.76	−34	−26	−14
Simple effects:							
proprioceptive							
Walk–ride	NONE						
Ride–walk	Parahippocampus R.	36	109	7.60	28	0	−28
	Mid. Occipital R. (hMT+)	39	527	7.34	46	−78	18
	Cuneus R.	18	230	6.72	6	−78	26
	Mid. Occipital L. (hMT+)	39	118	6.24	−40	−74	16
	Fusiform R.	20	132	6.88	32	−30	−24
	Mid. Frontal L.	8	41	6.32	−26	22	62
Ride–stand	Mid Orbitofrontal L.	46	83	10.03	−44	46	−4
	Mid Occipital L (hMT+)	37	67	7.53	−50	−68	6
	Postcentral L.	3	113	7.03	−52	−22	56
Stand–ride	Sup. Temporal L.		33	7.44	−52	0	2
	Midbrain		114	7.39	14	−12	−8
	Sup. Temporal R.		29	5.28	50	−2	6
Walk–stand	NONE						
Stand–walk	Cuneus R.	18	12	6.89	24	−64	24
	Mid. Frontal R.	6	26	5.97	42	8	58
	Cerebellum 9 L.		30	5.68	−12	−46	−42
	Cerebellum 9 R.		16	5.60	14	−44	−40

Significant interactions denote dependencies between the sensory base for motor imagery (displayed here as the subtraction proprioceptivevisual) and movement task. Significant interactions indicate that simple effects must be examined. Simple effects represent the movement tasks for each sensory input type separately.

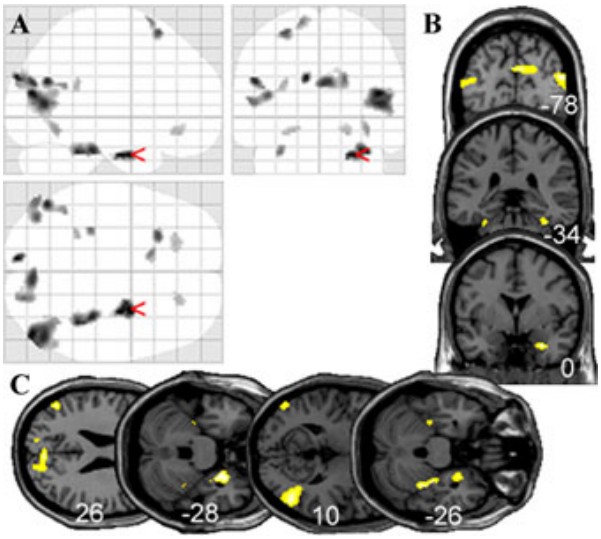

Figure 1. Whole brain activations for the contrast ride–walk ($P < 0.001$ unc.) in a glass brain view (**A**). Coronal (**B**) and axial (**C**) slices with y- and z-coordinates, respectively, showing activations in the bilateral parahippocampus (predominately right), cuneus, bilateral hMT +, and cerebellum.

ride condition used here, has until now never been studied with motor imagery. Although little to no imagined proprioceptive input was available, the ride condition lead to significant brain activation compared with either walk or stand. The parahippocampus and human motion complex (hMT+)[7] were activated bilaterally, although the right side was stronger, and the cuneus and cerebellum were also activated (Fig. 1). These regions are known to be involved in navigation,[8,9] suggesting that cortical activity during virtual reality navigation may in part be due to the passive nature of virtual reality stimulation. The passive movement task was trained with approximately twice the velocity of active locomotion, which could explain the cuneal and parahippocampal activity where cells are known to respond in a velocity dependent manner.[10,11] In conclusion, 1) passive movement stimulates a different cortical network than active movement, 2) proprioceptive-based motor imagery leads to different activity patterns than visual-based motor imagery, and 3) proprioceptive input during training is crucial for performing motor imagery.

Conflicts of Interest

The authors declare no conflicts of interest.

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Research report

Moving and being moved: Differences in cerebral activation during recollection of whole-body motion

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ABSTRACT

While moving through the world, humans as well as animals can make use of motion cues during both active and passive whole-body motion to track their own position in space. However, the functional neuroanatomy of self-motion processing remains poorly understood. In the present study we aimed to characterize brain networks reflecting whole-body self-motion experience. We used retrieval of previously experienced events, which is known to involve cortical representations of the modalities used to perceive these events. Recollection of self-motion experience may thus engage motor and sensory brain areas, reflecting the active or passive nature of the experienced movement, but may engage also common brain areas processing self-motion. We further compared the retrieval networks of self- and observed motion: even though actual action observation has been shown to recruit brain networks similar to those active during mental simulation, it is unclear to which extent recollection networks of these experiences overlap. Brain activation patterns were recorded using fMRI during mental simulation of recent episodes of (1) experiencing linear whole-body motion (active locomotion and passive transport) and (2) observing another person performing the same tasks. Following the experiential phase, participants recalled the episodes during a MR session. We found that primary sensorimotor brain areas dominate the composition of the recollection network of active walking, while recalling passive transport recruits higher level association areas. Common to both self-motion conditions was activation in the medial temporal lobe. Recollection of self-experienced and observed movement overlapped in motor planning areas. Our results provide evidence that the medial temporal lobe is specifically relevant for retrieval of self-motion information and that motor coding during action observation is reflected in recollection networks.

1. Introduction

One fundamental component of our daily sensorimotor experience is related to whole-body motion, e.g. during locomotion or driving a car. During self-motion, specific sensorimotor signals inform us, whether we move ourselves or are moved by something else [1–4]. Sensorimotor cues arising from self-motion contribute to visual information to update self-position in space [2]. Behavioral studies have shown that self-motion cues are sufficient for accurate spatial updating during active movement and passive transport [5–8]. However, little is known about the neural circuits processing self-motion during those experiences. In the present study we characterize brain networks reflecting whole-body self-motion experience. Specifically, we record activation in brain networks during recall of recent experiences of active or passive whole-body motion with functional magnetic resonance imaging (fMRI).

Recalling recent experiences has emerged as a tool in fMRI to address questions on the composition of brain networks during specific actions. For example neuroimaging studies of locomotor control often use protocols in which participants imagine previously experienced movements like walking or running [9–13]. The success of these protocols is based on the neural foundation of the encoding–retrieval relationship [14]: when humans recollect recent events from their own life, these memories are composed of rich contextual details which reflect the sensory, emotional and spatial experience during which they were encoded [15–18]. The neural basis of this vividness might be the mental simulation of these events in brain areas active during their encoding [14,19–21]. Self-motion perception during walking and passive transport relies in part on common sensory inputs (vestibular, proprioceptive) and

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in part on input only available during active motion (motor efference copies), which might be reflected in the respective retrieval network. Furthermore, processing of active and passive self-motion contributes to common computations such as spatial updating, which might be processed in overlapping networks.

Following theories on action–perception coupling, we were further interested to which extent recollection networks of self-experienced and observed whole-body motion overlap. The mental simulation theory asserts that the brain areas activated while mentally simulating movement overlap with those of observing the same movement [22]. Together with the discovery of the mirror neuron system [23,24] this theory supports the concept of a 'common coding principle' [25–27] which suggests that executing, simulating and observing actions share common mental representations. Supporting these theories, many neuroimaging studies show brain networks of action observation that partly overlap with networks of execution and mental simulation [28,29]. The observation of gait has also been found to activate motor areas relevant for execution [30] and shows overlapping activity in motor planning areas active during mental simulation of gait. Here we addressed the open question whether memory recollection networks of self-experienced and observed whole-body motion show overlapping activity patterns.

To this end, participants experienced sequences of whole-body motion, which they subsequently recalled during fMRI. In the first experiment participants were asked to actively walk or passively ride on a cart and to remember these whole-body self-motions. Standing was chosen as reference to specifically concentrate on the movement component of the experience. To direct attention to proprioceptive experience, participants performed the experiment with eyes closed. Importantly, subjects were led to the training environment already blindfolded and therefore did not have a visual image of the spatial layout. In the second experiment, the same participants observed another person walking or riding on a cart. We used observing another person standing as reference condition. After the experiential phase of each experiment participants recalled the respective episodes in the MR scanner.

In our study we compared networks of active and passive movement recall to test which brain areas represent the experience common to whole-body movement. Regarding sensory and motor areas, we tested whether motor areas were specifically recruited during active movement simulation, and whether structures involved in somatosensory or vestibular processing were common to both self-motion conditions. We were further interested whether structures of the medial temporal lobe were active to the same extent during all recall conditions, or whether we find differences for the self-motion conditions. Findings of motion-specific hippocampal activity during active [32,33] and passive movement [4,34] in rats and monkeys and the general importance of the medial temporal lobe in spatial updating [35–37] suggest that this region is specifically active during the experience of self-motion through space. We further tested whether recall of the observation condition activated an action observation network as described for real observation [28,29]. Based on reports of a general memory brain network for recollection [38,39], we tested whether we find activations common to all retrieval conditions.

2. Methods

2.1. Participants

21 healthy participants gave written informed consent to participate in this study. The study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of the medical faculty of the Ludwig-Maximilians-University Munich. Handedness was determined according to a ten-item excerpt of the 'Handedness Inventory' [40], resulting in +100 in 16 participants, one with +9, one with −40 and one with −100. Handedness scores were entered as covariate in the group analysis. None of the participants were taking medication or had any history of neurological disease. Two participants were excluded from the analysis, one due to anatomical abnormalities, one due to scanner artifacts, resulting in a final cohort of 19 participants (mean age 26, range 20–40; 9 female).

2.2. Experimental design and procedure

Participants conducted the two experiments on the same day. In the first experiment they experienced and recalled self-movement (body experience, BE) and in the second they observed and recalled movement of another person (visual experience, VE). Each experiment contained an experiential phase outside of the scanner and a recollection phase within the scanner. In the experiential phase, participants physically executed the tasks, which they then recalled in the scanner (see Fig. 1 for a schematic of the paradigm). Participants were instructed to keep their eyes closed during the entire functional MR experiment. Participants were debriefed after the scanning sessions.

2.2.1. Experiment 1: body experience

Participants were asked to (1) walk (active movement, BEA), (2) ride in a stance position on a cart (passive movement, BEP) and (3) stand (control, BEC) in a long open corridor. An experimenter walked next to the participant in both movement conditions to prevent participants from colliding with the walls, but did not otherwise touch the participant. Participants were instructed to concentrate on how their body feels during this task and not to visually imagine the task. Each experience lasted 16 s and was repeated three times. Participants were instructed to choose their individual walking speed. The cart was pushed by always the same experimenter at average walking speed (about 1.3 m s^{-1}). Participants were blindfolded before they were led into the practice environment and during the entire experiential phase to prevent the semantic–contextual effects of seeing their surroundings. Subsequently, participants recalled the experienced conditions in a randomized block design, cued by auditory commands in the MR scanner. The commands were the German equivalent to 'I walk', 'I ride' and 'I stand'.

2.2.2. Experiment 2: visual experience

In the second experiment participants were led again to the practice environment, this time with their eyes open (visual experience, VE). In this experiment, they observed another person performing all the tasks they previously performed; active movement (VEA): observing a person from behind, walking away from them; passive movement (VEP): observing how the other person was moved on a cart pushed by an experimenter, moving away from them (participants were instructed to concentrate on the person moving on the cart); control (VEC): observing the person standing in front of them (with the back to the observer). Each experience lasted 16 s and was repeated three times. This experiment always followed the first to prevent potential visualization during BE recall. All participants observed the same female person performing the task. In the MR scanner they recalled these conditions in a randomized block design, cued by auditory commands. The commands were the German equivalent to 'she walks', 'she rides' and 'she stands'.

2.2.3. Self reports

After the two experiments, participants were debriefed on the ease of imagery during recollection. Participants were asked which condition (active movement (A), passive movement (P) or control (C, stand)) was easiest to imagine, or if the conditions were equally easy to imagine. Subject responses for A and P were numerically coded and then used as covariate in the group analysis of the fMRI data (C was not explicitly modeled in the general linear model). The answers were coded by weighting the individual task difficulty: if a participant answered A, a code weighing the four conditions as BEA: 1, BEP: 0, VEA: 1, VEP: 0 was created for this participant. If a participant answered 'all the same', the code was BEA: 1/4, BEP: 1/4, VEA: 1/4, VEP: 1/4.

2.3. fMRI acquisition

Functional imaging was performed on a 3T MR-Scanner (GE Sigma HDx) with a standard 8 channel head coil using a gradient echo-planar imaging sequence (repetition time: 2250 ms, echo time: 40 ms, flip angle: 90) to acquire 35 axial slice volumes. Voxel size was 3.5 mm × 3.5 mm × 3.5 mm with no gap. The first five volumes of each run were discarded to account for T1 effects, resulting in a final 147 volumes per run. Four runs per participant were performed, two for BE, two for VE. Participants left the scanner between the experiments BE and VE for conducting the second experiential phase. The experiment consisted of a block design with randomized stimulus presentation (Fig. 1B) lasting 7 scans (15.75 s) for a total of 7 repetitions per condition.

2.4. fMRI analysis

Image processing and statistical analysis were performed using SPM5 (www.fil.ion.ucl.ac.uk/spm/). All volumes were realigned to the first volume, spatially normalized using coregistration to the individual anatomical image and segmentation into MNI standard coordinate space and finally smoothed using a 8 mm full-width at half-maximum isotropic Gaussian kernel.

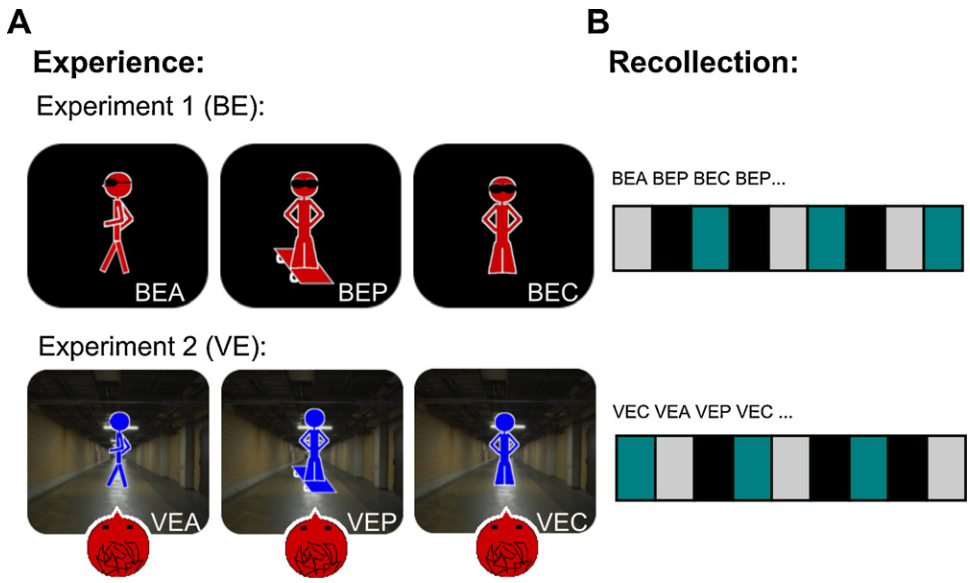

Fig. 1. Experimental setup. Schematic drawing of the experimental procedure. Experiment 1 (BE: body experience): participants first experienced blindfolded walking, riding or standing (A, upper panel). They were then instructed by auditory commands to recall these sequences in a randomized fashion in the subsequent scanning session (B, upper panel). Experiment 2 (VE: visual experience): subjects observed another person walking, riding or standing (A, lower panel) and recalled these sequences in the following scanning session (B, lower panel). BEA: body experience active, BEP: body experience passive, BEC: body experience control, VEA: visual experience active, VEP: visual experience passive, VEC: visual experience control.

At the single-subject level, we applied a high-pass filter (cut-off 128 s) to remove baseline drifts. For each participant we defined regressors of interest for the four recall conditions BEA, BEP, VEA, VEP. They were entered into a general linear model (GLM) as boxcar functions convolved with the hemodynamic response function. Regressors of no interest modeled the data variability due to auditory commands and head movement. The control (C) was not explicitly modeled. Scanning sessions (experiments 1 and 2) were modeled in a single design matrix to control for session-specific effects. Effects of interest were tested on a voxel by voxel basis using linear contrasts of the parameter estimates. The corresponding contrast images were subsequently entered into a group level random effects model that contained the four resulting conditions as well as subject effects. Handedness and the individual score on ease of imagery were entered as additional covariates to the group level model. The handedness covariate consisted of a numerical code determined from the 'Handedness Inventory' (from −100 fully left handed to +100 fully right handed). The covariate on ease of imagery was created from questionnaire data collected during debriefing (the answers were coded by weighting the individual task difficulty: if a participant answered A, a code weighing the four conditions as BEA: 1, BEP: 0, VEA: 1, VEP: 0 was created for this participant. If a participant answered 'all the same', the code was BEA: 1/4, BEP: 1/4, VEA: 1/4, VEP: 1/4). The latter was chosen, as we aimed to correct for inter-subject variability, which is known to be pronounced for imagery ability [41] and neurophysiologic changes during mental imagery [42]. Main and simple effects were tested with linear contrasts of the parameter estimates. We considered voxels to be significant when they exceeded a threshold of $p < 0.05$ false discovery rate (FDR) corrected for multiple comparison. Only clusters exceeding 10 voxels are reported. The SPM conjunction null method [43] was used to assess activation common to two conditions. A region of interest analysis was performed with an anatomical mask comprising hippocampus and parahippocampus as defined by the Wake Forest University PickAtlas [44].

We tested for overall habituation of the blood oxygen level-dependent response (BOLD) with time by creating regressors that were parametrically modulated with time, starting with the onset of a run, a session or the whole experiment. Habituation effects were tested with linear contrasts of these regressors and assessed in a random effects model with one-sample *t*-tests.

To test for hemispheric differences, a lateralization analysis was performed, as described previously [45,46]. Contrast images from the single subject models of each of the four conditions were flipped by 180° about the *y*-axis. Original and flipped contrast images were then entered in a random effects model and effects were assessed with a paired *t*-test.

Percent signal change plotted were calculated per subject by averaging over the whole-brain beta values of the voxels of a sphere with the diameter of the smoothing kernel applied (8 mm), positioned on the local maxima of a region determined by conjunction analysis on the group level. Their use was exploratory, statistical inference is only drawn from the results of the random effects model. Coordinates are reported in MNI-space. The nomenclature of anatomical structures follows the Harvard–Oxford structural atlas and the Juelich histological atlas [47].

3. Results

3.1. Networks specific to active and passive self-motion

Comparing the brain networks involved in recall of locomotion and recall of passive transport, we found that the primary sensorimotor aspect of experience was clearly reflected in the network of active but not passive self-motion. During recall of walking (BEA), the supraspinal locomotor network was activated [10,48] (Fig. 2A): BOLD signal increased in subcortical areas like the caudate nucleus, thalamus and pallidum, as well as in the cerebellum and the brainstem (Fig. 2B, Table 1). Activation in the cortex was found in motor planning areas like the premotor cortex and supplementary motor area (SMA), but also in the primary motor cortex, which has up to now been described by studies on real [49] but not by studies on mentally simulated locomotion [10,11] (Table 1).

In contrast, during recall of passive transport, BOLD signal increased in higher association areas rather than in primary sensorimotor areas: we observed activation in the anterior dorso-medial frontal cortex (pre-SMA), the left precuneus (corresponding to BA7) [50] and in the posterior parts of BA31 bilaterally, which we will subsequently call posterior cingulate cortex after Vann et al. [51]. We furthermore observed activation at the left junction of mid-occipital cortex and medial temporal gyrus (Fig. 3, Table 1). The differences between the two self-motion conditions were confirmed by the contrast BEA–BEP which revealed activations in a network of motor areas, while the contrast BEP–BEA showed BOLD signal increase in higher visual and parietal regions when lowering the statistical threshold to $p < 0.005$ uncorrected (Table 2).

3.2. Common activation in self-motion conditions

Importantly, both types of self-motion simulation activated the posterior medial temporal lobe. Activations were located at the transition of posterior hippocampus to posterior parahippocampus, which we will further call pHC/PHC (Fig. 4). We observed a slightly differing distribution for activated voxels in BEA compared to BEP: clusters of pHC/PHC from both conditions were overlapping,

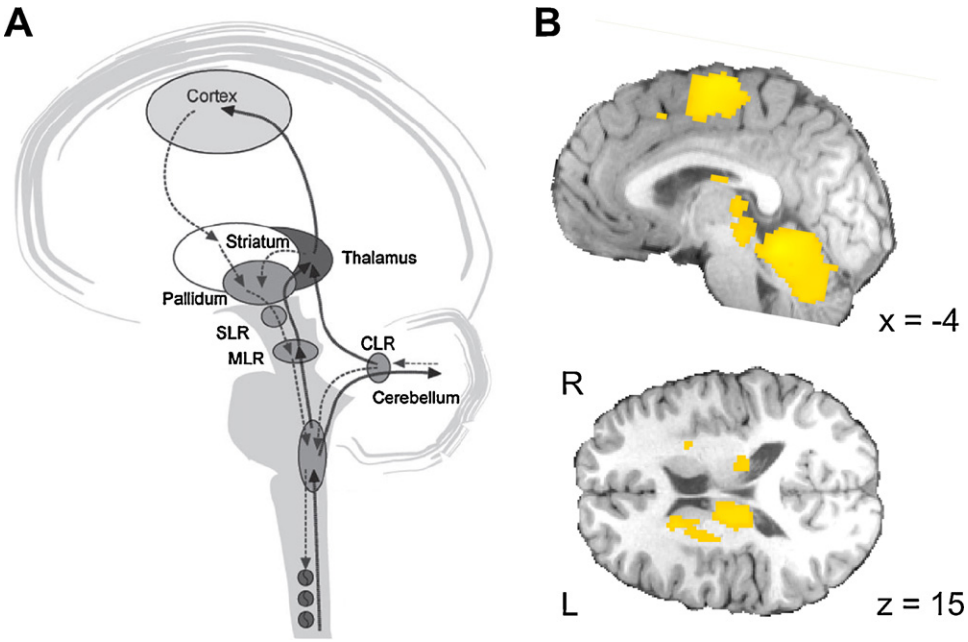

Fig. 2. Supraspinal motor network. Schematic drawing of the hierarchical locomotor control from cortex to spinal cord (A) and group analysis *t*-maps of BOLD signal increase for the condition BEA overlayed on a MNI-standardized anatomical image of one of the measured participants (B). BOLD signal increase was found in the following areas belonging to the supraspinal motor network: precentral gyrus, dorso-medial frontal cortex, cerebellum, brainstem, thalamus, caudate nucleus, pallidum. *t*-maps thresholded at $p < 0.05$, corrected for multiple comparisons. CLR: cerebellar locomotor region, MLR: mesencephalic locomotor region, SLR: subthalamic locomotor region.

