Human self-motion perception

Sensory processing, adaptation and training
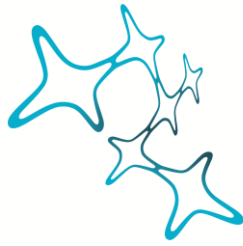
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Abstract

Every day, we move through the world, walking or driving, uphill or downhill, on high heels or sneakers, maybe balancing if the street is frozen or sidestepping people in the crowded pedestrian zone. When we move, our environment is constantly changing and although it appears easy to us to adapt to these changes, the performance of our brain in this task is astonishing. A multitude of signals from different modalities needs to be evaluated and combined continuously regarding their informative value and matching motor and cognition responses have to be induced. Knowledge about how this is achieved is still far from complete. However, approaches come from a number of different research fields. In this thesis, I present three studies measuring human performance in, and cortical processes of uni- and multisensory self-motion perception. In the first study, we evaluated the effect of prior expectation on our sensory self-motion estimates, in the second study we looked at the cortical processing of a visual self-motion stimulus and in the third study we investigated how long-term sensory modifications of self-motion perception affect brain anatomy. I draw conclusions about how short- and long-term sensory modifications affect self-motion perception and how these changes can be explained based on existing theories of multisensory cue integration, and I present a framework of sensory cue processing during visual self-motion perception.

Overview

This thesis is structured in five chapters. In the first part of the introduction, I present three sensory systems that closely interact when we are moving through our environment: Vision, vestibular sensation and somatosensation. I review theories on their integration and respective calibration. In the second part of the introduction, I summarize how the human cortex is organized to allow for the perception and interaction with our environment and I review what we currently know about the cortical processing of self-motion perception.

In chapters two to four research on these topics is presented in form of two articles published in peer-reviewed journals (Chapters 2 and 4), and one article (Chapter 3) prepared for submission.

In the first study (Chapter 2) we explored how important the upright body position, i.e. the body position we are most used to, is for our ability to estimate the direction we are moving to, our heading direction. Eleven subjects estimated their perceived heading directions from visual or vestibular cues and we evaluated how accuracy and precision differ between upright and supine body positions. We observed strong vestibular, but almost no visual effects of body position and draw conclusions about our prior expectation on the direction of gravity and the reliability of our visual system during heading estimation.

In chapter three we investigated the cortical representation self-motion direction. In an fMRI study, 26 subjects performed a visual heading discrimination task and we evaluated the cortical activation patterns during the estimation of eight different heading directions. We observe sensitivities to the direction of a self-motion consistent optic flow in all stages of visual and multisensory cortical processing. We present a theoretical approach on how a visual self-motion stimulus is processed along the human cortex and identify different factors of heading encoding.

In chapter four we evaluated the long-term effects of sensory loss and balance training on brain anatomy. Using diffusion tensor imaging (DTI), we measured white matter properties of a group of patients suffering from bilateral vestibular failure, a group of balance trained dancers and slackliners and their respective control groups. We observed similar reductions in white matter fractional

anisotropy and an increase in radial diffusivity in both groups. We concluded that this finding likely is due to an increased amount of fiber crossings in these regions, representing the strengthening of intersensory and sensorimotor connections, as a result of the increased demand of balance in both groups.

In the discussion, I review the outcome of the three studies in regard to their contribution to two major topics of self-motion perception: 1. Its ability to adapt to a changing environment and 2. the underlying cortical processes.
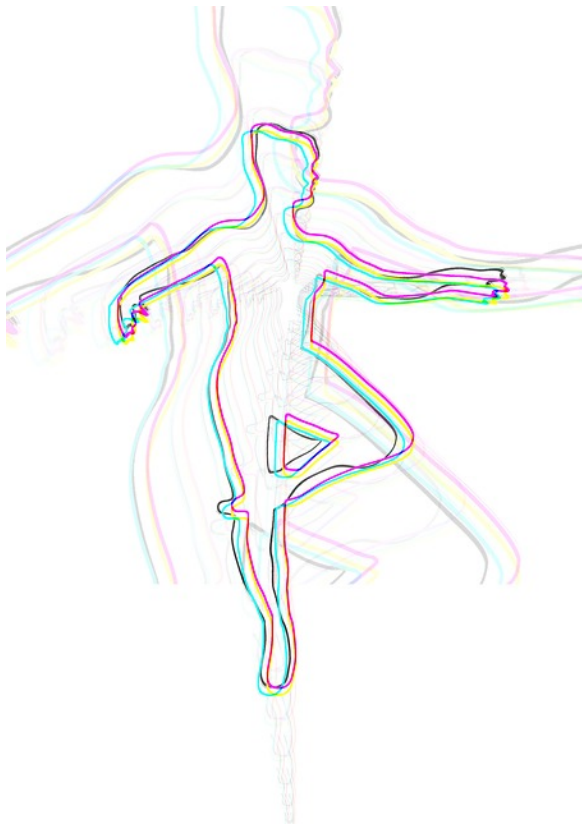
Contents

CHAPTER 1

General introduction

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The human body consists of approximately 650 muscles, 206 bones and around 360 joints. This is a large number, considering that most of the time we are moving, we do not actively think about how to coordinate every involved muscle, bone and joint. During walking, running, dancing or balancing, we can coordinate our body - some more, others less - and adjust its position to our environment so that our movement looks natural, we avoid obstacles and we do not fall. Furthermore, we are able to estimate the speed, direction and distance covered by our motion, and if we are told to walk towards a specific location we can usually follow the instructions easily. Perceiving how we move through our environment therefore represents also an essential part of our ability to orient and navigate. All of our sensory systems work together to continuously provide us with information about our body and our environment and our brain evaluates each system's input, combines them to accurate estimates of our current state and dynamically produces matching motor responses.

To understand the complex mechanisms underlying self-motion perception, we need to understand every single step of the process. The focus of this thesis will lie on how we process sensory information about our body position relative to our environment, how important our different sensory systems are and what happens if we modify one of them.

1.1 Sensory systems involved in self-motion perception

Practically every sensory system of our body can transfer self-motion specific information. For example, when we cross a street, our eyes and ears tell us if there are cars approaching, and our proprioceptive and vestibular systems control our body position when we walk. Even the distribution of blood in our body or the smell of our favorite food place across the street, they all can provide information about our state of self-motion. Here, I would like to introduce the three systems that are considered the most important for optimal self-motion perception: Visual, vestibular and somatosensory system, and their respective strengths and weaknesses during self-motion perception.

1.1.1 The visual system

For humans, as well as for many other species, the visual sense dominates over all other senses. The reason is that the visual system provides the best ratio between distance and accuracy: Other systems like hearing and smell reach far, but are often imprecise in source localization, while touch and taste are very accurate, but only for objects that are in contact with our body. When we move through the environment, a so-called optic flow is created by our motion, which produces a pattern of light on our retinae (Gibson, 1950) (Figure 1). This motion pattern provides reliable estimates, for example about the direction of our motion or about the collision probability with surrounding objects, even if no other sensory input is provided. When we move forward, and look in the direction of our motion, the optic flow field is a radial motion pattern, with all objects looming radially from a centered focus of expansion. For forward motion, the position of this point corresponds to the direction of our self-motion and can be estimated by evaluating the global motion pattern and local cues of relative object motion (for a review see Lappe et al., 1999). Behavioral studies show that the threshold of visually discriminating a heading direction from straight ahead can be as small as 1.2° (Warren & Hannon, 1988). In the following chapters I will use the terms 'heading direction' and 'singularity of flow (SoF)' when referring to the direction of linear self-motion with the gaze directed at straight ahead, and to the focus of expansion (for forward motion) and the focus of contraction (for backward motion), respectively.
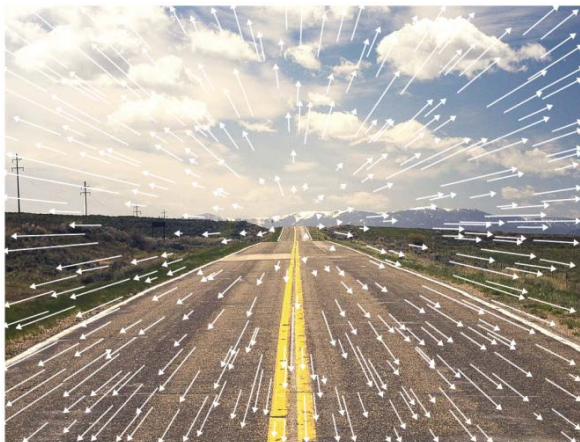
Figure 1. Optic flow illustration. When an observer moves forwards, while looking to the same direction, an optic flow is created, with all objects expanding radially from a central focus of expansion (FoE). Image used and modified under the license CC0 from www.pixabay.com (08/22/2016; 01:39 PM)

The use of virtual visual environments, provides an astonishing way to investigate the visual importance for self-motion perception. Three dimensional environments can be simulated and presented via head mounted stereo systems, which sometimes even adapt to head movements. Even if no other sensory input is provided, a very realistic percept of self-motion through the virtual environment is created. In the studies described in this thesis, we made use of such a kind of setup to simulate realistic visual self-motion stimuli.

1.1.2 The vestibular system

The vestibular system, a system that developed specifically to serve balance and spatial orientation, is located in our two inner ears. It is a twofold system, consisting of the three semicircular canals for the perception of head rotations, and the two otolith systems utricle and saccule, which perceive linear body accelerations and head tilts. The receptors in both systems are hair cells - the name deriving from the hair bundles that protrude from the apical surface of the cell. These bundles contain a number of hair-like structures, the stereocilia, and one longest cilium, the kinocilium. A deflection of the stereocilia in the direction of the kinocilium, causes a depolarisation of the hair cell, a deflection in the opposite direction causes a hyperpolarisation of the hair cell, both leading to a change in the afferent activity. For the semicircular canals, these receptors are located at the bases of each of the three roughly orthogonal canals. While the canals are filled with fluid endolymph, the stereocilia of the hair cells stick into the gelatinous cupula. Head rotations cause the fluid in the canals to move and push against the cupula, which bends the cilia of the hair cells. In utricle and saccule, the hair cells sit in a layer of supporting cells, called the maculae. The cilia reach into a polysaccharide layer, on which little calcium carbonate crystals, the otoliths ('ear stones'), are mounted. These crystals add weight and inertia to the membrane, acting as an amplifier of linear forces. When we move, gravity is always acting on these sensors, which means that the force that deflects the stereocilia is a combination of gravity and inertia (gravito-inertial force). The maculae of utricle and saccule are oriented roughly orthogonal to each other, so that the utricle is maximally sensitive to horizontal translation and the saccule is maximally sensitive to vertical translations. The curved

structure of the two systems and the different orientations of the hair cells in the maculae allow for a 3D perception of different linear accelerations.

The importance of the vestibular system to self-motion perception becomes apparent from reports of patients suffering from vestibular disorders. They suffer from balance problems and frequent falls and also have problems in navigation (e.g. Brandt et al., 2005). The vestibular system also plays an important role during heading estimation. In macaques, heading discrimination thresholds in darkness after bilateral labyrinthectomy increase by more than 10-fold (Gu et al., 2007). The precision, i.e. the reliability of the vestibular system, during a heading estimation task, where subjects need to indicate their heading direction e.g. with a pointer, is often reported to be lower than that of the visual system (Butler et al., 2010; Ohmi, 1996; Telford et al., 1995). Vestibular heading discrimination thresholds, on the other hand, are only slightly higher than visual heading discrimination thresholds (Butler et al., 2015; Butler et al., 2010; Gu et al., 2007) and the reported biases for oblique heading directions are usually much smaller (Crane, 2012; Cuturi & MacNeilage, 2013).

1.1.3. The somatosensory system

The somatosensory system responds to physical contact with the external world (touch) and monitors the internal state of the body (proprioception). Different receptor types (mechanical, chemical, thermal, and nociceptors) in e.g. joints, muscles and tendons transport information about the position of our body and of different body parts with respect to each other, mostly over three long neurons to our somatosensory cortex. Somatosensation is particularly relevant for active self-motion, where proprioceptive information produces quick reflexive sequences of motor patterns. Its role during passive self-motion should, however, also not be underestimated. Like the vestibular system, gravitoceptive information can also be delivered via somatosensory receptors (Mittelstaedt, 1992; Trousselard et al., 2004; Vaitl et al., 2002). While our vestibular system fails at the task to differentiate between a linear acceleration and a head tilt in the dark, proprioceptive receptors in our neck provide us with the necessary information about the relationship between head and body position (for a review see Pettorossi & Schieppati, 2014), and the sensitivity of the somatosensory

system to perceive a self-motion is reported to be higher than that of the vestibular system (Hlavacka et al., 1996; Hlavacka et al., 1992).

1.2 Multisensory self-motion perception

None of our sensory systems are perfect. Depending on the situation, some systems provide more reliable, others less reliable input. This is why when we move in real life, we usually are provided not only with one, but with a multitude of different sensory inputs. Usually, the sum of the multisensory inputs allows us to give a more precise estimate than each single sensory input alone (Alais & Burr, 2004; Butler et al., 2010; Ernst & Banks, 2002; Knill & Saunders, 2003). For example, try balancing on one leg, once with eyes open and once with eyes closed. The task will be much harder when the visual input is missing, and we need to rely only on vestibular and proprioceptive information.

How close our different sensory systems are connected becomes apparent, for example, if we sit on a train in the station and the train next to us starts moving. Although neither vestibular nor somatosensory motion cues exist, the visual cue produces a vestibular sensation, so that we feel as if we were moving. This phenomenon is known as 'vection' (Brandt et al., 1972; Mach, 1875), and reveals a close visuo-vestibular connection. Similarly, if we tilt the head to one side, vertical objects might appear tilted to the other side (Aubert, 1861). This 'Aubert-effect', named after the researcher who first described it, is caused by the close connection between graviceptive and visual systems (Mittelstaedt, 1983). Also, if an apparent conflict between visual and vestibular cues exist, like for example when we read a book in a driving car, our body might react with motion sickness (for a review see Bertolini & Straumann, 2016).

When we receive input from different sensory systems during a self-motion, our brain evaluates and weighs each sensory cue, and then integrates them, according to their respective reliability. The performance of our brain in this process becomes even more astonishing, when we consider the flexibility with which it can adapt to changing conditions. These changes can happen short-term, e.g. when we close our eyes while balancing, we might first sway strongly

but then regain balance over our body, or they can happen over longer periods of time, for example after losing one sense through a disease, or an accident: Patients with vestibular disorders, for example, suffer from imbalance and falls in the beginning, but can learn over months and years to rely more on visual and proprioceptive cues to regain their balance (Hillier & McDonnell, 2011; Krebs et al., 1993).

In this chapter I would like to present two mechanisms that allow us to succeed in these tasks: Sensory cue integration and sensory cue calibration. These two mechanisms are closely related, and each is essential for a statistically optimal self-motion perception. Sensory cue integration describes the process of combining different sensory cues to a more precise, combined estimate, while sensory cue calibration refers to the calibration of each single sensory system in order to gain accurate unisensory estimates.

1.2.1 Optimal Bayesian cue integration

Precision during a self-motion task, like heading discrimination, is higher if two sensory inputs are provided simultaneously than if provided separately (Butler et al., 2010). Evidence is growing, that during self-motion perception as well as during many other processes of multisensory perception, our brain integrates different sensory estimates in a Bayesian optimal way (e.g. Alais & Burr, 2004; de Winkel et al., 2013; Ernst & Banks, 2002; Fetsch et al., 2009; Knill & Pouget, 2004).

When we want to estimate a specific state, for example our current body position, we receive information from our different sensory systems, e.g. our eyes tell us about the orientation of objects in our environment, which we can use as a reference, our vestibular system provides information about the position of our head relative to gravity, and our proprioceptive system tells us how certain body parts are located in respect to each other. Each of these inputs has a certain reliability, or precision, that depends on the situation, for example in darkness, our vision might be less reliable, while it is a very dominant cue under different circumstances. Further, each sensory input underlies independent Gaussian noise. With this information we can set up probability distributions for each sensory input at the given state, the so called 'likelihood'

of the state given this sensory input. If the single sensory estimates are independent of each other, they can be combined according to a linear cue combination strategy, i.e. by calculating the weighted average of all estimates (Cochran, 1937; Landy et al., 1995).

While this cue combination strategy alone usually suffices to describe our behavior in well controlled experimental setups, it often fails to describe human behavior in real life. This is because apart from the current sensory input, our decisions rely heavily on our previous experience, knowledge and memories. For example, when we estimate our body position, we tend to judge it biased towards upright, because we are used to upright positions in everyday life (Mittelstaedt, 1983). In Bayes theory, this so called 'prior' distribution is combined with the state likelihood estimated from our current sensory input to create a 'posterior' distribution that then becomes the new prior and can be further updated by new sensory input.

In mathematical terms, this relationship is formulated as

$$P(A|B) = P(B|A)\, P(A) / P(B)$$

where A is the state that we want to estimate, and B is the given sensory input. P(A|B) describes the posterior distribution, that is estimated from the product of likelihood P(A|B) and prior distribution P(A). The term P(B) describes a normalizing constant term, scaling the probabilities over all possible states to sum up to one.

1.2.2 Sensory cue calibration

In regard to multisensory perception, we need to distinguish between sensory precision, and sensory accuracy. While the precision of a sensory system describes the variability of sensory estimates, and thus the reliability of the sensory cue, the accuracy of a cue describes how exact the sensory input describes a specific state. According to the principle of linear cue combination, the highest weight is assigned to the most reliable input. If this input is, for some reason, defective or biased, the combined estimate will be shifted misleadingly in the direction of the inaccurate estimate. The ability to optimally

integrate different sensory cues develops only late in adolescence, suggesting that our sensory systems are calibrated first to ensure possibly accurate estimates of each sensory system (Gori et al., 2008; Nardini et al., 2008). However, also during adulthood calibration mechanisms still exist (Zaidel et al., 2013; Zaidel et al., 2011). Internal (e.g. in form of another sensory estimate that serves as comparison) or external (e.g. somebody telling us how accurate we are) feedback allows us to estimate the accuracy of our sensory estimate and to adjust it accordingly. For example, if two reliable systems provide conflicting sensory estimates, the estimates will adapt towards each other in a fixed-ratio attitude (Zaidel et al., 2011).

In order to fully understand multisensory perception, it is thus important that we understand how accurate and precise each contributing sensory system is, and how these factors change when combined. Also it is interesting, how the systems adapt to manipulations, e.g. how does the modification of one sensory input affect the accuracy and precision of this system, and how does it affect the estimates of another system? Some of these points will be addressed in this thesis.

1.3 The neuronal basis of self-motion perception

In the previous chapters, I described the sensory systems and the basic principles of self-motion perception. In this chapter I would like to introduce the neuronal mechanisms that underlie these processes. Knowledge about how self-motion is processed in our brain is still far from complete, but has been studied extensively over the last years. In this chapter, I would like to first provide a rough overview about the general cortical processing of multisensory input, before I go more into the cortical processing specifically related to self-motion perception.

1.3.1 General cortical stimulus processing

Uni- and multisensory input reaches the cortex through the thalamus. In the classical approach, it has been assumed that most sensory information, such as

visual and somatosensory cues, is first projected to unimodal primary and association cortices, dedicated exclusively to the input of these specific modalities. Figure 2 shows an example processing of a visual and a somatosensory stimulus through the cortex, according to this classical view.
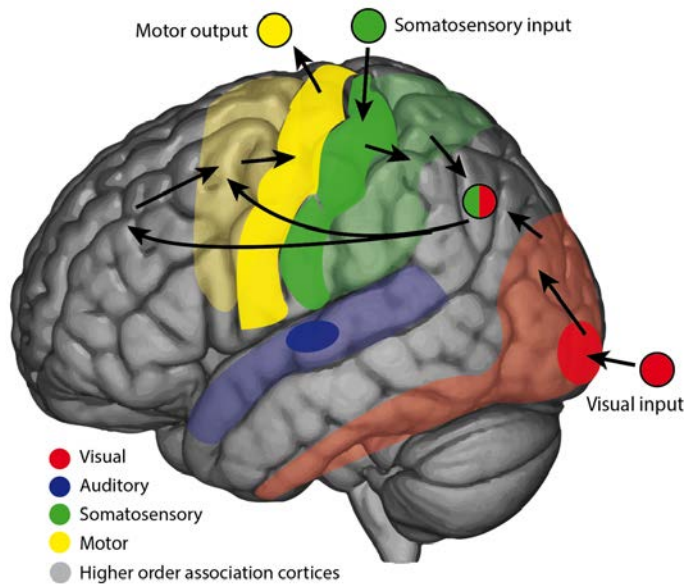
Figure 2. Primary sensory cortices (solid colors), association cortices (faded colors) and higher order association cortices (grey). This figure illustrates an example pathway of a visual and a somatosensory cue through the cortex. Both cues are first processed in their respective primary cortices, then forwarded to association cortices, where more complex unisensory associations occur. In higher order association cortices the preprocessed cues of all sensory modalities can be combined and the output is projected to areas of cognition and motor control. From here, top-down processes create matching motor responses. Image produced based on data from http://www.indiana.edu (06/08/2016 10:35AM)

Somatosensory (S1) and visual (V1) primary cortices first map very basic characteristics of the respective sensory stimulus: V1 provides a retinotopic map, which means the image that is depicted on our retinae is projected in a similar way on our primary visual cortex, all information of the right visual field onto the left hemisphere and all information of the left visual field onto the right hemisphere. Similarly, the somatosensory map of S1, the so called homunculus, represents sensitivities of our whole body surface to touch. The sensory information is then further processed in secondary and higher unisensory association cortices. These cortices are highly developed in humans and enable us to recognize more complex aspects of our environment, like

recognizing objects or their spatial relationship. In the next step, the preprocessed unimodal information is then transported to higher association areas, which receive multisensory input. These areas finally carry out the actual cue integration and forward the output to areas of motor control, decision making and memory to create matching motor and behavioral responses. More recent findings further suggest that multisensory processes can be observed already on the level of primary sensory cortices (Kayser & Logothetis, 2007).

1.3.2. Cortical processing of self-motion stimuli

While the performance of self-motion perception can be tested relatively easy, e.g. by asking 'What was your self-motion direction?', exploring the underlying cortical processes constitutes a much harder task. Observing the healthy human brain in action is possible nowadays, but faces certain limitations. For example, the resolution of an fMRI scanner is too low to measure neuronal responses, as one functional voxel comprises around 630,000 neurons[1]. This limitation has been tackled recently by developing new evaluation methods, such as multi-variate pattern analysis (MVPA, Haxby et al., 2001). This approach is not limited to the voxel-level, because it evaluates patterns of voxel intensity instead of single-voxel activation levels. It has been claimed that MVPA allows for the detection of neuronal firing patterns within cortical visual orientation columns (Kamitani & Tong, 2005). Although this claim is still discussed (Freeman et al., 2011; Pratte et al., 2016), general consensus exists that MVPA allows for the detection of more subtle differences across conditions than classical evaluation approaches (Haxby et al., 2014). Measuring cortical activations specifically during the perception of a self-motion with fMRI, faces two further limitations. First, subjects in the fMRI scanner should move as little as possible, to avoid motion artifacts in the data. This obviously makes it difficult to measure self-motion perception. Second, the supine body position required during fMRI data acquisition could interfere with our prior experience of moving in upright positions. The relevance of this latter problem is explored in the first study of this thesis, described in chapter 2. To address the problem of motion suppression in the scanner, most fMRI studies on human self-motion

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[1] number from: https://cfn.upenn.edu/aguirre/wiki/public:neurons_in_a_voxel 06/04/2016 09:25 a.m.

perception use visual stimuli to simulate an egomotion. This approach provides several advantages 1) The visual sense is our dominant sense, and highly important for self-motion perception, thus it is likely that areas that process visual self-motion stimuli are also involved in 'real' self-motion perception. 2) The visual sense is the best investigated of all senses. 3) Compared to other sensory systems, it is uncomplicated to create visual self-motion stimuli and present them in the fMRI scanner. 4) Certain factors of self-motion, like the estimation of a heading direction, can be done very accurately only from visual input and do not necessarily need other sensory estimates, and 5) Visual perception can induce an actual percept of self-motion, called vection. This opens up the possibility to investigate visual-vestibular integration using unimodal stimulation.