Table 1
Simple effects BE. All significant activations (clustersize > 10 voxels, $p < 0.05$, FDR corrected) for the conditions BEA and BEP are listed. 3D coordinates refer to the MNI standard space. Anatomic labels follow the Harvard–Oxford structural atlas and the Juelich histological atlas. RH: right hemisphere, LH: left hemisphere.

Spatial coordinates of the local maxima in the group analysis ($p < 0.05$, FDR)			
Region	Coordinates (*x*, *y*, *z* mm)		*t*-score
	LH	RH	
BEA			
Cortical			
Middle frontal gyrus	−36, 14, 52		3.43
Anterior cingulate cortex	−14, 12, 24		3.84
Dorso-medial frontal cortex	−6, −2, 62		6.52
		2, −2, 64	5.14
Precentral gyrus lateral	−54, −8, 40		4.65
		60, 6, 26	4.02
Precentral gyrus dorso-medial	−14, −8, 70		6.61
		14, −18, 68	6.52
Hippocampus/parahippocampus	−36, −36, −6		4.67
		30, −36, 6	4.70
Cuneus		14, −74, 22	4.63
Calcarine gyrus	−18, −82, 2		4.00
		18, −62, −2	4.95
Subcortical			
Caudate nucleus	−18, 14, 18		3.86
		28, 10, 16	4.12
Pallidum		20, −8, −2	4.45
Thalamus	−14, −20, 20		5.16
		16, −26, 20	4.50
Brainstem and cerebellum			
Cerebellum	0, −48, −12		9.07
Brainstem	−4, −34, 0		3.45
BEP			
Cortical			
Dorso-medial frontal cortex	−12, 6, 64		4.46
Hippocampus/parahippocampus	−24, −30, −6		3.94
		30, −40, −6	4.66
Precuneus	−14, −70, 52		5.08
Posterior cingulum (posterior BA31)	−16, −68, 26		4.14
		26, −62, 22	4.03
Mid-occipital cortex	−44, −66, 16		4.67
Subcortical			
Pallidum		20, −10, 0	5.77

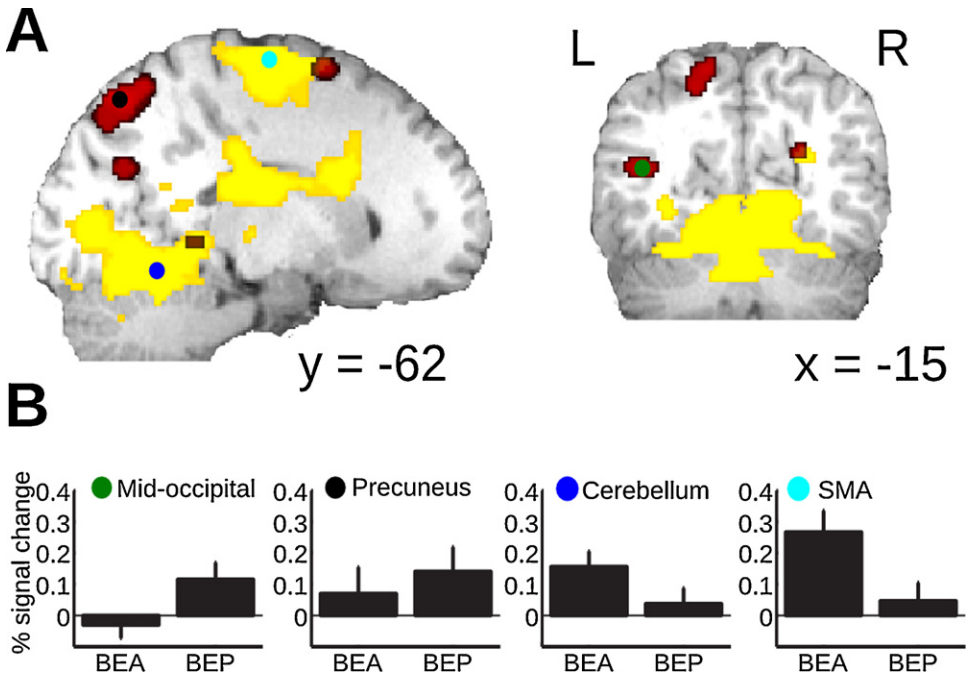

Fig. 3. Differential activations for recall of active and passive movement. Shown are group *t*-maps for BEA (yellow) and BEP (red) (A) and bar plots of percent signal change over subjects in the indicated regions (B). While the BEA condition evokes activation in a motor network, BEP shows activation in parietal and occipital areas and the pre-SMA. Both conditions show activation in the hippocampal formation. All *t*-maps thresholded at $p < 0.05$, corrected for multiple comparisons.

but while more voxels showed activation anterior than posterior for BEA, the pattern was the opposite for BEP (Fig. 4). The cluster size of the pHC/PHC activation also differed, larger clusters were elicited by BEA than by BEP (BEA: 255 voxel, BEP: 120 voxel, pooled for hemispheres). Common activations were also found in the right pallidum and the anterior dorso-medial frontal cortex (pre-SMA). A whole-brain conjunction analysis also showed the trend of common activations in pallidum, anterior dorso-medial frontal cortex and bilateral pHC/PHC ($p < 0.001$ uncorrected). To test for hemispheric differences in activity of these regions, we conducted a lateralization analysis. We found no significant lateralization of activity for neither condition.

3.3. Comparison of self- and observed motion

The most striking difference between the two conditions with body experience (BE) and observed movement of another person (VE), was that BE conditions elicited pHC/PHC activation, while VE conditions did not (Table 3). To further investigate this difference we performed a region of interest analysis of parahippocampal and hippocampal regions for the datasets from VE conditions, which again showed no significant activations. A direct comparison of recalling self-motion versus observed motion with the whole-brain contrast (BEA + BEP) – (VEA + VEP) revealed a trend for the left pHC/PHC ($p < 0.001$ uncorrected).

Testing for common activations in self-motion and observed motion conditions, a conjunction analysis of executed and observed walking recollection (BEA & VEA) found overlapping activity in the SMA (Fig. 5A). A conjunction analysis of the recollection of executed and observed riding (BEP & VEP) resulted in the left precuneus and right posterior cingulate cortex (Fig. 5B).

3.4. Imagery related areas across all conditions

We found that activations in the precuneus and the posterior cingulate cortex were common to all conditions, with exception of the simulated walking condition (BEA) (see Table 1 and Table 3). A conjunction analysis of the recollection of executed and observed

Table 2
Comparing BEA and BEP. Activations (clustersize > 10 voxel) are listed for BEA–BEP ($p < 0.05$, FDR corrected) and BEP–BEA ($p < 0.005$, uncorr.). 3D coordinates refer to the MNI standard space. Anatomic labels follow the Harvard–Oxford structural atlas and the Juelich histological atlas. RH; right hemisphere, LH; left hemisphere.

Spatial coordinates of the local maxima in the group analysis ($p < 0.05$, FDR)			
Region	Coordinates (*x*, *y*, *z* mm)		*t*-score
	LH	RH	
BEA–BEP			
Precentral gyrus dorso-medial	0, −12, 66		4.84
Cerebellum	0, −48, −12		5.37
Caudate nucleus	16, 0, 28		3.96
Thalamus	−22, −16, 22		4.15
		2, −16, 20	4.30
BEP–BEA uncorr. $p < 0.005$			
Inferior frontal gyrus	−54, 28, 8		3.26
Mid-occipital cortex	−42, −68, 16		4.25
		54, −56, 12	3.37
Precuneus	−18, −74, 42		3.13

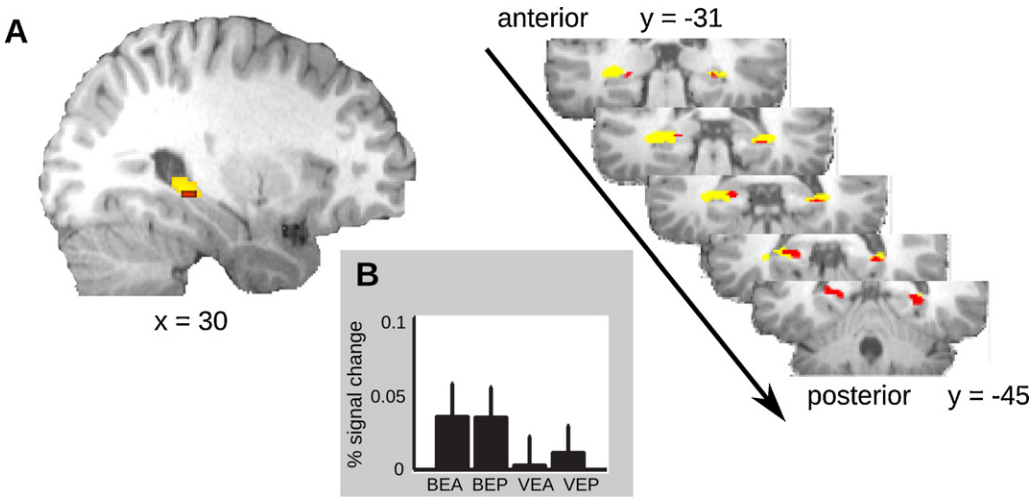

Fig. 4. Relative contribution of pHC/PHC regions during recall of self-motion. Shown are group *t*-maps of the medial temporal lobe for BEA (yellow) and BEP (red) (A) and a bar plot of percent signal change pooled over the right and left pHC/PCH, shown for all conditions (B). Larger clusters were found in BEA than in BEP (BEA: 255 voxel, BEP: 120 voxel, pooled over left and right pHC/PHC). The pHC/PHC cluster decreased from anterior to posterior for the BEA condition while it increased for the BEP condition. All *t*-maps thresholded at $p < 0.05$, corrected for multiple comparisons.

riding (BEP & VEP) resulted in the left precuneus and right posterior cingulate cortex (Fig. 5B). The conjunction BEP & VEA & VEP showed a trend for the left precuneus as an overlap between all three conditions ($p < 0.001$ uncorrected) whereas a conjunction of BEA & BEP & VEA & VEP, to test for activations accompanying recollection in general, did not reveal common activations even at uncorrected thresholds. Overall, the BEA condition was the most distinct from all other conditions. A conjunction analysis between BEA and any of the remaining three conditions revealed neither visual nor parietal activations.

3.5. Control for habituation effects

The VE experiment was always conducted after the BE experiment to prevent that visual contextual experience influenced the encoding of self-motion. We therefore investigated whether

Table 3
Simple effects VE. All significant activations (clustersize > 10 voxels, $p < 0.05$, FDR corrected) for the conditions VEA and VEP are listed. 3D coordinates refer to the MNI standard space. Anatomic labels follow the Harvard–Oxford structural atlas and the Juelich histological atlas. RH; right hemisphere, LH; left hemisphere.

Spatial coordinates of the local maxima in the group analysis ($p < 0.05$, FDR)			
Region	Coordinates (*x*, *y*, *z* mm)		*t*-score
	LH	RH	
VEA			
Cortical			
Inferior frontal cortex		34, 38, 16	4.86
Frontal operculum	−46, 10, 2		4.97
Anterior cingulate cortex	−6, 10, 20		4.60
		6, 8, 20	4.15
Dorso-medial frontal cortex	−2, 0, 66		5.44
Precuneus	−8, −78, 48		4.69
		20, −72, 38	4.64
Posterior cingulum (posterior BA31)		24, −60, 22	4.66
Angular gyrus		44, −78, 28	3.71
VEP			
Cortical			
Inferior frontal cortex		38, 40, 16	3.20
Superior frontal gyrus	−20, 22, 38		3.54
		18, 24, 42	5.17
Middle frontal gyrus	−44, 6, 50		4.66
		44, 18, 48	3.30
Frontal operculum	−44, 14, 3		3.53
		32, 14, 2	3.21
Anterior cingulate cortex		14, 42, 12	4.15
Lingual/fusiform gyrus	−32, −48, −10		4.36
		32, −48, −8	3.86
Precuneus	−10, −64, 52		6.67
		14, −68, 48	3.89
Posterior cingulum (posterior BA31)	−14, −58, 12		6.67
		20, −54, 18	7.05
Angular gyrus	−41, −68, 34		5.03
		48, −74, 32	6.46
Subcortical			
Caudate nucleus	−10, 6, 16		3.72

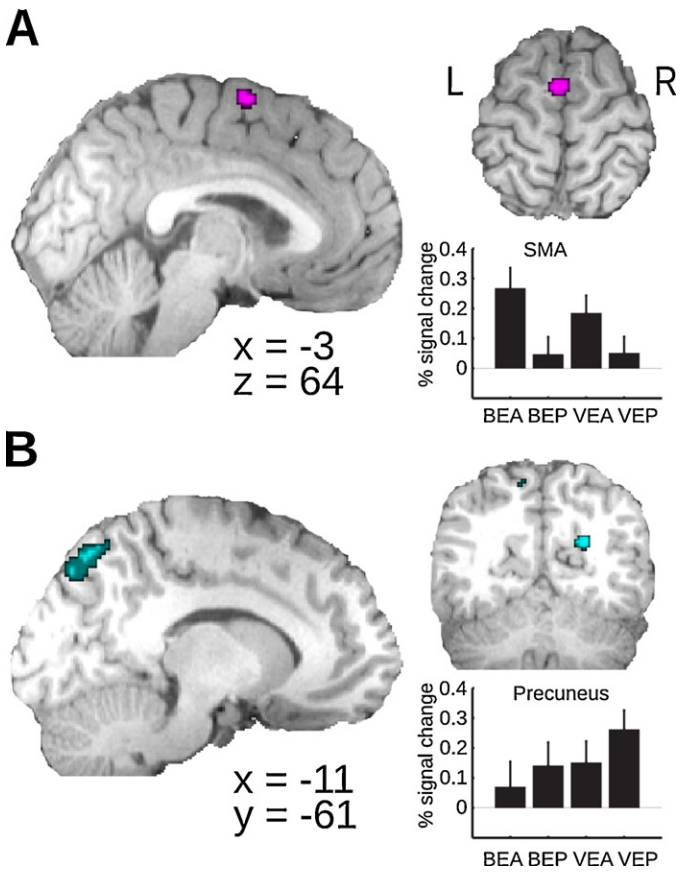

Fig. 5. Common activations over experiments. In both conditions of active and observed locomotion (body experience active, BEA and visual experience active, VEA), the supplementary motor area was activated. Shown are a conjunction analysis on the group level, BEA & VEA and percent signal change in the SMA for all conditions (A). A conjunction of the conditions involving riding a car (body experience passive, BEP and visual experience passive, VEP), revealed the left precuneus and right posterior cingulate cortex as common activation. Shown is also a barplot of percent signal change in the left precuneus over all conditions (B). All *t*-maps $p < 0.05$, corrected for multiple comparisons.

habituation effects resulting from the fixed order of conditions influenced our results. Habituation effects were neither found over individual runs nor over sessions nor over the whole experiment.

4. Discussion

The composition of activated recollection networks differed depending on the recalled condition, which makes us confident that we are observing differences due to the specific experience bound to that condition. This allows us to interpret the respective networks in relation to specific sensorimotor components involved in the underlying experience. Our results suggest that while recall of active movement involves sensorimotor areas activated during execution/perception, passive transport is simulated using mostly areas involved in higher level body representations. Importantly, recall of both self-motion conditions activated the posterior medial temporal lobe, while recall of observed motion did not. Both recalling oneself and another person walking involved the SMA, in accordance with what has been described for real action observation [28]. Finally, while most conditions activated areas described for mental simulation in general like the precuneus, recalling walking specifically did not.

4.1. High-level association areas active during passive transport simulation

In contrast to the recollection of blindfolded walking (BEA), which activated a supraspinal motor network known from real execution in cats [48,52] and humans [49], the recollection of being passively moved (BEP) did not seem to rely on primary sensory or sensorimotor areas. Rather, areas implicated in processing higher level body representations were recruited, such as the pre-SMA, the mid-occipital cortex and the posterior parietal cortex (precuneus): the pre-SMA has been implicated in the representation of complex movement sequences [53]; the coordinates at which we observed activations in the mid-occipital cortex have been described for the 'extrastriate body area' before, specialized for the (not only visual) analysis of human bodies [54]; and one of the many functions assigned to the posterior parietal cortex is the construction of a 'body image' [55]. The experience of passive transport therefore does not seem to leave a vivid imprint of the sensory processes involved in this experience, detectable in the brain network of its recollection. This is in clear contrast to the condition of recalling walking, where sensorimotor processes involved in the experience of walking are being re-activated during the simulation. The activated motor network found during BEA therefore appears to be specific for locomotion recall and is not always recruited, if whole-body self-motion has to be recalled.

Authors of behavioral studies which observe accurate spatial updating during linear passive transport in general suggest, that the vestibular system provides crucial sensory information for this computation [5,6]. However, some studies show that the influence of vestibular information on self-motion perception [56] and spatial navigation [57,58] is limited. These findings gave rise to the suggestion that spatial estimations during passive transport are derived by the participant based not only on sensory cues of self-motion, but also by using cognitive skill and prior experience [56]. Such cognitive processes could comprise time estimation or could involve mental simulations of whole-body movement based on prior experience [59,60]. Supporting the view that vestibular processing contributes a minor aspect to the passive transport experience, we did not observe activations in primary cortical areas processing vestibular information such as the insula. The activation of higher association areas that we found makes the view of an internal simulation of the body moving through space based on prior experiences more likely.

4.2. Activations in the medial temporal lobe: specific for processing self-motion information?

Interestingly we found significant activation in the medial temporal lobe while participants recollected events during which they experienced motion with their own body, but not while recollecting observing another person moving. One interpretation of this finding is that under both BE conditions the hippocampus and parahippocampus processes the aspect of moving the own body through space. Real walking [49,61] and mental simulation of walking [10,11,13,31] have often shown to involve hippocampal and parahippocampal areas. Some authors also describe an increased involvement of these regions with increasing complexity of the path to be completed [12].

However, another critical difference between the two encoding situations was the role of the participant: re-experiencing your own body moving necessarily involves the self as the object of experience, while observing someone else does not. The reference condition to recall oneself standing also involves the self as the object, but it likely induces a weaker body experience than the two self-motion conditions. Memory research shows superior memory for self-relevant items, referred to as the 'self-referential

effect' [62,63] as well as enhanced recall for self-performed over other-performed actions, also known as the 'self-enactment effect' [64,65]. This stronger impression of the experience might be reflected in enhanced activity in memory-related areas like the hippocampus during recall. To the best of our knowledge, memory studies have not yet compared specific hippocampal involvement in recollection of self-experienced versus observed actions (which would both fall in the domain of episodic memory). However, neuroimaging studies of mental simulations for self and other agency have not shown a preferential involvement of the medial temporal lobe in the self conditions [66–68]. The current study cannot differentiate between the above explanations for specific pHC/PHC activation, but our findings remain an interesting distinction between these different types of mental simulations, which should be further explored with appropriate designs in future studies.

The activation in the medial temporal lobe showed slight differences between conditions: the activations while recollecting walking comprised a larger area than during the recollection of riding. It is tempting to interpret this difference as reflecting the influence from the motor circuit on the medial temporal lobe, which would be in accordance with the animal literature: during real whole-body movement in rats, hippocampal place cells in rats show stronger firing and narrower tuning during active movement in comparison to riding passively on a cart [4]. Correspondingly, hippocampal theta rhythm and population firing rate are modulated by ambulatory signals such as running speed [32,33]. Connectionist models would be a fruitful approach for future studies to follow up on the question, if the medial temporal lobe is modulated specifically by motor circuits.

4.3. Perception for action

Comparing recall of walking oneself (BEA) and recall of observed walking (VEA), we found overlapping activity in the medial supplementary motor area (SMA). The SMA is known to be involved in motor planning but is also implicated in the action observation network [69,70]. A meta-analysis of the overlap between action observation and simulation has described areas including the premotor cortex, SMA, pre-SMA, inferior and superior parietal lobe as well as posterior medial temporal lobe over many studies [28]. The overlap we found was notably smaller, restricted to the SMA. The overlap is however in a likely spot, an area which controls lower limb motor function, which is in accordance with the findings that the observation of another agent's action is somatotopically organized [71]. The interconnection of action and perception also has been found for other locomotion studies investigating observed and simulated walking with visual stimuli [31]. It has been summarized as the 'common coding principle' [25–27] and based on our results we propose that this principle can be extended to the memory domain: overlap of neural circuitry of perception and recollection is well demonstrated [19–21], and such findings have been interpreted to substantiate theories on 'grounded cognition' which claim that cognitive phenomena like memory are strongly rooted in sensorimotor neural circuits of perception and action [72]. Some authors suggest, that memory entails mental simulation using the circuits by which information was encoded [14]. The observation of walking involves activations in motor areas [30,31], and we found that also the recollection network of this experience involves motor areas.

4.4. Different types of mental simulation during recollection

In a conjunction analysis of both motion observation conditions we found activity in the left precuneus and the right posterior cingulate cortex. Also in the recollection of passive self-motion we found activation in precuneus and posterior cingulum. These regions have strong reciprocal and bilateral connections in monkeys [73] and are activated during general memory retrieval and mental imagery [50,74,75]. Memory and imagery act in concert, mental imagery draws on memorized components, and visual, auditory or motor imagery occur during memory retrieval [15,74,76]. Nonetheless, not all recall is thought to depend on the parietal cortex: for example, recall of memorized simple visual patterns of stripes to mentally examine them for certain characteristics recruits only primary visual areas [77]. That activity in the primary perception or action system is sufficient for certain types of imagery and recollection might explain the lack of precuneus activation during the condition of simulated walking: the vivid impressions of the sensorimotor components of the walking memory, enhanced by our blindfolded training, might have made simulation of this experience in the primary perception and action system sufficient for successful recall.

5. Conclusion

We find that the specific sensorimotor experience of active self-motion during locomotion is embedded in the memorized episode, whereas recall of passive transport depends on frontal, occipital and parietal areas involved in higher level body representations. The self-motion information common to both self-experienced movements may drive medial temporal lobe activity. An important reservation to this interpretation is that perspective of experience was concurrently different between BE and VE conditions. Common areas for mental image inspection like precuneus and posterior cingulate cortex are found in all conditions except for the recollection of walking, thus demonstrating the distinctiveness of recollecting self-executed motor experiences. These results thus suggest that the precuneus is not involved in all forms of mental imagery and recall, but rather mediates visual imagery specifically. The overlap of SMA activity during recall of self-experienced and observed locomotion suggests that the common-coding principle, shown for execution, mental simulation and observation, extends to the recollection of actions as well.

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2.2 Multimodality in PPA

The following section consists of one research article:

- Wolbers, T., Klatzky, R.L., Loomis, J.M., **Wutte, M.G.**, Giudice, N.A., 2011. Modality-Independent Coding of Spatial Layout in the Human Brain. *Current Biology* 21, 984989.

This research article originates from work conducted during a 4 months research stay in the lab of Jack Loomis, University of California Santa Barbara. The project was based on a paradigm from Thomas Wolbers and Nick Giudice. The author of this thesis conducted pilot studies for this experiment, helped with data collection, preprocessing of the data and wrote the sections *Experimental Stimuli and Paradigm* and *Experimental Procedure* of the research article (see *Supplemental Experimental Procedures*).