Although the use of functional imaging methods to investigate human self-motion perception is promising, knowledge from other fields is highly valuable to create a common understanding of how we perceive self-motion. Electrophysiological single cell recordings in non-human primates, for example, provide relevant information on neuronal firing patterns. In particular the neuronal responses to self-motion stimuli within the occipito-temporal visual motion areas MT/V5 and MST have been explored extensively (e.g. Albright, 1989; Duffy & Wurtz, 1991a; Duffy & Wurtz, 1991b, 1995; Gu et al., 2008; Gu et al., 2007; Tanaka et al., 1986). On the other hand, reports from brain lesion studies reveal interesting insights into the function and importance of specific brain regions (Vaina, 1998; Vaina & Rushton, 2000; Vaina & Soloviev, 2004). For example, patients with occipito-parietal lesions perform well on low-level motion tasks, such as discriminating different object motion directions, but fail in higher-level motion tasks, like heading estimation. Patients with occipital lobe lesions show impairments in low-level motion tasks, but retain their ability to judge heading direction relative to a target. This suggests mechanisms of heading estimation in occipito-parietal regions, which do not necessarily depend on low-level motion estimates (Vaina, 1998).

A number of different brain regions has been suggested in the last years, which show characteristics making them highly interesting regarding their possible roles in self-motion perception. Most of these regions are primarily visual processing regions, that respond to visual motion (Sunaert et al., 1999) and have

large receptive fields, making them suitable for the evaluation of the global flow pattern of a retinal optic flow. Characteristic aspects of visual self-motion have been investigated in these and other regions to create a concept of cortical self-motion processing. For example, it was tested which regions differentiate between coherent and random patterns of object motion (de Jong et al., 1994), assuming that self-motion always creates coherent motion patterns. These findings were further refined by distinguishing different kinds of coherent motion: a self-motion consistent pattern, with only one SoF, was contrasted against a self-motion inconsistent pattern, with multiple SoFs (Cardin & Smith, 2010; Wall & Smith, 2008), different components of coherent flow stimuli (radial, circular, planar) were distinguished (Holliday & Meese, 2005, 2008; Morrone et al., 2000; Pitzalis et al., 2013), different SoF positions were compared (Cardin, Hemsworth, et al., 2012; Furlan et al., 2014), and the influence of vection during visual stimulation was investigated (Brandt et al., 1998; Brandt et al., 2002; Deutschlander et al., 2004; Kleinschmidt et al., 2002; Kovacs et al., 2008; Wada et al., 2016). Table 1 shows recently discussed areas and the most important findings on motion- and self-motion sensitivity in these areas.

Together with what we learned in the previous chapters, these findings suggest that the cortical processing of human self-motion perception includes a large network of unimodal and multimodal pathways of processing. Both unimodal and multimodal areas seem to be important for the evaluation of a specific self-motion state, however, our knowledge is still far from complete regarding the question, which areas are responsible for which tasks.

Table 1. Summary of regions responding to visual motion and their functions regarding visual motion evaluation

Visual association, dorsal stream	
V3A	- direction discrimination (Cornette et al., 1998)
	- complex flow evaluation (Cardin, Hemsworth, et al., 2012)
V5/MT (middle temporal area)	- SoF position (Cardin, Hemsworth, et al., 2012)
	- heading task > dimming task (Peuskens et al., 2001)
	- coherent > incoherent (Holliday & Meese, 2008; Morrone et al., 2000)
	- expansion > other transverse flow directions (Albright, 1989)
	- direction (Van Essen et al., 1981)
MST (medial superior temporal area)	- SoF position (Page & Duffy, 1999)(Duffy 1999)
	- flow components (Saito et al., 1986; Tanaka & Saito, 1989)
	- direction (Desimone & Ungerleider, 1986)
	- expansion, contraction, rotation (Saito et al., 1986)
	- speed (Tanaka & Saito, 1989)
	- multisensory (Page & Duffy, 2003)
V6	- EC > EI (Cardin & Smith, 2010)
	- flow components (Pitzalis et al., 2013)
	- stereoscopic depth (Arnoldussen et al., 2013; Cardin & Smith, 2011)
	- vection (Uesaki & Ashida, 2015; Wada et al., 2016)
	- coherent > random > static (Wada et al., 2016)
	- stimulus size (Wada et al., 2016)
Visual association, ventral stream	
LG (lingual gyrus)	- speed (Orban et al., 1998)
FG (fusiform gyrus)	- temporal comparison (Cornette et al., 1998; Orban et al., 1998)
	- expansion > random (de Jong et al., 1994)
Posterior parietal cortex	
VIP (ventral intraparietal area)	- SoF position (Bremmer, Duhamel, et al., 2002)
	- EC > EI (Wall & Smith, 2008)
	- flow components (Bremmer, Duhamel, et al., 2002)
	- multisensory (Bremmer, Klam, et al., 2002)
	- vection (Uesaki & Ashida, 2015)
PcM (precuneus motion area)	- first described by Cardin & Smith 2010: EC > EI (Cardin & Smith, 2010)
	- vection (Wada et al., 2016)
	- stimulus size (Wada et al., 2016)
	- coherent > Random > Static (Wada et al., 2016)
DIPSM/L (medial/lateral dorsal intraparietal sulcus)	- vection (Kovacs et al., 2008)
	- coherent > static (Kovacs et al., 2008)
	- heading vs. dimming task (Peuskens et al., 2001)
POIPS (parieto-occipital intraparietal sulcus)	- vection (Kovacs et al., 2008)
	- coherent > incoherent > static (Kovacs et al., 2008)
Higher cortices	
CsV (cingulate sulcus visual area)	- EC > EI (Wall & Smith, 2008)
	- changes in SoF position (Furlan et al., 2014)
	- vection (Wada et al., 2016)
	- coherent > static > random (Wada et al., 2016)
	- stereoscopic depth (Arnoldussen et al., 2013)
PIVC (parieto- insular vestibular cortex)	- vection (Brandt et al., 1998; Uesaki & Ashida, 2015)
	- multisensory, primarily vestibular (Brandt et al., 1998; Grusser et al., 1990)
p2v (putative area 2v)	- multisensory, primarily vestibular (Cardin & Smith, 2010; Guldin & Grusser, 1998)
	- EC > EI (Cardin & Smith, 2010)
FEF (frontal eye fields)	- multisensory heading sensitivity (Gu et al., 2015)
	- expansion > other transverse flow directions (Xiao et al., 2006)
	- active heading task > dimming task (Peuskens et al., 2001)

EC = egomotion-consistent, EI = egomotion-inconsistent, SoF = singularity of flow

1.4. About this thesis

We have seen that self-motion perception is a highly dynamic process, where different sensory systems continuously adapt to changes in the environment and are tightly connected to each other. Further, approaches to identify the cortical basis of self-motion perception were described. The studies described in the following three chapters of this thesis address these topics in different ways.

In the first study we chose the task of heading direction discrimination to explore the accuracy and precision of the visual and the vestibular system in this specific task. We then looked at how a sensory modification in form of a change to a supine body position affects the perception of the unisensory cues. This approach allows us, on the one hand, to estimate how important the upright body position is for our everyday motion. On the other hand it reveals interactions between the visual and the vestibular system, that might exist, even if no task-related feedback can be exchanged between the two systems. This study additionally provided the basis for our second study, by testing the feasibility of showing visual self-motion stimuli to supine subjects during fMRI.

In the second study, we explored cortical activation patterns during a visual heading discrimination task. We used univariate and multivariate data evaluation methods in order to identify cortical sensitivites to the direction of a self-motion consistent optic flow. We further evaluated which regions are sensitive to the pattern of the flow that is determined by the position of the SoF, and which regions show a sensitivity to the temporal sequence of the pattern, i.e. if the motion is to the left or to the right, forwards or backwards, independent of the SoF position. We hoped to gain knowledge about the cortical processes underlying the estimation of our heading direction from optic flow.

While the first two studies refer to performance and neuronal processing of a specific self-motion task, and the first study evaluates short-time effects of multisensory adaptation and interaction, the last study looks at a more general aspect of self-motion perception and the long-term effects of multisensory adaption and interaction. We compared patients that suffered from bilateral vestibular loss, normal control subjects, and subjects trained in a balance sport (e.g. ballet) to evaluate how the different distributions of visual, vestibular and proprioceptive input affect cortical connectivity.

CHAPTER 2

The effect of supine body position

on human heading perception
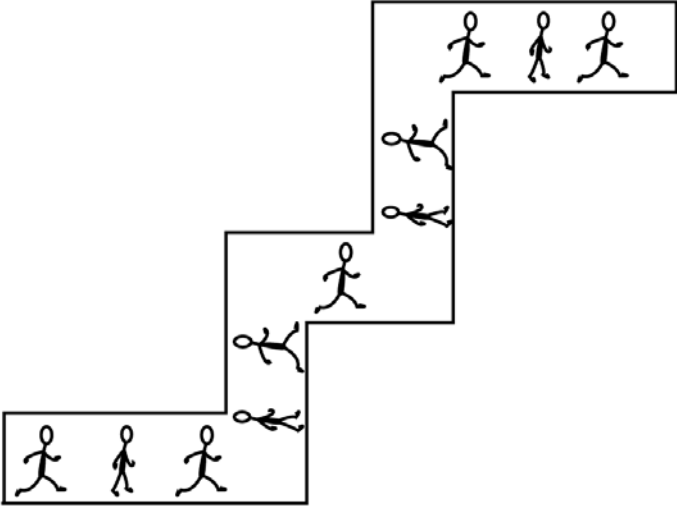
Author contributions

P.R.M. and V.L.F. conceptualized the study

N.H., L.F.C., P.R.M. and V.L.F. designed the study

N.H. programmed the visual stimuli

L.F.C. and P.R.M programmed the vestibular stimuli

N.H. and L.F.C. conducted the experiments

N.H. analyzed the data

N.H., P.R.M. and V.L.F. interpreted the data

N.H. wrote the manuscript

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Image created with Adobe Illustrator CS6

The effect of supine body position on human heading perception

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The use of virtual environments in functional imaging experiments is a promising method to investigate and understand the neural basis of human navigation and self-motion perception. However, the supine position in the fMRI scanner is unnatural for everyday motion. In particular, the head-horizontal self-motion plane is parallel rather than perpendicular to gravity. Earlier studies have shown that perception of heading from visual self-motion stimuli, such as optic flow, can be modified due to visuo-vestibular interactions. With this study, we aimed to identify the effects of the supine body position on visual heading estimation, which is a basic component of human navigation. Visual and vestibular heading judgments were measured separately in 11 healthy subjects in upright and supine body positions. We measured two planes of self-motion, the transverse and the coronal plane, and found that, although vestibular heading perception was strongly modified in a supine position, visual performance, in particular for the preferred head-horizontal (i.e., transverse) plane, did not change. This provides behavioral evidence in humans that direction estimation from self-motion consistent optic flow is not modified by supine body orientation, demonstrating that visual heading estimation is one component of human navigation that is not influenced by the supine body position required for functional brain imaging experiments.

Introduction

The use of virtual environments in combination with functional brain imaging provides an important meth-

odological tool for understanding human spatial navigation and self-motion perception. Because fMRI does not allow for actual physical movement, these studies rely on visual stimulation to simulate self-motion (e.g., Cardin & Smith, 2010; Kovacs, Raabe, & Greenlee, 2008; Wall & Smith, 2008). The visual input is usually provided in the form of a self-motion consistent optic flow stimulus, from which the direction, speed, and duration of self-motion can be successfully estimated (Bremmer & Lappe, 1999; Gibson, 1950; Warren & Hannon, 1988).

One assumption inherent to performing these tasks during fMRI is that perceptual performance is comparable between upright and supine body positions. However, the differing vestibular and proprioceptive signals between upright and supine body positions may modify heading perception. We are not accustomed to move in a supine body position, and this prior experience could lead to differential performance between upright and supine postures. Such differential performance may generalize for heading perception across both visual and vestibular modalities. Alternatively, effects of body orientation on heading perception may depend on modality. For the vestibular system, a change in body orientation amounts to changing the direction of the static gravitational stimulus, which could directly impact low-level processing of dynamic vestibular heading stimuli. In contrast, low-level visual processing will be unaffected by the direction of the static gravitational vestibular stimulus. To determine whether effects of body orientation on heading perception are modality-specific, it is necessary to measure and compare heading perception across modalities.

In an upright body position, humans show systematic biases when estimating heading directions from optic flow (Crane, 2012; Cuturi & MacNeilage, 2013). These biases have been ascribed to a neuronal preference for lateral motion. When the same visual stimuli are rendered to subjects in a supine body position, multisensory interactions may prompt the interpretation of movement in the earth vertical plane because nonvisual sensory signals indicate that subjects are lying on their back. Could this affect the appearance of the visual heading biases?

On a neuronal level, visual and vestibular signals are combined relatively early in sensory processing pathways (Dichgans, Diener, & Brandt, 1974; Gu, DeAngelis, & Angelaki, 2007), suggesting a close interdependence between visual and vestibular processing. Body tilts away from upright lead to decreased reliability of vestibular sensory estimates (Graybiel & Patterson, 1955; Quix, 1925), causing a reweighting of other sensory inputs, including vision (Dichgans et al., 1974; Fetsch, Turner, DeAngelis, & Angelaki, 2009). This can lead to modifications in visual perception, for

example, in the perception of the orientation of lines or objects (Aubert, 1861; Mikellidou, Cicchini, Thompson, & Burr, 2015). The perception of the own body and its orientation relative to extrapersonal space is created by a combination of vision, body position, and gravity (Dyde, Jenkin, Jenkin, Zacher, & Harris, 2009; Harris, Herpers, Hofhammer, & Jenkin, 2014). In a supine body position, the direction of gravity in relation to the body changes, causing a shift in the perceptual upright that could also affect visual motion perception. Varying the body position can lead to systematic biases in estimating the direction of forward movements relative to the horizon from optic flow (Bourrelly, Vercher, & Bringoux, 2010) and increase the threshold of vestibular as well as visual heading direction discrimination close to straight ahead (MacNeilage, Banks, DeAngelis, & Angelaki, 2010). Similarly, effects of body orientation have been found for distance estimation (Harris & Mander, 2014) and the sensation of vection (i.e., the illusory perception of self-motion that develops during prolonged viewing of optic flow) (Kano, 1991; Thilo, Guerraz, Bronstein, & Gresty, 2002).

The aim of this study was to investigate the influence of the supine body position on visual heading estimation performance in humans. For comparison purposes, we also acquired supine and upright vestibular heading performance as a behavioral measure for the effect of a supine body position on vestibular perception. Biases and variability in heading estimation were compared between upright and supine body positions as a measure of performance and uncertainty. Because heading perception depends strongly on the stimulus type (Fetsch et al., 2009), motion plane (Crane, 2014a; MacNeilage et al., 2010), and heading angle (Crane, 2012; Cuturi & MacNeilage, 2013), we chose a paradigm that covered different factor combinations of visual and vestibular stimulation, transverse and coronal stimulus planes, and 24 heading angles within each plane. We expected stronger biases and larger errors in both visual and vestibular heading estimation in the supine position than in the upright position because human self-motion systems are most specialized for processing heading with upright posture.

Methods

Subjects

Eleven subjects (five females), mean age 27.55, range 24–32 years, participated in the study. They had normal or corrected-to-normal vision and no history of neurological disorders. All subjects gave written informed consent to participate in the study, which was
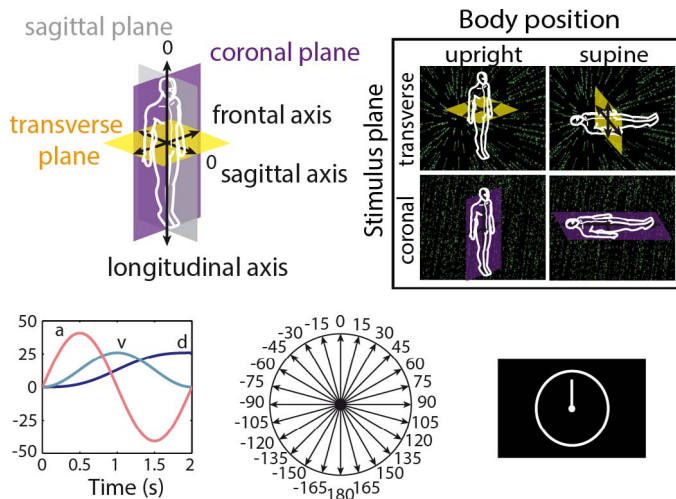
Figure 1. Experimental procedure, conditions, and nomenclature. During the experiment, all combinations of the three factors, body position (supine/upright), stimulus type (visual/vestibular), and stimulus plane (transverse/coronal), were tested. The stimulus profile (lower left corner) shows acceleration in cm/s^2 (a), velocity in cm/s (v), and displacement in cm (d) during the 2-s stimuli for both optic flow and platform motion. Twenty-four heading directions (lower row, center) were presented in the coronal and the transverse plane, respectively (six repetitions). Zero degrees corresponded to a movement straight forward or upward. Negative heading directions refer to leftward self-motion, positive heading directions to rightward self-motion. After each stimulus, the response screen (lower right corner) was shown. Subjects estimated their perceived heading direction by moving the arrow around the dial via button press.

approved by the ethics committee of the medical faculty of the Ludwig Maximilians University and performed in accordance with the Declaration of Helsinki.

Stimuli

Stimuli were either visual (optic flow) or vestibular (passive acceleration/deceleration) with identical stimulus profiles for both types of stimulation. One stimulus profile lasted 2 s and represented a linear translation in one of 24 directions. All translations had a sinusoidal acceleration profile with a total displacement of 26 cm, a peak velocity of 26 cm/s, and a peak acceleration/deceleration of 41 cm/s^2 (Figure 1). Translational motion can be described in world-centered, i.e., earth-horizontal or earth-vertical, or body-centered coordinates, i.e., sagittal, coronal, and transverse. However, previous research has shown that heading discrimination is influenced by changes in the stimulus plane in body-centered and not world-centered coordinates (MacNeilage et al., 2010). Therefore, we refer to the two stimulus planes in the present study with respect to

body coordinates as transverse and coronal translations (Figure 1). Body-centered optic flow stimulus planes also correspond to the same physical stimulus projected onto the head mounted display (HMD), see Visual stimuli; therefore, we define stimulus planes in body-centered coordinates in this study. Both visual and vestibular heading estimation were tested in each stimulus plane in both an upright and a supine body position.

For each plane, we tested 24 heading directions covering the whole plane in 15° steps, i.e., 0°, 15°, 30°, 45°, etc. All directions are labeled in relation to 0° or straight ahead/upward such that left (counterclockwise) heading directions are negative (−15° to −165°) and right (clockwise) directions are positive (15° to 165°, Figure 1). All trials took place in a darkened room, and in the vestibular condition, subjects were additionally instructed to close their eyes during stimulus presentation. Acoustic white noise was played over headphones during stimulus presentation to eliminate auditory self-motion cues. In the upright position, the subject sat in a racing chair; his or her head was positioned against a form-fitting vacuum headrest, and a headband fixated the forehead to the chair. In the supine position, the subject was placed on a form-fitting vacuum mattress, and forehead, body, and legs were fixated with mattress belts.

Visual stimuli

Three-dimensional optic flow stimuli were created in Matlab (The Mathworks Inc., Version R2009b) using the OpenGL library and Psychtoolbox-3 (Brainard, 1997). Stimuli were rendered on a head-mounted stereo display (HMZ-T2, Sony Corporation) with a binocular horizontal field of view of 45°, a display resolution of 1,280 × 720 pixels and a refresh rate of 60 Hz. Stimuli simulated linear transitions through a cloud of randomly placed triangles. For stimulus creation, 13,366 green, two-dimensional, frontoparallel triangles (base and height 0.5 cm) were placed at a density of 0.04 triangles/cm^3 in a black rectangular room with a three-dimensional volume of 122.30 × 170.76 × 210 cm^3 (height, width, depth). The near and far clipping planes were at 50 cm and 400 cm, respectively.

Vestibular stimuli

Vestibular stimuli were delivered by a six-degree-of-freedom motion platform (Moog© 6DOF2000E). Subjects were placed, either seated (upright position) or lying (supine) on the platform. The subject was then moved passively in one of the directions described above following the motion profile described above. After response collection, the platform moved to the origin that was required for the next trial.

Experimental procedure

The procedure was identical in all trials: After an acoustic signal, subjects started the trial via button press. The heading stimulus was presented, and afterward, subjects indicated the perceived heading direction by adjusting the orientation of an arrow on the screen via button press. The arrow was presented within a white circle on a black background (Figure 1). Four buttons allowed for rough adjustments of 2° and fine adjustments of 0.2° per registered key press. Subjects confirmed their estimate by pressing a different button. Haptic cues on the buttons allowed subjects to distinguish all five buttons without visual feedback, and subjects quickly learned the positions of the buttons without seeing them.

The experiment was performed over 4 days, and stimuli were presented block-wise with four blocks per day. Each block consisted of 74 trials. Within one block, only one stimulus type (visual or vestibular), one body orientation (upright or supine), and one stimulus plane (coronal or transverse) was presented. This means, three (of, in total, six) repetitions of the 24 heading directions of one specific condition were presented in random order. Within the same day, stimulus type and body orientation never changed, but two blocks of each stimulus plane were acquired. The order of presentation of stimulus type, body orientation, and stimulus plane was counterbalanced across subjects. Before a new condition began, subjects received 10 training trials that accustomed them to the new condition.

Feedback as to subject's performance was only given during the 10 training trials. This was done primarily to ensure that subjects were not judging object motion in the visual heading conditions, which would lead to errors of ~180° (see also Crane, 2012; Cuturi & MacNeilage, 2013). Despite training, subjects occasionally judged object motion instead of self-motion, leading to large errors that are unrelated to the perceptual biases under investigation. Therefore, a deviation of more than 90° from the target angle was considered an erroneous estimate of subjective heading (see also Crane, 2012; Cuturi & MacNeilage, 2013). This was the case in 54 out of 6,336 visual trials (0.85%). These trials were identified immediately, recollected at a later time within the same block, and excluded from further analysis.