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Report

Modality-Independent Coding of Spatial Layout in the Human Brain

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Summary

In many nonhuman species, neural computations of navigational information such as position and orientation are not tied to a specific sensory modality [1, 2]. Rather, spatial signals are integrated from multiple input sources, likely leading to abstract representations of space. In contrast, the potential for abstract spatial representations in humans is not known, because most neuroscientific experiments on human navigation have focused exclusively on visual cues. Here, we tested the modality independence hypothesis with two functional magnetic resonance imaging (fMRI) experiments that characterized computations in regions implicated in processing spatial layout [3]. According to the hypothesis, such regions should be recruited for spatial computation of 3D geometric configuration, independent of a specific sensory modality. In support of this view, sighted participants showed strong activation of the parahippocampal place area (PPA) and the retrosplenial cortex (RSC) for visual and haptic exploration of information-matched scenes but not objects. Functional connectivity analyses suggested that these effects were not related to visual recoding, which was further supported by a similar preference for haptic scenes found with blind participants. Taken together, these findings establish the PPA/RSC network as critical in modality-independent spatial computations and provide important evidence for a theory of high-level abstract spatial information processing in the human brain.

Results

To test our hypothesis that the human brain would show modality-independent responses to spatial layout, we used functional magnetic resonance imaging (fMRI) while presenting participants with a modified version of a paradigm previously shown to activate scene-sensitive regions in sighted humans [4]. Specifically, we used Lego bricks to construct (1) 27 indoor scenes that were matched in size and complexity but differed with respect to their geometric properties and (2) 27 abstract geometric objects. We then administered a delayed matching-to-sample (DMTS) task that required participants to compare the spatial layout of four sequentially presented stimuli to a final sample stimulus (Figure 1). This behavioral task was administered separately in two versions, a visual version during which subjects saw grayscale photographs of the stimuli and a haptic version during which they acquired the geometric structure of the stimuli via exploration with the right hand.

Spatial Layout Processing in Sighted Subjects

Whereas reaction times in the visual version of the DMTS task did not differ between objects and scenes ($p > 0.5$), the parahippocampal place area (PPA) (identified in each subject with a functional localizer; see Supplemental Experimental Procedures available online) responded more vigorously when subjects were attending to the geometric structure of indoor scenes than objects ($t = 10.22$, $p < 0.001$, $d = 1.92$; Figure 2A). Importantly, activation differences between objects and scenes did not correlate with differences in reaction time (left PPA: $r = 0.21$, $p > 0.5$; right PPA: $r = -0.64$, $p > 0.1$) or accuracy (left PPA: $r = 0.29$, $p > 0.5$; right PPA: $r = 0.63$, $p > 0.1$), and they did not differ between the right and left PPA ($F = 4.108$, $p = 0.09$; condition by hemisphere interaction: $F = 0.437$, $p = 0.533$). These results replicate previously reported differences between Lego scenes and objects in the PPA during passive viewing and during a continuous one-back task [4]. Voxel-wise whole-brain analyses revealed similar effects in retrosplenial cortex (RSC) and in the superior frontal gyrus (Table S1). By comparison, the reverse contrast (objects > scenes) did not reveal any significant results, and we did not observe any voxels that showed a significant correlation with behavioral performance.

In the haptic version of the DMTS task, reaction times also did not differ between the two stimulus types ($p > 0.05$), and we observed significantly stronger responses in the PPA when subjects explored the scenes by touch as compared to the objects ($t = 2.45$, $p < 0.05$, $d = 0.40$; Figure 2A). Again, larger activation differences between scenes and objects were not associated with larger differences in reaction time (left PPA: $r = -0.32$, $p > 0.4$; right PPA: $r = 0.25$, $p > 0.5$) or accuracy (left PPA: $r = -0.59$, $p > 0.1$; right PPA: $r = -0.02$, $p > 0.5$), and treating the right and left PPA as separate regions of interest (ROI) did not reveal a main effect of hemisphere ($F = 0.009$, $p = 0.93$) or an interaction between task and hemisphere ($F = 1.753$, $p = 0.23$). These results demonstrate that coding for spatial layout in the PPA can be driven by modalities other than vision. In addition, because the match and sample stimuli differed with respect to the presence of furniture and toy characters (see Supplemental Information), we reran our analyses while only focusing on the sample stimuli. These analyses replicated all the results reported for the sighted and the blind participants (see below); hence, only the results from the analyses that included the match stimuli are reported here.

Given that (1) haptic experiences can be recoded into visual mental images [5] and (2) visual imagery of scenes can elicit both occipital and PPA responses [6], the PPA responses

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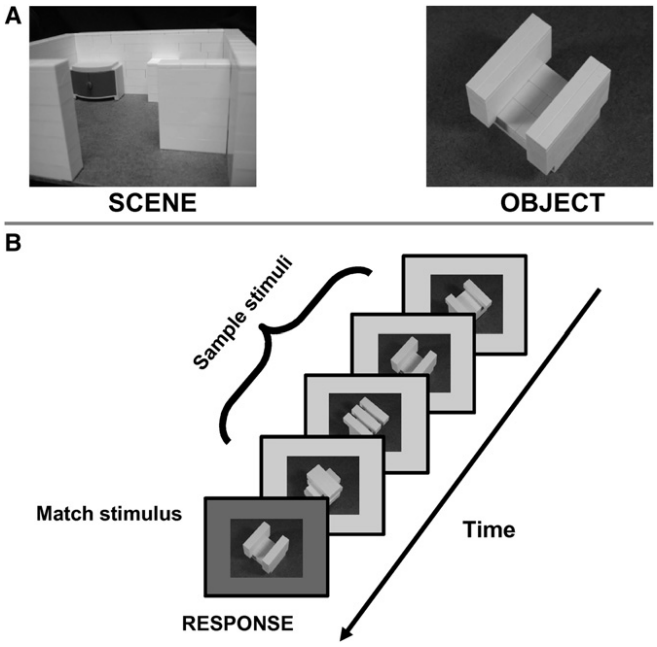

Figure 1. Experimental Paradigm of the Delayed Matching-to-Sample Task

(A) We constructed 27 scenes and 27 objects with different geometric layouts. To make the rooms distinguishable, we manipulated the number, size, and position of the interior walls, thereby giving each room a unique geometric layout. Because the PPA is believed to represent navigable spatial layouts in which one can move about [2], the scenes also contained toy characters and small furniture. In addition, we acquired digital images of each room and each object and rendered them in grayscale. In the visual condition, stimuli were displayed as photographs on a screen inside the bore of the MRI scanner. Six blocks of objects and six blocks of rooms were presented in alternating order, with intervening rest periods (duration 16 s) during which subjects fixated a white cross on a black background. In the haptic condition, the physical models were placed on a tray positioned on the upper right thigh, and participants explored the stimuli with the right hand. For further information about the stimuli, see Figure S1.

(B) Each trial started with the presentation of four sample stimuli, followed by a fifth stimulus, the match stimulus (shown here for the object scenario). In the case of scenes, furniture was removed from this final match stimulus to emphasize that the geometric properties were the relevant dimension. In the visual task, each image was shown for 3 s, followed by a 1 s interstimulus interval (ISI). In the haptic task, each stimulus was presented for 12 s, followed by a 4 s ISI. Participants decided with a two-alternative forced-choice button press whether or not the geometric structure of the match stimulus was identical to any of the previous four sample stimuli. Six blocks of objects and six blocks of rooms were presented in alternating order, with the initial block type randomized across participants.

that we observed during haptic exploration could, in principle, reflect a visual representation of scene geometry. Visual information reaches the posterior parahippocampus via direct projections from multiple occipital regions [7, 8]; hence we addressed this recoding hypothesis with functional connectivity analyses. Specifically, for both DMTS tasks, we tested whether occipital regions showed a scene-specific increase in coupling with the PPA (collapsed across hemispheres). In contrast to the visual task, we did not observe any significant voxels in the haptic task, indicating that the covariation between occipital and PPA responses did not differ between scene and object blocks during haptic exploration. Direct comparisons supported these findings by revealing multiple clusters in occipital cortex in which the scene-related increase in coupling with the PPA was significantly stronger under visual than haptic stimulation (Figure 2B; Table S2).

Spatial Layout Processing in Blind Subjects

Experiment 1 suggests that scene-selective responses in the human brain can be driven by modalities other than vision. Given the absence of context-dependent coupling between occipital cortex and the PPA during haptic exploration, these results are unlikely to arise from occipital processing during nonvisual stimulation, which would have been indicative of mental imagery. However, because occipital activation has not always been reported in studies on mental imagery [9], we performed a second, complementary test of the recoding hypothesis with age- and gender-matched blind participants. Analogous PPA/RSC involvement in the blind participants would rule out the possibility of recoding based on visual experience and provide evidence for multimodal processing of spatial layout.

Like the sighted participants, those who were blind responded as quickly to scene stimuli as to objects ($p > 0.1$). Because a paradigm to localize the PPA in blind subjects has yet to be established, we followed a previously established approach [10] and used the group results from the functional localizer task in the sighted subjects to define an average PPA ROI for the blind participants (Figure 3). As Figure 3 demonstrates, activation profiles in the blind participants were highly similar to the sighted: blood oxygenation level dependent (BOLD) responses were significantly greater when subjects haptically explored the scenes than when they explored objects ($t = 4.19$, $p < 0.01$, $d = 0.62$) but did not differ between the right and left PPA (main effect of hemisphere: $F = 0.07$, $p = 0.80$; task by hemisphere interaction: $F = 1.26$, $p = 0.30$). Moreover, differences in BOLD responses did not correlate with differences in reaction time (left PPA: $r = -0.32$, $p > 0.4$; right PPA: $r = 0.32$, $p > 0.4$) or accuracy (left PPA: $r = 0.54$, $p > 0.2$; right PPA: $r = 0.13$, $p > 0.5$). Outside the PPA, both groups showed stronger bilateral activation for haptic exploration of scenes in RSC (Figure 4; Table S1); however, in the left hemisphere, the cluster of significant voxels extended into the parieto-occipital sulcus. Similar results were observed in area 7p [11] of the superior parietal lobe and in the middle frontal gyrus. Because the RSC appeared to show deactivation for objects in the blind subjects, we tested for a negative effect but did not observe any significant voxels in the sighted or the blind subjects. Importantly, we did not observe differences between scenes and objects in primary motor cortex, suggesting that the amount of motor exploration did not differ between stimuli. Furthermore, the reverse analysis (objects > scenes) did not reveal any significant effects, and we did not observe any voxels that showed a significant correlation with behavioral performance.

Finally, we tested for overlapping and differential responses between sighted and blind participants with a whole-brain analysis on the haptic task. A conjunction analysis [12] revealed that both blind and sighted participants recruited a large network of regions during haptic exploration of scenes and objects, with the maximum responses in areas implicated in motor control and sensorimotor processing (Table S5). In addition, although blind and sighted subjects did not differ in their overall reaction times ($F = 0.054$, $p > 0.5$), blind subjects exhibited stronger activation in occipital and middle temporal areas (Table S2). These findings support previous reports showing that blind humans recruit occipitotemporal cortices during tactile exploration of objects [13, 14] and Braille reading [15, 16]. However, similar to the sighted participants, a functional connectivity analysis did not reveal any clusters in

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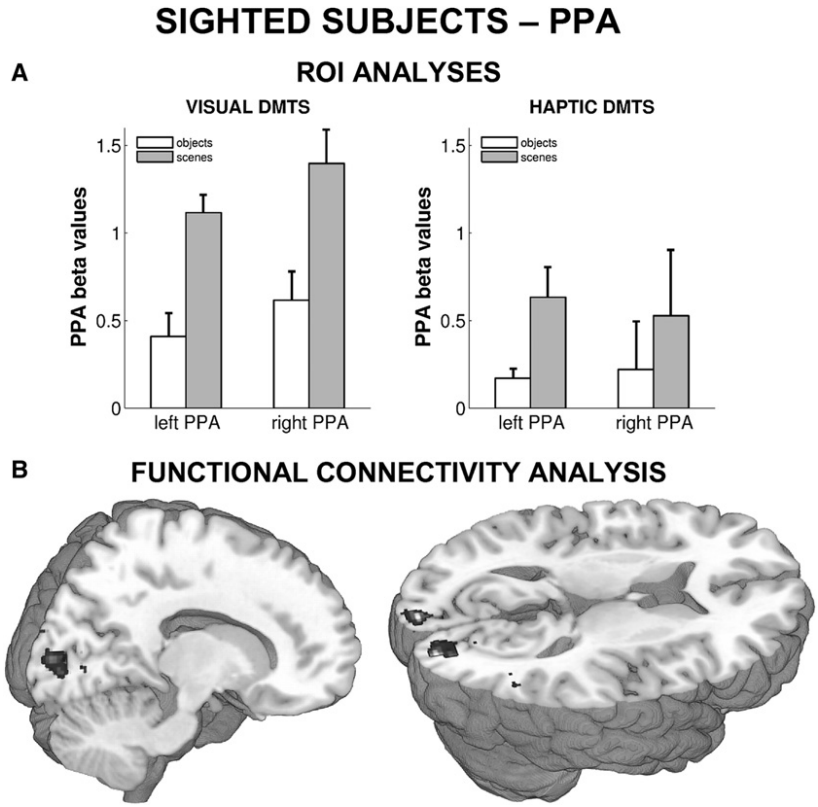

Figure 2. Modality-Independent Scene Processing in the PPA of Sighted Subjects

(A) In the visual version of the delayed matching-to-sample task, the PPA responded more strongly when subjects were viewing and memorizing scenes as compared to objects (left). Similar results were observed in the haptic condition (right) when subjects manually explored the stimuli. For each subject and condition, we extracted the responses for scenes and objects and averaged them across all voxels in the individual PPA regions of interest (as identified by the functional localizer). The graph shows the mean activations (+ standard error of the mean [SEM]) in the PPA averaged across participants. Effect sizes for the differences between scenes and objects were as follows: visual DMTS: left PPA (d = 1.68), right PPA (d = 1.57); haptic DMTS: left PPA (d = 1.21), right PPA (d = 0.29). See Table S1 for additional whole-brain analyses and Figure S2 for data from individual subjects.

(B) Given that the PPA receives direct projections from various occipital areas, we performed functional connectivity analyses with the PPA as a seed region to identify voxels whose activation showed a stronger covariation with the PPA during scene than during object blocks. After performing this analysis separately for the visual and the haptic DMTS task, a paired t test revealed multiple clusters in occipital cortex in which the context-dependent coupling was significantly stronger during visual than during haptic stimulation. To show the subthreshold extent of the effect, we displayed the results of the random-effects analysis on the MNI template brain with a threshold of $p < 0.001$ uncorrected. See Table S2 for complete voxelwise statistics.

occipital cortex that showed a stronger covariation with the PPA during scene than during object blocks.

Discussion

These studies investigated whether regions such as the PPA and the RSC can be recruited for computation of spatial layout, independent of a specific sensory modality. In experiment 1, sighted subjects showed stronger PPA/RSC responses for visually presented scenes than for objects, which replicates previous findings. Similar differences were observed when stimuli were apprehended via haptic exploration, suggesting a targeted network that can be driven both by visual and nonvisual spatial information. Importantly, functional connectivity analyses and a similar PPA/RSC preference for scenes in blind participants showed that these effects were not related to a recoding of haptic experiences into visually dependent mental images. Taken together, our findings strongly support a theory of modality-independent coding of spatial layout in the brain, which adds to the growing evidence for multimodal coding in other specialized processing regions such as the fusiform face area [17, 18] or the object-sensitive ventral visual pathway [10, 19].

Although previous research on the spatial functions of the PPA and RSC has focused on visual processing, spatial information can be acquired and represented from multiple nonvisual sources [20]. For example, in rodents, position signals in place and grid cells and orientation signals in head direction cells not only are sensitive to visual landmarks but also can be updated by body-based cues when the animal moves around in darkness [1, 2]. In addition, human behavioral studies suggest that both visual and nonvisual cues influence our navigational behavior [21–24]. Taken together, this evidence indicates that various types of spatial information can be acquired from different sensory modalities and ultimately represented in a common, modality-independent format, thus supporting mental computations and spatial behaviors independent of the input source. This hypothesis has been elaborated in several ways, including the spatial representation system [25], the spatial image [26], and the notion of metamodal brain organization [27].

The present results extend this claim by showing that the scene-specific responses in the human brain are not restricted to visual input but can also arise from haptic exploration. Our findings are parallel to those of Mahon et al. [10], who showed that preferences for object categories in the ventral visual stream do not require visual experience. Here, when scenes and objects were presented as grayscale photographs to the sighted subjects, we observed the well-established PPA preference for scenes. When corresponding information was acquired from haptic exploration of the physical models, a similar PPA preference for scenes emerged. Although this effect could have been driven by a recoding of haptic experiences into visual mental images, this account appears unlikely for two reasons. First, the coupling between occipital cortex and the PPA was selectively enhanced during visually presented scene blocks, which argues against an imagery-related occipital contribution. Second, we observed the same PPA selectivity for scenes in blind participants during haptic exploration. Although the definition of the PPA in the blind bears some anatomical uncertainty—as a result of the absence of an established functional localizer for this population—our data suggest that the PPA intrinsically functions to represent spatial layout in a format that is not tied to a specific sensory modality.

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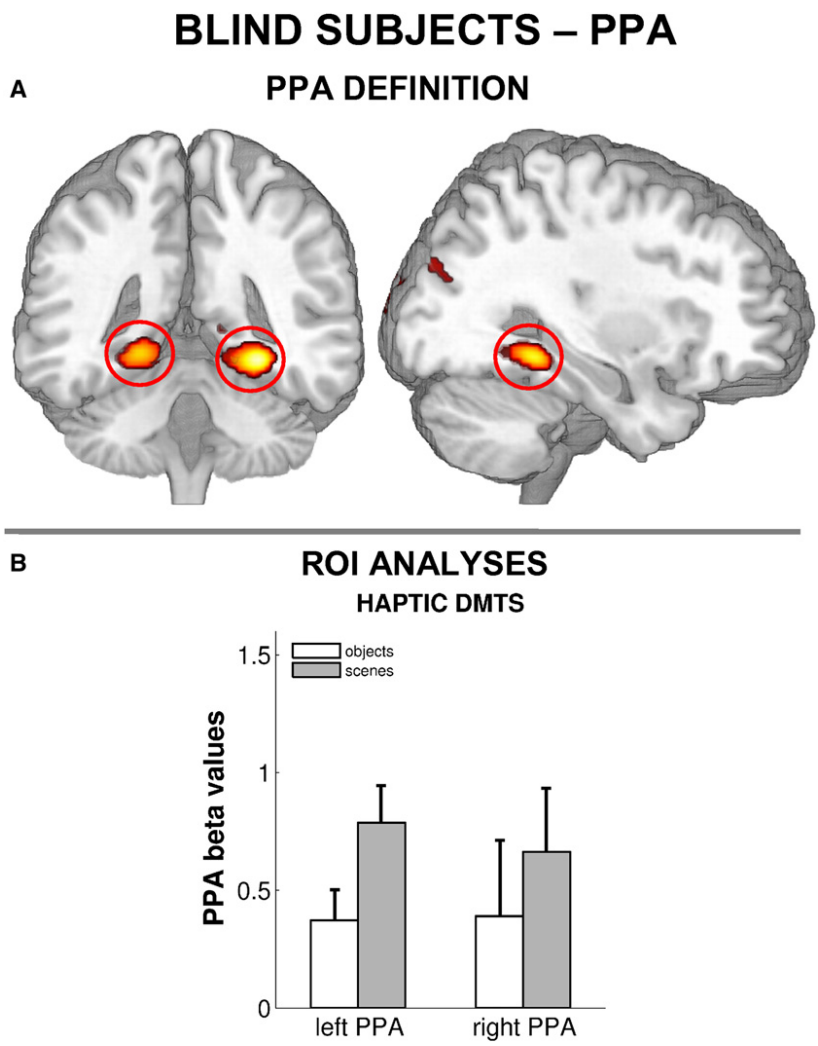

Figure 3. Haptic Scene Processing in the PPA of Blind Subjects

(A) Given the absence of a functional PPA localizer for blind subjects, we defined the PPA based on the results from the functional localizer task in sighted subjects. The panels show the results of a fixed-effects analysis in the sighted subjects that tested for differences between scenes and objects. Results are displayed on the MNI template brain, using a threshold of $p < 0.05$ corrected for multiple comparisons. For each of the blind subjects, we extracted the responses for scenes and objects and averaged them across all voxels in the right and left PPA.

(B) In the haptic version of the task, blind participants showed stronger PPA activation for scenes than for objects, thus replicating the results of the sighted subjects. The graph shows the mean activations (+SEM) in the PPA ROIs, averaged across participants. Effect sizes for the differences between scenes and objects were as follows: left PPA ($d = 1.04$), right PPA ($d = 0.28$). For detailed demographic data on the blind participants, see Table S3.

In addition to the PPA, we observed stronger responses to scenes in RSC, independent of the encoding modality. Although several proposals exist with regard to the precise navigational functions of the RSC [28–30], our tasks are fully consistent with studies reporting strong RSC responses to unfamiliar scenes that provide ample geometric information [29]. Our results show for the first time that scene sensitivity in the RSC, as in the PPA, is not restricted to the visual modality but also emerges when spatial layout information is acquired from haptic experiences. Given the extensive network of afferent projections to the RSC [31], it therefore appears likely that various streams of spatial information processing converge in the RSC to support the encoding, storage, and manipulation of spatial layout information.

In both the PPA and the RSC, the overall activation and the scene-specific increases were weaker in the haptic than in the visual condition. These differences are likely related to differences in sensory processing: haptic input is slower to apprehend, as a result of serial versus parallel encoding, and tactile resolution and bandwidth capacity are far lower than that of vision [32]. As such, one would expect it to be a slower and noisier signal to use for building up a scene representation. Behavioral findings support this assumption because visual maps are faster to learn and yield less overall variability at testing than the same learning and testing from haptic maps, but both input modalities show an almost identical pattern of speed and error performance on spatial updating tasks [33]. These results indicate the building up and accessing of a multimodal representation, which is consistent with our findings of the PPA and the RSC processing information from multiple input sources. Importantly, future studies—potentially using intracortical recordings—are needed to ultimately verify the idea that identical neuronal populations are driven by visual and haptic inputs.

In conclusion, we have shown that the PPA and the RSC, two key regions of the human spatial navigation network [3], respond both to visual and haptic presentation of spatial layouts. Together with the multisensory properties of other spatial systems such as the head direction, grid, and place cell networks, our findings provide further evidence for the notion that the mammalian brain may code for spatial information in a format that is not tied to a specific sensory modality. Given that spatial properties (size, distance, direction, etc.) are fundamental dimensions of the physical world that do not require a specific type of sensory processing, it is tempting to speculate that cortical systems have evolved to construct this abstract format.