Control condition for response bias

Response collection methods may lead to systematic differences between the intended and indicated heading direction. As our response dial was slightly different than what has been used in the past (Cuturi & MacNeilage, 2013), we performed two additional blocks in which we measured heading estimation for "written" directions, similar to the spoken condition in Crane's (2012) study. Instead of presenting a motion stimulus, the actual direction was presented as a written number on the screen, e.g., "−45°." Using this measure helped us to identify to what extent responses given by subjects were biased by their interpretation of the angles on the response device. For example, subjects may not be able to set the line accurately to 45° although, if asked what visual or vestibular heading angle they received, they would respond "45°." For this control experiment, six repetitions of each direction were acquired, again with 15° spacing, once in a supine and once in an upright body orientation. To ensure that the additional knowledge of stimulus magnitude did not affect heading estimation, the control experiment was always performed after the main experiment. Subjects were informed about the relationship between each written value and its relative location within the circle prior to performing the task.

Analysis

The error between the response direction and the actual heading direction was extracted from each trial by subtracting the final position of the arrow within the dial in each trial from the presented heading direction, resulting in the heading bias (Crane, 2012; Cuturi & MacNeilage, 2013). Additionally, we calculated absolute bias to obtain a measure of the magnitude of the heading bias, independent of its direction. This is convenient, for example, for comparing accuracy of heading perception across body orientations. In addition, variability was calculated as the standard deviation of the bias across the six repetitions.

We performed a 2×24 repeated-measures (rm-)ANOVA with factors body orientation (upright/supine) and heading direction (24 directions per plane) for each of the three measures in each stimulus plane for visual stimuli as well as for vestibular stimuli and for the written control condition. If significant interactions between body orientation and heading direction were found (i.e., $p < 0.05$), we evaluated the differences by calculating paired t tests for each heading direction.

Results

In this study, we compared visual heading estimation for upright and supine body positions to test whether the change in vestibular sensory information (i.e., the direction of gravity in head coordinates) influences optic flow–based heading perception. We also tested

	Visual						Vestibular						Written					
	BP		HD		BP-HD		BP		HD		BP-HD		BP		HD		BP-HD	
	F	p	F	p	F	p	F	p	F	p	F	p	F	p	F	p	F	p
Bias																		
Transverse	0.37	0.55	89.76	<0.0001	1.44	0.093	5.52	0.041	2.85	<0.0001	7.19	<0.0001	0.61	0.45	3.37	<0.0001	0.77	0.77
Coronal	5.50	0.041	10.23	<0.0001	1.21	0.24	25.29	0.00051	3.30	<0.0001	4.59	<0.0001						
Variability																		
Transverse	0.27	0.61	11.08	<0.0001	1.58	0.049	6.78	0.026	4.59	<0.0001	1.62	0.041	7.01	0.024	4.04	<0.0001	1.50	0.072
Coronal	0.018	0.90	7.60	<0.0001	1.65	0.034	11.65	0.0066	5.66	<0.0001	2.58	0.00019						
Absolute bias																		
Transverse	1.05	0.33	32.54	<0.0001	1.31	0.16	0.018	0.90	3.42	<0.0001	1.00	0.47	4.23	0.067	3.39	<0.0001	0.86	0.65
Coronal	0.050	0.83	5.78	<0.0001	0.98	0.49	25.68	0.00049	4.68	<0.0001	1.77	0.019						

Table 1. F values and p values for the repeated-measures ANOVAs performed. *Notes:* BP = main effect of body position, *df:* 1,10; HD = main effect of heading direction, *df:* 23, 230; BP-HD = interaction between the body position and heading direction, *df:* 23, 230.

vestibular heading estimation performance in both body positions to estimate the change in vestibular heading perception induced by a change in body orientation.

The rm-ANOVAs revealed a main effect of heading direction for all conditions, consistent with what has been shown previously in an upright position (Crane, 2012, 2014a; Cuturi & MacNeilage, 2013). However, because we were interested in the effects of body orientation, we have focused the results on the main effect of body orientation and the interactions with heading direction. The results of the rm-ANOVAs are summarized in Table 1.

Visual heading perception

Similar heading biases were found between upright (Figure 2A, green) and supine (Figure 2A, blue) body positions using optic flow. This was true in both the transverse and coronal stimulus planes although heading bias showed a very different pattern between stimulus planes. For transverse stimuli, no main effect of body position or interaction between body position and heading direction was found. For stimuli in the coronal plane, a weak main effect of body position existed, $F(23, 230) = 5.50$, $p = 0.041$, but no interaction, $F(23, 230) = 1.21$, $p = 0.24$. Inspection revealed that this effect is due to a small offset between supine and upright heading estimates. Biases were in general more positive (i.e., clockwise) when subjects were sitting than when they were lying on their back.

This offset was not correlated to the effects of body position we measured for vestibular heading perception in the same stimulus plane ($r = -0.019$, $p = 0.76$). It could also not be explained by differences in the absolute bias or variability. Both of these variables showed no main effect of body position (Figure 2B, C), suggesting that the bias offset is neither caused by a change in the subjects' uncertainty about heading direction nor by generally greater or smaller errors. Bias variability showed a significant interaction between body position and heading direction for both stimulus planes. The interaction was due to a difference in bias variability between upright and supine body position for individual heading directions (Figure 2C), but no consistent pattern of significance across similar heading directions was found that could explain the general offset in heading bias.

Vestibular heading perception

The lack of effect of body position on visual heading estimation could result from little or no effect of body position on heading judgments in general. However,
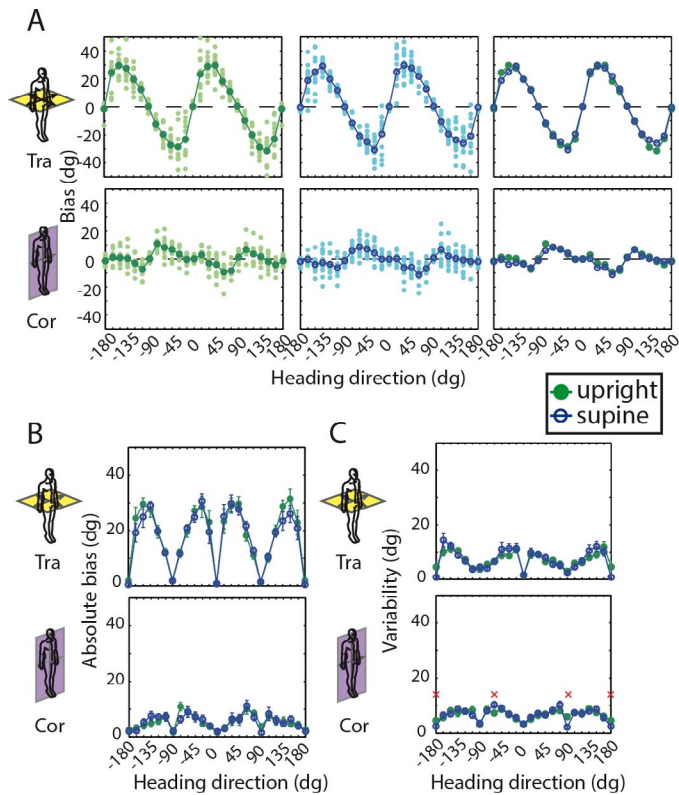
Figure 2. Visual heading perception. Top rows always show results in the transverse stimulus plane and bottom rows the coronal stimulus plane. Green: upright body orientation, blue: supine body orientation. (A) Biases in heading direction estimation. Left: mean bias across subjects ($n = 11$, green) and mean bias for each individual ($n = 6$, bright green) for the upright body orientation. Center: mean bias across subjects ($n = 11$, blue) and mean bias for each individual ($n = 6$, cyan) for the supine body orientation. Right: Mean bias across subjects plotted for both upright versus supine body orientations. (B) Mean absolute bias $\pm$ SE across subjects. (C) Mean variability (standard deviation of the biases) $\pm$ SE across subjects. Red ticks delineate significant differences between upright and supine as calculated by t tests ($p < 0.05$).
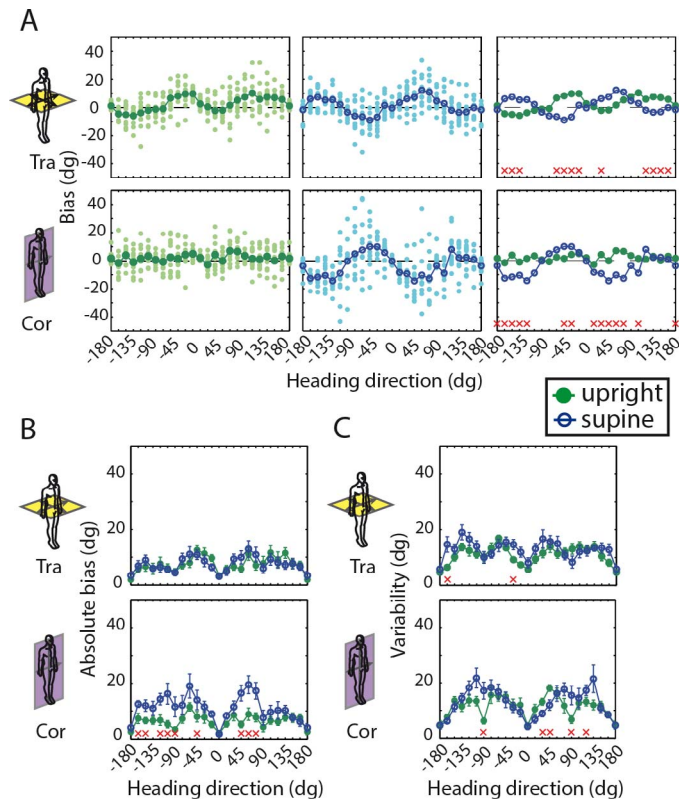

Figure 3. Vestibular heading perception. Color coding for body orientation and location for stimulus plane are the same as in Figure 2. (A) Left: mean bias across subjects ($n = 11$, green) and mean bias for each individual ($n = 6$, bright green) for the upright body orientation. Center: mean bias across subjects ($n = 11$, blue) and mean bias for each individual ($n = 6$, cyan) for the supine body orientation. Right: Mean bias across subjects plotted for both upright versus supine body orientations. (B) Mean absolute bias $\pm$ SE across subjects. (C) Mean variability (standard deviation of the biases) $\pm$ SE across subjects. Red ticks delineate significant differences between upright and supine as calculated by t tests ($p < 0.05$).

consistent with previous research, vestibular heading biases were strongly affected by body position (Figure 3). These effects varied depending on the stimulus plane.

In the transverse stimulus plane, oblique direction biases went in approximately opposite directions for upright (Figure 3A, top row, green) versus supine (Figure 3A, top row, blue) body position, corresponding to a weak main effect of body position and a significant interaction (Table 1). Significant differences between supine and upright biases were seen in almost all oblique heading directions ($-165°$, $-150°$, $-135°$, $-60°$, $-45°$, $-30°$, $-15°$, $45°$, $120°$, $135°$, $150°$, and $165°$, $p < 0.05$). In the coronal stimulus plane, a strong main effect of body position and significant interaction was found (Table 1). The upright (Figure 3A, bottom row,

green) body position showed no obvious directionality in heading bias. However, distinct heading biases were seen in the supine (Figure 3A, bottom row, blue) body position. Oblique forward heading directions were underestimated and oblique backward heading directions, in particular movements to the left, were overestimated. In other words, subjects showed a bias toward the longitudinal body axis for supine heading estimates, which they did not show in an upright position.

Absolute bias and variability (Figure 3B, C) were further analyzed to determine the effects of body position on vestibular heading accuracy and precision. For transverse movements, absolute biases did not show significant effects of body position, but variability increased significantly in a supine body position (Table 1). For coronal stimuli, both absolute bias and
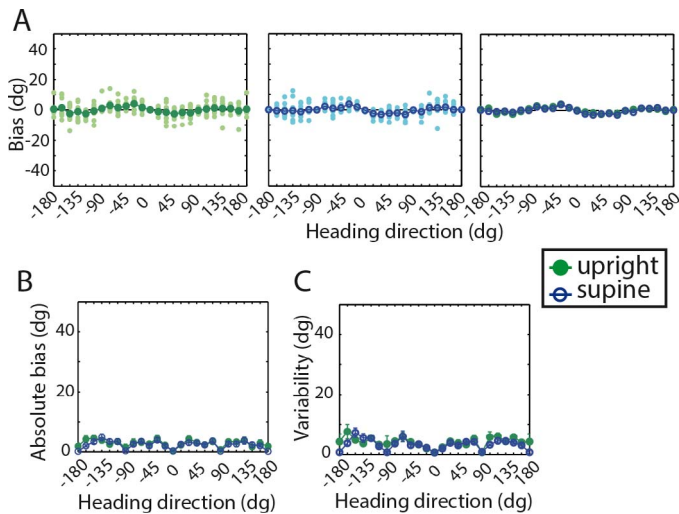
Figure 4. Written heading estimation. Color coding for body orientation is the same as in Figure 2 and 3. (A) Left: mean bias across subjects ($n = 11$, green) and mean bias for each individual ($n = 6$, bright green) for the upright body orientation. Center: mean bias across subjects ($n = 11$, blue) and mean bias for each individual ($n = 6$, cyan) for the supine body orientation. Right: Mean bias across subjects plotted for both upright versus supine body orientations. (B) Mean absolute bias $\pm$ SE across subjects. (C) Mean variability (standard deviation of the biases) $\pm$ SE across subjects.

variability showed a significant main effect of body position (greater values in supine position) and an interaction between heading direction and body position. In general, the effects of body position were stronger for the coronal stimulus plane than for the transverse plane.

Written heading estimation

To explore possible effects of response modality on heading errors, subjects were also asked to move the arrow to angles that were written out numerically on the screen. Subjects tended to underestimate forward/upward and to overestimate backward/downward directions. The magnitude of the biases measured was much smaller than those seen for visual and vestibular heading estimation (Figure 4), suggesting that response bias cannot explain the heading biases. Statistics on heading biases corrected for response bias (i.e., after subtraction of the response bias from the heading bias), showed very similar results as on the original heading biases. However, the weak main effects we found for body position for visual stimuli in the coronal plane, before correction: $F(1, 10) = 5.50$; $p = 0.041$; after correction: $F(1, 10) = 2.78$; $p = 0.13$, and vestibular stimuli in the transverse plane, before correction: $F(1, 10) = 5.52$; $p = 0.041$; after correction: $F(1, 10) = 2.52$; p

$= 0.14$, lost significance when accounting for the response bias. Body position had a significant main effect on variability and, by trend, also on the absolute response bias but in the opposite direction than the expected one. Greater errors and higher variability were seen for the upright rather than the supine condition. This may be attributable to the fact that the HMD was more comfortable and more stable in a supine position. However, the main effect was opposite from the effects we found for visual and vestibular heading biases. Thus, the results of the written experiment do not explain the overall effects of body position on heading biases.

Discussion

In this study, we compared visual and vestibular heading biases between upright and supine body positions. We found that visual heading perception is basically unaffected by the change in body position. Vestibular heading biases, on the other hand, were strongly modified. The effect of a supine body position extended to the direction, size, and variability of the vestibular heading biases and depended on the heading angle and the stimulus plane.

Visual heading perception

Humans can estimate their heading direction based solely on optic flow stimuli (Warren & Hannon, 1988). However, heading estimates can be strongly modified by other sensory inputs, such as vestibular, proprioceptive, and somatosensory cues (DeAngelis & Angelaki, 2012). The supine body position that is required during functional imaging scanning is very uncommon when we move in everyday life; during supine orientation, gravity acts along the sagittal rather than the longitudinal axis of the head and body. Is visual heading performance, when measured in a supine body position, comparable to upright performance? We found that visual heading estimates are very similar between upright and supine body positions. In particular for the transverse plane, the most common plane of movement, we do not find significant differences in performance. This suggests that visual heading performance is not affected by a supine position and that the estimates are based exclusively on the visual stimuli, which are identical between body positions. A change in body position appears to affect vestibular heading perception as supported by the results of our vestibular heading experiment. However, the vestibular and proprioceptive sensory signals that differ between upright and supine body positions seem not to interfere

with our visual perception. This is consistent with the theories of optimal Bayesian cue integration in heading perception (Knill & Pouget, 2004; Saunders, 2014). When only visual stimuli are provided for heading perception, input from nonvisual sensory systems may be considered inaccurate or unreliable. This results in a predominant weighting of the more reliable, visual input (Fetsch et al., 2009). It has further been suggested that if a sensory system is considered inaccurate or unreliable, it can be eliminated from the weighting process (Brandt et al., 2002). If a purely visual heading stimulus is shown, vestibular brain regions are even deactivated (and vice versa) (Brandt, Bartenstein, Janek, & Dieterich, 1998; Brandt et al., 2002; Wenzel et al., 1996). Thus, although noisy or conflicting information may exist between visual and nonvisual systems due to the supine body position, this suppression could explain why our visual estimates are unaffected.

For visual stimuli in the coronal body plane, the differences we find between upright and supine body positions are very small. There is weak evidence that subjects perceived the presented heading direction more counterclockwise in the supine position compared to when they were upright. Because biases may exist in both body positions, we cannot say whether the estimates improve or deteriorate in a supine position. Such an offset may be a true property of perceptual processing or an artifact of the experimental manipulation. Correcting the heading biases for errors induced by the response device removes the reported main effect, favoring the latter explanation.

Taken together, we found no evidence that visual heading estimation performance is impaired by a supine body position. Although this first appears in conflict with previous work (Bourrelly et al., 2010; MacNeilage et al., 2010), we believe that the effects are a result of the different experiments performed. MacNeilage et al. (2010) examined heading discrimination for roll-, not pitch-tilts, of the body. The task in Bourrelly et al. (2010) was to judge heading elevation in the sagittal plane, and they did not examine supine body orientation. In addition, subjects were instructed to judge heading in world rather than body coordinates. Visual motion perception may still depend on the task and the complexity of the visual stimulus. Studies on navigation, for instance, usually use complex structured environments (Doeller, Barry, & Burgess, 2010; Spiers & Maguire, 2006) that might be less compatible with the supine body position. The relative weighting of earth- to body-related reference frames will likely play a stronger role in these more complex structured environments (Bourrelly et al., 2010).

Although heading biases have not been investigated previously for a supine body position, heading accuracy and precision based on optic flow stimuli have been extensively studied for an upright body position (see

Lappe, Bremmer, & van den Berg, 1999, for review). The systematic heading biases we observe for upright individuals estimating heading directions from coronal and transverse optic flow are consistent with previous studies using similar heading range, optic flow type, and stimulus characteristics (Crane, 2012, 2014a; Cuturi & MacNeilage, 2013; however, see de Winkel, Katliar, & Bulthoff, 2015). In the transverse plane, biases are systematically oriented toward lateral directions (Crane, 2012; Cuturi & MacNeilage, 2013). These biases have been explained using population vector decoding models based on the distribution of directionally selective neurons in the dorsal medial superior temporal areas (MSTd) of primates (Gu, Fetsch, Adeyemo, DeAngelis, & Angelaki, 2010). MSTd is known to integrate visual and vestibular stimuli, and a larger number of left/right–sensitive neurons have been found compared to fore/aft–sensitive neurons, which may lead to the lateral bias. For coronal optic flow, we find biases similar to those described by Crane (2014a). He also reports weak visual biases with a high precision compared to vestibular estimates and a tendency to overestimate the vertical component of the heading directions. Our error sizes are considerably larger (around twice as large) than those found in Crane's (2014a) study, and our subject's variabilities are considerably smaller, which may be due to the higher number of repetitions in our study.

Vestibular heading perception

We also measured the effect of a supine body position on vestibular heading perception. The vestibular system is directly affected by the change in body position because the otoliths transduce the combination of gravity and linear acceleration stimuli. We hypothesized that a supine body orientation would have a significant effect on vestibular heading perception, and this hypothesis was confirmed. The effect extended to the direction, magnitude, and variability of the vestibular heading biases. We assume that this is caused by the change in the position of the otoliths relative to gravity (i.e., a pure effect of body orientation regardless of movement direction). Alternatively, it could be due to a change in the orientation of the stimulus plane relative to gravity (i.e., an effect of movement direction in world coordinates). Our experimental design does not allow us to tease apart these two possibilities. However, heading discrimination has been shown to depend on body orientation relative to gravity and not on movement direction in world coordinates (MacNeilage et al., 2010). We therefore favor the same explanation for the current effects. In MacNeilage et al. (2010), the best performance (i.e., the smallest thresholds) on the heading discrimination task was observed in an upright position with a horizontal (transverse) accelera-

tion, and the worst performance was observed in a side-down body position together with a vertical (sagittal) stimulus plane. Here, we found that the effect of the supine body position on absolute bias and variability was larger in the coronal plane than in the transverse plane in support of previous results. Because we most often move in the horizontal (transverse) plane, it is conceivable that we are better able to compensate for the effects of a supine position on vestibular sensitivity when moving in the transverse plane than for vertical planes of movement, such as the coronal plane.

Analogous to visual heading biases, previous studies have most frequently investigated upright vestibular heading biases in horizontal and vertical stimulus planes (Crane, 2012; Cuturi & MacNeilage, 2013; Telford & Howard, 1996). In the present study, upright, transverse, vestibular heading estimates were systematically biased toward straight ahead, similar to the findings of Telford and Howard (1996), who measured visual and nonvisual heading biases for a limited range of heading directions. However, our results are contrary to the biases shown in Crane (2012) and Cuturi and MacNeilage (2013), who reported the biases to be systematically biased toward lateral directions. For visual biases, the absolute bias was much larger than the variability (i.e., constant error was large relative to variable error; Figure 2B, C) whereas approximately equal values of absolute bias and variability were found for vestibular heading perception (Figure 3B, C). This suggests that the subjects were relatively uncertain when giving their estimates (i.e., variable error was large relative to constant error). As a consequence, small variations in the experimental design might affect the biases measured. Our study used a HMD for presenting the response dial. This adds inertia to the head that must be stabilized by neck muscle commands, which have been recently shown to impact perception of linear translation (Crane, 2014b). This stabilization behavior could lead to a reversal in the direction of the observed biases relative to prior research. Additionally, the amount of stabilization will obviously differ between upright and supine positions, contributing to differences in the observed biases depending on body orientation. Indeed, the pattern of biases observed in the supine orientation, in which HMD inertia would play less of a role, are more similar to biases reported previously for the transverse plane in upright subjects (i.e., overestimation of oblique heading angles). Our response dial did not include tick marks for various angles as in Cuturi and MacNeilage (2013), and the written heading estimates show slight biases toward straight ahead (Figure 4A). Control data (not shown) suggest that the absence of tick marks may have also contributed slightly to observing biases toward rather than away from straight ahead in the upright, transverse condition.

Only one previous study has looked at vestibular heading biases in the coronal plane (Crane, 2014a) and only with subjects upright. This study described stronger vestibular biases than visual biases and in the opposite direction. Vestibular biases were consistent with overestimation of the horizontal component of the heading stimulus. The vestibular biases we observed for the coronal plane were smaller and showed no systematic pattern. This difference could again be due to the HMD adding inertia to the head, leading to increased estimates of the vertical motion component. Biases observed while supine were in the direction opposite to those reported by Crane (2014a), inconsistent with explanations based on a generalized underestimation of head-vertical relative to head-horizontal motion components. Within-subject variability was considerably lower in our study compared with Crane's (2014a). In general, we suggest that due to the high degree of variability in vestibular heading estimation, a high number of repetitions per heading direction should be acquired.

Conclusions

In this study, we explored the effects of a supine body position on visual heading perception in order to understand the behavioral consequences of the position imposed by functional imaging data acquisition. We found that vestibular heading perception is strongly modified by a change in position; however, our perception of heading direction from 3-D optic flow is not affected. Visual motion direction identification is comparable for supine and upright body orientation.