Experimental Procedures

Subjects

Eight healthy volunteers (six right-handed, one ambidextrous according to [34], and one unknown), all with normal or corrected-to-normal vision, participated in experiment 1, and eight blind volunteers (all right-handed Braille readers), matched for age and sex, participated in experiment 2. Because one blind participant in experiment 2 had to be removed because of excessive head movement, we removed the corresponding sighted subject as well. Therefore, the final data sets comprised seven sighted subjects (two female, age range 22–77 yrs) and seven blind subjects (two female, age range 22–75 yrs). See Table S3 for further information on the etiology and age of onset of blindness.

Image Processing and Statistical Analysis of fMRI Data

Image processing and statistical analysis were carried out using SPM8 (Wellcome Department of Imaging Neuroscience, London). All volumes

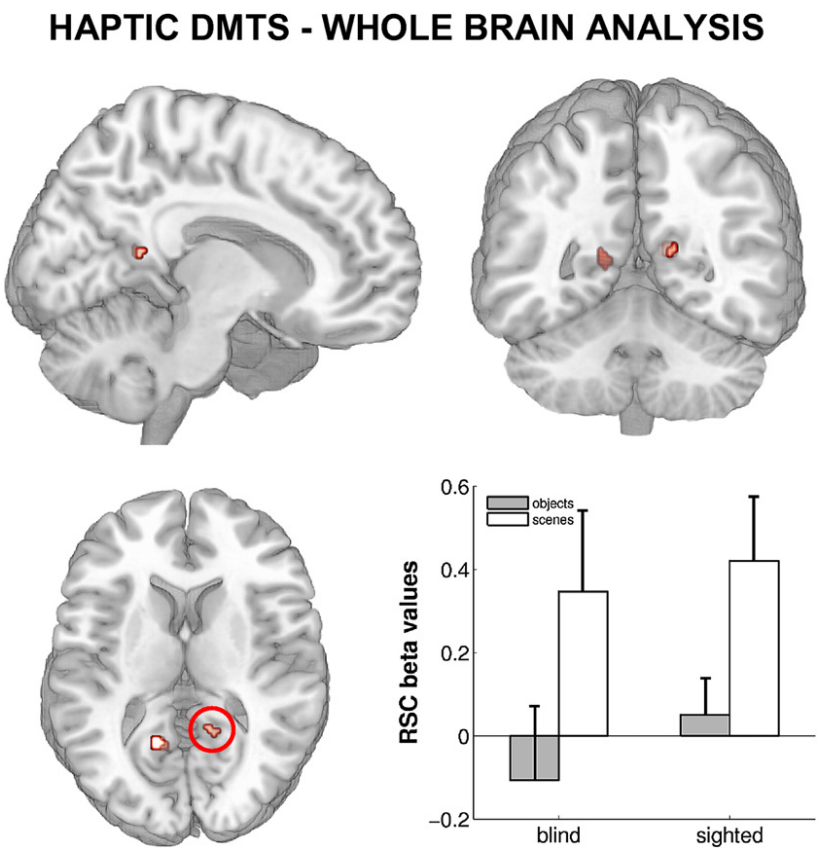

Figure 4. Haptic Scene Processing in Retrosplenial Cortex

Whole-brain analysis showing regions beyond the PPA that responded more strongly to haptic exploration of scenes than objects in both groups. Consistent with our findings on visual processing, bilateral effects were observed in retrosplenial cortex, and scene selectivity did not differ between blind and sighted participants. In all panels, results of the random-effects analysis are displayed with a threshold of $p < 0.05$ corrected for multiple comparisons. The lower right panel shows the mean activations (+SEM) of all voxels in the right retrosplenial cortex, averaged across participants. Similar results were obtained in superior parietal cortex and middle frontal gyrus (see Table S4). For further activations common to both subject groups, see Table S5. For signal time courses from the RSC and the PPA, see Figure S4.

were realigned to the first volume, spatially normalized to an Echo Planar Imaging (EPI) template in a standard coordinate system [35], and finally smoothed using a 9 mm full-width at half-maximum isotropic Gaussian kernel.

In the sighted subjects, we identified the PPA in each subject with a functional localizer task (see Supplemental Experimental Procedures). We also performed a whole-brain fixed-effects analysis across all sighted subjects to define a PPA ROI for the blind subjects, given the absence of an established PPA localizer for this population. We then estimated statistical models for the DMTS tasks in the PPA ROIs of each participant and entered the resulting parameter estimates into paired t tests. To test for regions outside the PPA showing differences between objects and scenes, we performed whole-brain random-effects analyses as implemented in SPM8.

The functional connectivity analyses were performed with the functional connectivity toolbox (http://web.mit.edu/swg/software.htm)—one for the visual and one for the haptic condition—to identify voxels in occipital cortex whose activation showed a stronger covariation with the PPA during scene than during object blocks. Detailed information about experimental procedures, MRI acquisition, image processing, and statistical analysis of fMRI data is given in the Supplemental Experimental Procedures.

Supplemental Information

Supplemental Information includes six figures, one table, and Supplemental Experimental Procedures and can be found with this article online at doi:10.1016/j.cub.2011.04.038.

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Supplemental Information

Modality-Independent Coding of Spatial Layout in the Human Brain

Thomas Wolbers, Roberta L. Klatzky, Jack M. Loomis, Magdalena G. Wutte, and Nicholas A. Giudice

Supplemental Inventory

Figure S1, related to Figure 1.
Representative floor plans and screenshots of the scene stimuli.

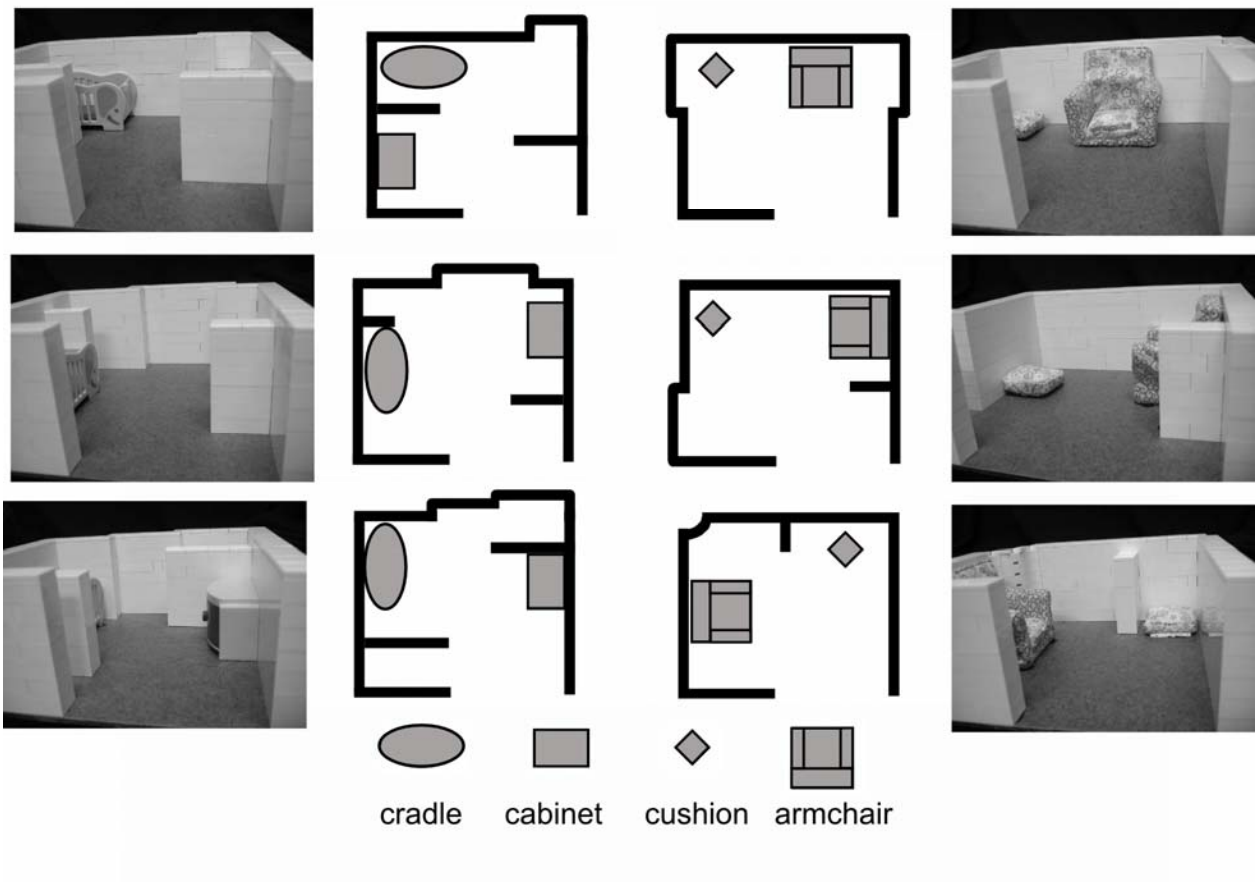

Figure S2, related to Figure 2.
Single subject data showing the difference in PPA activation between scenes and objects for the different tasks / groups. In the visual condition, stronger PPA responses to scenes vs. objects were seen in all sighted subjects. In the haptic task, 6 out of the 7 sighted and 7 out of the 7 blind subjects showed the same effect, albeit when compared to the visual task, the magnitude of the response differences was smaller for most participants.

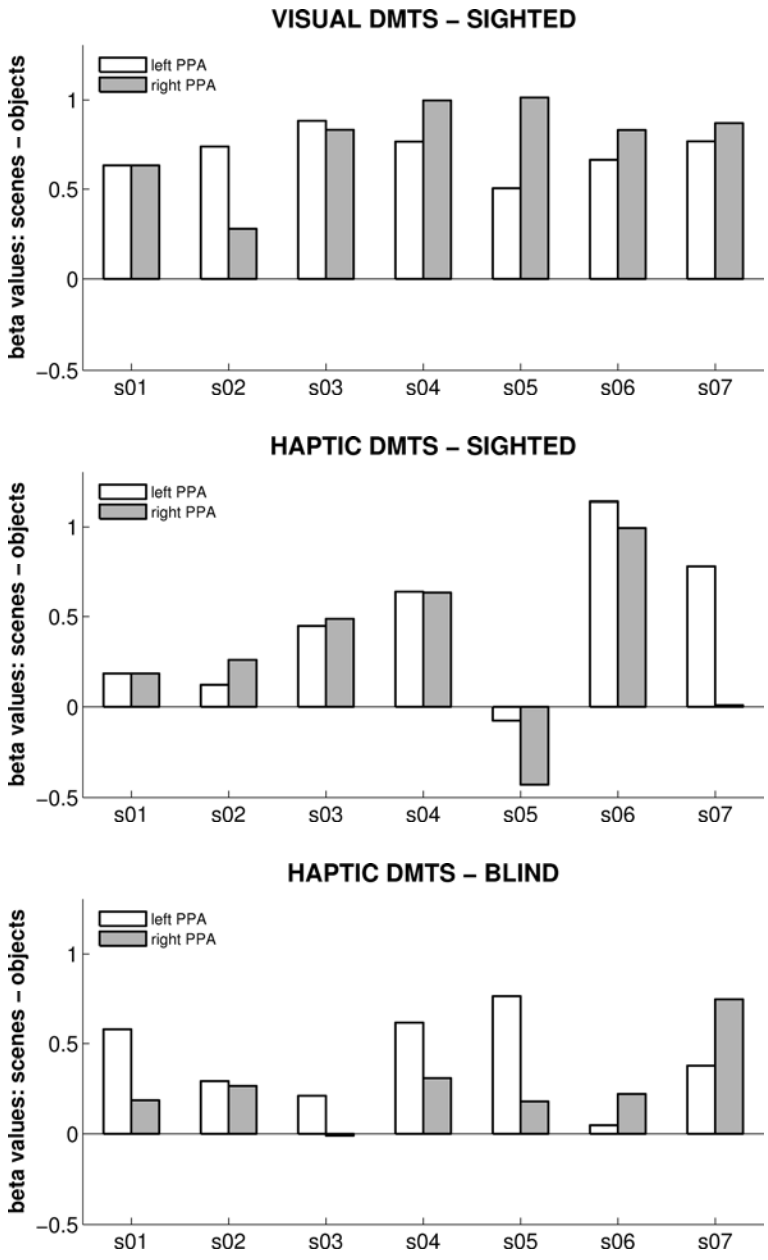

Figure S3, related to Figure 4.
Averaged time courses (+/- sem) for the haptic DMTS task for the left PPA, the right PPA and the RSC. For the PPA, time courses were calculated by averaging across all voxels in the subject specific PPA-ROI's. For the RSC, time courses were calculated by averaging across all voxels in retrosplenial cortex as identified by the whole brain analysis that included both groups (see Figure 4). The plots are aligned with the presentation of the first stimulus in a block and cover the entire duration of a block.

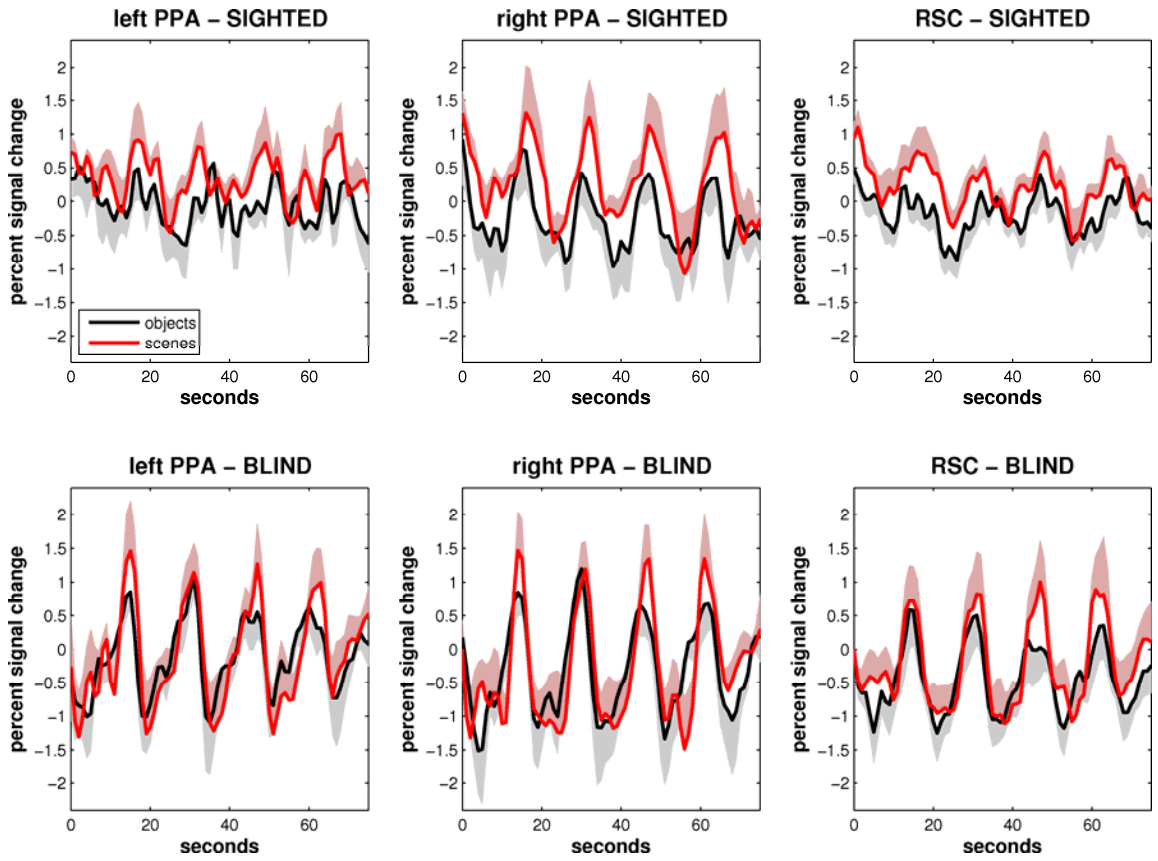

Table S1. Whole Brain Analyses for the Visual DMTS Task in the Sighted. Related to Figure 2

Spatial coordinates of the local maxima		
Region	Coordinate (x, y, z, in mm)	Voxel-level (t-score)
	LH RH	
Contrast: scenes > objects		
Retrosplenial cortex	10, -54, 12	46.44
Superior frontal gyrus	22, -2, 64	34.65
Contrast: objects > scenes		
No significant voxels		

RH/LH – right/left hemisphere; threshold: $p<0.05$ corrected

Table S2. Functional Connectivity Analyses in Sighted Subjects. Related to Figure 2

Spatial coordinates of the local maxima in occipital cortex showing a stronger coupling with the PPA for scene than for object stimuli			
Region	Coordinate (x, y, z, in mm)		Voxel-level (t-score)
	LH	RH	
Visual DMTS > Haptic DMTS			
Calcarine gyrus	-8, -94, 12		11.79
Superior occipital gyrus	-10, -94, 18		13.54
		16, -96, 24	12.65
Inferior occipital gyrus		38, -72, -10	9.69
Cuneus	-10, -92, 16		18.98
Haptic DMTS > Visual DMTS			
No significant voxels			

RH/LH – right/left hemisphere; threshold: $p<0.05$ corrected

Table S3. Demographic Information on the Blind Participants. Related to Figure 3

Sex	Etiology	age of onset	years blind	Residual Vision
M	Retinitis Pigmentosa	birth	54	None
F	Cancer	6 months	22	None
M	Retinitis Pigmentosa	24	25	None
M	Lebers Congenital Amaurosis	birth	34	light perception
M	Retinopathy of Prematurity	birth	62	None
F	Retinitis Pigmentosa	35	16	light and near shape perception
M	Optic Nerve Atrophy	25	50	None

Table S4. Main Effects of Task and Group in the Haptic DMTS Task. Related to Figure 4

Spatial coordinates of the local maxima			
Region	Coordinate (x, y, z, in mm)		Voxel-level (t-score)
	LH	RH	
Blind > Sighted (pooled across scenes and objects)			
Superior parietal lobe		36, -56, 62	10.27
Precuneus		10, -78, 48	9.03
Cuneus	-14, -88, 38		10.81
Middle temporal gyrus	-42, -62, 2		9.35
Superior occipital gyrus	-24, -88, 28		11.51
		24, -84, 34	9.09
Middle occipital gyrus	-26, -90, 18		8.94
Scenes > Objects (pooled across blind and sighted participants)			
Retrosplenial cortex	-14, -56 10		9.86
		14, -50, 14	10.19
Superior parietal lobe (area 7p)	-16, -76, 52		8.45
		24, -74, 50	11.41
Middle frontal gyrus	-32, 24, 28		8.28
Objects > Scenes (pooled across blind and sighted participants)			
No significant voxels			

RH/LH – right/left hemisphere; threshold: $p<0.05$ corrected

Table S5. Conjunction Analysis: Activation Common to Both Groups during Haptic Exploration of Scenes and Objects. Related to Figure 4

Spatial coordinates of the local maxima for the contrast: (scenes sighted & objects sighted) & (scenes blind & objects blind)			
Region	Coordinate (x, y, z, in mm)		Voxel-level (t-score)
	LH	RH	
Inferior frontal gyrus		56, 6, 34	10.06
Superior frontal gyrus	-4, -4, 54		12.05
		8, 4, 52	15.80
Precentral gyrus	-36, -20, 56		37.57
	-54, 2, 38		17.97
		24, -8, 54	15.91
		38, -14, 56	13.60
Postcentral gyrus	-60, -22, 32		33.61
	-46, -34, 52		44.98
		32, -44, 64	33.75
		64, -20, 36	27.73
Parietal Operculum	-54, -18, 16		20.21
		62, -18, 20	11.23
Supramarginal gyrus	-52, -30, 48		52.38
		64, -24, 26	22.88
Superior parietal lobe	-16, -66, 56		22.98
	-14, -52, 68		11.33
		24, -64, 60	17.78
		14, -54, 60	11.19
Inferior parietal lobe	-34, -56, 60		17.95
		38, -46, 52	23.07
Inferior temporal gyrus	-46, -56, -2		18.10
		44, -58, -8	14.26
Superior occipital gyrus	-22, -78, 36		10.91
		26, -68, 26	10.92
Cerebellum	-26, -56, -16		19.95
	-32, -50, -18		19.66
		22, -48, -20	29.60
		30, -46, -24	24.91

RH/LH – right/left hemisphere; threshold: $p<0.05$ corrected

Supplemental Experimental Procedures

Experimental Stimuli and Paradigm

We used Lego blocks to construct 27 abstract geometric objects and 27 indoor scenes (furnished rooms). Previous paradigms have shown that viewing similar Lego stimuli reliably activates the PPA [1]. The outer walls were identical in each room, and the entry door was always located at the same position. To make the rooms distinguishable, we manipulated the number, size, and position of the interior walls, thereby giving each room a unique geometric layout. Because the PPA is believed to represent navigable spatial layouts in which one can move about [2], we added toy characters and small furniture. In addition, we acquired digital images of each room and each object and rendered them in grayscale to eliminate any color differences between stimuli (see Figures 1 and S1 for examples). For the rooms, photographs were taken from a first person perspective through the entry door, applying the same angle for each room (see Figure S1 for examples).

In experiment 1, sighted subjects first performed a haptic and then a visual version of a delayed matching-to-sample (DMTS) task in which they attended to the geometric structure of the stimuli (Figures 1 + S1). In the visual task, each trial began with a visual presentation of a block of four sample stimuli (four different rooms or four different objects). Each image was shown for 3s, followed by a 1s interstimulus interval. Subjects were instructed to memorize the geometric structure of each sample stimulus and to compare it to the structure of a subsequent match stimulus. Specifically, subjects had to decide whether or not the geometric structure of the match stimulus was identical to any of the four sample stimuli. In the case of rooms, furniture was removed from this final match stimulus to emphasize that the geometric properties were the relevant dimension. Subjects indicated match or no-match by pressing one of two buttons on a keypad. Six blocks of objects and six blocks of rooms were presented in alternating order, with intervening rest periods (duration: 16s) during which subjects fixated a white cross on a black background. Initial block type was randomized across subjects.

In the haptic version of the task, room and object models were placed on a tray positioned on the upper right thigh, and subjects explored the stimuli with the right hand only. We first ran two pilot experiments to establish optimal movement trajectories and temporal periods for exploration. Based on these experiments, each stimulus was presented for 12s, followed by a 4s interstimulus interval (ISI). Given that subjects could not know when a new stimulus had been delivered, an auditory command (delivered via headphones) instructed them to start exploring the current stimulus immediately after the ISI. For the sample stimuli, the instruction was ’explore’, for the match stimulus it was ’compare’. As in the visual version of the task, subjects were instructed to memorize the geometric structure of each sample stimulus and to compare it to the structure of a subsequent match stimulus. In order to standardize hand movements across stimuli and subjects, they were instructed to move the hand in one fast, counterclockwise circle first to get a general impression of the geometric structure. Following this initial exploration pattern, they were free to return to whatever parts of the stimulus they felt they needed to explore further with no additional restrictions on hand movement. For the rooms, subjects were also instructed to stay within the interior perimeter of the room and to avoid moving along the outer side of the stimuli. This restriction reduced hand movement and ensured that the same stimulus information was available between the visual and haptic scenes. After exploring the matching stimulus, subjects heard an auditory signal cuing them to press one of two buttons to indicate match or no-match. Six blocks of objects and six blocks of rooms were presented in alternating order, separated by an intervening 16s rest period, with the initial block type randomized across subjects.