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CHAPTER 3

The neuronal representation of self-motion
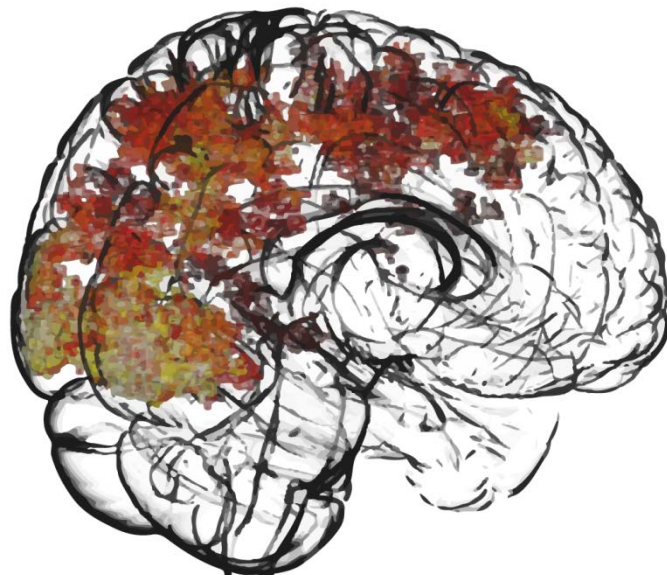
consistent, visual motion directions

Image created with MRIcroGL (http://www.mccauslandcenter.sc.edu)

The neuronal representation of self-motion consistent, visual motion directions.

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ABSTRACT

Self-motion through an environment creates visual motion patterns on our retinae. We can use these patterns to determine the direction of our self-motion. A number of brain regions have been suggested and investigated regarding their roles in this process. However, knowledge about the cortical processes from stimulus perception to heading estimate are still widely unknown. 26 subjects participated in an fMRI experiment, during which they discriminated self-motion consistent optic flow stimuli, simulating different heading directions on the transverse plane. Using classical univariate and modern multivariate analysis approaches, we evaluated cortical sensitivities to the direction of self-motion. Multivariate pattern classification allowed us to reveal differences in the activation patterns evoked by eight different self-motion directions across early visual and higher visual processing stages, posterior parietal association cortices and frontal and cingulate cortices of motor control and cognition. We evaluated regional contributions of different attributes, like the overall flow pattern and temporal sequence of the flow, to these findings and compared the location of these regions to regions discussed previously in the regard of self-motion perception (V3A, MT+, V6, VIP, CsV, as well as occipito-temporal visual association and frontal areas). We observe strong effects of the flow pattern, which is determined by the position of the flow origin and the type of self-motion. In particular radial flow is encoded uniquely compared to other flow types across all mentioned processing stages consistent with our behavioral results showing best performance for heading discrimination from straight ahead and straight backwards. We further observe a specific role of expanding vs. contracting flow in occipito-parietal and posterior parietal areas, consistent with the concept of cortical looming detectors, and a role of the temporal flow sequence in occipital regions. We conclude that a broad network of cortical regions is involved in the estimation process of heading direction from an optic flow stimulus and create a general concept about the stages of visual processing of a heading direction throughout the cortex.

INTRODUCTION

The human brain is constantly confronted with the processing of visual motion. Objects or individuals that are moving around us, but also movement of our own eyes, head and body create motion patterns on our retina. According to the most popular model, cortical visual processing from V1 on is divided on two main streams of processing, the dorsal ('Where') and the ventral ('What') stream (Ungerleider & Haxby, 1994; Ungerleider, 1982). Attributes of visual motion are evaluated throughout these processing streams. The dorsal stream passes V3A, V6 and the medial temporal complex MT+ on its way to the posterior parietal cortex (PPC). It is associated with spatial tasks and strongly connected to the frontal motor cortices, facilitating visually guided actions (Goodale & Milner, 1992). The ventral stream reaches the inferior temporal cortex via V2, V3 and V4 and is associated with the recognition of objects, colors and forms and temporal comparisons of visual motion (Corbetta et al., 1991; Cornette et al., 1998; Orban et al., 1998).

When we move through our environment, an optic flow is created on our retina. A characteristic of this self-motion consistent visual motion is that there is one singularity of flow (SoF), often referred to as the focus of expansion (FoE), from which all object motion originates (or closes to, in case of a backwards motion). We can estimate the direction of our self-motion, our heading direction, from the optic flow pattern, that is determined by the position of the SoF (Gibson, 1950). Knowledge about the cortical processing of this specific, self-motion consistent, visual motion comes from different research fields. Motion areas V5/MT and MST have been investigated extensively using electrophysiological methods (e.g. Albright, 1989; Duffy & Wurtz, 1991, 1995; Gu et al., 2007; Page & Duffy, 1999; Saito et al., 1986; Tanaka et al., 1986; Tanaka & Saito, 1989), showing neuronal sensitivity to motion direction and the global flow pattern. Area MST (Page & Duffy, 1999), and more recently ventral intraparietal area VIP (Bremmer, Duhamel, et al., 2002; Bremmer, Klam, et al., 2002), have further been described to respond to multisensory stimulation and to different SoF positions. In addition to single cell recordings, observations from patients with brain lesions provided valuable information about the importance of occipito-parietal regions for complex motion discrimination tasks, such as heading estimation (Vaina, 1998). More recently, non-invasive functional imaging methodologies, like fMRI or PET, have been used to investigate the role of specific brain regions during self-motion perception in the functioning human brain. Many more regions have since then been described to respond to self-motion consistent optic flow stimuli (Cardin, Hemsworth, et al., 2012; Cardin & Smith, 2010; Furlan et al., 2014; Pitzalis et al., 2010; Wall & Smith, 2008) or to visuo-vestibular self-motion sensations (Brandt et al., 1998; Indovina et al., 2005; Kleinschmidt et al., 2002; Kovacs et al., 2008). A general overview of regions involved in the estimation of a heading direction and their specific roles, is, however, still missing. Previous studies often focus on single regions of interest and use passive viewing or similar tasks instead of an actual heading estimation task. The fact that visual motion processing strongly depends on the actual task (Cornette et al., 1998;

Peuskens et al., 2001), suggests that these approaches might miss certain regions important for heading estimation.

Here we compared activation patterns evoked during the active judgment of eight different heading directions, using novel approaches of multivariate pattern classification (Haxby et al., 2001; Kriegeskorte et al., 2006). The heading directions represented eight linear self-motion directions on the transverse plane, i.e. our main motion plane, while keeping the gaze directed at straight ahead. Using a whole brain searchlight approach (Kriegeskorte et al., 2006), we identified brain regions showing self-motion direction specific activation patterns. We then compared pairs and groups of heading directions to reveal which attributes determine the activation patterns of different self-motion directions. We found above chance level classification accuracies across the eight self-motion directions in a broad cortical network of occipital, occipito-parietal, occipito-temporal, parietal, frontal and cingulate areas. All regions showed particularly unique activation patterns for radial, and specifically for straight forwards motion, compared to other flow types. We also identified a difference between looming (expanding) and contracting stimuli in regions involved in self-motion perception, and found evidence supporting the role of temporal comparison in ventral visual regions (Cornette et al., 1998; Orban et al., 1998).

METHODS

1. Subjects

26 subjects (eight females, mean age: 23.85, range: 19-32), participated in the study. They had normal or corrected to normal vision and no history of neurological disorders. All subjects gave written informed consent to participate in the study, which was approved by the ethics committee of the medical faculty of the Ludwig Maximilians University and performed in accordance with the Declaration of Helsinki.

2. Optic flow stimuli

Three-dimensional optic flow stimuli (Figure 1A) were created using the OpenGL library implemented in Matlab (The Mathworks Inc., Version R2009b). Stimuli were created so that the observer was put in a cloud of two-dimensional green triangles (with a base and height of 0.7 cm). The observer's viewing frustum had a vertical field of view (FOV) of 60°, a horizontal FOV of 91.49°, a near clipping plane at 20 cm and a far clipping plane at 200 cm. Linear translations through the cloud of triangles were simulated into eight transverse heading directions ('main directions', -135°,-90°,-45°, 0°, 45°, 90°, 135° and 180°) and specific comparison directions (details below). The number of triangles within the FOV of the observer was kept constant at approximately 800 throughout the

movement. One stimulus lasted two seconds, with a sinusoidal acceleration profile, a total displacement of 26 cm, a peak velocity of 0.26 m/s and a peak acceleration/deceleration of 0.41 m/s² (Fig. 1A, upper right corner). A fixation dot was located 150 cm away from the observer. Subjects were instructed to fixate that spot throughout stimulus presentation. Though this might affect task performance of the subjects slightly, it was necessary in order to avoid activations related to eye movements, and performance level played a minor role in this study.
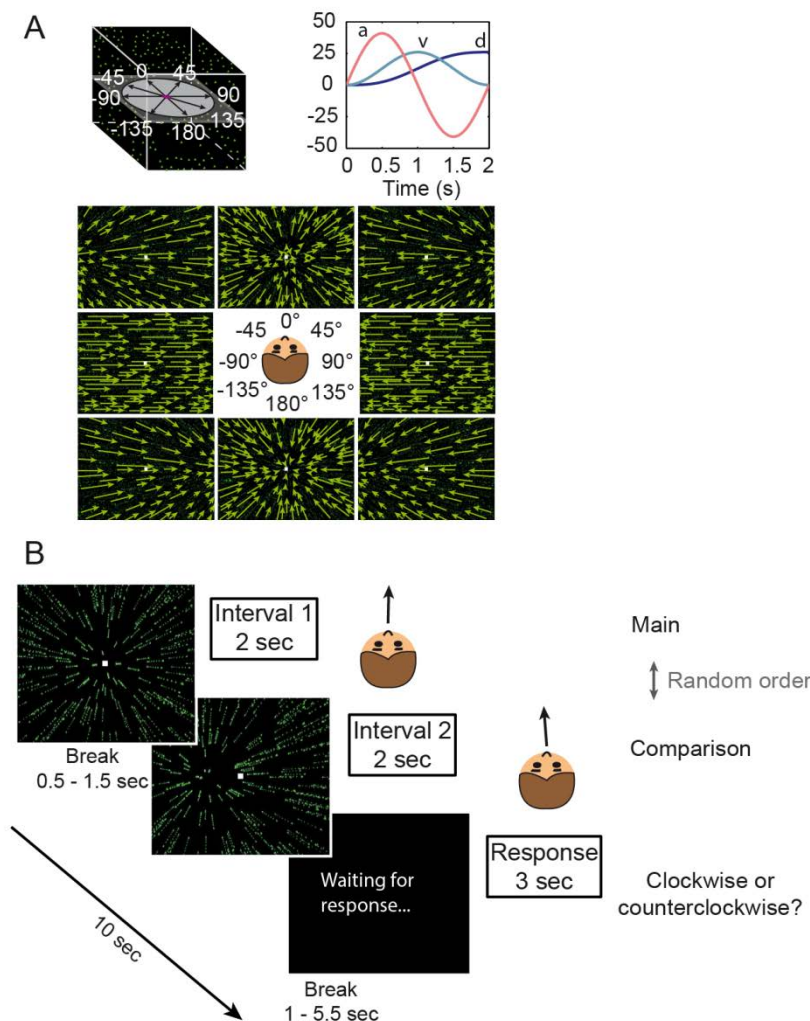
Figure 1. Stimulus profiles and task. A. Stimulus profile. The observer experienced translations through a 3D cloud of green triangles. Illustration of the motion patterns created by the eight directions of self-motion in the transverse plane, that were used for analyses. Green arrows represent object motion directions. Upper right corner: Speed profile of the simulated movements. a = acceleration (cm/s²), v = velocity (cm/s), d = distance (cm). B. Exemplary sequence of one fMRI trial (32 trials per run, 5 runs). Figure created with Matlab (The Mathworks Inc., Version R2009b) and Adobe Illustrator CS6.

3. Hardware for stimulus presentation

The experiment was divided into sessions outside the MR scanner (training and determination of the comparison interval, see below) and inside the MR scanner (actual fMRI experiment). For sessions outside the MR scanner, stimuli were rendered on a head-mounted stereo display (HMZ-T2, Sony Corporation) with a horizontal field of view of 45°, a display resolution of 1280x720 pixels and a refresh rate of 60 Hz. Inside the MR scanner, MR compatible stereo goggles with a horizontal FOV of ~30°, a display resolution of 800x600 pixels and a refresh rate of 60 Hz were used to render the 3D stimuli. Pilot experiments ensured that the results of the sessions outside the MR scanner were transferable to the scanning sessions.

4. Task

During the fMRI experiment, subjects performed a 2AFC heading discrimination task (Figure 1B). One trial consisted of two consecutively presented heading directions (each 2 seconds). Between the two intervals was a break of 0.5-1.5 seconds (to jitter the HRF). One of the two intervals contained one of the eight main directions, the other interval contained a comparison direction. The comparison direction was computed by adding or subtracting a fix number of degrees (determination described below), from the reference direction. The subject should then decide, if the second heading direction was clockwise or counter-clockwise compared to the first. They were instructed and trained to judge self-motion, and not object-motion. After the end of the second interval, they had three seconds to give their response per button press. The duration of one trial was kept fix at 10 seconds. The scanning session consisted of five runs. Each run had four repetitions for each of the eight reference directions, i.e. 32 trials per run, presented in random order. It was shown in a previous study that the supine body position, required by the fMRI scanner, does not affect our visual estimates of heading direction (Hummel et al., 2016).

5. Behavioral experiment

The experiment was divided on three sessions. The fMRI data was acquired only in the third session. The two previous sessions were used to train the subjects in the task and to simultaneously determine the respective comparison directions for all eight main directions. Because the goal of our fMRI experiment was to compare brain activation across eight different heading directions, we needed to ensure, that the heading estimation process was equally difficult for all main directions. Otherwise, differences in brain activation could have been due to differences in the level of difficulty. This means, that before fMRI measurement, we determined one heading direction for each main direction, which the individual subjects could discriminate in 90% of the cases from the respective main direction. Pilot

measurements in the MRI scanner showed, that this level was not too easy but feasible, so that subjects would neither lose concentration, nor reply randomly.

To find the heading directions corresponding to this level, subjects performed a very similar paradigm to the one used during fMRI data acquisition, with the difference that the direction of the comparison interval varied according to a Bayesian adaptive staircase algorithm, described as the PSI method (Kontsevich & Tyler, 1999; Prins, 2009, http://www.palamedestoolbox.org). This method can be used to determine the threshold and the slope of a psychometric function (PF). Instead of estimating threshold and slope, which usually requires about 300 trials, we only acquired the slope of the PF, and kept the threshold constant at $0°$ (difference between the two presented heading directions). This was possible, because we were not interested in the exact threshold value (which would be the direction, for which subjects chose correctly in 50% of the cases), but in the value representing 90% correct responses. To ensure reliability of our acquired slope estimate, we performed two sessions (on separate days) of 50 trials for each reference direction, and compared the resulting slope estimates of both sessions with a paired t-test. If a significant difference existed, which was the case in 4.8% of the tests, the staircase was repeated for the concerned direction. We used the slope estimate of the last trial of the last session to plot a cumulative normal PF (threshold $0°$, guess rate 0.02, lapse rate 0.02) and determined the difference in degree between reference and comparison direction, for which a correct response was given in 90% of the cases. This difference was then equally often added and subtracted from the reference direction and formed the comparison interval in the fMRI session.

6. fMRI data acquisition & analysis

Image acquisition was performed on a 3T MRI Scanner (Siemens Skyra) with a standard 8-channel head coil. Scanning was divided into five runs of task performance, followed by one functional localizer run and one anatomical scan. 34 contiguous transverse slices (slice thickness 3 mm, no gap), covering the cerebrum, were acquired using a gradient echo echo-planar-imaging (EPI) sequence. The MR parameters were: TR 2.4 s, TE 30 ms, flip angle $75°$, resolution 2×2 mm, matrix size 100×94 voxel, FOV 192 mm. The 3D T1-weighted high-resolution structural image of the entire brain ($0.8 \times 0.8 \times 0.8$ isotropic voxel size) was acquired using a fast spoiled gradient recalled sequence.

6.1 Functional Localizer

Many regions of the human brain have been described to respond to visual motion (Dupont et al., 1994; Sunaert et al., 1999). We used a functional localizer scan, where we contrasted coherent and incoherent visual motion versus a static image to identify different brain regions, that are discussed to be involved in the analysis of self-motion consistent visual motion.

One trial of our functional localizer consisted of three blocks, each lasting 16 seconds. The first block (COH) showed coherent optic flow, a radial optic flow pattern, similar to the 0° and 180° conditions of the main experiment, which alternatingly expanded and contracted with a frequency of two seconds. The second block (INCOH) showed incoherent object motion, i.e. random motion of the triangles, independent to one another, and inconsistent with self motion. In the third block (STA), static triangles were shown. Breaks of altogether five seconds per block were jittered between the blocks. The localizer consisted of eight trials, thus lasting around seven minutes, and was performed directly following the experiment. To sustain the subjects' attention, a counting paradigm was included in the session: the fixation spot changed its color with a frequency of one second. Subjects were instructed to count the number of times the fixation spot turned blue. Data were preprocessed including realignment to the mean image, coregistration to the corresponding anatomical image, segmentation and normalization into MNI space and smoothing with an 8-mm FWHM Gaussian kernel. Using the GLM, blocks of motion (COH & INCOH) were contrasted against blocks of no motion (STA), for each subject individually. We then identified clusters corresponding to motion responsive regions of primary visual, visual association cortices, and higher association cortices. The primary visual cortex V1 is the first stage of cortical visual processing, and provides an analysis of basic motion properties within small receptive fields. Along the dorsal visual stream, we identified visual association areas V3A, MT+ and V6, which all show large receptive fields and have been discussed regarding their importance of global flow field computations (Cardin, Hemsworth, et al., 2012; Cardin, Sherrington, et al., 2012; Cardin & Smith, 2010; Morrone et al., 2000; Pitzalis et al., 2010; Tootell et al., 1997; Zeki et al., 1991) and the ventral intraparietal area VIP, a region of the posterior parietal association cortex, which shows, besides a large receptive field, sensitivity to multisensory stimulation and to the position of the SoF, and is therefore considered to play an important role during heading perception (Bremmer, Duhamel, et al., 2002; Bremmer, Klam, et al., 2002; Wall & Smith, 2008). Of the ventral visual stream, fusiform (FG) and lingual (LG) regions of visual association cortices are specifically activated by successive motion discrimination tasks and thus presumably involved in the judgment of temporal factors (Cornette et al., 1998; Orban et al., 1998). Further we looked at two frontal regions, corresponding to the same ROIs described by Sunaert and colleagues (Sunaert et al., 1999), one located within the precentral gyrus (PreC), thus likely associated with motor execution, and one within the superior frontal gyrus (SFG) of the prefrontal cortex, which is associated with tasks involving cognition, memory and decision making. We also identified the cingulate sulcus visual area (CSv), that is discussed regarding its role in self-motion perception (Furlan et al., 2014; Wall & Smith, 2008).

For each subject and each cortical hemisphere, we searched for these regions of interest (ROIs) in the motion vs. static contrast, and then calculated the mean across the coordinates of all subjects showing corresponding activations. Around these mean coordinates a sphere of 8mm radius was built using MarsBaR 0.43 (Brett, 2002) to form the ROIs. For the results of all subsequent whole-brain analyses,

we then determined the extent of the overlap with these ROIs in order to make statements corresponding to specific motion sensitive brain regions.

6.2 Experimental Runs

In this section, we describe the preprocessing and analyses of the fMRI data acquired during the five runs of task performance.

Preprocessing & Preparation. All functional imaging data were preprocessed using Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, University College London) on Matlab 8.2.0.701 (R2013b). All images were slice time corrected, realigned to their mean image and coregistered to their corresponding anatomical image. The anatomical image was segmented into tissue probability maps based on MNI space, and used to normalize the functional volumes. Smoothing of the functional data was performed using a 4-mm FWHM Gaussian kernel. Single subject data was high-pass filtered with a cut-off 128 s. Eight regressors were modeled, representing the eight main directions -135, -90, -45, 0, 45, 90, 135, 180, and convolved with the hemodynamic response function (HRF). The regressors were then, together with the motion parameters of the realignment, fed into a general linear model (GLM).

Voxelwise differences. Voxelwise T-contrasts were modeled for each direction on the single subject level and then compared pairwise across the eight directions using an F-contrast on group level. After FWE correction only two early visual clusters remained, so we show uncorrected maps here (p <= 0.001). Voxels that shared a face were combined to clusters, and clusters < 10 voxels were discarded. This type of analysis tells us where in the brain we find direction-specific differences in the activation level of single voxels. This means it can only find differences that are caused because some directions evoke a stronger or a weaker activation than others.

Searchlight MVPAs. Multivariate pattern analyses (MVPAs) were performed using the toolbox cosmomvpa (http://cosmomvpa.org/, Oosterhof et al., 2011) running on Matlab. In this type of data analysis the data is divided into training and test sets. A classifier is used to identify class-related differences of activation patterns across a predefined number of voxels in the training data set, and its resulting classification accuracy is then determined by testing it on the test data set. In contrast to the single-voxel analysis described above, this approach can identify more subtle differences between the single directions. In the searchlight approach, one MVPA is performed for each voxel included in the analysis (i.e. in our case, all cerebral voxels), thereby considering activation patterns within a number of neighboring voxels to identify class-related differences. First, we tested from which brain regions we could successfully predict which of the eight heading directions was being presented, i.e. which brain regions show direction-specific activation patterns.

We then further explored these results in follow-up analyses, to evaluate how the single directions or factors that determine the direction of heading in an optic flow stimulus, might contribute to the overall result. We therefore performed single searchlight MVPAs for each pair of direction (in total 28 comparisons), and for groups of directions according to certain factors that determine the visual appearance of a heading direction (Figure 2). We distinguished between the factors 'pattern' and temporal attributes 'looming' and 'laterality'. With 'pattern', we refer to the pattern of flow that is determined by the position of the SoF and the type of self-motion, independent of temporal attributes. For example, 0° and 180° show the same flow pattern (central SoF, linear translation, i.e. a radial pattern), but considering temporal sequences, they can be expanding (0°) or contracting (180°). This means, when we explore the classification accuracies for the factor 'pattern', we group directions with identical SoF positions: 0° & 180° vs. 45°&-135° vs. -45° & 135° vs. -90 & 90°. For the factor 'looming', we group expanding (-45°, 0°, 45°) vs. contracting (-135°, 180°, 135°) directions and for the factor 'laterality', we group leftwards (-45°,-90°,-135°) vs. rightwards (45°, 90°, 135°) self-motion directions.
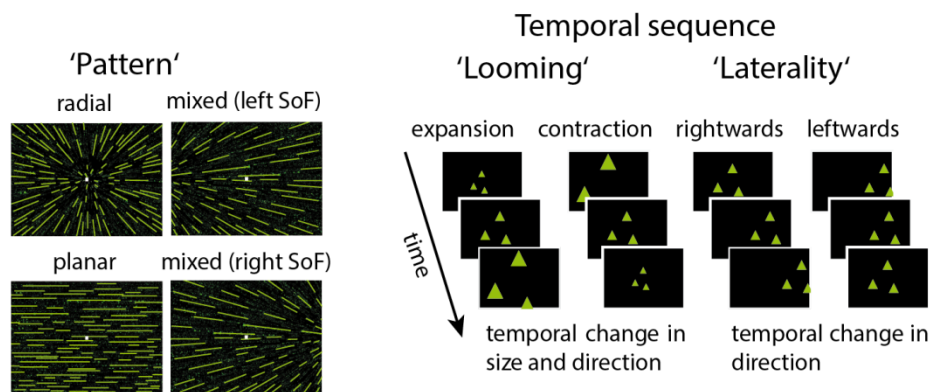
Figure 2. Factors determining a heading direction from optic flow. We distinguished between factor 'Pattern': groups of directions with identical SoF positions (0°+180°, -90°+90°, -135°+45°, 135+-45°) and factors determined by the temporal sequence of the flow ('Laterality': left vs. rightwards flow, and 'Looming': expanding vs. contracting flow). Figure created with Adobe Illustrator CS6.

For all analyses, we used a spherical searchlight of 100 voxels size. Training and test data were defined using a leave-one-run-out crossvalidation strategy. We used the support vector machine LIBSVM as linear classifier (Chang & Lin, 2011). Whole brain input beta images were masked with the group image containing only common voxels of all subjects.

The resulting accuracy maps of all subjects were statistically evaluated using random-effect cluster statistics corrected for multiple comparisons implemented in cosmomvpa, with threshold-free cluster

enhancement and 10000 permutations (Smith & Nichols, 2009; Stelzer et al., 2013, p <= 0.05). This method estimates the probability to generate above-threshold clusters of a specific size with an identical data set, but with randomized targets (i.e. simulating a situation where the classifier necessarily fails) and compares the actual accuracy levels and cluster sizes to this threshold instead of comparing single voxel accuracies against a fix (and possibly less realistic) chance-level.

RESULTS

1. Behavioral data

Table 1. Difference to main direction in degrees for 90% correct responses

Main directions								
	-135	**-90**	**-45**	**0**	**45**	**90**	**135**	**180**
Mean*	9.68	11.09	10.35	2.75	9.04	10.36	11.81	2.71
SD*	4.36	5.91	4.45	1.63	5.27	5.10	4.95	1.79

* across all subjects (n = 26).

In the pre-scan training sessions we attained subject-specific values for task performance. Table 1 shows the mean (+-SD) difference in degrees, for which subjects could successfully discriminate comparison and main direction in 90% of the cases. Best task performance was shown for 0° and 180°. For all other directions, the 90% threshold was significantly increased (one-way ANOVA across directions: $F_{(7)} = 17.47$, $p < 0.0001$).

For each subject, these individual threshold values were used to create the comparison intervals during fMRI data acquisition. This should ensure equal levels of difficulty across all eight main directions, so that direction specific differences in signal intensity were independent of direction specific levels of difficulty. This measure was successful, as no significant differences in task performance during scanning could be found across the eight directions ($F_{(7)} = 0.98$, $p = 0.45$). The mean percentage (±SD) of correct responses during scanning was 78.94 ± 5.88 %. We expected the decrease in performance due to the differences in hardware between training and scanning sessions (see Methods section *3. Hardware for stimulus presentation*). By choosing the 90% threshold from the training sessions, we thus attain still clearly above chance level performance during scanning.

2. fMRI data

2.1 Localizer

Table 2. ROI coordinates

	x,y,z (mm)	
	LH	RH
Primary		
V1	-6,-82,-1	6,-82,0
Visual association - Dorsal		
V3A	-18, -92, 12	17, -90, 14
MT+	-44, -72, 5	48, -68, 4
V6	-16,-77,30	16,-79,31
Higher association - Dorsal		
VIP	-26, -49, 51	26, -49, 47
Visual association - Ventral		
FG	-24, -64, -11	26, -63, -6
LG	-15, -79, -12	15, -79, -8
Frontal/Cingulate		
PreC	-51, -1, 43	50, -2, 41
SFS	-34, -4, 55	35, -7, 54
CSv	-15,-21,41	15, -22, 44

Contrasting coherent and incoherent object motion patterns against static objects from our functional localizer allowed us to identify motion-responsive regions of the human brain. We created spherical ROIs (radius 8mm) for the primary visual area V1, visual association areas V3a, MT+ and V6 and the parietal higher association area VIP of the dorsal stream, and visual association areas LG and FG of the ventral visual stream, as well as for frontal (PreC, SFS) and cingulate (CSv) regions involved in visual motion perception. With the described localizer scan we could identify all ROIs in at least 11 of 52 hemispheres (26 subjects --> 52 hemispheres). Table 2 shows the location of these regions, i.e. the coordinates of the mean local maxima across all subjects. Figure 3 shows the spherical ROIs build around those center voxels with an 8 mm radius.
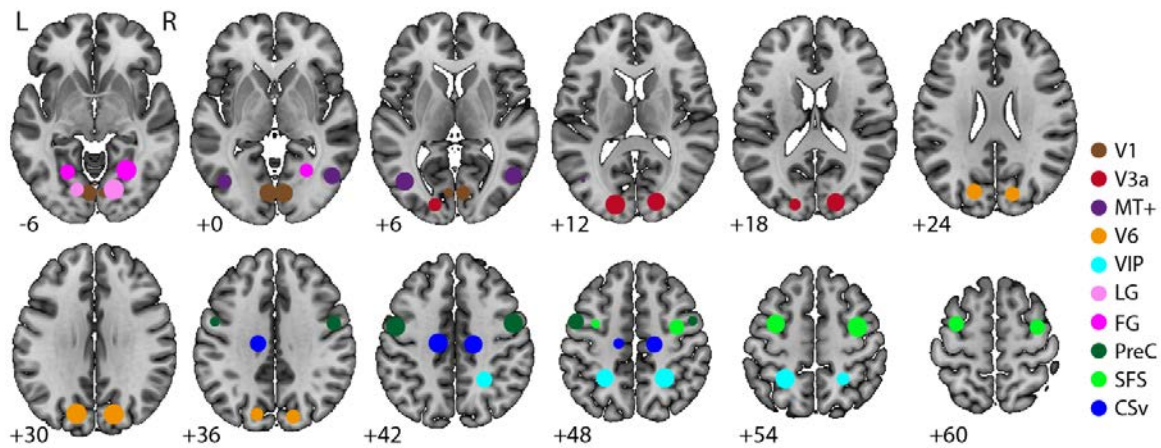
Figure 3. ROIs. Spherical ROIs (radius 8mm) were built around the mean coordinates across all subjects showing activation in the respective regions in the motion vs. static condition of the localizer. Figure created with MRIcroGL (Version 11 October 2014, www.mccauslandcenter.sc.edu) and Adobe Illustrator CS6.

In the following sections, we will evaluate the extent to which our results overlap with the location of these regions, in order to make statements regarding the sensitivity of specific regions, discussed in the literature regarding their role in self-motion perception.

2.2 Single-voxel activity

In a first approach to identify self-motion direction sensitive brain regions, we looked at voxelwise signal intensities during the estimation of the eight main heading directions.

Clusters of voxels, showing significant activation differences across directions were found bilaterally in occipital, occipito-temporal and occipito-parietal brain regions, along the intraparietal sulcus of the right hemisphere, and within two frontal regions in the area around the anterior middle frontal gyrus / frontal pole of the right hemisphere. Figure 4A shows these clusters, together with the ROIs from Figure 3 overlaid on 12 axial slices of the standard MNI brain. The ROIs V1, LG, FG, V3a and also V6 overlap to some extent with significant clusters. The clusters along the intraparietal sulcus seem a bit more lateral than area VIP. In figure 4B, the clusters are shown on a glass whole brain view. The bar plots illustrate mean cluster activities for each of the eight heading directions. Each color represents one cluster. Clusters were defined by grouping significant voxels that shared a face. It is apparent, that most occipital clusters show a preference for either 90° or -90°, while left-hemispheric clusters seem to prefer rightwards heading directions and vice versa. This suggests a role of flow laterality in these regions. The two intraparietal clusters show a different pattern: All cardinal directions (0°,+-90° and 180°) evoke activations, while oblique directions do not. A similar pattern, although less clear, is shown in the two frontal clusters.

After FWE-correction only few occipital clusters along V1 and the lingual gyrus remain. The results were independent of task performance during scanning, because they did not change when we added task performance as a covariate.
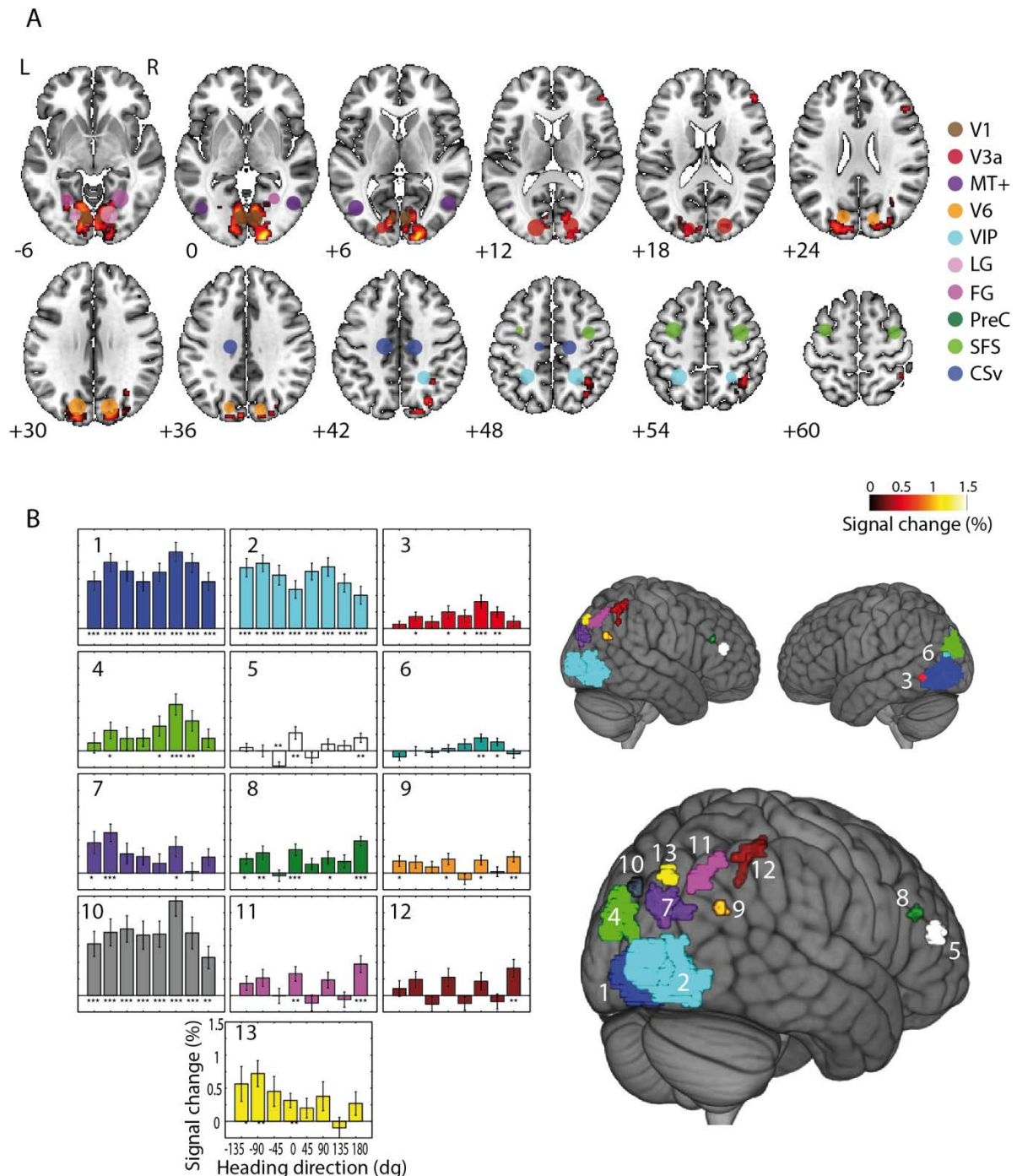
Figure 4. Results of the univariate analysis. A) Brain regions showing differences in single voxel intensities across eight different directions of self-motion (red-yellow, p < 0.001, uncorr., only clusters >10 voxels) are shown together with predefined ROIs (colored circles) overlaid on 12 axial slices of the standard MNI brain. B) Significant voxels sharing a face were grouped to clusters. For each of the 13 clusters, we determined the mean percent signal change (± SE) across the eight heading directions. Colors refer to the single clusters, and are not related to A. Figure created with MRIcroGL (Version 11 October 2014, www.mccauslandcenter.sc.edu) and Adobe Illustrator CS6.

2.3. Searchlight MVPA: All eight directions

In contrast to univariate analyses which are limited to voxelwise comparisons, multivariate analyses look at patterns of activity within a set of voxels, and thus allow us to reveal also subtle differences across conditions. Here we used a searchlight analysis to identify brain regions where our classifier could, on the basis of activation patterns within a set of 100 voxels, successfully identify which of the eight heading directions has been presented. Classification accuracies above chance level (random-effect cluster statistics, FWE-corrected, 10000 permutations, $p < 0.05$) were found bilaterally (with a left-hemispheric dominance) throughout the occipital cortex and the parietal lobe, as well as in frontal motor regions, the cingulate gyrus and parts of the prefrontal cortex (Figure 5). The general accuracy level in these regions is not particularly high (max. mean accuracy across subjects: 19.71%), however, many neighboring voxels show above-threshold classification, supporting the validity of the results. The results suggest that in early visual cortices, as well as in visual association cortices and higher association cortices of multimodal integration and in frontal and cingulate association cortices some form of pattern evaluation takes place. A closer evaluation of these findings is given in the next sections.
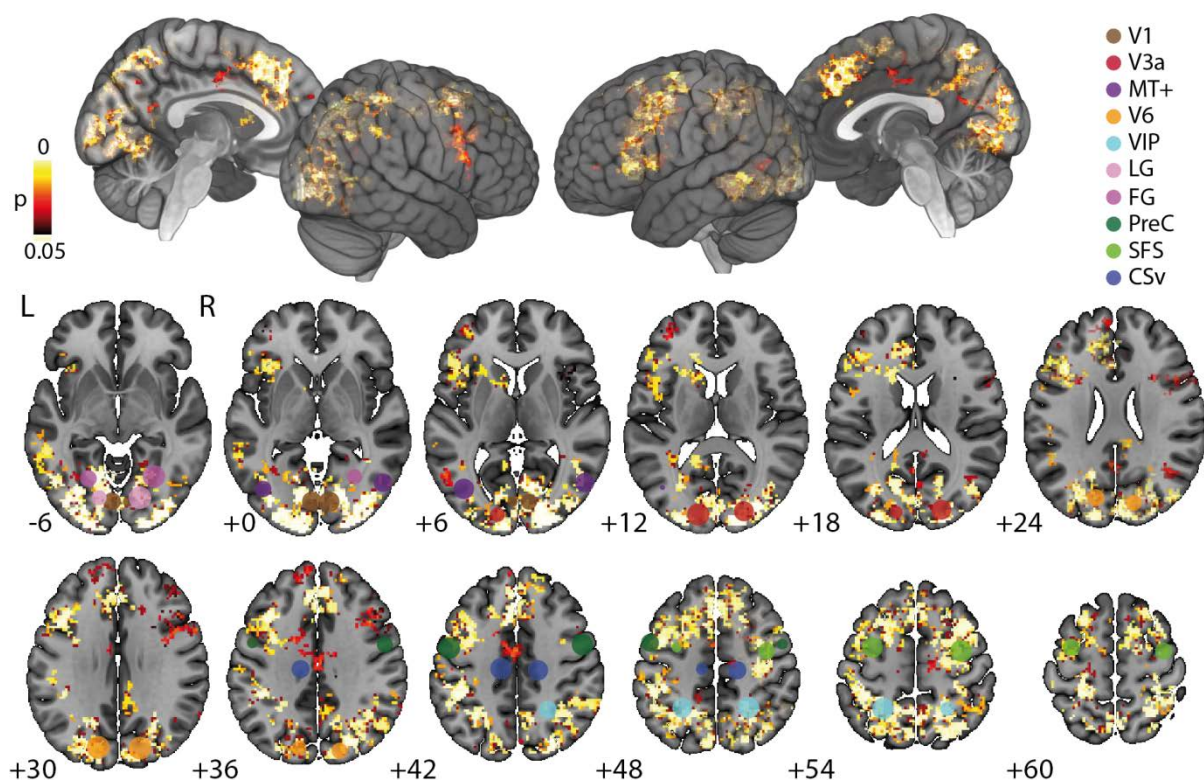
Figure 5. Results of the searchlight MVPA across all eight directions. These regions showed significant above chance-level classification of the eight heading directions (random-effect cluster statistics, FWE-corrected, 10000 permutations, $p < 0.05$) The colored circles represent the localized ROIs. Figure created with MRIcroGL (Version 11 October 2014, www.mccauslandcenter.sc.edu) and Adobe Illustrator CS6.

When we compare our results with the locations of our motion-sensitive ROIs, we find that almost all ROIs overlap to some extent with these regions (Figure 5). The overlap is negligible for areas CSv, PreC, and MT+, suggesting that these regions might not be particularly involved in visual heading discrimination on the transverse plane. Cingulate areas showing significant results are more anterior than CSv, adjacent to the supplementary motor area. CSv has been described to distinguish between self-motion consistent and self-motion inconsistent optic flow (Wall & Smith, 2008), it also has been shown to respond less to random than to static motion (Wada et al., 2016), suggesting a very specific role of area CSv in detecting self-motion. Our results suggest that this role does not necessarily include heading discrimination. Regarding frontal motor regions, mainly areas of the premotor cortex and the SMA show significant results, more than the primary motor cortex itself. This suggests that planning and control of motor function is more affected than motor execution. We also observe only a partial overlap with area MT+, which is somewhat surprising because this region is known to be highly sensitive to the (uniform) direction of object motion, and its subregions MT/V5 and MST have been reported to be involved strongly in the evaluation of optic flow patterns and heading perception. However, the tasks of areas MT/V5 and MST in self-motion perception seem to differ (Morrone et al., 2000), and the position of these regions can vary considerably across subjects. Thus it is conceivable that our approach of determining the amount of overlap with a spherical ROI that has been meaned across subjects misses out important functions of either one of these subregions.

2.4. Searchlight MVPA: Pairwise

The results of the classification searchlight across all eight directions reveal where in the brain a differentiation between the eight directions is possible. It cannot, however, tell how the single directions contribute to this differentiability. Therefore, we performed post-hoc pairwise classification searchlights, where we tested the separability between each pair of directions. Figure 6 shows areas of above threshold classification (random-effect cluster statistics, FWE-corrected, 10000 permutations, $p < 0.05$) overlaid on a glass brain. Obviously the most unique patterns of activation are evoked by a heading direction of 0°. This seems to be the case particularly in frontal cortical regions, where differences can be found in regions of motor planning, motor execution, decision and memory. The most distinct difference seems to be between 0° and +-90°, i.e. between a radially expanding and a lateral planar optic flow. Differences between a radially expanding (0°) and a radially contracting (180°) radial flow are found more dominantly along the inferior parietal lobule and the anterior intraparietal sulcus, as well as in a lateral occipital region and a posterior temporal region. In contrast to 0°, 180° can be separated from other directions almost exclusively in V1. We further find a cluster in the area of the posterior cingulate gyrus / parietal precuneus which shows different activation patterns for -90° vs. +90°, i.e. planar leftwards vs. planar rightwards optic flow, and in V1 and some frontal areas +90° and -90° can be separated from oblique flow patterns. A separation between of

different oblique directions is almost not possible, only one small cluster in the precuneus exhibits successful classification of -135° vs. 45°.

The results of the pairwise classifications reveal only very little overlap with our ROIs. This suggests that the differentiation between two presented heading directions from activation patterns in these regions is hardly possible. Together with the finding that a differentiation across all eight direction is, in contrast, possible, we conclude that it is probably not the 'direction' itself that is encoded in the activation patterns of these brain regions, but rather a common factor between different directions. The results of the model searchlight analysis, described in the next section, helps us to investigate this hypothesis.
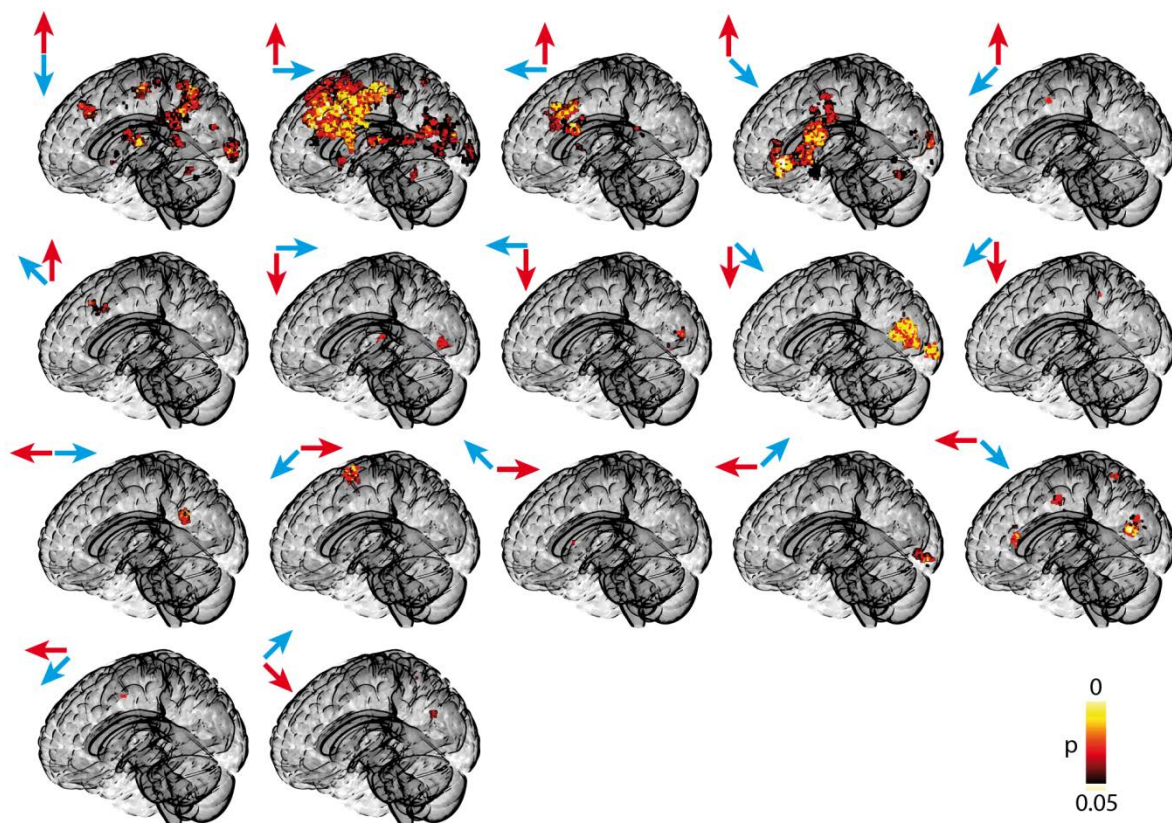
Figure 6. Results of the pairwise searchlight MVPAs. These regions showed successful (random-effect cluster statistics, FWE-corrected, 10000 permutations, p < 0.05) classification between pairs of directions. Overlaid on a glass brain. Figure created with MRIcroGL (Version 11 October 2014, www.mccauslandcenter.sc.edu) and Adobe Illustrator CS6.