Although our formal emphasis in the behavioral pilot studies was on quantifying a temporal measure, it is important to note that none of the participants self-reported being confused between what was a scene and what was an object nor did any report having trouble differentiating the stimuli. Furthermore, during fMRI scanning, auditory instructions informed subjects about the type of stimuli (rooms/objects) to be presented in each block. Thus, there was never any possible confusion whether the haptic stimulus was a scene or an object.

Finally, we localized the parahippocampal place area in each subject individually with a functional localizer. Following previously established procedures [3], we presented 20 color pictures of indoor scenes (furnished rooms) and 20 color pictures of everyday objects (e.g. brush, cup). Each stimulus was shown for 400ms, followed by an interstimulus interval of 480ms. Subjects performed a continuous one-back task by pressing a button whenever two successive images were identical. Stimuli were shown in three blocks of rooms alternating with three blocks of objects, with each block containing 22 items (2 targets) presented in a randomized order. Blocks were separated by rest periods (duration: 16s) during which subjects fixated a white cross on a black background.
In experiment 2, the blind subjects performed the haptic version of the DMTS task. The stimuli and experimental paradigm were identical to experiment 1.

Experimental Procedure
In experiment 1, the sighted participants first performed the haptic version of the task to prevent them from using a memory representation of the visual stimuli during the haptic task. Detailed instructions about the task were followed by a training session without concurrent fMRI recording to eliminate learning and habituation effects. The training session was identical to the subsequent experimental session, except for the fact that subjects were given feedback about their performance. Importantly, subjects were never allowed to see any of the models, both during training and during experimental sessions. Haptic stimuli were placed on a tray on the right thighs of the subjects by the experimenter, so that they could reach them easily with their right hand, without extensive arm movement. Subjects were instructed to move their arm as little as possible, instead relying on hand movements to explore the stimuli. Button presses were always performed with the left hand. Following the haptic task, subjects performed the visual version and finally the functional localizer. In experiment 2, the blind subjects performed the haptic version of the DMTS task, using the same procedures for training and experimental sessions.

Image Processing and Statistical Analysis of fMRI Data
Image processing and statistical analysis were carried out using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). All volumes were realigned to the first volume, spatially normalized to an EPI template in a standard coordinate system [4] and finally smoothed using a 9 mm full-width at half-maximum isotropic Gaussian kernel. At the single-subject level, we applied a high pass filter (cut-off: 256s) to remove low frequency artifacts.
In experiment 1, we first created regions of interest (ROI) for the PPA in each of the sighted participants. To achieve this goal, we analyzed the data obtained from the functional localizer and specified design matrices with separate regressors for scenes and objects. Blocks of stimuli were modeled as boxcar functions convolved with a hemodynamic response function. We then identified the PPA as the cluster of contiguous voxels in the posterior part of the parahippocampal gyrus that showed stronger BOLD responses for scene than for object stimuli, using an uncorrected threshold of $p<.001$. Replicating previous findings [1, 3, 5], this approach proved successful since we were able to identify the PPA bilaterally in each sighted subject. For the subsequent analyses, we created both separate ROI's for the left and right PPA and a combined ROI by collapsing voxels from both hemispheres into one ROI.
Next, we estimated statistical models for the visual and the haptic DMTS task in the PPA-ROIs of each participant. We specified design matrices with separate regressors for scenes, objects and button presses, and blocks of stimuli were modeled as boxcar functions convolved with a hemodynamic response function. To account for potential confounds due to head motion, we also included six movement regressors (three translations and three rotations) as obtained from the realignment procedure. We then used the Marsbar toolbox to extract the mean time course across all voxels in the PPA-ROI, estimated the statistical model for the averaged time course, and entered the resulting parameter estimates for scene and object stimuli into a random effects paired t-test as implemented in the Matlab Statistics toolbox (version 7.4). Effect sizes were calculated by taking into account the correlation between both variables [6].
To look for regions outside the PPA showing differences between objects and scenes in the visual DMTS task, we performed a random effects whole-brain analysis. Specifically, the contrast images coding for the

main effects of both stimulus types were analyzed with a paired t-test as implemented in SPM8. Moreover, due to the relatively long block duration in the haptic condition, we estimated two models to test whether the PPA responses showed a habituation of the BOLD response over time. In the first model we tested for across block habituation by adding regressors in which the predicted hemodynamic responses for both conditions (scenes / objects) were parametrically modulated with the repetition of blocks (i.e. first object block, second object block etc.). In the second model, we modeled each stimulus as a separate event and added regressors that coded for the position of a stimulus within a block (within block habituation). For both models, the resulting parameter estimates for the parametric modulation regressors were then entered into random effects one-sample t-tests, but we did not observe any evidence for habituation effects (visual DMTS: within blocks – objects: $t=-0.05$, $p>0.5$; scenes: $t=1.54$, $p>0.1$; across blocks – objects: $t=0.05$, $p>0.5$; scenes: $t=0.70$, $p>0.5$; haptic DMTS: within blocks – objects: $t=-0.10$, $p>0.5$; scenes: $t=0.05$, $p>0.5$; across blocks – objects: $t=0.56$, $p>0.5$; scenes: $t=0.07$, $p>0.5$).

Because the match and sample stimuli differed with respect to the presence of furniture and toy characters (see Experimental Stimuli and Paradigm), we reran all analyses while only focusing on the sample stimuli and modeling the match stimuli as a separate regressor of no interest. These analyses replicated all the results reported in the main text; hence, the absence of the furniture and the toy characters in the match scenes did not seem to have a biasing effect.

Given the absence of a standard paradigm for localizing the PPA in blind people, we followed previously established procedures [7] and used the data from the functional localizer task of the sighted participants to define an average PPA ROI for experiment 2. Specifically, we performed a whole-brain fixed effects analysis in the sighted subjects and defined the PPA as the cluster of contiguous voxels in the posterior part of the parahippocampal gyrus that showed stronger BOLD responses for scenes than for objects. All subsequent analyses proceeded as for the sighted subjects.

As shown in table S3, our sample of blind participants was not completely homogeneous; hence factors such as age of onset of blindness or residual light perception could have had an unintended effect on our results. We believe this is unlikely given that each of the blind participants showed stronger activation for scenes than for objects, the fact that none had any more than light and minimal shape perception, and that the average duration of blindness was more than 37 years. Moreover, congenitally and adventitiously blind groups showed similar differences in PPA responses between scenes and objects (data not shown).

Finally, to test for overlapping and differential activations between blind and sighted subjects in the haptic delayed matching-to-sample task, we also performed a random effects whole-brain analysis across both groups. The contrast images coding for the main effects of both stimulus types in both subject groups were analyzed with a flexible factorial design as implemented in SPM8. To account for non-sphericity due to our repeated measures design, we explicitly modeled dependent error terms.

For each of the whole brain group analyses, correction for multiple comparisons (using a threshold of $p<.05$ corrected) was based on the entire brain and was performed using Gaussian Random Field Theory as implemented in SPM8. In contrast, note that the ROI analyses did not require correction for multiple comparisons as the subject specific statistical models were estimated for the mean time courses (averaged across all voxels in the respective ROI). As a consequence, for each participant, only one regression coefficient for scenes and one for objects entered the subsequent random effects models.

Functional Connectivity Analysis

How can we characterize potential mechanisms that could explain the scene sensitivity of the PPA in sighted subjects? Humans can extract the global structure of a visually presented scene as a combination of low-level filters of the type found in early visual areas, which is presumably read out by higher order areas. Given that the posterior parahippocampus receives direct projections from various occipital areas such as V2 and V4 [8, 9], we hypothesized that the stronger responses to scenes in the PPA might result from a stimulus-dependent modulation of the coupling strength between occipital cortex and the PPA. Moreover, we predicted similar effects in the haptic condition if subjects were engaging in visual mental imagery. We therefore performed two functional connectivity analyses with a functional connectivity toolbox (web.mit.edu/swg/software.htm) – one for the visual and one for the haptic condition – to identify

voxels in occipital cortex whose activation would exhibit a stronger covariation with the PPA during scene than during object blocks.

For each participant, we first removed several sources of confounding variance from the smoothed data through linear regression: estimated motion parameters, global average BOLD signal, average BOLD signals in ventricular and white matter ROIs and variance related to the main effects of the tasks. In addition, the data were high-pass filtered (cut-off: 256s) to eliminate low frequency drifts. Next, we extracted the mean time course across all voxels in the PPA as defined by the functional localizer and correlated it with all voxels in occipital regions V1, V2, V3, and V4 as defined by the SPM Anatomy toolbox [10]. Note that the PPA voxels from both hemispheres were combined as we did not observe hemispheric differences in the ROI analyses. We then tested for voxels in which this correlation was stronger during scene than during object blocks. Finally, the resulting contrast images were entered into a random effects paired t-test to assess differences between visual and haptic conditions. To take into account the anatomically motivated hypotheses, we applied multiple comparisons correction based on the four occipital regions of interest, again using Gaussian Random Field Theory.

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2.3 Inter-individual differences in hMT+

The following section consists of one research article:

Wutte, M.G., Smith, M.T., Flanagin, V.L., Wolbers, T., 2011. Physiological signal variability in hMT+ reflects performance on a direction discrimination task. *Frontiers in Psychology* 2, 185.

This research article originates from a collaboration with the lab of Thomas Wolbers, Center for Cognitive and Neural Systems, University of Edinburgh. This project benefited greatly from the collaboration with the computer scientist Michael T. Smith, who contributed the noise analysis and the final pattern classification analysis of the fMRI dataset. The author of this thesis collected the psychophysical and fMRI data, analyzed the psychophysical data, did preprocessing, GLM analysis and preliminary pattern classification analysis on the fMRI data, and wrote the research article.

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Physiological signal variability in hMT+ reflects performance on a direction discrimination task

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Our ability to perceive visual motion is critically dependent on the human motion complex (hMT+) in the dorsal visual stream. Extensive electrophysiological research in the monkey equivalent of this region has demonstrated how neuronal populations code for properties such as speed and direction, and that neurometric functions relate to psychometric functions within the individual monkey. In humans, the physiological correlates of inter-individual perceptual differences are still largely unknown. To address this question, we used functional magnetic resonance imaging (fMRI) while participants viewed translational motion in different directions, and we measured thresholds for direction discrimination of moving stimuli in a separate psychophysics experiment. After determining hMT+ in each participant with a functional localizer, we were able to decode the different directions of visual motion from it using pattern classification (PC). We also characterized the variability of fMRI signal in hMT+ during stimulus and rest periods with a generative model. Relating perceptual performance to physiology, individual direction discrimination thresholds were significantly correlated with the variability measure in hMT+, but not with PC accuracies. Individual differences in PC accuracy were driven by non-physiological sources of noise, such as head-movement, which makes this method a poor tool to investigate inter-individual differences. In contrast, variability analysis of the fMRI signal was robust to non-physiological noise, and variability characteristics in hMT+ correlated with psychophysical thresholds in the individual participants. Higher levels of fMRI signal variability compared to rest correlated with lower discrimination thresholds. This result is in line with theories on stochastic resonance in the context of neuronal populations, which suggest that endogenous or exogenous noise can increase the sensitivity of neuronal populations to incoming signals.

Keywords: inter-individual differences, motion perception, direction sensitivity, hMT+/V5, fMRI, BOLD signal variability, multi-voxel pattern classification

INTRODUCTION

Accurate perception of visual motion is a key function of the human brain, enabling us to interpret the world around us, to predict trajectories of moving objects and to steer vehicles and control locomotion. While many psychophysical and neurophysiological studies have revealed common processing of visual motion information across participants, perceptual capabilities can differ substantially between individuals (Halpern et al., 1999). Though classical behavioral experiments average these difference to focus on the mean tendency, heterogeneity in visual motion perception can provide information on perceptual functioning. Describing performance profiles of motion perception might, for example, help to distinguish subgroups in phenomena like dyslexia or describe aging processes in the visual system (Talcott et al., 2000; Slaghuis and Ryan, 2006; Bennett et al., 2007; Billino et al., 2008). Exploring the relation between differences in performance on motion tasks and physiological signals in the visual dorsal stream can shed light on the relationships between cortical processing and perception.

Motion perception in humans critically depends on area hMT+ (also known as V5, for a review see Born and Bradley, 2005). Extensive research on its equivalent in monkeys (MT) has shown that neurons in this region are selective for the direction and speed of moving stimuli. Direction sensitive neurons show columnar organization, with columns of smoothly changing preferred directions abutting columns of the opposite preferred direction (Born and Bradley, 2005). Relating neuronal characteristics to behavior, neurometric functions of single-neurons were shown to correlate with psychometric functions in a direction discrimination task (Britten et al., 1992). More evidence for a direct link between MT neuronal properties and perception comes from studies which show that microstimulation can considerably bias performance (Cohen and Newsome, 2004) and that deteriorated neuronal speed and direction selectivity accompanies aging (Yang et al., 2009; Liang et al., 2010).

In humans, hMT+ lies in an anatomically variable region and shows variation in histological and functional anatomy across individuals (Dumoulin et al., 2000; Huk et al., 2002; Malikovic et al.,

2007). Studies exploring neurophysiological properties of hMT+ have worked with exogenous variation of the stimulus (e.g., coherence of movement) to describe related modulations of the blood oxygen level dependent (BOLD) signal. Other studies have considered endogenous signal changes in hMT+ during the presentation of ambiguous stimuli, reflecting switches between percepts (for example Castelo-Branco et al., 2002; Muckli et al., 2002). The latter line of research shows the informative value of looking at endogenous fluctuations in hMT+, an approach we took in the current study to describe inter-individual physiological differences. While structural differences in the visual stream have been shown to correlate with individual psychophysical thresholds (Kanai and Rees, 2011), the connection between individual physiological properties of hMT+ and inter-individual differences in psychophysical tasks is less explored.

On a neuronal level, a possible reason for different perceptual sensitivity for direction could be the relative width of directional tuning curves. Sharper tuning curves lead to an unambiguous population signal in hMT+, which could be reflected in more distinct patterns for different directions of motion. On the behavioral level, this might translate into lower psychophysical thresholds when an individual has to make fine discrimination between different directions of motion (Purushothaman and Bradley, 2005; Liang et al., 2010). A potential candidate for revealing such physiological differences in fMRI is multi-voxel pattern analysis (MVPA) which is able to resolve fine grain patterns of hMT+ organization invisible to univariate techniques (Kamitani and Tong, 2006). Individual differences in decoding accuracy might indicate the distinctiveness of the hMT+ population pattern and correlate with perceptual performance.

Another method which has been recently suggested as a good gauge for inter-individual comparisons is variability analysis of the BOLD signal (Garrett et al., 2010; Mohr and Nagel, 2010; Samanez-Larkin et al., 2010; Mennes et al., 2011). Measurements of variability aim to describe endogenous background fluctuations in the signal, which appear independent of the timecourse of the experimental manipulation. An important confound for accurately measuring such endogenous variability is that the relationship between the stimulus and the BOLD signal has to be described as precisely as possible. Only if this is achieved can one investigate if the observed physiological variability has functional significance. A growing body of studies suggests that neurophysiological variability patterns can be understood as (functional relevant) "signal" rather than (function disturbing) "noise" (Faisal et al., 2008; McDonnell and Abbott, 2009; Garrett et al., 2010). Population signal variability in hMT+ could have different effects on performance accuracy: higher overall variability levels in hMT+ could be detrimental for discrimination performance if they would have an destabilizing effect on the hMT+ population signal as some authors suggest for the dopamine system (Winterer et al., 2006; Samanez-Larkin et al., 2010). Alternatively, a certain level of variability has been described to improve the sensitivity of systems, e.g., by stabilizing synchronized oscillating populations (Ermentrout et al., 2008), an observation described as stochastic resonance (Emberson et al., 2007; McIntosh et al., 2008; McDonnell and Abbott, 2009; Garrett et al., 2010).

In the present study, we set out to characterize brain activity that correlates with inter-individual variability in the accuracy of visual motion perception. We used multivariate pattern classification (PC) to describe hMT+ population patterns and we characterized the variability of the hMT+ BOLD signal during perception of motion in different directions. We investigated if these measures can serve as sensitive indicators for inter-individual performance differences on a motion direction discrimination task.

MATERIALS AND METHODS

PARTICIPANTS

Fifteen healthy subjects gave written informed consent to participate in this study. The study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of the medical faculty of the Ludwig-Maximilians University Munich. Handedness was determined according to a 10-item excerpt of the "Handedness Inventory," coding the degree of handedness (+100: exclusively right handed, −100: exclusively left handed; Oldfield, 1971). It resulted in +100 in 13 subjects, one with +64 and one with +81. All subjects had normal or corrected-to-normal visual acuity as determined binocularly with a Snellen table (0.8 on 6 m or better). None of the subjects were taking medication or had any history of neurological disease. All subjects understood the instructions without difficulty. One subject was excluded from the MR analysis due to excessive motion resulting in a final cohort of 14 subjects (age range: 21–27, 6 female). These 14 subjects consecutively also took part in the psychophysical task on direction discrimination. Three subjects were excluded from psychophysical data analysis, as their measurements did not fulfill stability criteria as described below.

PSYCHOPHYSICS

Apparatus

Stimuli were generated by a Fujitsu Siemens Pentium(R) 4 CPU at a frame rate of 85 Hz and displayed on a 40-cm × 30-cm Conrac Elektron CRT monitor driven by a NVIDIA Quadro Pro2 graphics card. The monitor resolution was set to 1280 × 1024. White and black pixel had a luminance of 25.3 and 0.1 cd/m^2, respectively, resulting in a maximum Michelson contrast of 99%. Experiments were conducted in a darkened room and subjects were seated in 60 cm distance from the monitor.

Stimulus

Stimuli were programmed in Matlab 7.3 using the Psychophysics Toolbox extensions (Brainard, 1997). Coherent translational flow fields were presented in a circular aperture (11.4° × 11.4°), containing 300 white dots (diameter: 0.1°) at a time on a black background. All dots of one stimulus moved in a upward direction either vertically or at a small tilt from the vertical with a speed of 8°/s. Dots moving out of the aperture reappeared at new random positions (at the bottom of the aperture). Stimulus intensity was defined as the degree of tilt of the match stimulus (clockwise or anticlockwise) in respect to the upward (0°) reference stimulus.

Procedure

A two-alternative-forced-choice task was used to determine individual thresholds and psychometric functions of direction sensitivity. Reference stimulus and match stimulus were presented consecutively

(stimulus duration: 1.5 s, inter stimulus interval: 0.25 s, intertrial interval: 1.25 s). While fixating on the center of the aperture, subjects indicated with a buttonpress whether the second stimulus (match) was tilted clockwise or anticlockwise with respect to the first, upward moving reference stimulus (compare **Figure 1A**). After initial training with feedback (60 trials), preliminary thresholds were determined by two repetitions of a 3-down-1-up adaptive double-staircase method (140 trials). The staircase measure was defined as stable if the slope of the linear fit from the last 12 reversals was less than 0.02. All but one subject achieved stable staircase measurements (this subject belonged also to the outliers in the measurement of constant stimuli, defined as subjects whose threshold exceeded the fourth quartile, see 2.2.4). Consecutively, the method of constant stimuli was used to sample the psychometric function, the range of sampling was set around the threshold determined by the staircase measurements. Tilt was varied between seven different intensities and each intensity was presented in 30 trials, resulting in a total of 210 trials. Subjects answered following the second stimulus and both speed and accuracy of the response were emphasized. Response times were measured from the moment the second stimulus ended until the moment of response. No feedback was given in staircase or constant stimulus measurements.

Data analysis

Data was analyzed using psignifit toolbox (Wichmann and Hill, 2001a,b) in Matlab 7.3. Final thresholds were obtained by fitting the percentage of correct responses determined by the method of constant stimuli with a cumulative Weibull distribution using a maximum likelihood procedure. Free parameters were threshold, slope, and lapse rate, which was kept variable between 0 and 0.5 (Wichmann and Hill, 2001b). Thresholds were taken as the 0.5 cut-off from the fitted function, corresponding roughly to a performance level of 75% correct (see **Figure 1B**).

To ensure data reliability, those subjects whose thresholds exceeded the fourth quartile were excluded from further analysis (2 of 14). Subjects were furthermore excluded if the fit of their psychometric function did not meet goodness-of-fit criteria in the sensitivity analysis. Summary statistics yielded good fits between the psychometric function and the data for 11 of the 12 remaining subjects. Ninety-five percentage confidence intervals (CI) were calculated for the thresholds of each subject using the bootstrapping method (sampling with replacement, 1999 repetitions).

A one-way Kruskal–Wallis ANOVA tested for inter-individual differences in the behavioral thresholds, using the bootstrapped results.

Averaged reaction times (RT) were calculated as the arithmetic mean over the whole constant stimuli experiment. RT consistency was calculated as the SD over the experiment.