2.5. Searchlight MVPA: Models

We formed groups of directions according to two attributes of a self-motion consistent flow pattern a) the overall pattern that is determined by the position of the SoF (factor 'Pattern') and b) temporal attributes, where we distinguish expansion vs. contraction (factor 'Looming') and leftwards vs. rightwards flow (factor 'Laterality'). Figure 7 shows the results of these model classification analyses.
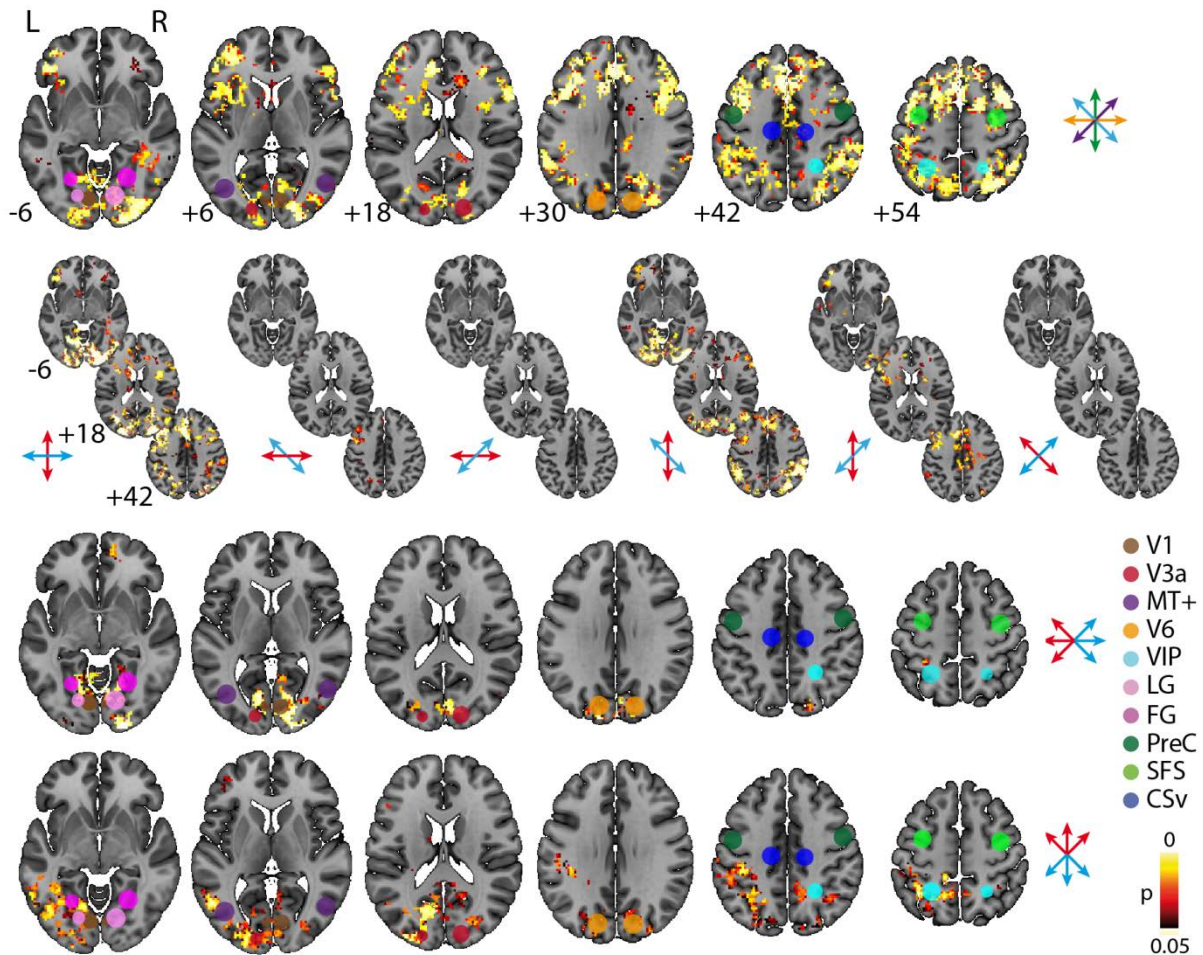
Figure 7. Results of the model searchlight MVPAs. Separate searchlight MVPAs were made for the factors pattern (first two rows), laterality (third row) and looming (last row). Red-yellow regions showed successful classification performance (random-effect cluster statistics, FWE-corrected, 10000 permutations, p < 0.05). Factor pattern: Classification across four different optic flow patterns (top row) and across each pair of flow pattern (second row). Factor laterality: Classification between left- and rightward flow sequence. Factor looming: Classification between for- and backward flow sequence. Colored circles represent the localized ROIs. Results are overlaid on 6 (respectively 3) axial slices of the MNI standard brain. Figure created with MRIcroGL (Version 11 October 2014, www.mccauslandcenter.sc.edu) and Adobe Illustrator CS6.

The factor 'Pattern' evokes clearly separable activation patterns in occipital, posterior parietal and frontal regions (Figure 7, first row). The regions are very similar to the regions that showed successful classification across all eight directions of heading (Figure 5), suggesting that the previous findings

were to some extent driven by the difference in the flow pattern. All ROIs overlap to some extent with the significant areas. When we further evaluate the classification abilities for each pair of flow patterns (Figure 7, second row), it becomes evident that radial flow can be well distinguished from other flow patterns in these regions, while less differences exist between lateral and mixed flow types, and none can be found between mixed flow patterns, composed of identical amounts of radial and lateral flow, but with different FoE positions. This is consistent with our findings from the pairwise classifications and shows that the significance of the results increases, if we consider flow patterns instead of single heading directions. The factor 'Laterality' can be decoded predominantly in regions of the occipital cortex. This includes primary visual, occipito-temporal, and occipito-parietal regions of visual processing, and implies the ROIs V1, V3a, V6, LG & FG. This is consistent with the findings of our univariate analyses, which suggested a hemisphere-dependent left-/ right- discrimination. The factor 'Looming' can be decoded from similar occipital regions, but also in more lateral occipital regions, medial occipito-parietal and in regions along the intraparietal sulcus, including also the ROI of area VIP. Both factors, 'Laterality' and 'Looming', refer to temporal sequences of the optic flow. However, while the only difference between left- and rightwards optic flow is the direction of the flow, expanding and contracting optic flow can also be differentiated by changes in the object size (Figure 2). This 'looming' factor seems to be particularly relevant for occipito-parietal and posterior-parietal regions, while more ventral areas seem to be similarly relevant for both temporal factors, suggesting a general role in temporal processing.

DISCUSSION

In this study we identified brain regions showing (visual) heading direction selective activation patterns. Activation patterns during the active judgment of eight linear self-motion directions on the transverse plane, i.e. our main motion plane, while keeping the gaze directed at straight ahead, can be differentiated on the level of single-voxel and multi-voxel activation patterns. In contrast to the univariate analysis, the multivariate analysis reveals above chance-level classification of the eight heading directions in a broad cortical network, including stages of visual processing, higher associative processing, motor control and cognition. Further inspection revealed that in all of these regions unique activation patterns are produced by the overall flow pattern, in particular for radial flow. We were also able to identify sensitivities to the temporal sequence of the flow in early visual and visual association cortices of the dorsal and ventral streams.

A whole cortical network is involved in heading estimation

The extent of sensitivity to the direction of self-motion from optic flow stimuli is much greater than expected from previous studies. It has been shown that many more regions than only occipital visual

cortices are active during the perception of visual motion (Sunaert et al., 1999), and a sensitivity to the direction of (planar) motion has been reported in particular for early visual cortices V1-V4 and area MT (Kamitani & Tong, 2006; Weliky et al., 1996; Zeki et al., 1991). Studies on self-motion perception usually focus on specific areas that show the ability to extract global visual pattern information, or are sensitive to different sensory modalities. A cortical sensitivity to the direction of self-motion from optic flow to the extent we observe in this study, has, to our knowledge, not been predicted from any previous study.

Aspects of our task design and our multivariate evaluation approach might explain these findings. First, extrastriate brain regions are specifically activated if an active heading task is performed compared to a passive viewing task (Peuskens et al., 2001). While the heading estimation task in Peuskens et al. was to decide if an FoE was left or right from straight ahead in a 2D optic flow field, our task required the active imagination of self-motion from object motion, thus suggesting a higher cognitive demand and a stronger activation of extrastriate brain regions. Further, we used 3D stereoscopic optic flow, to which some brain regions respond specifically (Arnoldussen et al., 2013; Cardin & Smith, 2011). Second, comparing the results between our single- and multi-voxel approaches reveals that, in particular higher cortical sensitivities to the direction of heading, are evident only on the multivariate level. MVPA looks at patterns of activation across several voxels instead of judging the absolute level of activation within one voxel, and is thus a much more sensitive method to detect differences across conditions (Haxby et al., 2014). While on the single-voxel level, which is typically used to analyze fMRI data, differences across the eight directions were evident only across medial occipital and few intraparietal and frontal regions (uncorrected for multiple comparisons), we could identify direction-specific multi-voxel patterns of activation in many more regions, including early visual regions, association cortices of visuo-spatial processing, dorsolateral and medial prefrontal cortices and frontal motor cortices. Third, this is, to our knowledge, the first study that combines a whole brain evaluation and a multivariate pattern classification approach, using the searchlight method suggested by Kriegeskorte and colleagues (Kriegeskorte et al., 2006), to investigate the sensitivity of cortical regions to self-motion consistent stimuli. Related previous studies either look at univariate effects across the whole brain (Pitzalis et al., 2013) or used MVPA on specific regions of interest (Furlan et al., 2014; Kamitani & Tong, 2006; Wada et al., 2016) to identify optic flow related cortical responses.

Which regions show heading sensitivity and why?

We observe sensitivity to the direction of self-motion in primary visual areas, visual association cortices of the dorsal and ventral stream, the posterior parietal cortex and in a large network of frontal and cingulate regions. We assume that the factors contributing to the heading direction sensitivity in these areas are diverse, depending on regional characteristics. For example, small receptive fields in

V1 make an evaluation of the global flow pattern in these regions rather unlikely. Uniform object motion direction can, however, be decoded (Kamitani & Tong, 2006), suggesting that the pattern differences we observe in V1 derive from local object motion differences. Extrastriate visual association cortices, such as V3A, MT, MST and V6, in contrast, can extract global motion information (de Jong et al., 1994; Furlan & Smith, 2016). Here, we do not find evidence that area MT+ is particularly involved in differentiating self-motion consistent optic flow directions, other dorsal and ventral visual association areas, in contrast, such as V3A, V6, LG and FG show direction specific activation patterns. It is, however, conceivable that by evaluating the overlap between our results and area MT+ we miss subregion-specific heading sensitivities. We can indeed observe a partial overlap with our ROI, and nearby regions show successful classification across the eight directions. This suggests that subregions of MT+ might still show heading sensitivity. We also find heading direction sensitivities along the PPC. This region is related to spatial perception and included in a variety of tasks, involving sensorimotor transformation, attention and working memory, which require a connection between posterior and frontal cortices (for a review see Culham & Kanwisher, 2001). Although we only looked at the overlap with area VIP, our results suggest that regions along the whole intraparietal sulcus (IPS), and also in the dorsal and ventral parietal lobules and the precuneus are involved in heading estimation. This includes areas such as DIPSM/L, POIPS (Kovacs et al., 2008; Sunaert et al., 1999) and PcM (precuneus motion area, Cardin & Smith, 2010), that have previously been described regarding their roles in self-motion perception. Differences in the activation patterns observed in the PPC likely reflect a differentiation of self-motion directions (Kovacs et al., 2008). The role of the frontal 'network' is harder to evaluate, because clusters spread across regions of motor control and execution, decision making and memory. Different activation patterns in these regions could be partially created by eye movements (which we tried to suppress by central fixation), or by differences in the cognitive process during task performance, which is more likely as our task is cognitively quite demanding.

Factors of heading discrimination

In an optic flow field, the position of the focus of expansion determines the pattern of the flow and thus, our heading direction. However, when we consider transverse self-motion directions across the whole 360° range, forwards and backwards heading directions with the same SoF produce identical flow 'patterns' but have different temporal sequences. Closer inspection of the differences in activation patterns across the eight heading directions revealed, that in contrast to single pairs of heading direction, these features of optic flow can be classified in specific cortical regions. We found that the results of the classification across different flow patterns, in particular if one of them is a radial optic flow, are very similar to the results of the classification across all eight directions. This suggests that the fact that radial optic flow is encoded uniquely across the human cortex drives the accuracies of classification analyses involving either 0° or 180°. The unique role of radial flow patterns has been

described in previous studies reporting a) firing preferences of neuronal populations to different optic flow components (Bremmer, Duhamel, et al., 2002; Saito et al., 1986; Tanaka & Saito, 1989) b) a radial orientation and motion bias in certain brain regions (Raemaekers et al., 2009; Sasaki et al., 2006) c) superior performance for tasks involving radial flow patterns over other flow patterns (Beardsley & Vaina, 2005; Burr et al., 1998; Crane, 2012; Cuturi & MacNeilage, 2013; Hummel et al., 2016). Our results suggest that radial flow patterns, and in particular radial expanding flow, produce unique activation patterns throughout all stages of visual processing, sensorimotor transformation and cognition. These findings are consistent with our measured heading discrimination thresholds, which were strikingly lower for radial than for other flow types. Although we matched task difficulty across motion directions, we observe these unique patterns for radial flow. This suggests that our behavioral observations can be explained by firing preferences for specific flow types in neuron populations, which is consistent with previous suggestions (Crane, 2012, 2014; Cuturi & MacNeilage, 2013; Gu et al., 2010). From our pairwise comparisons, we can also conclude that in particular 0° can be well distinguished from other heading directions. As we are used to forwards motion in everyday life, it makes sense that this motion direction is uniquely represented in different stages of cortical processing, including the analysis, spatial association and multisensory integration of the visual stimulus, but also the transformation from sensory estimates to motor response and cognition.

With the factors 'Laterality' and 'Looming' we compared groups of directions with identical flow patterns, but different motion sequences. While for the former factor, temporal differences exist only in regard to the motion direction (left- vs. rightwards object flow), the latter factor describes temporal changes in motion direction and object size (Figure 2). Previous studies suggested the existence of cortical detectors that respond specifically to 'looming' optic flow, i.e. a radially expanding optic flow with increasing object size (Regan & Beverley, 1978) and several studies reported a preference for radial expansion over other types of optic flow in different brain regions (Albright, 1989; Steinmetz et al., 1987; Xiao et al., 2006). It is interesting that we observe significant classification results for both of the factors Laterality and Looming in more ventral occipital regions, but we found above chance-level classification also in occipito-parietal and posterior parietal regions only for the factor Looming. This suggests that the temporal evaluation of motion direction might occur particularly along more ventral occipital areas, which is consistent to previous findings, reporting a role of the fusiform gyrus in the temporal comparison of motion directions (Cornette et al., 1998; Orban et al., 1998). The posterior parietal cortex, on the other hand, could indeed respond specifically to looming stimuli, which would confirm the claim for cortical looming detectors (Regan & Beverley, 1978) and underline its important role in the perception of self-motion.

Conclusions

Taken together, our findings show that we can decode activation patterns of eight different directions of self-motion in primary visual areas, dorsal & ventral visual association cortices, and higher association cortices including posterior parietal, frontal and cingulate regions. We could identify different factors of heading direction from the activation patterns in different brain regions. Radial optic flow is uniquely represented throughout these processing stages, consistent with the fact that we observed lowest heading discrimination thresholds for radial flow patterns. Apart from differences in the global flow pattern, we could decode temporal aspects of flow direction and object size from occipital primary visual and visual association cortices. We conclude that a broad network of brain regions is involved during the performance of a heading discrimination task. The extent of cortical sensitivity to self-motion consistent optic flow is larger than expected from univariate evaluation approaches. Here, we delineated a general concept of the processing stages and the possible roles of the involved regions.

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CHAPTER 4

Vestibular loss and balance training cause similar changes in human cerebral white matter fractional anisotropy

K.H., O.K., and V.L.F. conceptualized the study

K.H. designed the study

O.K. recruited subjects and conducted behavioral experiments

K.H. and V.L.F. conducted DTI experiment

O.K. analyzed the behavioral data

N.H., T.S. and V.L.F analyzed the DTI data

N.H., K.H. and V.L.F. interpreted the data

N.H. wrote the manuscript

K.H., T.S., J.L., O.K., T.B. and V.L.F. critically revised the manuscript

PLOS ONE

Vestibular Loss and Balance Training Cause Similar Changes in Human Cerebral White Matter Fractional Anisotropy

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Abstract

Patients with bilateral vestibular loss suffer from severe balance deficits during normal everyday movements. Ballet dancers, figure skaters, or slackliners, in contrast, are extraordinarily well trained in maintaining balance for the extreme balance situations that they are exposed to. Both training and disease can lead to changes in the diffusion properties of white matter that are related to skill level or disease progression respectively. In this study, we used diffusion tensor imaging (DTI) to compare white matter diffusivity between these two study groups and their age- and sex-matched controls. We found that vestibular patients and balance-trained subjects show a reduction of fractional anisotropy in similar white matter tracts, due to a relative increase in radial diffusivity (perpendicular to the main diffusion direction). Reduced fractional anisotropy was not only found in sensory and motor areas, but in a widespread network including long-range connections, limbic and association pathways. The reduced fractional anisotropy did not correlate with any cognitive, disease-related or skill-related factors. The similarity in FA between the two study groups, together with the absence of a relationship between skill or disease factors and white matter changes, suggests a common mechanism for these white matter differences. We propose that both study groups must exert increased effort to meet their respective usual balance requirements. Since balance training has been shown to effectively reduce the symptoms of vestibular failure, the changes in white matter shown here may represent a neuronal mechanism for rehabilitation.

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Introduction

Peripheral bilateral vestibular failure is a disorder of various etiologies characterized by a lack of vestibular input due to vestibular nerve or hair cell damage. Patients suffer from severe difficulties in maintaining balance, causing unsteadiness of gait and a high risk of falls. Symptoms can also include dizziness, nausea and oscillopsia, as well as cognitive impairments, although the causal relationship between vestibular failure and cognitive deficits is still unclear [1,2]. The non-invasive method of vestibular rehabilitation therapy, which comprises different balance tasks and exercises, is used to treat symptoms of vestibular failure [3,4].

Various sports also put a high demand on the ability to maintain balance, and require the use and interpretation of vestibular information to correctly perform e.g. a dancer's pirouette, without a sense of vertigo. Ballet dancers can reduce their vestibular-ocular reflex (VOR) in response to spinning [5,6] suggesting that their vestibular system is affected by the training required to perform

their sport. Slacklining, a relatively new balance sport, was also shown to decrease reflectory muscle reactions and have a positive influence on postural control [7], another behavior where vestibular information is quite important.

Both training [8] and disease [1] have been shown to lead to significant changes in brain structure, or plasticity. Vestibular failure in humans causes volumetric decreases in gray matter structures involved in vestibular processing such as the thalamus, parietal-temporal regions, area MT/V5 and the hippocampus [1,9]. Ballet training has a reductive effect on grey and white matter volume and on fractional anisotropy within frontal and motor areas [10]. Figure skating and slacklining also show structural modifications in the brain [11]. Each of these balance sports have different requirements in terms of interpreting sensory-motor information, but all require a reinterpretation of vestibular information, which is also necessary after bilateral vestibular loss. However, a comparison of the effects of vestibular loss and professional balance training on the brain structure has yet to be

done. This comparison may prove useful in understanding the mechanisms underlying vestibular disease, training and rehabilitation.

In this study, we investigated the differential effects of increased and decreased balance ability on white matter plasticity using diffusion tensor imaging (DTI). This method can be used to detect microstructural changes in white matter by measuring the water diffusion directionality in nerve fibers [12]. The fractional anisotropy (FA) of the diffusion tensor can be separated into axial (AD, parallel to nerve fibers) and radial diffusivity (RD, perpendicular to nerve fibers) components. Here, we compared the FA, RD and AD of patients with chronic bilateral vestibular failure, healthy balance trained subjects, such as ballet dancers, figure skaters and slackliners and their respective control groups to identify 1) plastic white matter changes that are related to vestibular input in general and 2) overlapping regions of white matter restructuring in both disease and training.

Methods

Ethics statement

All subjects gave written informed consent to participate in the study, which was approved by the ethics committee of the medical faculty of the Ludwig Maximilians University and performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The use of minors was accepted by the ethics committee and we obtained written informed consent from the parents or guardians of the subjects, as well as written informed consent from the subjects that were under age.

Subjects

13 patients with bilateral vestibular failure (BVF, six females, mean age: 65.38, range: 44–86), their healthy controls (BC, n = 13, five females, mean age: 63.54, range: 42–80), 18 balance trained persons, including five ballet dancers, five figure skaters, one person doing both, ballet dancing and figure skating and seven slackliners (T, eight females, mean age: 25, range 16–43) and their healthy controls (TC, n = 17, ten females, mean age: 26.18, range 21–39) participated in the study. Control subjects were matched for age and sex. TC were additionally matched for the amount of leisure sports. In other words, the controls had a certain level of physical activity, i.e. they performed leisure sports, like swimming, jogging, dancing etc., that the trained group also did in addition to their balance sport. The range of leisure sports and the overall amount of additional physical activity were comparable between the two groups. All healthy participants had no history of neurological disorders and no history of dizziness or vestibular disorders. Head impulse tests were done on all subjects to check vestibular function. Ballet dancers and figure skaters had been training for 11–34 years (16.4±6.88 years; mean ± SD), slackliners for 1–8 years (2.79±2.53 years; mean ± SD). All members of group T trained at least two hours a week, except for one dancer who had a foot injury at the time of measurement. Further details about training load, i.e. the current amount of hours spent training per week and the overall training experience can be found in Table 1. A heterogeneous balance trained group was purposefully chosen to look for overall effects of balance training, independent of the specific type of sport done.

The patients (Table 2) in this study were recruited from the Interdisciplinary Dizziness Clinic of the German Center for Vertigo and Balance Disorders, Munich and met the following inclusion criteria: 1) bilateral pathological head impulse test and 2) bilateral reduced (mean slow phase eye velocity ≤6°/s) or absent

responsiveness in the bithermal caloric irrigation 3) no clinical signs indicating cerebellar dysfunction and 4) no additional neurological diseases. All patients suffered from chronic bilateral vestibular hypofunction, i.e. at the time of measurement, they have been living with the disease for at least two years. None of the patients had regularly undergone vestibular rehabilitation therapy at the time of measurement. One patient had a mean slow phase eye velocity of 6.4°/s which marginally exceeds the lower limit of 6.0°/s. We decided to include this patient because all other inclusion criteria were matched and the limit violation was only small. Heterogeneity of disease etiology was deliberate to ensure that our findings are most likely due to a decrease or lack of vestibular sensory input and not the result of other unforeseen factors related to a specific disease.

Diffusion-weighted image acquisition

Image acquisition was performed on a 3T MRI Scanner (*Signa HDx, GE Healthcare, Milwaukee, USA*) with a standard 8-channel head coil. A diffusion weighted single shot spin-echo sequence (repetition time 10000 ms, echo time 84 ms, b-value = 1000 s/mm^2, 20 directions, 256×256 matrix, 2.5 mm slice thickness, 40 slices, FOV 25 cm, with one b0 image without diffusion weighting) was collected along with a high-resolution T1-weighted anatomical sequence (0.8 mm isotropic voxel size).