MAGNETIC RESONANCE IMAGING

Experimental stimulus and procedure

Visual stimuli were projected with a LCD projector on a screen placed behind participants in the MR-scanner, which they viewed through a mirror placed above them at 45°. Vizard 3.0 (Worlviz)[1], was used to produce coherent translational flow fields presented in a circular aperture (300 dots per display, aperture size 11.4° × 11.4°). Participants watched flow fields in one of four possible directions (0°, 90°, 180°, and 270°), shown in a randomized order, while fixating on a cross in the middle. Using a block design, 18 s task periods were interleaved with 10 s rest periods, during which subjects continued fixating. One block consisted of four trials, in which direction of motion was kept constant. Subjects performed a two-alternative forced-choice speed discrimination task, to keep their attention directly related to the movement of the stimulus while incidentally coding stimulus direction. In each trial, two consecutive

[1]http://www.worldviz.com/

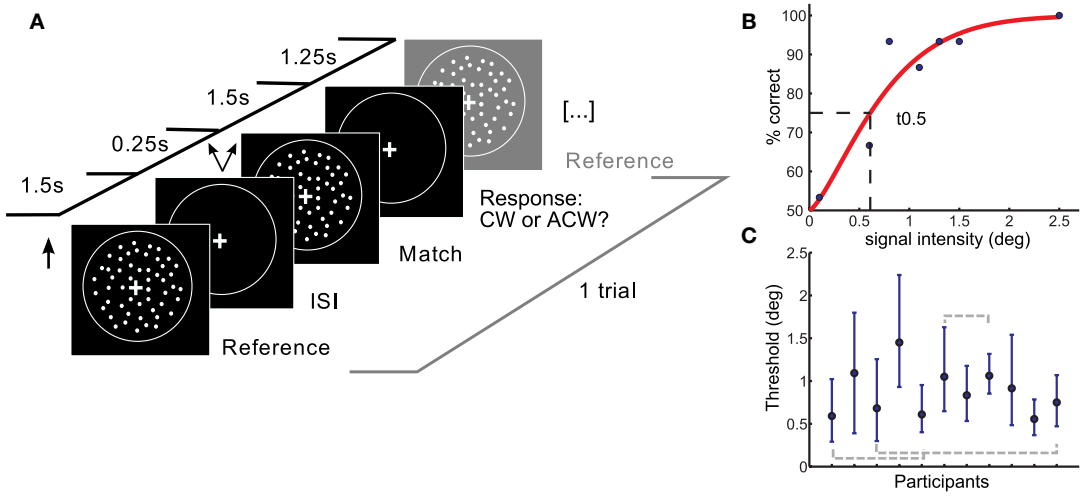

FIGURE 1 | Setup and results of the psychophysical experiment. (A) A coherent flow field of white dots was moving in an upward vertical direction followed by a match stimulus moving upward with a slight tilt clockwise or anticlockwise from vertical. Participants responded following the match stimulus. One trial is depicted. **(B)** Psychometric function of one representative subject. Percent correct responses are plotted as a function of the deviation (in degree) of the match stimulus from the reference stimulus. Thresholds were taken at the mid-point of the psychometric function (t0.5, shown by dotted lines). **(C)** Subjects yielded different thresholds. Shown are individual t0.5 thresholds with errorbars depicting the 95% confidence intervals. Subjects which were not found to be different in a *post hoc* test are shown with gray dotted lines. deg, degree tilt from vertical; ISI, interstimulus interval; CW, clockwise; ACW, anticlockwise.

stimuli were shown, a reference speed of 8°/s and a match stimulus of faster speed randomly distributed to the first or second presentation (stimulus duration: 1.5 s, interstimulus interval: 0.25 s, intertrial interval: 1.25 s, as for the psychophysical stimulus). Subjects reported the order-position of the faster stimulus with a buttonpress (see **Figure 2A**). For keeping task difficulty constant, individual speed discrimination thresholds were kept at a task performance of about 80% correct with an adaptive staircase procedure (QUEST, Watson and Pelli, 1983). Subjects performed 8 runs for a total of 32 repetitions per direction. Participants practiced the task outside the MR-scanner until they reached a satisfactory performance level (2 runs in which participants had to be error-free for 12 trials (fixed velocity difference) after which a staircase procedure started, on which subjects had to demonstrate a stable 80% correct threshold for at least 12 trials). They also practiced inside the bore of the MR-scanner, until they were comfortable conducting the task in a supine position.

A separate fMRI experiment was conducted to functionally localize hMT+ in each subject, according to previously established procedures (Morrone et al., 2000; Huk et al., 2002). Briefly, a stimulus of alternating moving and stationary dot patterns was presented in a circular aperture with interleaved rest periods. Moving dots (velocity: 17.1°/s) traveled toward and away from the fixation cross for 16 s, followed by a 16-s stationary dot field, and a 20-s blank screen. Subjects fixated at all times.

fMRI acquisition

Imaging data were acquired on a 3T MR-Scanner (GE Sigma HDx) with a standard 8 channel head coil using an echo-planar imaging sequence (TR: 2 s, echo time: 40 ms, flip angle: 70°) to acquire 25 slice volumes (interleaved acquisition, no gap), centered on the area of interest (medial temporal lobe). Voxel size was 1.75 mm × 1.75 mm × 2.4 mm. In total, 8 runs of 225 volumes for

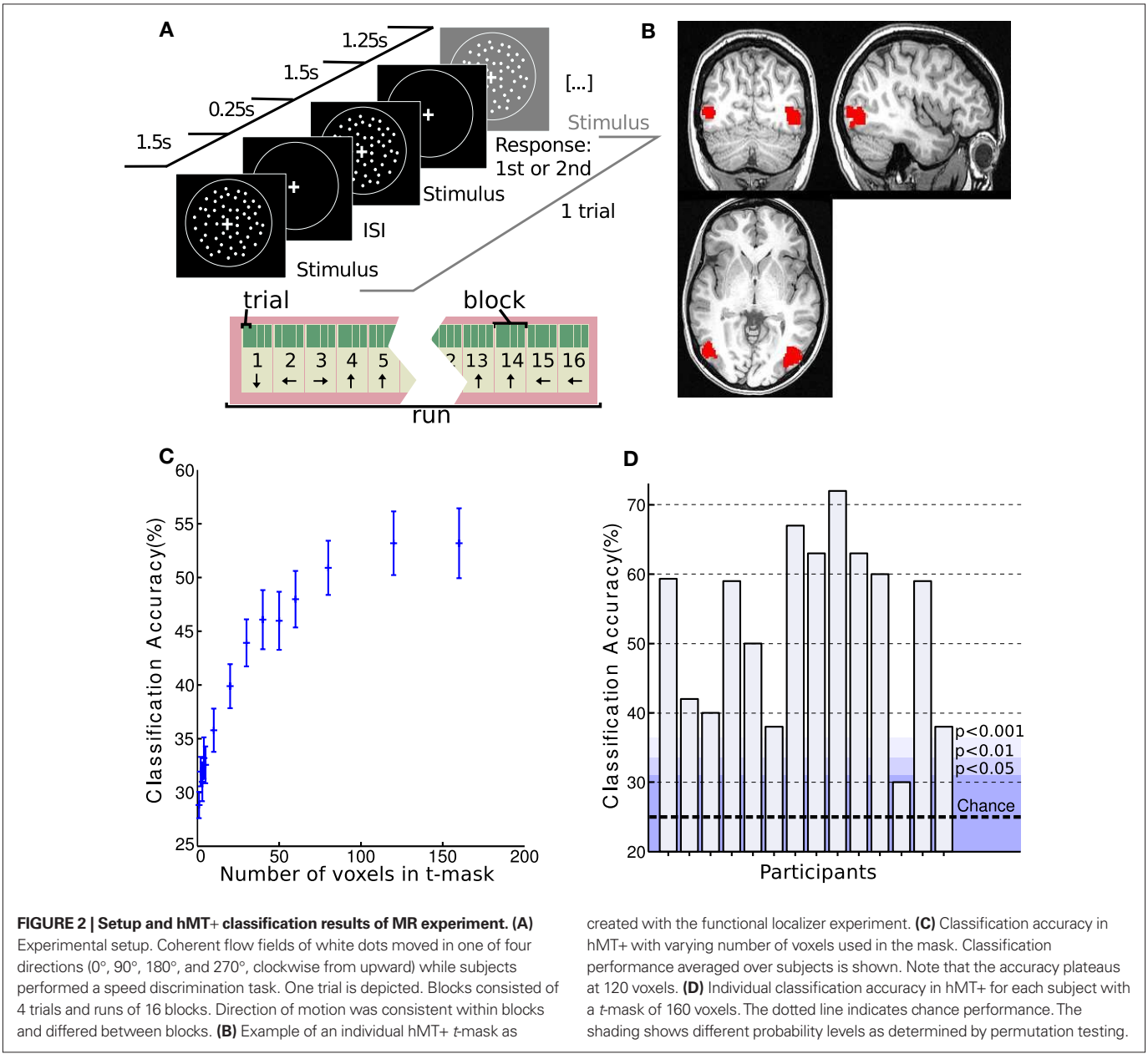

FIGURE 2 | Setup and hMT+ classification results of MR experiment. (A) Experimental setup. Coherent flow fields of white dots moved in one of four directions (0°, 90°, 180°, and 270°, clockwise from upward) while subjects performed a speed discrimination task. One trial is depicted. Blocks consisted of 4 trials and runs of 16 blocks. Direction of motion was consistent within blocks and differed between blocks. **(B)** Example of an individual hMT+ *t*-mask as created with the functional localizer experiment. **(C)** Classification accuracy in hMT+ with varying number of voxels used in the mask. Classification performance averaged over subjects is shown. Note that the accuracy plateaus at 120 voxels. **(D)** Individual classification accuracy in hMT+ for each subject with a *t*-mask of 160 voxels. The dotted line indicates chance performance. The shading shows different probability levels as determined by permutation testing.

the experimental condition and 1 run of 132 volumes for the functional hMT+ localizer were acquired in each subject. In addition, a T1-weighted anatomical volume was acquired.

Defining hMT+ and V1 masks

To define functional regions of interest, fMRI data from the functional localizer were realigned to the first volume of the timeseries and smoothed with a kernel of 4 mm FWHM as implemented in SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). Data were processed in individual space. A general linear model analysis comprising regressors for motion and stationary conditions was performed. Contrasting motion and stationary regressors identified clear delineated clusters for hMT+ (FWE, $p < 0.05$ in all but two subjects, who showed hMT+ clusters only at $p < 0.001$ uncorrected). See **Figure 2B** for an example. The clusters from the two hemispheres were combined to make a hMT+ mask of voxels for further analysis.

The V1 mask was created using anatomical and functional constraints. V1 was determined anatomically using FreeSurfer's cortical parcelation algorithms in every subject, based on anatomical constrains described by Hinds et al. (2008). The final mask consisted of voxels within this anatomically defined V1 which showed significant activation in the functional localizer, using the motion–stationary contrast.

Multivariate pattern classification and preprocessing

We used the Princeton Multi-Voxel Pattern Analysis Toolbox (MVPA)[2], to test whether voxels within hMT+ or V1 contained information about the direction of the stimulus. Data were prepared by unwarping, realigning (SPM8), and detrending (MVPA) the timeseries to remove linear trends and high-pass filtering (cut-off: 128 s) to remove low frequency noise. Z-scoring of response amplitudes for stimulus periods of individual voxels was applied to minimize baseline differences across runs and to reduce the impact of outliers. To account for the latency of the hemodynamic response, all stimulus onset times were shifted forward in time by 4 s as described previously (Kamitani and Tong, 2006). Data were neither smoothed nor spatially normalized, to avoid signal degradation and preserve inter-individual differences. The nine image volumes from each block of four trials were combined to generate a single average volume for each block.

The 160 voxels with the highest *t*-values in the functional localizer experiment were selected from the hMT+ or V1 masks respectively for decoding analysis. We tested different mask sizes, but found no improvement in classification accuracy beyond 160 voxels (see **Figure 2C**).

The lSVM (linear support vector machine) classifier was chosen as it provided stable results across participants without overfitting. It was used with a fixed cost, $c = 1$. Classification used standard leave-one-out cross-validation, in which the data set was divided, with seven runs in the training set and one run in the testing set. The test was repeated eight times, with each different run being the test set (Pereira et al., 2009). The accuracy scores reported represent the proportion of blocks in which the classifier correctly decoded directions.

[2]www.pni.princeton.edu/mvpa

Generating a stability index to quantify head motion

An index was designed to assess data stability for individual subjects. Head-movement causes image shifts between classifier training and test periods which are detrimental for MVPA. Specifically, a movement in the middle of the acquisition is more detrimental than a movement at its start or end because there will be more cross-validation iterations in which the training set contains volumes misaligned with the test set's volumes. Our stability index (SI) roughly represents the longest stable stretch of head orientation during data acquisition. For each volume, the location of the center of hMT+ is estimated from the realignment parameters generated during image preprocessing. Each volume is compared with all others. At each comparison (e.g., between volumes *i* and *j*), the distance, d_{ij} between the estimated locations of hMT+ is calculated and a number, A_{ij}, assigned describing how aligned the pair of volumes are. This alignment score is

$$A_{ij} = \frac{1}{1 + d_{ij}} \tag{1}$$

The similarity S_i of each volume with all the other volumes is summarized by summing over all of its alignment scores:

$$S_i = \sum_j A_{ij} \tag{2}$$

Finally, the whole recording session is given a SI, which is the score for the volume with the highest similarity score:

$$\mathrm{SI} = \max_i S_i \tag{3}$$

Figure 3A illustrates how the similarity value varies for different time points over a fictitious series of volumes. The example shows little head motion during the longest part of data acquisition and a single large head motion toward the end. Similarity values for volumes in the long stable period are higher than for those after the movement, because the volumes in the former are similar to many more timepoints than a volume taken after the movement.

Estimating BOLD signal statistics using a generative model

Variability of the timecourses of the 160 voxels from the above described hMT+ and V1 masks was assessed with a generative model for stimulus (SDstim) and rest periods (SDrest) (see **Figure 4B** for an illustration of the model). In addition, variability was estimated in a white matter region to quantify the contribution of non-physiological variability to noise, as those regions show little change in local metabolism (Rostrup et al., 2000). Spheres of 80 voxels in each hemisphere were selected from the anterior portion of the corona radiata (CR), as determined by the Harvard–Oxford structural atlas (see **Figure 3C** for an example).

Timecourses were high-pass filtered before model analysis. The temporal properties of the BOLD signal were described by modeling all eight events within a stimulus block as box-cars (1.25 s duration), which is similar to modeling them as delta functions as used in event-related designs. Box-cars were then convolved with the canonical hemodynamic response function (HRF), to account for the latency of the BOLD signal. A mixing parameter α_i was generated by this function and assigned to each volume *i*, describing the proportion of the signal recorded at that timepoint that was provided by the stimulus periods.

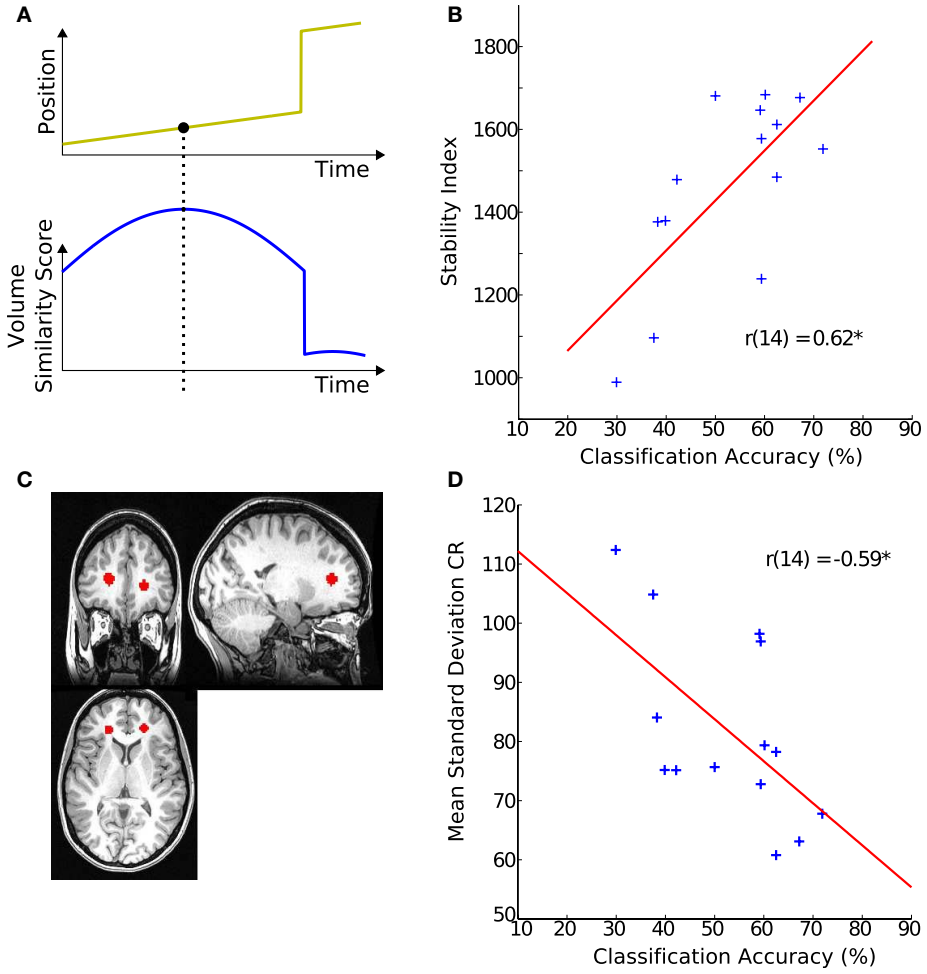

FIGURE 3 | Origins of classification variability. (A) Schematic of the stability index. The upper plot shows simulated movement of a participant across a scanning session. The lower plot indicates how similar each of the volumes is to all the other volumes in the scan. For example the last few volumes are very dissimilar to the rest of the scan. The value of the volume with the highest similarity score is used as this participant's overall stability index. **(B)** Stability index and hMT+ classification accuracy. The stability index was positively correlated with decoding accuracy. **(C)** Region of interest in white matter. The region is defined by placing two spheres of 80 voxels each in the anterior portion of the corona radiata (CR). **(D)** Signal variance in white matter and hMT+ classification accuracy. The individual SD during block-periods in CR was negatively correlated with the decoding accuracy in their hMT+.

For the generative model, both stimulus and rest periods were modeled as gaussian distributions (stimulus: mean μ_s, variance σ_s^2 rest: mean μ_r, variance σ_r^2). The proportion of each of these distributions included in the final signal was estimated using maximum likelihood estimation (MLE). The estimate of the signal for a particular time point was calculated by finding the weighted sum of the two distributions. The mean and variance of the sum of two independently distributed gaussian random variables was found by adding the means and variances of the two distributions. So the mean and variance of the new distribution for time point *i* could be written as:

$$\mu_{ci} = \alpha_i \mu_s + (1-\alpha_i)\mu_r \tag{4}$$

$$\sigma_{ci}^2 = \alpha_i^2 \sigma_s^2 + (1-\alpha_i)^2 \sigma_r^2 \tag{5}$$

this allows one to write the probability of value x_i as

$$p(x_i) = N(\mu_{ci}, \sigma_{ci}^2) \tag{6}$$

Assuming independent and identically distributed sampling, the likelihood of the whole timeseries is:

$$p(x) = \prod_i N(\mu_{ci}, \sigma_{ci}^2) \tag{7}$$

The log likelihood therefore is:

$$LL(x) = \sum_i log\, N(\mu_{ci}, \sigma_{ci}^2) \tag{8}$$

$$LL(x) = -\sum_i \tfrac{1}{2} log\, \sigma_{ci}^2 - \sum_i \frac{(x_i - \mu_{ci})^2}{2\sigma_{ci}^2} \tag{9}$$

The four parameters were estimated by maximizing this function with respect to each of them.

Finally, the arithmetic difference between the SD within stimulus periods (σ_s) and within rest periods (σ_r) was calculated for each participant (SDdiff).

Adaptation model. The above model is not the only conceivable description of the signal timecourse. An alternative model was tested to assess the stability of our results yielded with the first approach. In this alternative model, possible signal adaptation in hMT+ over a block was accounted for by introducing a exponential decay term with a time constant of 5 s. This reduced the (pre-HRF convolved) box-car signal exponentially while the stimulus was applied, and allowed it to recover using the same exponential function during the stimulus-off periods. A maximum reduction of 14% in the BOLD response due to the adaptation was assumed, based on electrophysiological studies (Petersen et al., 1985; Krekelberg et al., 2006). The model was tested at four values of the time constant: 5, 10, 20, and 40 s. All other parameters of the model were kept constant.

ASSESSING EYE MOVEMENTS FROM fMRI DATA

Although subjects were instructed to fixate, we were concerned that systematic eye movements occurred. It has been shown previously that eye movements can be estimated from fMRI data by analyzing the timecourse of fMRI signal in the vitreous of the eye (Beauchamp, 2003). We took this retrospective approach in those subjects in which the eyeball was partially contained in the field of view (FOV; in 3 of 11 participants the eyeballs were to 33, 40, and 46% contained in the FOV, see **Figure 5**). We defined a region of interest for the available section of the eyeball using FreeSurfer. The mean timecourse was extracted using marsbar in SPM8. To estimate the dependency between eyeball signal and the rest of the brain, we used the eyeball timecourse as regressor in a GLM, as has been described previously (see Muckli et al., 2009 supplementary material).

CORRELATION OF BEHAVIORAL DATA WITH MR MEASUREMENTS

A Pearson correlation was calculated between individual thresholds from the behavioral experiment (t0.5) and the individual noise difference between block and rest periods as determined by the generative model (SDdiff). Additionally, a Spearman correlation was performed which also showed a significant correlation. The robustness of the significant Pearson correlation was estimated using bootstrapping, sampling with replacement with 2000 iterations, to produce 95% CI for the r distributions.

RESULTS

INTER-INDIVIDUAL VARIABILITY IN DIRECTION DISCRIMINATION

On average, direction discrimination thresholds were found to be similar to previous results (Westheimer and Wehrhahn, 1994). We observed significant differences in discrimination thresholds between subjects (Kruskal–Wallis ANOVA, $p < 0.001$). *Post hoc* analysis also revealed similarities in subgroups of subjects, in three subject pairs (see **Figure 1C**: there was no significant difference between subject 1 and 4, between subject 3 and 11 and between subject 6 and 8). Note that data stem from 11 subjects, as three subjects did not reach reliability criteria explained in Materials and Methods. Slopes of the individual psychometric functions were heterogeneous as well and showed a negative correlation with threshold (the higher the slope, the lower the threshold). The width of subjects 95% CI also differed between subjects. Average RT and RT consistency varied between subjects (max: 460 ms, min: 176 ms, SD: 67 ms, and SD max: 149 ms, SD min 57 ms respectively). RT means or variability did not correlate with individual direction discrimination thresholds.

PATTERN CLASSIFICATION IS CONFOUNDED BY RESIDUAL HEAD MOTION AND CANNOT EXPLAIN PERCEPTUAL DIFFERENCES

Replicating previous results (Kamitani and Tong, 2006), the linear SVM was able to discriminate between the four motion directions in hMT+ with above chance accuracy ($\mu = 53 \pm 13\%$, $p < 0.002$ using permutation testing) in all but one participant (see **Figure 2D**). Also consistent with previous results, classification accuracy was still higher in V1 ($\mu = 65 \pm 12\%$, $p < 0.001$).

To test if individual classification scores in hMT+ or V1 were related to performance on the direction discrimination tasks, a correlation analysis between scores and psychophysical thresholds (t0.5) was performed which showed no significant effect (hMT+: $r = 0.15$, $p = 0.64$; V1: $r = 0.16$, $p = 0.64$).

To investigate possible reasons for inter-individual differences in classification scores, we looked at its correlation with non-physiological noise of the MR signal. Classification accuracy correlated significantly with variability (SDstim) in the white matter region CR ($r = -0.59$, $p < 0.03$, **Figure 3D**), from which we concluded that the level of global noise determined the differences in decoding success rather than local hMT+ noise.

To test this, we looked at one of the largest methodological contributors to variability in MR signal: head-movement (Friston et al., 1996; Lund et al., 2005). A strong correlation was observed between the SI reflecting stability of the signal and classification accuracy ($r = 0.62$, $p < 0.02$, **Figure 3B**).

This implies that noise induced by subject movement is the predominant cause for differential classification accuracies in subjects. Being this sensitive for head-movement artifacts, PC differences between subjects are unlikely to be a viable method to investigate physiological differences between subjects.

A GENERATIVE MODEL FOR ASSESSING BOLD SIGNAL VARIABILITY

We used the arithmetic difference between SD of block and rest periods (SDdiff) to look at variability of the MR signal in hMT+ and V1 in individual participants. Being a relative measure, it was assumed to be largely resistant to movement induced artifacts and background scanner noise, as those would influence both periods to the same extend.

Considerably more variability was found in the hMT+ region than in a white matter region (CR), both within stimulus blocks, and rest periods (SD was 30% higher in hMT+ and V1 than in CR). The SDdiff was also found to be larger in hMT+ and V1 than in CR (36%).

Importantly, subjects with a larger noise difference in hMT+ between rest and blocks did not have larger SI scores ($r = -0.4810$, $p = 0.0695$) which demonstrates that SDdiff is less affected by head motion.

VARIABILITY PATTERNS IN hMT+, BUT NOT V1, CORRELATE WITH DIRECTION SENSITIVITY

In the final analysis, we tested whether inter-individual variability of perceptual performance was correlated with variability characteristics of the hMT+ signal. As can be seen in **Figure 4A**, we observed a significant correlation between psychophysical threshold and SDdiff: participants with a greater SDdiff showed better behavioral performance (smaller thresholds) compared to participants with a smaller SDdiff ($r = -0.61$, $p < 0.046$, bootstrap CI 95% for r: −0.87 to −0.23). In other words, the larger the difference in variability (stimulus block minus rest), the lower the threshold the respective subject achieved. Similar correlation results were found for estimating SDdiff with an alternative model taking into account adaptation effects within blocks ($r = -0.59$, $p < 0.058$, bootstrap CI 95% for r: −0.84 to −0.20).

To investigate the specificity of this effect, we also correlated SDdiff in the CR with the psychophysical thresholds which was not significant ($r = -0.35$, $p = 0.29$, **Figure 4C**, lower panel). To test another region involved in direction coding, we correlated SDdiff of V1 with psychophysical thresholds. We did not observe a significant correlation in V1 neither ($r = -0.44$, $p = 0.181$, **Figure 4C**, lower panel).

When the MR-blocks were split into those with stimuli of different directions, the effect remained significant for vertical but not horizontal motion (see **Figure 4C**, upper panel). Given that the stimulus in the psychophysics experiment were visual flow fields moving vertically upward, this might indicate that we are observing a phenomenon specific for vertical motion. Alternatively, one could interpret this observation as showing a general bias for vertical versus horizontal motion in hMT+. Further studies are necessary to clarify this point.

EYE MOVEMENT ANALYSIS

The hMT+ is known to be influenced by eye movements (Dukelow et al., 2001; Acs and Greenlee, 2008). For this reason we instructed subjects to fixate, with which they reported no difficulties. We can not exclude however, that eye movements occurred. To investigate this, we used a retrospective approach to assess, if the signal timecourse of the eyeballs taken from the EPI images correlates with fluctuations in hMT+. In the three subjects analyzed, we did not observe significant correlations of eyeball signal timecourse with fluctuations in area hMT+ (see **Figure 5**).

DISCUSSION

We demonstrate in the current study that inter-individual differences in performance on a direction discrimination task of visual motion are correlated with signal variability characteristics of hMT+ but not V1. We furthermore show that PC, though being able to decode direction from hMT+ within subjects, is a poor tool to describe inter-individual differences. Assessing individual BOLD signal variability difference in stimulus and rest periods is shown to be a better measure for such comparisons, being less influenced by non-physiological noise.

Differences in psychophysical thresholds between subjects show that perceptual sensitivity for motion direction is variable even within a homogeneous sample. Worse or better perception of motion stimuli in subjects with normal visual acuity has been suggested to reflect changes in higher level visual cortical areas rather than in the peripheral apparatus (Halpern et al., 1999).

Relatively little is known about hMT+'s contribution to worsening of direction perception (Bennett et al., 2007; Billino et al., 2008), although concepts like the "magnocellular theory" behind learning disorders like dyslexia attribute a partial cause of the phenomenon to perceptual malfunctioning in the dorsal visual stream (Stein, 2001). Other authors already suggested that BOLD signal variability over the whole brain (Garrett et al., 2010) or in specific regions like the nucleus accumbens (Samanez-Larkin et al., 2010) might have predictive value for degradation of function during aging. Our method of characterizing signal variability in hMT+ could help the clinical understanding of degraded motion perception in aging or disorders like dyslexia.

Better performance in the psychophysical task suggests higher perceptual sensitivity in that particular participant and thereby most likely more effective processing in the brain. Our results show that variability characteristics in hMT+ but not V1 correlate with psychophysical thresholds. This might indicate that we observe individual differences not at the initial encoding of the visual information in V1, but rather during a more complex motion processing step in hMT+, an area thought to drive perceptual decisions in higher cortical areas.

We find lower thresholds correlating with larger variability differences between stimulus and rest periods which mean higher variability levels in stimulus periods (but see the below discussion on model bias as a limitation to this claim). How could increased random physiological signal be beneficial for the sensitivity of a system? An influential theory based on the phenomenon of stochastic resonance advertises "[...]randomness that makes a non-linearity less detrimental to a signal." (McDonnell and Abbott, 2009). The theory asserts that a certain level of noise can actually be beneficial for signal transmission. Studies have shown that a certain level of endogenous noise can make synchronized oscillating populations more stable (Ermentrout et al., 2008; Ghosh et al., 2008) and benefits the emergence of fast oscillations in local field potentials (Brunel and Wang, 2003). For us this means that detecting higher levels of endogenous variability in the hMT+ population signal might actually reflect a more robust signal.

Other fMRI and EEG studies have described lower levels of cortical noise in senior subjects (Garrett et al., 2010) and children (McIntosh et al., 2008) compared to young adults. This has been discussed as neurophysiological noise being inversely related to the well described U-shaped function of performance during the lifespan (MacDonald et al., 2006; McIntosh et al., 2008).

More specifically for our case of signal variability in the visual system, Bair et al. (2001), recording single-neurons in macaque MT, describe that those neuron pairs with high signal correlations also showed an increase in the correlation of noise. Clearly, given the coarse MR resolution, correlated noise would be more detectable at the fMRI level than uncorrelated noise. Our results suggest that greater variability differences between stimulus and rest periods might be beneficial for perceptual sensitivity in hMT+. The basis for signal variability could be caused by individual neurophysiological characteristics of hMT+.

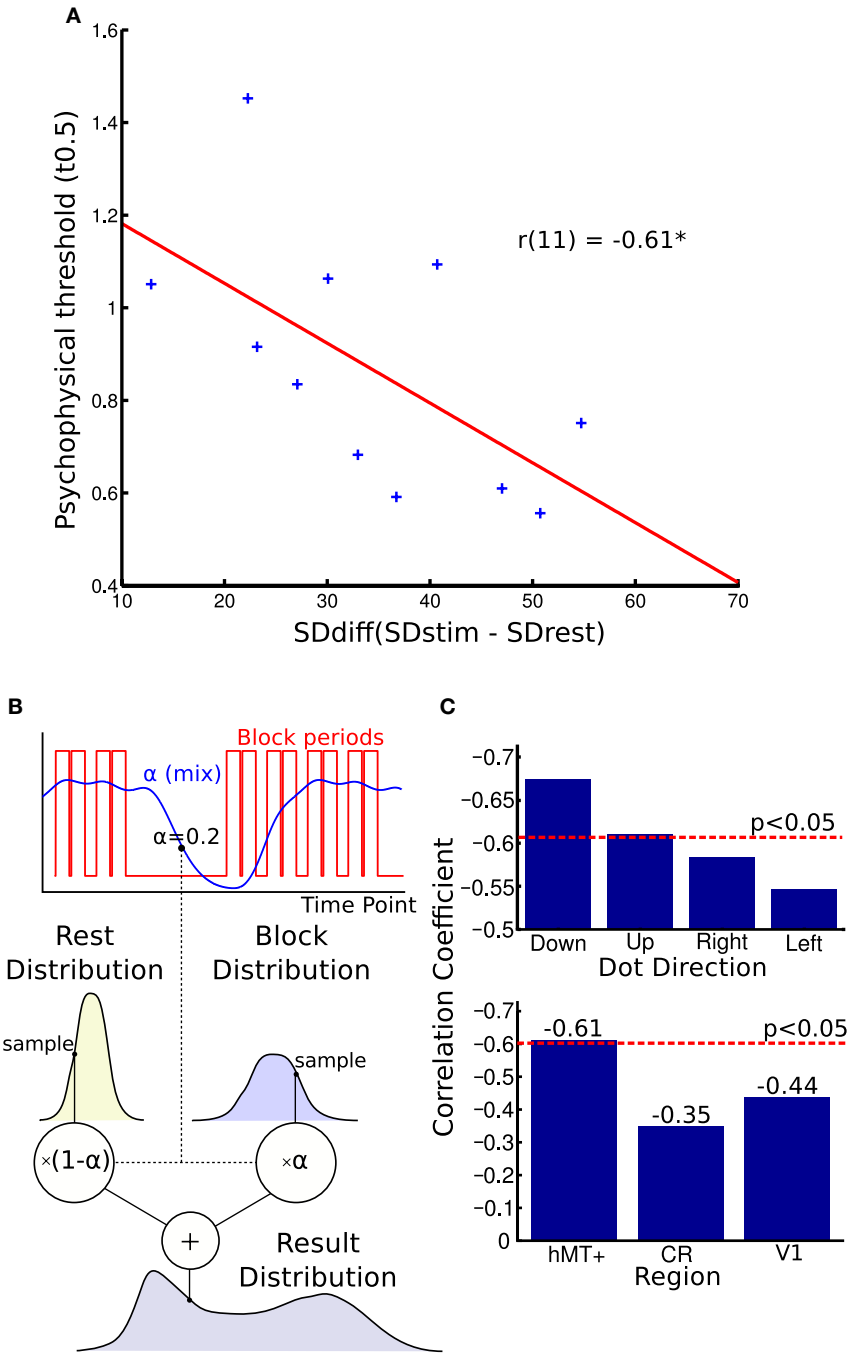

FIGURE 4 | Blood oxygen level dependent (BOLD) signal variability and behavioral performance. (A) Correlation of BOLD signal variance and direction discrimination threshold. The difference in individual SD between the blocks and rest periods correlated with single-subject thresholds from the psychophysics experiment. A larger variability difference is correlated with lower direction discrimination thresholds. **(B)** This figure illustrates the generative model used to estimate the parameters of the two distributions. The graph shows how the alpha "mix" values are calculated from the block times. Each volume's alpha value is used to estimate what proportion of the signal is from the stimulus and what proportion is from the rest period. These two distributions are sampled and their weighted sum is found. This is used to generate the distribution. The log likelihood of the real distribution being generated in this way is calculated. The parameters of the block and rest distributions are then altered to maximize this log likelihood. **(C)** Top graph: Comparing correlations for different stimulus directions. Splitting the block and rest periods in the four directions shown during the MR experiment, we observed small differences in correlation strength. Bottom graph: Comparing correlations over different brain regions. The correlation between noise difference and psychophysical threshold was smaller and not significant in the white matter region CR and V1. CR, corona radiata.

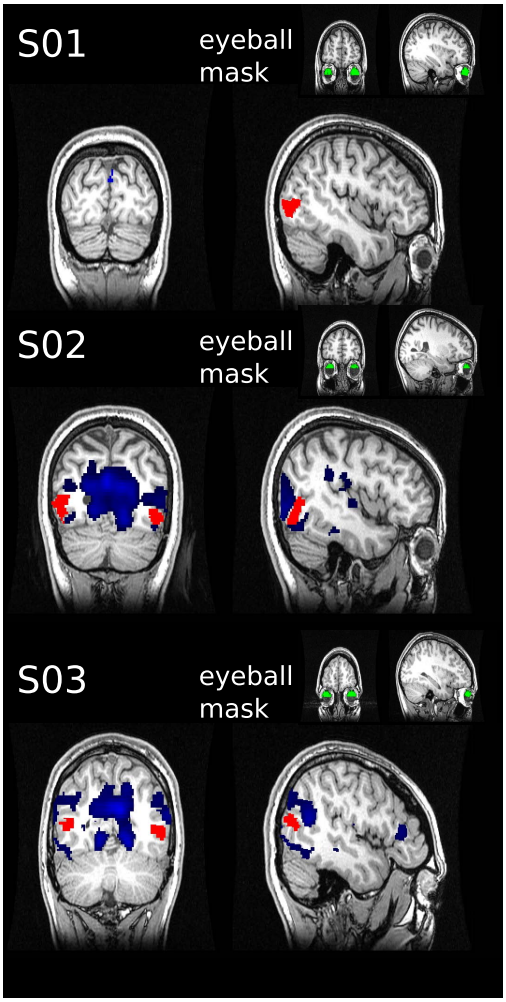

FIGURE 5 | Retrospective eye movement analysis. The mean timecourse was extracted from the eyeball ROIs (green) defined for three subjects. The timecourses were used as regressors in general linear models to assess correlated activity in the rest of the brain (blue). No overlap was found with the hMT+ masks (red).

A confound that must be considered before interpreting our variability signal is signal fluctuations in hMT+ caused by eye movements. Participants were instructed to fixate, but as we used translation stimuli, an automatic smooth pursuit must have been suppressed which individual subjects might have achieved with more or less success over the timecourse of stimulation. However, we did not find that the signal timecourse from the eyeball ROIs as measured in a subgroup of subjects correlated with hMT+ signal fluctuations. Participants furthermore did not report difficulties fixating. Although we cannot exclude an influence of eye movements on the hMT+ signal, we believe it is not the strongest component causing the observed inter-individual differences in fluctuation of the hMT+ signal.

Also non-perceptual phenomena like individual motivation or attentional levels could explain our results, influencing both physiological and perceptual measurements. It has been shown that hMT+ BOLD signal is modulated by attention (Berman and Colby, 2002; Liu et al., 2011; Stoppel et al., 2011), and those participants able to apply attention most accurately to the stimulus are not only likely to do well in the psychophysics direction discrimination task, but may also show the BOLD signal variability we observe. Top-down control by areas described for internally evoked attention processes like the intraparietal cortex and superior frontal cortex could play a role in inducing the individual hMT+ signal variability we observe (Corbetta and Shulman, 2002).

From the methodological point of view, we demonstrate that PC is a poor method to determine between subject differences. Although it could decode directional information from hMT+ activity in individual subjects, its ability to describe the relative difference between subjects was confounded by individual head-movement and scanner artifact differences. Filtering out movement artifacts has been a challenge in the field of MR, as it contributes the greatest amount of non-physiological noise (Friston et al., 1996; Lund et al., 2005). Although successful methods have been established for reducing the effect of head-movement in univariate analysis based on the general linear model (Friston et al., 1996; Andersson et al., 2001), the specific influence of residual artifacts on new methods like PC is less well documented. Beyond this methodological confound, other evidence exists that classification accuracy may not be an appropriate metric to compare experimental conditions, brain regions, or participants. Smith et al. (2011) for example suggest that classifier performance is influenced by other factors besides neural specificity such as response amplitude. Using MVPA for between subject comparison might therefore require further corrections to guarantee comparability.

Head-movement artifacts can also confound measures of signal variability. Garrett et al. (2010) show that the predictability of a noise measure was greatly improved by the extensive preprocessing of the data, beyond the conventional steps of realignment and normalization. Their methods included artifact correction via independent component analysis (Beckmann and Smith, 2004) and regressing out motion parameters. For future analysis of both PC and BOLD signal variability, this seems to be a fruitful approach. In the current study we used the relative value of noise differences between stimulus and rest periods, which minimizes the movement confound, as both periods should be equally affected by movement.

Critically, all assumptions on signal variability characteristics depend on the validity of our method to estimate the variability in the hMT+ signal. We used a generative model to estimate variability in the fMRI signal, modeling all eight events within a stimulus blocks separately as box-cars convolved with the HRF. The model furthermore accounted for the HRF-induced overlap of stimulus blocks and rest periods by assigning mixing values to each individual volume, based on the estimation of the relative contribution of stimulus and rest periods to the signal in that particular volume. Compared to other methods to assess variability in the BOLD signal, our method is quite complex. Garrett et al. (2010) for example directly calculated the SD over blocks. Considering that the physiological response in hMT+ to our stimulus periods probably consisted of a sustained elevation in BOLD signal, overlaid with single spikes evoked by the eight single events, simply calculating the SD would have not allowed us to separate the endogenous from the stimulus induced variability. The current model is

designed to account for the stimulus induced modulation of the BOLD signal, leaving us with the endogenous variability. Certain stimulus induced modulation of the BOLD signal might still not have been accounted for, such as repetition suppression which might occur due to repetitive stimulus display during a block. An alternative model taking this adaptation effect of the signal into account yielded similar results as our initial model. Extending our model to include an adaptation effect therefore seems to have little consequence for our measure of variability.

The model, in its current form, has also important limitations. By using non-uniformly distributed mixing parameters (e.g., the stimulation and rest periods), a bias is introduced as the maximum likelihood estimator assigns more of the variance in the data to the more frequent parameter (the stimulus period). Critically, though, this does not affect their use to compare subjects, as the bias will influence all subjects equally.

Another point to be considered is that the mixing parameter was calculated by convolving the stimulus events with the HRF, while the remaining signal was assumed to stem from the rest periods. Other ways to model the data are conceivable, e.g., convolving both rest and block-periods with the HRF. The ratio or sum of the two could then be used to model the data. Different modeling schemes remain to be explored systematically, to find which best estimates the contributions of the two distributions.

Taking the relative difference as a measure and not absolute variance, we are however confident that we observed physiological differences in hMT+ correlating with perceptional sensitivity. We conclude by suggesting that modeling variability difference between rest and stimulus cycles is a promising method to investigate physiological differences between subjects. We furthermore suggest that perceptual sensitivity in direction discrimination might be associated with noise characteristics in hMT+. This could ultimately help to understand normal and pathological changes in visual motion perception.

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3 General Discussion

While it is known that self-motion cues contribute to the formation of spatial representations, it remains an open question which neural circuitry underlies the extraction of spatial information from such cues. This thesis aimed to characterized neural networks of sensorimotor movement and motion representation as well as regions which interface between these networks and the neural spatial representation system.

3.1 Characterization of self-motion circuits

The interaction between self-motion processing and spatial representation circuits in the brain is poorly understood. Even in the field of rodent navigation research, where experimental manipulation is possible in the freely moving animal, the question where in the brain spatial information is extracted from self-motion cues remains open. While the neural network underlying spatial representations in this model animal begins to take shape, a recent review affirms: "The origin of the self-motion signals and the mechanisms for integration of self-motion signals with extrinsic sensory inputs have not been determined." (Moser et al., 2008).

Brain research on moving humans (or primates in general) faces technical limitations, which is why the connection between moving through space and the neural spatial representation system can only be investigated using detours. One approach to study underlying circuits are virtual reality environments, where subjects navigate with buttonpresses or joysticks. Numerous studies have used this technique to study neural systems processing visual navigation (Cornwell et al., 2008; Doeller et al., 2010; Ekstrom et al., 2005; Hartley et al., 2003; Spiers and Maguire, 2007). Some studies also work with environments without geometric features, to concentrate on the self-motion component of visual information. In such setups, spatial computations are based solely on the integration of optic flow (Wolbers et al., 2007, 2008). Still, these approaches rely entirely on the visual sense. The neural networks found by such studies might therefore capture only a specific visual navigation network. Important internal self-motion cues however arrive from proprioceptive, vestibular and motor systems.

Brain research in rodents and primates has revealed that signals from moving and being moved evoke differential response on a neural level - a necessary prerequisite for successful sensorimotor action (Cullen, 2004). Nonetheless, on a behavioral level humans can accurately extract spatial information from both active movement and passive transport, as shown by studies on path integration and spatial updating (Israël et al., 1997; Frissen et al., 2011). Some authors interpret this similarity as a sign for common physiological processes (Israël et al., 1997). Other studies however show that passive and active movement as a source for spatial processing are not completely functionally equivalent: closer analysis of path integration data under both conditions reveals differences in error profiles (Mittelstaedt and Mittelstaedt, 2001). And animal studies found greater accuracy of spatial estimations during active movement (Etienne et al., 1988), which is reflected on the physiological level in sharper place cell tuning curves during active compared to passive movement (Terrazas et al., 2005). While the latter results do not exclude partial common physiological processes, they however point to an influence of the movement experience on the spatial computation. Wutte et al. (2011a) provide insight into the underlying physiology by characterizing brain networks during recall of walking and passive transport. The results show that retrieval networks of active walking and passive transport are different in large parts, with the active experience being reflected in primary sensorimotor areas, while the passive transport experience recruits a network of higher-level association areas. However an overlap between both networks in the posterior medial temporal lobe (MTL) was observed, which could accommodate the "common physiological processes" Israël et al. (1997) might have thought of.

The results of Wutte et al. (2011a) also indicate an influence of the movement experience on the activation size in the posterior MTL. This might point to a modulation of this region by the rest of the network, contributing more or less reliable information on self-motion. Passive self-motion stimulates significantly less sensory inputs, and indeed, to the current date it is not resolved how linear self-displacement during passive transport is computed at all. Does it rely on the remaining sensory information from the vestibular system, or is it rather a internal simulation based on experience? Experiments addressing this issue gained mixed results: some suggest vestibular processing to be important (Berthoz et al., 1995; Israël et al., 1997), others show that vestibular signals are only sufficient when speed can be inferred from vibrations of the transporting device (Seidman, 2008; Yong et al., 2007), and again others conclude, that cognitive processes based on time estimation and prior knowledge are crucial for accurate self-motion perception (Wertheim et al., 2001).

The results of Wutte et al. (2011a) add to these findings that passive transport is recalled recruiting a network of higher-level association areas, and does not activate cortical or subcortical areas implicated in primary vestibular or somatosensory processing. That no activity in such sensory areas was found supports the view that vestibular processing contributes a minor aspect to the passive transport experience. The activation of higher association areas makes the explanation of an internal simulation of the body moving through space based on prior experiences more likely.

In future studies, the reasons for activations in the higher-association areas during recollection of passive transport could be further explored. Do they represent a general network underlying simulations of whole-body movement through space, in the absence of motor information? How would the network change if a spatial task was added? Does the network overlap with areas which are recruited in time estimation tasks? The comparison of recall of passive transport with different cognitive tasks on mental exploration and time estimation might be a fruitful approach for future studies to understand in detail, what is actually processed by this network.