Image processing and data analysis

All preprocessing and whole brain analyses were carried out with FMRIB Software Library FSL, version 4.1.8 [13] following the protocol described in Smith et al. (2007) [14]. Diffusion data from every subject was corrected for head motion and eddy current effects using the eddy current correction tool of the FMRIB's Diffusion Toolbox (FDT). Brain images were extracted using the brain extraction tool (BET) [15]. Diffusion tensors were fitted with the FDT's dtifit tool. Voxelwise analysis of the data was carried out using TBSS (Tract-Based Spatial Statistics) [16] in FSL. All subjects' FA data were aligned into a common space (defined by the FMRIB58_FA template in FSL) using the nonlinear registration tool FNIRT [17], which uses a b-spline representation of the registration warp field [18]. Next, single subject FA images were averaged. This mean FA image was thinned using a threshold of 0.2 to create a mean FA skeleton, representing the centers of all white matter tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxelwise cross-subject statistics.

Statistics

We conducted statistical analyses to test for differences in FA between the four groups (BVF, T, BC, TC). We identified the source of the FA differences by further determining radial and axial diffusion components (RD and AD respectively). Additionally, we conducted correlation analyses to identify the effects of age and measures of cognition, training load and disease characteristics. We also tested if differences in FA exist between the different balance sports in group T. For all analyses, whole brain voxelwise statistical analyses were carried out using a Monte Carlo permutation method provided by the Randomise tool in FSL. Note that unless otherwise stated 5000 permutations were used and age was always added as a covariate of no interest in statistical designs. P-value statistical images were fully corrected for multiple comparisons across space and were generated using threshold-free cluster enhancement (TFCE) [19]. All analyses and results were considered significant if they survived the corrected threshold of

Table 1. Characteristics of subjects trained in balance sports.

ID	Sex	Age	Training type	Training (yrs)	Current training (h/ week)	Experience[a]
T01	f	40	Ballet	34	3	2040
T02	f	19	Ballet	11	48	528
T03	m	26	Ballet	19	30	570
T04	f	23	Ballet	12	7.5	90
T05	m	29	Ballet	20	42	840
T06	m	25	Figure skating	16	6	224
T07	f	17	Figure skating	13	0	130
T08	m	17	Figure skating	13	7.5	97.5
T09	f	16	Figure skating/ballet	13/12	3	130
T10	f	16	Figure skating	14	10	140
T11	f	17	Figure skating	12	10	96
T12	m	28	Slacklining	4	6	24
T13	m	24	Slacklining	1	10	8
T14	m	43	Slacklining	1	2	6
T15	f	38	Slacklining	8	6	48
T16	m	21	Slacklining	1.5	10	15
T17	m	27	Slacklining	1.5	6	9
T18	m	24	Slacklining	2.5	3	5

[a]Experience was calculated by multiplying the hours of training per week averaged over the past year by the number of years the individual had been practicing the activity.
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$p < 0.05$. White matter tracts were specified using the JHU DTI-based white-matter atlases [20] included in FSLView.

Age related issues. A major challenge of the statistical analysis of our data was that the two study groups, BVF and T, respectively their control groups, BC and TC, differed notably in age. This was inevitable, as mainly young persons regularly perform balance sports, while bilateral vestibular failure usually occurs at an advanced age. White matter FA shows considerable changes over the lifespan. It increases during childhood and adolescence, reaches a peak during adulthood and from middle age on decreases [21]. This issue made it hard to directly compare the young with the old groups. For our statistical analyses we compensated for this in several ways: Wherever possible, we compared groups that were age-matched. This applies to the separate comparisons of BVF vs. BC and T vs. TC as well as to the combined comparison of BVF+T vs. BC+TC. Additionally, we added age as a covariate in these analyses to avoid any age-related confounds.

Table 2. Characteristics of patients with bilateral vestibular failure.

ID	Sex	Age	Etiology	Time since onset (yrs)	Caloric mean SPEV[a] (°/s)
BVF01	m	79	Aminoglycosides	10	0.875
BVF02	f	86	Meningitis	69	0
BVF03	m	58	Idiopathic	4	0
BVF04	f	67	Borreliosis	14	1.175
BVF05	m	58	Traumatic	14	4.5
BVF06	f	68	Autoimmune	12	1.575
BVF07	m	65	Meningitis	35	0
BVF08	m	63	Idiopathic	2	1.75
BVF09	f	44	Idiopathic/familial	10	0
BVF10	m	61	Idiopathic	2	0
BVF11	f	66	Ménière's disease	13	6.4
BVF12	f	59	Idiopathic	2	5.25
BVF13	m	78	Idiopathic	5	2

[a]SPEV = slow phase eye velocity.
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However, the direct comparison between the two different study groups remains an interesting topic. We therefore directly compared the two study groups using age as a covariate. As the strong confound of age might overshadow actually present differences between the groups, we additionally conducted an analysis to compare BVF and T, by subtracting age-related effects beforehand. We created new FA "difference" maps reflecting the difference between BVF and BC and T and TC respectively, by subtracting the skeletonised FA map of the age-matched control from the respective study subject FA map. In this way, we created 13 difference maps for BVF - BC and 18 difference maps for T – TC. The missing TC control subject was replaced by the mean FA skeleton of group TC. We then performed the voxelwise statistical analysis on these difference maps.

We further investigated the general effect of age on FA by analyzing the correlation between age and FA. This analysis was performed by adding contrasts investigating the effect of the covariate age to the design matrix containing all subjects of the four groups.

Group comparisons. For group comparisons a model was used in which each of the four groups were modeled as a separate column, and age was a regressor of no interest. First, we compared BVF and T separately to their respective control groups. This analysis showed us where patients had FA changes compared to their healthy age- and gender-matched controls and independent of this, where trained individuals significantly differed from their control group. We then tested for differences between study and control groups, by comparing BVF and T, respectively BC and TC, first directly with age as a covariate, then by using the age-matched difference maps of FA.

In a last analysis, we compared BVF and T as a single group, to their control groups. Using the original model from the first analysis, we looked at the difference between the study groups as a whole (BVF+T) compared to the two control groups (BC+TC).

Analysis of axial and radial diffusivity. Water diffusion within the white matter of the brain is commonly used as an indicator of fiber integrity. This is because the fatty myelin layers and the cytoskeleton of the nerves determine a principal diffusion direction which is axial, i.e. parallel to the nerve fibers. Consequently, a loss of fiber integrity as well as fiber crossings within a specific region reduce diffusivity along that principal axis and promote perpendicular diffusion directions [12,22,23]. To understand the nature of the differences in FA, we calculated RD and AD for all voxels in each subject. FA is calculated in FSL according to formula (1) from the three eigenvalues ($\lambda 1, \lambda 2, \lambda 3$) that describe the size and shape of the diffusion tensor. One can see that decreases in FA can either be caused by increases in RD, decreases in AD or a combination of the two [23]. FSL output images representing the voxelwise eigenvalues (L1, L2 and L3) were used to calculate the RD and the AD according to the formulas (2) and (3).

$$FA = \sqrt{\frac{1}{2}} \frac{\sqrt{(\lambda 1 - \lambda 2)^2 + (\lambda 3 - \lambda 1)^2 + (\lambda 2 - \lambda 3)^2}}{\sqrt{\lambda 1^2 + \lambda 2^2 + \lambda 3^2}} \qquad (1)$$

$$RD = \frac{\lambda 2 + \lambda 3}{2} \qquad (2)$$

$$AD = \lambda 1 \qquad (3)$$

For all analyses showing significant differences in FA, we conducted identical whole brain voxelwise statistical analyses for RD and AD, to identify the driving tensor component that caused the changes in FA. For each analysis, 500 permutations were run.

Behavioral analyses. Because of the heterogeneity of the groups tested, we also collected data about cognitive and memory performance from all of the subjects in this study. All subjects performed the MWT-B ("Mehrfachwahl-Wortschatz-Intelligenztest B") and the Doors A and B subtest of the Doors and People test [24]. The MWT-B is a German-language modification of the National Adult Reading Test of Nelson and measures premorbid intelligence. The Doors test provides an estimate for visual recognition memory asking the subject to memorize a colored door and to identify it in an array of four doors. The two parts of the Doors test each have a maximum score of 12 points, the results of which were averaged into a single test score per subject. The MWT-B had a maximum score of 37. Using a one-way ANOVA with four levels, we compared the group means of the test results to test for significant differences in intelligence or memory between the different groups. Further, we correlated the individual test results with the voxelwise FA values to test for inter-subject interdependencies between FA and cognitive performance. Correlation analyses were performed on the demeaned test values using the Randomise tool in FSL with 500 permutations. For six subjects (1 BVF, 2 T, and 3 TC), no data of the MWT-B test could be collected. For these subjects, the average MWT-B score across all four groups was substituted in place of the missing data.

It is well known that patients suffering from vestibular loss usually show spatial memory deficits [1], and that the virtual Morris Water Task provides useful behavioral measures for spatial memory performance. However, the virtual Morris Water Task must be altered for ageing populations such that a direct comparison of spatial memory performance using this task was not possible [1,25].

In addition to cognitive and memory performance, we also looked at whether training or disease-related measures correlated with white matter FA values. For the BVF study group, we chose the caloric mean slow phase eye velocity, which is a well-known measure of the nystagmus following vestibular loss, and the time since onset of the disease as disease-related measures. As a measure of training in the T study group, we used the current training load (h/week) and the overall training experience. Training experience was calculated from the weekly training time in hours averaged across the last year multiplied with the number of years since beginning the training [11]. We also tested if differences in FA existed depending on the kind of balance sport (ballet, figure skating or slacklining) the individuals of group T performed by performing a whole brain voxelwise one-way ANOVA across the FA values within the three different subgroups of T. These analyses were done with the Randomise tool in FSL with 500 permutations.

Results

1. Comparisons between study groups and their controls

Each study group was compared to their respective control group. The comparison between patients and their control group showed that BVF patients had a reduced FA in distributed white matter pathways (Figure 1A). Affected fibers could be found in the corpus callosum, the anterior and posterior forceps, the right anterior thalamic radiation, the fornix, the left external capsule, the left uncinate and superior longitudinal fasciculus and bilaterally in the inferior fronto-occipital fasciculus.

The analysis of the axial and radial diffusion components showed an increase in RD in similar brain regions for BVF
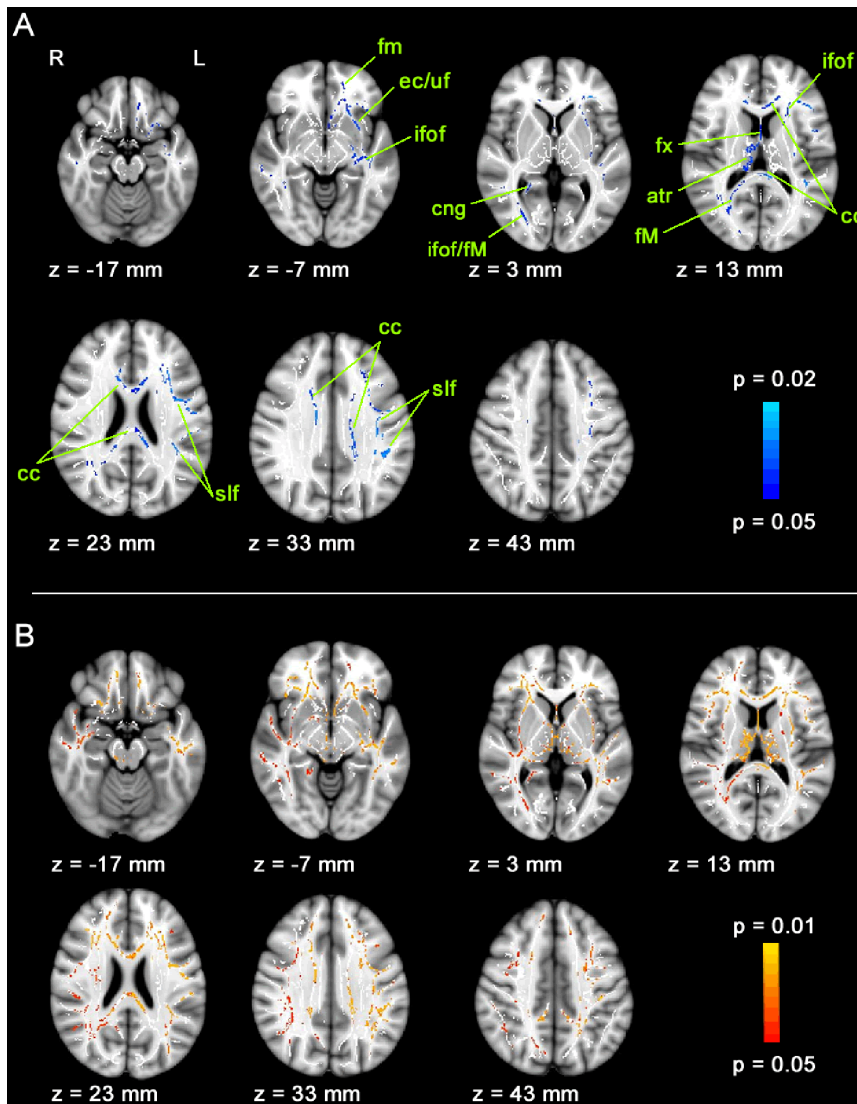
Figure 1. Fractional anisotropy and radial diffusivity changes in patients suffering from vestibular loss. A. FA is reduced in patients compared to their healthy control group. Voxels showing a significant lower FA of BVF compared to BC are shown in blue. Altogether, 11,546 voxels were significant; atr = anterior thalamic radiation, cc = corpus callosum, cng = cingulum, ec = external capsule, fm = forceps minor, fM = forceps major, fx = fornix, ifof = inferior fronto-occipital fasciculus, uf = uncinate fasciculus, slf = superior longitudinal fasciculus. B. RD is higher in patients compared to the control group in similar areas (red-yellow). Significant voxels are overlaid on seven axial slices of the MNI152_T1_1mm_brain standard image included in FSL and the mean FA skeleton mask (white).
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compared to BC (Figure 1B), while AD was also slightly but not significantly increased (p = 0.078). This suggests that the reduced FA is a result of a stronger radial diffusion rather than of less axial diffusion.

No significant differences in FA were found between trained subjects and their control group.

2. Differences between patients and trained persons

No significant differences were found for BVF and T, nor for BC and TC, when comparing them directly, with age as a covariate. In order to compare patients and trained persons without the confound age, we created and compared the FA difference maps of the two study groups and their respective control groups. Significant differences were found only in a small region of the corpus callosum (Figure 2). In this region, the difference in FA was significantly greater between BVF and BC

than between T and TC. We then looked at those voxels in the mean FA maps for each group. BVF showed a lower FA in this region than BC, while T had a higher FA than TC. No significant differences were found for the comparison of the RD and AD maps.

3. Comparison of both study groups together to their controls (BVF+T vs. BC+TC)

Patients and balance trained subjects showed similar changes of FA compared to controls in widespread white matter tracts (Figure 3A). All affected brain regions showed a reduction of FA in the study groups compared to the control groups. No regions showed a significant increase of FA. Areas of reduced FA in patients and trained individuals can be sorted into different functional categories. First, the corpus callosum, which is the main connection between the two hemispheres, was affected. Second,
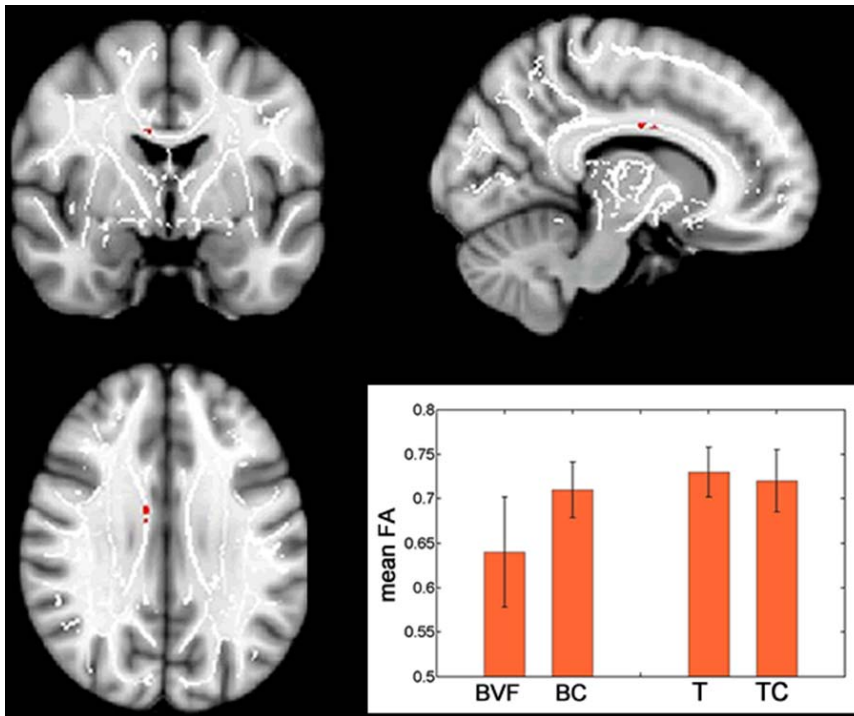
Figure 2. FA difference map comparison. FA difference maps were created and compared for BVF-BC and T-TC. These maps differed in a small area of the corpus callosum (red). Within this area, patients (BVF) had a lower FA compared to their control group (BC), while balance trained persons (T) had a slightly higher FA compared to their control group. Significant voxels are overlaid on the MNI152_T1_1mm_brain standard image (x = 10 mm, y = −3 mm, z = 29 mm) included in FSL and the mean FA skeleton mask (white). The cluster of significant voxels comprised 53 voxels.
doi:10.1371/journal.pone.0095666.g002

the thalamus, which is the main relay station for peripheral fibers running to the cortex, showed reduced FA in its entire white matter skeleton. Then, the internal capsule, carrying fibers of the corticospinal tract, the main motor pathway, showed reduced FA. The fornix, an intralimbic communication center connecting various limbic structures including the hippocampus, the septal region, the mammillary bodies, the prefrontal cortex and the cingulum was also affected. Finally, FA reductions also apply to association fibers. The inferior fronto-occipital, superior longitudinal and uncinate fasciculus, which all connect the frontal lobe to rostral parts of the brain, all had a reduced FA. The analysis of the diffusion components showed, that the increase in FA in these areas is a result of a significantly higher RD in the two study groups compared to the control groups (Figure 3B). AD was also slightly, but not significantly increased. Mean FA, RD and AD within significant voxels are summarized in Table 3.

4. Effects of age on FA

Across all subjects of the four groups, FA showed a significant negative correlation with age in wide-spread white matter regions (Figure 4). Interhemispheral connections, i.e. fibers of corpus callosum, forceps minor and forceps major, connective fibers between thalamus and frontal cortex (anterior thalamic radiation) as well as between thalamus and visual cortex (optic radiation), the fornix of the limbic system and association fibers of the uncinate and inferior-occipital fasciculus showed significant FA decreases with age.

5. Behavior and FA changes

To test for cognitive differences in the study groups, all participants performed the MWT-B and the Doors test. The

one-way ANOVA showed significant differences between the groups on both tests (MWT-B: $F(60) = 3.89$, $p = 0.013$, Doors: $F(60) = 3.02$, $p = 0.037$). The results are shown in Table 4. No single group showed systematic performance on the cognitive tests. Mean MWT-B scores (± SD) were 32.45 (±2.58) for BVF, 31.77 (±2.71) for BC, 28.82 (±4.64) for T and 31.15 (±1.81) for TC out of a total score of 37, and the mean Doors test scores were 8.42 (±2.14) for BVF, 9.15 (±1.34) for BC, 9.75 (±1.51) for T and 10.05 (±1.30) for TC out of a total score of 12. Interestingly, the patients performed better on the MWT-B test than trained subjects, whereas TC performed better on the Doors test than patients.

We also correlated the test scores of the cognitive tests with the voxelwise FA values for each subject, to test if the neuropsychological tests correlated with white matter diffusivity. However, no significant correlations between cognitive performance and FA values were found, suggesting that the results that we do see, are not related to cognitive performance.

We also assessed whether disease- or training-related measures were correlated with differences in FA. We did not find significant differences in FA between the different balance sport types ballet, figure skating and slacklining within the trained group. Further, current training load and training experience did not correlate with the FA. Also, patients' FA did not correlate significantly with the caloric mean slow phase eye velocity or the time since onset of the disease. Taken together, these results suggest an overall effect of balance effort on FA changes instead of specific training or disease-related effects.
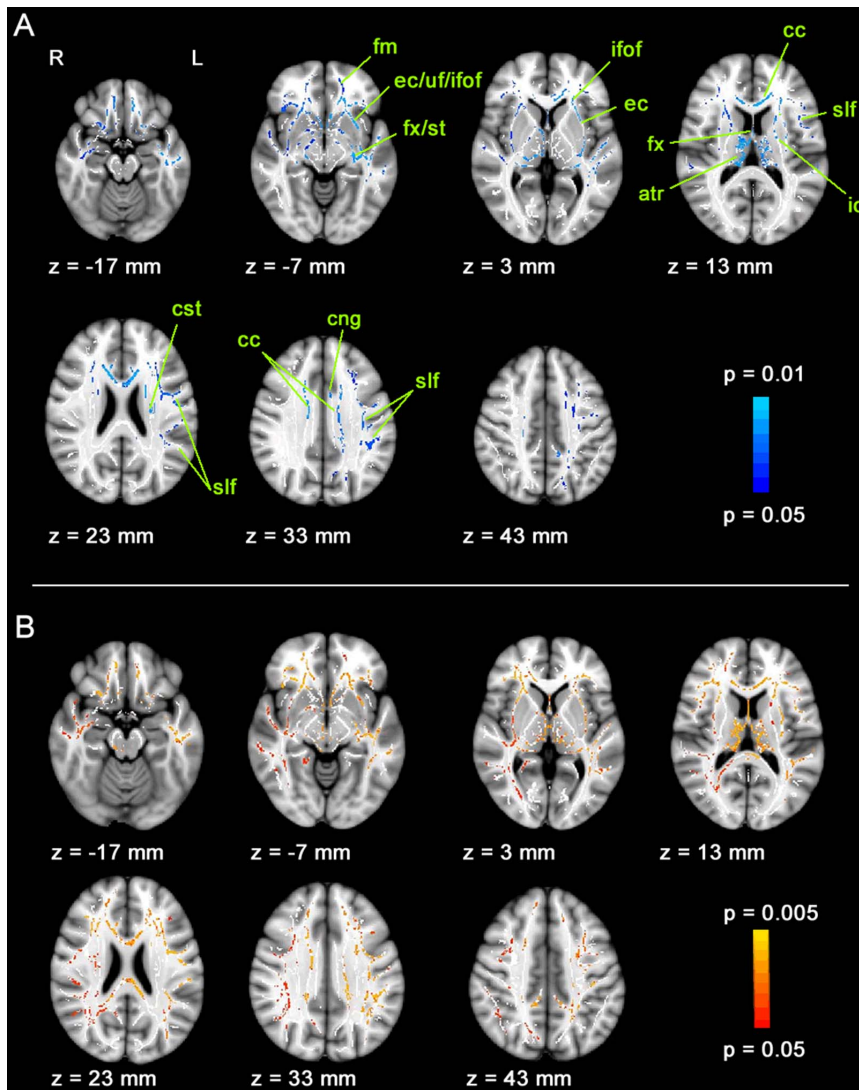
Figure 3. Fractional anisotropy and radial diffusivity changes of patients and balance trained persons. Both study groups, patients with bilateral vestibular loss and balance trained individuals show FA reductions and RD increases compared to their control groups. A. Voxels showing a significant lower FA of BVF+T compared to BC+TC are shown in blue. Altogether, 21,933 voxels were significant; atr = anterior thalamic radiation, cc = corpus callosum, cng = cingulum, cst = corticospinal tract, ec = external capsule, fm = forceps minor, fx = fornix, ic = internal capsule, ifof = inferior fronto-occipital fasciculus, uf = uncinate fasciculus, slf = superior longitudinal fasciculus, st = stria terminalis. B. RD is higher in the study groups compared to the control groups in similar areas (red-yellow). Significant voxels are overlaid on seven axial slices of the MNI152_T1_1mm_brain standard image included in FSL and the mean FA skeleton mask (white).
doi:10.1371/journal.pone.0095666.g003

Table 3. Mean FA, RD and AD ($\pm$ SD) across all voxels that survived thresholding for the comparison between study groups and control groups.