3.2 Extracting spatial information from movement: the role of category-specific regions

To understand where the self-motion circuits and the neural spatial representation system interface, the activation of self-motion circuits have to be investigated during a spatial task. Insight on this subject can be provided by describing the overlap between the study of Wutte et al. (2011a) on whole-body motion and the study of Wolbers et al. (2011a) on haptic exploration of spatial layout. Both of these studies involved self-motion experience, whether executed hand movement (Wolbers et al., 2011a) or recollected whole-body movement (Wutte et al., 2011a). In addition, the study on haptic exploration involved a spatial task: spatial layout had to be inferred from motor, proprioceptive and tactile cues during haptic exploration.

In both studies, the posterior MTL was activated. Importantly, (Wolbers et al., 2011a) showed that haptic exploration of spatial layouts activated the posterior MTL stronger than exploration of objects. Taking these results together, two points can be learned about this region: Firstly, it does not seem to process spatial content exclusively, as the study on whole-body self-motion recollection did not involve a spatial task. One interpretation of the activation of this region during retrieval of whole-body motion is that is specifically processes self-motion. Secondly, the posterior MTL does not process movement information independent of its content, but rather is modulated by the type of information this movement conveys. The results indicate that this region is particularly sensitive to spatial information, independent of the encoding modality.

The posterior MTL is presumably not activated in isolation but as part of a greater network. It might therefore shed more light on its role in self-motion and spatial processing if the co-activated brain areas are considered. The first observation is that during both recollection of walking and haptic exploration, the posterior MTL is activated together with a motor network. The co-activation of this region with motor-circuits has been found by many studies in humans and animals. Based on this evidence, a school of thought asserting its role in motor control and sensorimotor integration has developed the "sensorimotor model for the hippocampal formation theta subsystems" (Bland and Oddie, 2001; Vanderwolf, 2001). Early on, motor behavior and theta rhythm in the hippocampus have been shown to correlate (Vanderwolf, 1969). Different types of motor behavior have meanwhile been found to follow this pattern, predominantly whole-body movements (running, walking, swimming etc), but to a lesser extend also limb movements (e.g. during food ma-

nipulation) (for an overview see (Vanderwolf, 2001)). Further evidence stems from studies on hippocampal stimulation and lesion which have an impact on motor function. And anatomically, descending pathways from the hippocampus to several nuclei of the basal ganglia represent a realistic interface for hippocampal-motor interaction (for an overview see Vanderwolf (2001)).

However, outside this specific school of thought it is generally agreed upon that the function of the hippocampal formation goes beyond mere motor control. Activations in this region are found also without any activations in motor systems, and today the most influential theories implicate this structure in memory and space processing. The second observation of co-activation which can be drawn from the results of Wolbers et al. (2011b) and Wutte et al. (2011a) is more in accordance with theories on the spatial function of the posterior MTL: in both mental simulation of passive transport and haptic exploration of spatial layouts, areas of the retrosplenial complex and the posterior parietal cortex were

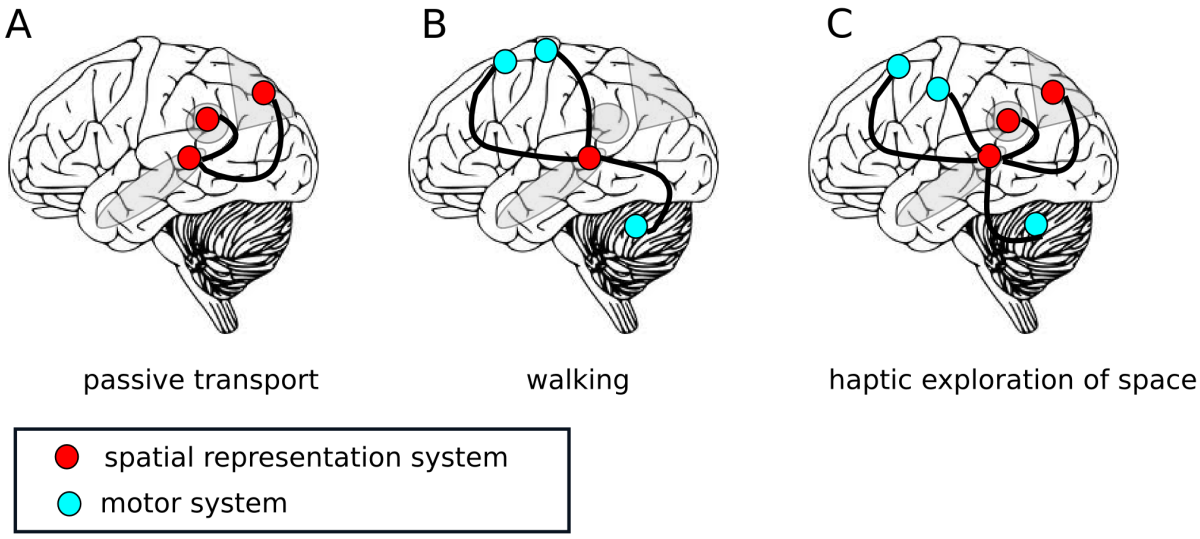

Figure 3.1: Piecing together the neural spatial representation system. Activation in the posterior MTL was observed in three conditions: A) recollection of passive transport, B) recollection of walking and C) haptic exploration of spatial layout. The three findings might draw a complementary picture of the interaction of the motor circuits and the neural spatial representation system, outlined in the following suggestion: during passive transport, movement was simulated by posterior parietal cortex, retrosplenial complex and posterior MTL; the simulation of walking relied on motor-circuits (SMA, M1, cerebellum) together with the posterior MTL; and during real exploration in a spatial task, both motor circuits and the retrosplenial-parietal network were active together with the posterior MTL. The posterior MTL might therefore serve as a hub, mediating between motor-circuits and parietal lobe.

co-activated with the posterior MTL. Those regions are frequently found to be involved in spatial tasks (Epstein et al., 2008; Sack et al., 2008) and occupy a crucial role in neural models of spatial representation (Byrne et al., 2007; Whitlock et al., 2008). The three conditions in which posterior MTL activity was observed therefore seem to tell a complementary story: During simulated walking, posterior MTL activation was found together with a locomotor network, but no parietal or retrosplenial activations were observed. During simulated passive transport, mostly parietal and retrosplenial regions were activated, which might reflect the necessity to simulate the own body moving through space. And finally, in haptic exploration, a motor network was activated *together* with parietal and retrosplenial areas (for a schematic overview see Figure 3.1).

These results suggest that the posterior MTL processes movement information, but is particularly sensitive to the spatial content of this movement information. Taken together with its role in visuo-spatial layout processing (Epstein et al., 2008), this area seems to function as mediator between the neural systems receiving spatial information, whether motor circuits or the visual system, and the system storing and processing abstract spatial information (retrosplenial and parietal areas). It appears to gather information concerning a specific conceptual domain from any modality conveying such information. Other such 'category-specific' regions in the human brain are known, such as the fusiform face area (FFA) (Kanwisher et al., 1997), the lateral occipital complex (LOC) for object-shape (Malach et al., 1995), or the motion-sensitive hMT+. Similar to PPA in the posterior MTL, most of these regions were initially described as 'higher-visual areas', because they were first discovered using visual stimuli. But in particular studies in blind participants discovered that these regions are not primarily visual, but rather category specific, and develop independent of visual information: the FFA for example has been shown to be activated by tactile perception of faces (Goyal et al., 2006), the LOC was found to process object information learned by haptic exploration (Mahon et al., 2009) and the hMT+ has been shown to respond to tactile and auditory motion information (Poirier et al., 2006; Ricciardi et al., 2007; Wolbers et al., 2011b). Another important notion can be drawn from these findings: while traditionally, multimodal processing is thought to happen in late processing stages taking place in the parietal cortex, evidence accumulates that multimodality already starts in category-specific regions along the temporal lobe. It remains to be explored, if the multimodality in these regions does merely consist of parallel processing, with integration happening only in the parietal cortex, or if a merging of different sensory information already happens on this stage.

3.3 Category-specific regions reflect perceptual differences

The category-specific region hMT+ is specialized for motion, and results on its involvement in visual path integration suggest that its computations contribute to the construction of neural spatial representations (Wolbers et al., 2007). Individual differences in spatial performance show quite plainly that psychological space is a construct, passing through many computation steps before its neural representation can be used to organize behavior. On every processing stage errors can occur, which the organism can compensate under natural conditions by continuously updating its inner representation with information from the external world. Errors also accumulate in the circuits processing motion. Wutte et al. (2011b) addressed, on which stage of visual motion processing individual performance levels would be reflected in the brain activation pattern. To address this question the stage of primary visual encoding in V1 and the stage of more complex processing in hMT+ were compared.

Results from psychophysical experiments show that performance on visual motion tasks differs between individuals: Halpern et al. (1999) report that 20 participants differed significantly on direction of motion detection and velocity discrimination tasks. Importantly, their test of direction of motion detection was similar to our task and revealed performance which varied about 100% between participants. The general assumption is that these differences stem from central neural processing, but which brain structures specifically are responsible for such differences remains an open question. Wutte et al. (2011b) found that signal variability characteristics on the stage of hMT+ but not V1 reflected individual performance scores on a direction discrimination task. This result suggests that the crucial difference between subjects, leading to different performance, was not the primary encoding of visual information, but concerned the step of motion-extraction from this information. hMT+ is meanwhile seen as an area which is not primarily sensory, but rather constructs the motion percept from available sensory information, and is involved in perceptual decision (Goebel et al., 1998; Muckli et al., 2002). The results of Wutte et al. (2011b) show that the amount of neural signal variability is negatively correlated with perceptual thresholds, which suggests that low levels of signal variability in hMT+ reflect less efficient processing. Less efficient processing in hMT+ might have several reasons: on the one hand, the neuronal properties of the individual hMT+ could entail these differences. Aging studies in macaque for example show a relation between widening of tuning

curves of direction selective neurons and perceptual performance on a direction discrimination task (Liang et al., 2010). On the other hand, hMT+ has been shown to be strongly modulated by attention (Corbetta and Shulman, 2002): top-down signals could modulate either its capability to 'read out' primary visual information, its internal computations to construct a percept or its capability to transfer its 'decision' to the motor circuits. Connectivity studies between hMT+, V1 and primary motor cortices comparing participants with different motion direction-discrimination thresholds could help to further understand the causal relation between hMT+ properties and behavioral outcome.

3.4 Physiological conclusion

In summary, the results of this thesis show that spatial computations based on experiences like active and passive whole-body movement can rely on computations in quite different neural networks. During recollection of these experiences, active movement reflected the sensorimotor experience, while passive movement recruited higher association areas which might show that prior experience was taken into account. The posterior MTL was commonly involved, and showed furthermore to play a key role in extracting spatial layout from haptic exploration and visual input. Spatial representations are built from many input modalities, as the single systems would not be sufficiently reliable to determine a percept from them. Every neural system accumulates errors, and the degree to which this happens varies from person to person, as the results for direction of motion coding in hMT+ indicate. To compensate for this the human brain uses many sources to construct a reliable representation of space. A physiological point of convergence, where multiple types of information - from sensory and motor systems but also from simulations based on prior experience - come together, appears to be the posterior MTL.

3.5 Novelties in paradigm and analysis

Study design and analytical tools were two important foci during this thesis. In the studies of this thesis novelties in paradigm and analysis were introduced, of which three will be discussed in detail: 1) the usefulness of blindfolded training in the study of simulated movement, 2) the confounds which render the measure of classification accuracy unreliable for comparison between participants, and 3) variability analysis of the BOLD signal as a useful novel way to look at physiological characteristics with fMRI.

3.5.1 Using blindfolded training to prepare for body imagery

Research groups use different designs to study mental simulation of movement in the MR scanner, spanning from imagery supported by video display, optic flow, training the movement beforehand to mere instructions (see Box 1 for an overview). All of those paradigms involve a visual component, either movies are shown, or the imagery/memory is based on experience involving vision. As an example, one popular paradigm used by several locomotion studies is based on shortly before experienced locomotion which participants subsequently recall in the MR scanner (Jahn et al., 2004, 2008; la Fougère et al., 2010; Wagner et al., 2008). The training is usually conducted with the instruction to concentrate on the body-perception during the movement, however, the experience also includes visual informations as participants have their eyes open during training. The following imagery in the MR scanner therefore includes a visual memory component. The paradigm used by Wutte et al. (2011a) however excluded this visual component and focused the experience exclusively on the perception of sensorimotor information, by blindfolding subjects before leading them to the training environment. The first version of this paradigm was used by Flanagin et al. (2009). In this study, subjects were lead to the training environment and were blindfolded immediately before the actual training. However, this might still have given participants an impression of the spatial layout of the environment in which they were trained, which rendered a visual simulation of the trained experience possible. To improve this first version of the paradigm, the following study by Wutte et al. (2011a) used a slightly different approach: participants were lead already blindfolded to the training environment (a journey which took 5-10 minutes), and therefore had a longer period to get used to the blindfolded state and to concentrate on their body. Furthermore they did not get an impression of the spatial layout in which they were experiencing self-motion.

Using this paradigm resulted in slightly different results compared to previous studies:

comparing the results of Wutte et al. (2011a) to the results of Jahn et al. (2004, 2008) and Wagner et al. (2008), additional activation in the precentral gyrus was observed, where the primary motor cortex lies. The primary motor cortex was also found in neuroimaging studies on real locomotion (la Fougère et al., 2010; Fukuyama et al., 1997). Further, the results of Wutte et al. (2011a) showed no activation in the precuneus, angular gyrus and mid-occipital cortex, which have been implicated in visual and visuo-spatial imagery (Astafiev et al., 2004; Cavanna and Trimble, 2006).

The exclusion of visual experience might therefore have led to more focus on the body-related sensorimotor experiences, and more towards a simulation of this body experience rather than a recall of the visual aspects of the task. It has been suggested before that focusing attention on the proprioceptive-motor part rather than the visuo-spatial part of experience might increase the involvement of motor areas and decrease the involvement of visuo-spatial areas: Sacco et al. (2006) examined the impact of extended training of complex movements (learning tango steps) and the respective motor imagery on mental simulation of gait. They found increase of activity in motor areas and a decrease of activity in visual and parietal areas after training. They interpreted their findings as representing an increased focus on body-experience mediated by the extensive training.

Some visual imagery might however have occured in the study by Wutte et al. (2011a), as activations in primary visual areas (calcarine sulcus, cuneus) were observed. A unexpected result was that no activation was observed in the insula, which is implicated in somatosensory and vestibular processing. This is in contrast to previous studies of simulated and real walking which report activation at the transition of anterior insula to inferior to frontal gyrus (Jahn et al., 2004, 2008; la Fougère et al., 2010). However, a meta-analysis on fMRI studies from various fields shows that the anterior insula is one of the areas found by most imaging studies which casts doubts on the specificity of such activation (Yarkoni et al., 2011). Nonetheless the further differences in paradigm and analysis between Wutte et al. (2011a) and the studies of Jahn et al. (2004, 2008), la Fougère et al. (2010) and Wagner et al. (2008) should be noted when comparing the results. Different to the before mentioned studies was for example the factorial GLM used for analysis and the different baseline condition (imagery of stance was used while previous studies used imagery of lying). A systematic comparison of mental simulation based on visual training and blindfolded training in the same subjects could be the next step to elucidate the differing results found further.

BOX 1: Paradigms of Whole-Body Movement in Neuroimaging

Different paradigms have been used to examine neural correlates of whole-body movements with mental imagery:

1) Instructions

Szameitat et al. (2007) instructed participants to imagine whole-body movements like swimming, running, dancing or digging a hole. Participants were given the instructions to imagine these movements while concentrating on the kinesthetic aspect of the movement. They were further instructed to imagine the movement with intense engagement and at a high frequency. To ensure comparability, participants filled in questionnaires on vividness and familiarity of the tasks. Imagery took place with eyes closed.

2) Prior visual training

One study on imagery of gait prepared participants by showing them videos before the scanning session (Malouin et al., 2003). The videos showed movement from a first-person perspective along a corridor. Participants were instructed to engage in gait imagery while watching the video. Questionnaires on motor imagery vividness and chronometry during imagery were also applied. Imagery took place with eyes closed.

3) Movement training shortly before

Subjects were made familiar with the movement to be imagined in the scanner by actually executing it before the scanning session. This paradigm has been used for walking along straight (Jahn et al., 2004) or curved paths (Wagner et al., 2008) and running (Jahn et al., 2008). A slightly different approach was taken by a study investigating the difference between normal and precision gait (Bakker et al., 2008). In this latter study, additional to prior training, participants were reminded of the training environment with photographs between imagery sessions. Imagery took place with eyes closed.

4) Movement training over an extended period

Sacco et al. (2006) were interested whether motor and imagery training of a complex movement, which needs close focus on the own body (Tango steps), influences networks during motor imagery of gait. To this end, two groups were compared, one training and one control group. All participants were scanned two times while mentally simulating walking, with a delay of a week. In the interim, the training group underwent five 1 hour Tango lessons and mental training of the learned steps. The control group received no training. Imagery took place with eyes closed.

5) Videos during mental simulation

Some researchers showed participants a video recorded by a cameraman moving through a outdoor or indoor scenes from a first-person perspective during scanning (Iseki et al., 2008; Wang et al., 2008). While watching the video, participants mentally simulate walking. In those studies, imagery took obviously place with eyes open.

3.5.2 Pattern classification to investigate inter-individual differences

To analyze patterns of brain activity with the use of machine learning algorithms is a novel approach in functional neuroimaging. Therefore its use for different scientific questions is still in the trial-and-error phase. While its metric of classification accuracy is still mostly used to answer true/false questions (e.g. if a particular region in a particular subject contains information about a stimulus feature or not), more and more studies use it also as absolute measure to compare subject groups, or brain regions (e.g. to answer the question if region A contains more information than region B). A recent study for example compared a group of healthy participants with a group of schizophrenic patients. They interpreted a difference in the pattern classification score as a group differences which the traditional GLM approach was not able to detect (Yoon et al., 2008). Especially for resolving subvoxel differences, pattern classification seems to be the method of choice: studies on direction discrimination in hMT+ could decode seen direction of motion from physiological activity in hMT+ (Kamitani and Tong, 2005, 2006). These two approaches were combined by Wutte et al. (2011b) to investigate physiological differences in direction coding between subjects in hMT+, which was hypothesized to be reflected in differences in classification accuracy. As studies in monkeys suggest (Liang et al., 2010), sharpness of neuronal tuning curves in hMT+ could be reflected in individual perceptual thresholds. In a fMRI study, such differences in neuronal tuning curves between subjects might be reflected in the bias a specific voxel has towards a direction, and this could be quantified with the measure of pattern classification accuracy. But although the results demonstrated differences in classification accuracy, this was due to the fact that the method was highly sensitive to noise introduced by head-movements. This sensitivity to head-movement makes this method a poor tool for the detection of fine differences in receptive fields of direction-sensitive neurons. In fact, as this novel way of analyzing fMRI data is increasingly used, more and more evidence accumulates to treat the metric of classification accuracy with caution: Smith et al. (2011) for example report that classification accuracy changes linearly with the amplitude of response. So while this technique can sometimes reveal physiological signals to contain information where the GLM approach fails, better ways of correcting for head-movement induced noise and individual differences in response amplitude have to be found, to use this technique to compare between brain regions, individuals or groups.

3.5.3 Variability of the BOLD signal

The study of Wutte et al. (2011b) applied analysis of BOLD signal variability, which is a novel analytical tool for fMRI datasets. Traditionally, analytical tools for fMRI data localize brain areas, in which the BOLD signal correlates with a stimulus timecourse. Also the shape of the BOLD signal as well as its amplitude have often been of interest. Recently, more and more studies have started to investigate the variability of the BOLD signal or electroencephalographic (EEG) signals, as an indicator for age-related (Garrett et al., 2010, 2011; McIntosh et al., 2008; Samanez-Larkin et al., 2010), disease-related (Winterer et al., 2006) or inter-individual differences (Emberson et al., 2007) in neurophysiology. Surprisingly, it has been shown that the well-described U-relationship between age and behavioral variability (children and seniors are more variable in behavioral tasks than young adults) (MacDonald et al., 2006), is inversely related to the variability of their neurophysiology: seniors as well as children show less noise of EEG and BOLD signals than young adults (Garrett et al., 2010, 2011; McIntosh et al., 2008). Some authors conclude on the basis of such findings that high variability levels found in EEG and BOLD signal measurements are not necessarily a sign for ineffective processing but might indicate a greater cognitive capacity of the brain (Emberson et al., 2007; McIntosh et al., 2008). Before this topic reached the domain of neuroimaging, the possible benefit of variability (or 'noise') in the brain has been discussed extensively in cellular and systemic electrophysiology. Faisal et al. (2008) describe in their review on noise in the nervous system the possible benefits of noise for information processing: in sensory systems, neurons have been found with properties of 'stochastic resonance' for signal transduction processes. The term 'stochastic resonance' describes a phenomenon, by which thresholded systems get more sensitive to a signal when a certain level of noise is present. Crayfish mechanoreceptors for example have the highest sensitivity when an intermediate level of noise is present (Douglass et al., 1993). The same has been described for visual neurons in the cat (Longtin et al., 1991) and human muscle spindles (Cordo et al., 1996). At the same time, it has been shown that the spiking of neurons can be influenced by noise: when a signal is too weak to cross the threshold to induce firing, noise can render it more likely to still cross the threshold. Noise can also improve neural network behavior, and neural networks which develop under noisy conditions appear to be more robust (Faisal et al., 2008).

Studying signal variability in fMRI datasets is a relatively recent approach which was used by Wutte et al. (2011b) to relate neurophysiological characteristics to a behavioral measure. Some methodological improvements are still necessary to fully exploit the poten-

tial of this approach, such as better head-movement correction. With such improvements, measuring noise characteristics in specific brain areas will develop into a valuable tool, not only for studies exploring inter-individual differences on a behavioral and neurophysiological level.

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List of Publications

- Mockett, B.G., Guvremont, D., **Wutte, M.**, Hulme, S.R., Williams, J.M., Abraham, W.C., 2011. Calcium/calmodulin-dependent protein kinase II mediates group I metabotropic glutamate receptor-dependent protein synthesis and long-term depression in rat hippocampus. *Journal of Neuroscience* 31,7380-7391.

- Flanagin, V.L.,**Wutte, M.**, Glasauer, S., Jahn, K., 2009. Driving dreams: cortical activations during imagined passive and active whole body movement. *Annual New York Academy of Science* 1164, 372-375.

- Wolbers, T., Klatzky, R.L., Loomis, J.M., **Wutte, M.G.**, Giudice, N.A., 2011. Modality-independent coding of spatial layout in the human brain. *Current Biology* 21, 984-989.

- **Wutte, M.G.**, Smith, M.T., Flanagin, V.L., Wolbers, T., 2011. Physiological Signal Variability in hMT+ Reflects Performance on a Direction Discrimination Task. *Frontiers in Psychology* 2, 185

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Eidesstattliche Versicherung

Ich versichere hiermit eidesstattlich, dass die vorgelegte Dissertation von mir selbständig und nur unter Verwendung der angegebenen Hilfsmittel angefertigt wurde.

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Magdalena Wutte
Marseille, den