	FA	RD (* 10^{-4})	AD (* 10^{-3})
BVF	0.45$\pm$0.029	6.61$\pm$0.72	1.35$\pm$0.056
T	0.50$\pm$0.0082	6.61$\pm$0.19	1.54$\pm$0.040
Ballet	0.50$\pm$0.0081	6.59$\pm$0.28	1.53$\pm$0.023
Figure skating	0.49$\pm$0.0064	6.65$\pm$0.15	1.53$\pm$0.041
Slacklining	0.50$\pm$0.0075	6.62$\pm$0.22	1.55$\pm$0.049
BC	0.49$\pm$0.017	5.86$\pm$0.29	1.32$\pm$0.030
TC	0.52$\pm$0.014	6.30$\pm$0.26	1.53$\pm$0.046

doi:10.1371/journal.pone.0095666.t003
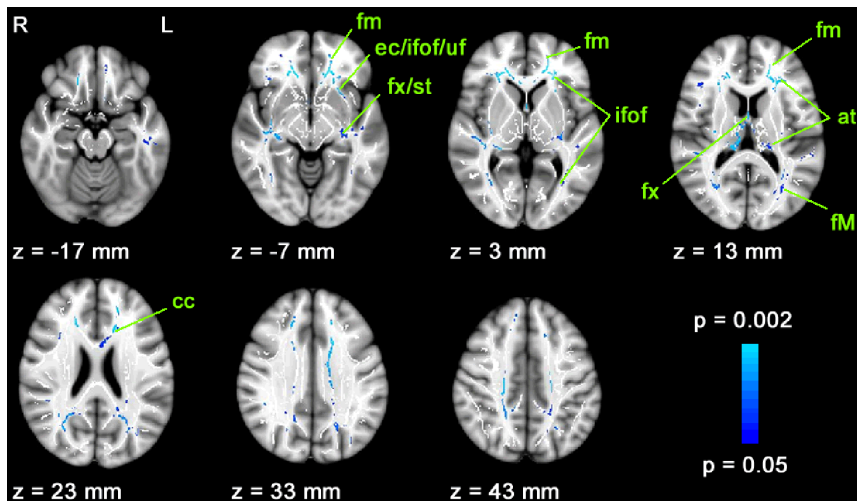
Figure 4. Fractional anisotropy correlates with age. FA values decrease with increasing age in widespread areas of white matter tracts. WM tracts showing significant correlation between FA and age of all 61 subjects are shown in blue. Altogether, 12,868 voxels were significant; atr = anterior thalamic radiation, cc = corpus callosum, ec = external capsule, fm = forceps minor, fM = forceps major, fx = fornix, ifof = inferior fronto-occipital fasciculus, uf = uncinate fasciculus, st = stria terminalis. Significant voxels are overlaid on seven axial slices of the MNI152_T1_1mm_brain standard image included in FSL and the mean FA skeleton mask (white).
doi:10.1371/journal.pone.0095666.g004

Discussion

The separate comparison of our study groups versus their respective control groups shows significant FA reductions for patients compared to their healthy control individuals, while FA reductions for trained subjects compared to their control group are not significant. Considering the small effect sizes and large number of statistical tests performed, we cannot conclude from our findings that no difference in FA exists between balance trained individuals and their controls. The mean FA over the entire white matter tract of T was lower than that of TC, which was also reflected in the comparison of both study groups together to the two control groups. This suggests, that the reductions in FA in balance-trained individuals, although not significant, affect the same white matter tracts than the FA reductions caused by bilateral vestibular failure. These tracts include widespread sensory, motor, limbic and association pathways.

Hänggi et al [10] found significantly reduced FA as well as changes in white- and gray-matter volume in professional ballet dancers. Although in our study the reduction of FA for balance trained individuals was not significant, we believe that our results are consistent with this study. Hänggi et al. tested only young female ballet dancers between 18 and 25 years, who had been training for 14.2±3.3 years. Our test subjects were female and male ballet dancers, figure skaters and slackliners between 16 and 43 years, whose total training period ranged from 1 to 34 years. We believe that the differences in groups, and in particular the heterogeneity in our trained group makes direct comparisons between the two studies difficult. However, the combined analysis of both study groups compared to the control groups shows reduced FA in areas that overlap with those found in the Hänggi et al. study.

The direct comparison of T and BVF was partially confounded by the age differences between patient population and balance-trained individuals. Using age as a covariate for the comparison of BVF and T respectively of BC and TC, we found no significant changes in FA between the groups. The negative correlation between age and FA in our data affects a broad network of white matter fibers, consistent with the literature on age-related changes in FA [21,26]. Still, using difference maps to subtract out possible age-related effects, differences between study groups were limited to a small area within the corpus callosum. Here patients showed a lower FA than their controls, while trained subjects show a higher FA than their controls. The corpus callosum is involved in a wide range of processes and connects primary and secondary motor areas between the two hemispheres [27] and as such may represent a real effect of increased vestibular training that is then decreased with less vestibular input. However, the nature of the analysis done can artificially inflate spurious differences between individuals; therefore these results should be regarded with skepticism before they are confirmed by future work.

Taken together, we conclude from our findings that both, balance training and bilateral vestibular failure cause a decrease of white matter FA that affects very similar white matter tracts in the brain. Within affected white matter tracts we find a significant increase of the radial diffusivity component. Thus, the reductions in FA in our study groups were likely a result of an increase in water diffusivity along the perpendicular diffusion directions, and not a decrease in the diffusivity along the main direction of water diffusion. They were not correlated with measures of intelligence, memory, training load or characteristics of disease, and they existed independent of the age difference between the two study groups and independent of the kind of balance sport that the individuals of group T performed.

Why is it that patients with vestibular loss, who have severe problems maintaining balance, show the same pattern of white matter plasticity as subjects who regularly perform balance sports and can maintain balance in even the most difficult of situations? We cannot exclude that we are looking at separate but overlapping effects. For a defective functioning of a sensory system, a reduction of fiber integrity seems plausible and has been seen in the past [28–30]. In contrast, it is not likely that healthy balance trained subjects show a pathologically induced loss of fiber integrity in these same regions, but is more likely due to crossing fibers [10]. Because the changes in FA that we found did not correlate with disease characteristics, the changes seen here may not be directly related to the pathology of the disease. Diffusion spectrum imaging together with q-ball imaging [31] where a more complicated

Table 4. Results of the cognitive performance tests.

ID	Doors	MWTB	ID	Doors	MWTB
BVF01	5.5	N/A	BC01	10	31
BVF02	7.5	32	BC02	8	35
BVF03	9	33	BC03	10	34
BVF04	9.5	34	BC04	9.5	26
BVF05	6.5	30	BC05	11.5	29
BVF06	11.5	36	BC06	8	31
BVF07	10	29	BC07	8	30
BVF08	9	36	BC08	11.5	33
BVF09	11.5	32	BC09	9	35
BVF10	10.5	35	BC10	9	29
BVF11	6.5	35	BC11	7	33
BVF12	7	30	BC12	8.5	33
BVF13	5.5	29	BC13	9	34
T01	10	34	TC01	11.5	30
T02	8.5	N/A	TC02	8.5	33
T03	11.5	22	TC03	9.5	30
T04	11	33	TC04	9.425	N/A
T05	10.5	28	TC05	8	N/A
T06	9.5	27	TC06	7.5	34
T07	9.5	23	TC07	9.5	31
T08	7.5	19	TC08	10	30
T09	11.5	26	TC09	11.5	32
T10	11.5	27	TC10	10	33
T11	8	25	TC11	9.5	28
T12	10	34	TC12	12	32
T13	12	34	TC13	11.5	27
T14	6.5	34	TC14	10	32
T15	10	31	TC15	10.5	32
T16	8.5	N/A	TC16	10.5	33
T17	9.5	27	TC17	11.5	N/A
T18	10	33			

Values represent the amount of correct responses out of 12 possible responses for the Doors and out of 37 possible responses for the MWT-B test.
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model for diffusion is used, may help to differentiate between increasing crossing fibers, and a reduction in fiber integrity.

Alternatively, the highly similar changes in FA and RD across both study groups rather suggest common underlying causes. The most striking behavioral characteristic that T and BVF have in common compared to their control groups is the increased effort that they have to make in order to maintain balance. Both groups need to increase balance beyond the level that is usually needed or can be guaranteed by the available sensory input under normal circumstances [32–34]. To avoid imbalance and falls, patients suffering from bilateral vestibular failure must make an effort, in part by using other sensory inputs, to compensate for the missing vestibular information. Individuals of group T do not have problems in maintaining balance under normal conditions, but during training they too must use all available sensory inputs to maximize balance and reduce vertigo. The compensation process that follows vestibular loss [35] may be the key to the structural reorganization of white matter tracts involved in balance maintenance.

An alternative common mechanism for the decreased FA in both study groups is that they both might need to suppress or reinterpret vestibular input to maintain balance. Ballet dancers reduce vestibular responses to increase balance during a pirouette [5]. When a slackliner balances on the shaking rope, typical postural responses would induce compensatory movements that could cause falls. A suppression of the vestibular information and an enhancement of visual and proprioceptive input instead would be beneficial in these cases, and have been seen for these populations [5,7]. For patients who suffer from bilateral vestibular failure, the vestibular input is reduced or non-existent. Thus, the effects on white matter could be similar to the effects in balance trained persons who suppress vestibular responses. It is even possible that a defective rest vestibular input remains in patients [36]. In this case, a suppression or reinterpretation of this vestibular input would help to maintain balance [11], particularly after compensation has occurred.

Central vestibular processing is spread across multiple brain regions, that integrate multimodal information [37]. The extent to

which short-range as well as long-range white matter fibers were affected in our study is consistent with the multimodal nature of cerebral vestibular processing. The entire thalamus was affected, suggesting the affliction of both bottom-up and top-down pathways, including sensory and motor fibers. The corpus callosum is involved in a wide range of processes and connects primary and secondary motor areas between the two hemispheres, and as such is important for the coordination of movements [27]. That both of these structures were affected suggests that the sensori-motor system was different between the study groups and their controls. The association fiber bundles that were affected play a role in various cognitive processes, e.g. visuospatial processing, object recognition and memory [38,39]. The long-range connection fibers are further an important messenger between different cortical areas.

The changes in the limbic system are particularly interesting with respect to the hippocampal atrophy and related spatial memory deficits seen in patients with BVF [1]: Vestibular failure is known to be associated with an increase in the level of glucocorticoids [40,41] and a reductive effect of these hormones on hippocampal volume was shown in various neuropsychiatric diseases [42]. Balance trained individuals have also shown a decrease in the anterior portion of the hippocampus [11], which is often related to emotional and chemical processing. The decrease in FA within the limbic system might therefore relate to a change

in relative levels of stress hormones released in these individuals, and warrants further investigation.

Although our data does not provide a definitive explanation for the similarities in white matter structure between BVF patients and ballet dancers, figure skaters and slackliners, we can conclude that bilateral vestibular loss and extensive balance training induce changes in similar white matter tracts. Balance training after vestibular loss is therefore very likely to have an effect on white matter plasticity that could help the coordination of different sensory systems for balance and postural control, and as such may represent a physiological mechanism for balance training as a method of rehabilitation.

Author Contributions

Conceived and designed the experiments: KH OK TB VF. Performed the experiments: KH TS OK VF. Analyzed the data: NH TS KH VF. Contributed reagents/materials/analysis tools: NH KH JL OK. Wrote the paper: NH KH TS JL OK TB VF.

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CHAPTER 5

General discussion

"Life is really simple, but we insist on making it complicated."

— Confucius

In this thesis, I presented three studies addressing different aspects of human self-motion perception.

In the first study (Chapter 2), we described visual and vestibular accuracy and precision in a heading estimation task covering heading directions across the coronal and the transverse motion plane, for upright and supine body positions. We found that subjects are usually very precise estimating cardinal directions, but show biases towards these directions when estimating oblique directions. The size and the direction of these biases depended strongly on the sensory cue modality, the motion plane and the body position. Further we found that a supine body position causes a decrease in vestibular estimate accuracy and precision, while visual estimates remain unaffected. We concluded that either no interactions between the task-unrelated and task-related sensory cues exist, or that due to the high visual reliability, possibly existing interactions do not have an effect (Hummel et al., 2016).

The second study (Chapter 3) looked into the still largely unknown cortical processes underlying self-motion perception. We found that multivariate activation patterns reveal sensitivities to the direction of a self-motion, encoded in an optic flow stimulus, throughout a cortical network of primary visual regions, ventral and dorsal visual association areas, posterior parietal areas of higher association and higher motor and cognition cortices. We further described, that the information encoded in these regions, corresponds less to the single heading directions than to common visual factors determining a heading direction. For example, directions with the same SoF, e.g. -45 and 135° show the same visual pattern, but different temporal sequences. We report that almost all regions show the ability to differentiate between radial and other flow patterns. Visual association cortices further seem to play an important role regarding the analysis of temporal flow sequences.

The third study (Chapter 4) addresses more general aspects of self-motion processing. We reported that patients with bilateral vestibular failure (BVF) show similar changes in white matter structure as balance trained individuals compared to control groups. Short- and long-distance connections showed a decrease in white matter fractional anisotropy, leading to the conclusion that the number of fiber crossings supposedly increased in these areas. This indicates that interactions between different sensory systems, as well as connections

between sensory cortices and higher motor and cognition cortices are strengthened in these groups. We concluded that the extensive amount of balance training, required for individuals of both groups, causes these effects (Hummel et al., 2014).

The findings of these studies contribute to the overall question on how we perceive self-motion, although in different ways. In the following sections, I would like to delineate, how they address two major topics of self-motion perception: 1. The ability to adapt self-motion perception to a changing environment and 2. the cortical processing of self-motion.

5.1. Adapting to a changing environment:
Processes of sensory adaptation and training

Multisensory plasticity allows us to compensate for temporary or long-term modifications of one or more sensory systems. If we had only one sensory system providing self-motion relevant information, we would have a hard time adapting to situations, where this modality is less reliable. By combining the inputs of different sensory systems according to their respective reliabilities, we can compensate for a sensitivity loss of one sensory modality. If one sensory modality is lost or defective, or if discrepancies between different sensory systems exist, calibration mechanisms of the single sensory systems can be observed (Zaidel et al., 2013; Zaidel et al., 2011). Two studies of this thesis (Chapters 2 and 4) focus on sensory input modifications and how they affect our perception.

In study 1 (Chapter 2) we investigated how a change in body position affects our visual and vestibular estimates of heading direction. We are used to move in upright positions, a change in body position thus conflicts with our prior expectation. A change in body position also means a change in the position of our vestibular periphery. How do these short-term changes modify our perception and can we draw conclusions about interactions between sensory systems? In study 3 (Chapter 4) we evaluated the effects of a long-term modification of sensory input. We investigated how brain anatomy is affected, if one sensory system is irreversibly damaged and compared it to the effects of

long-term training. What can we conclude about the long-term adaptation to a sensory modification?

5.1.1. Immediate effects of sensory input modification

During everyday life, we are often confronted with short-term modifications of the sensory input during self-motion perception. For example, when we put off our shoes and walk barefoot instead, when the structure or the solidity of the ground below our feet changes, or when lighting conditions change while we move. These changes can have a measurable effect on our behavior. Walking barefoot instead of in shoes might change the precision of our step, walking on shaky ground increases the amount of body tension, compensatory movements and gaze stabilization to maintain balance, walking in the dark causes us to feel our way, taking us much longer to arrive at our goal. Our brain allows us to adapt to these changes, estimating the reliabilities of our different sensory systems regarding the new situation and reweighting their respective contributions (Knill & Pouget, 2004). However, often we are tuned to certain 'usual' conditions. For example, we expect that the light comes from above ('light-from-above prior' (Sun & Perona, 1998), and that gravity acts along our longitudinal body axis ('upright prior' (MacNeilage et al., 2007; Mittelstaedt, 1983)). These priors can lead to misperceptions, if for any reason, they are not fulfilled, as for example described in the Aubert effect (Aubert, 1861).

By changing the body position in our experiment, we acted against our expectation to move upright, i.e. with our longitudinal body axis aligned to gravity, and manipulated the position of our vestibular periphery, while our visual input and the central connections between the sensory systems remained the same.

The effect of the position change on the vestibular heading estimates was striking. Estimate accuracy and precision both decreased, and the direction of the oblique heading biases changed. Figure 1 illustrates a theoretical approach to explain the effect of a supine body position on our vestibular receptors. Please note, that for reasons of complexity reduction, this approach regards the maculae of utricle and saccule as purely transverse, respectively purely sagittal. In an upright body position gravity acts perpendicular to the utricular plane,

which means that the utricular cilia are more or less unaffected by gravity, while the effect of gravity on saccular cilia is comparatively large. In a supine body position, the orientation of the cilia in respect to gravity changes, so that the effect of gravity on the utricular cilia increases. Our results suggest that this change of orientation of the otolith organs in respect to gravity causes changes in the accuracy and the precision of our vestibular heading estimates. The positioning of utricule and saccule in our vestibular periphery, making them most sensitive to motion in an upright body position, is a likely consequence of the upright prior in humans (Quix, 1925).
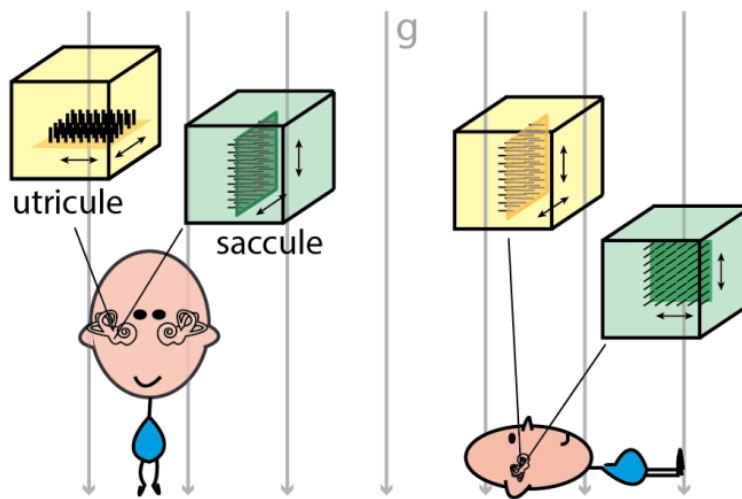
Figure 1. Simplified illustration of the position of saccule and utricle in upright and supine body position. The utricle is most sensitive to linear accelerations in the transverse plane, the saccule to linear accelerations in the sagittal plane. In an upright position, the utricle thus is unaffected by the direction of gravity, while gravity acts as a force deflecting the hair cells of the saccule. In a supine position, both, utricle and saccule are affected by gravity. orange and green planes represent the maculae of utricle and saccule, respectively. Little black stripes represent the hairs of the hair cells. Black double-headed arrows represent the deflection sensitivity of the hairs. The otolithic membrane is not shown.

In contrast to the vestibular estimates, we did not find an effect of body position on our visual estimates (Hummel et al., 2016). Previous studies suggested that body position can affect visual perception. It was concluded that the upright prior causes these effects (e.g. Aubert, 1861; Barnett-Cowan et al., 2013; Dyde et al., 2009; Harris & Mander, 2014; Kano, 1991; MacNeilage et al., 2010;

Mittelstaedt, 1983). Due to this prior we tend to perceive our body position biased towards upright. This leads to a reinterpretation, and thus a misperception, of the visual surround. Our results, however, indicated that visual heading perception is not modified in a supine position and we concluded that the high reliability of the visual estimates likely 'overrides' the effect of the upright prior on our visual estimates (Hummel et al., 2016).

For future experiments, it would be interesting to investigate how the combined visual and vestibular estimate is modified by a supine body position. This would allow to draw conclusions about the integration of visual and vestibular cues, and their dependency on body position, in the process. Our results show that the vestibular reliability decreases in a supine body position, while visual estimates stay precise (although strongly biased). According to prevailing cue combination strategies, this indicates a shift of the unisensory weights towards the visual cue. In an upright body position, the vestibular estimates are also less reliable than the visual estimates, but the vestibular cues are weighted stronger than a linear cue combination strategy would suggest (Butler et al., 2010). Is this vestibular overweighting related to the fact that we are used to move upright, i.e. our prior expectation? Or can we still observe it in a supine body position?

5.1.2. Long-term effects of sensory input modification

While the first study addressed the immediate effects of a short-term sensory modification on performance, study 3 (Chapter 4) provides valuable information regarding the long-term effects on multisensory plasticity. We compared individuals who lost bilateral vestibular sensitivity (bilateral vestibular failure, BVF), i.e. who suffered from a long-term loss of vestibular input and individuals who perform extensive balance training ('trained', T), i.e. ballet dancers, figure skaters and slackliners who require extraordinary balance skills to avoid falls, to a group of control subjects. We found that both groups show similar changes in white matter fractional anisotropy (FA) and radial diffusivity (RD), indicators of white matter integrity and structure, compared to the control group. FA was reduced throughout a network of sensory-motor and association pathways, while RD was increased. We suggested that these

differences were caused by an increased number of fiber crossings, representing training effects to the cortical network of multisensory interaction and sensorimotor transformation (Hummel et al., 2014).

How can we explain these changes in regard to multisensory integration and calibration during self-motion? Both groups, patients and trained individuals, are characterized by an extraordinary amount of balance training. Balance is a self-motion task, that is accomplished by an interplay of visual, vestibular and proprioceptive inputs. Balance training in healthy subjects allows for the performance of extraordinary types of self-motion, like pirouettes or walking on a thin and shaky line. For BVF patients it allows for the compensation of the permanent vestibular loss. According to Bayes rule, a multisensory estimate is formed by the combination of different task-related sensory inputs and our prior expectation (Knill & Pouget, 2004). In this content, the term training refers to a repeated updating of our prior distribution. When we try to balance on a slackline the first time, we will probably lose balance and fall. The reason is that we do not have any prior experience to this situation. Instead, our prior refers to the assumption that we are standing on solid ground. However, the next time we mount the line our prior will have been updated. We recognize the situation and know that an increased amount of balance will be necessary to avoid falling. By repeating this process over and over again, we will at some point be able to optimize balance, a process that goes along with structural changes in the brain (Bogdan Draganski et al., 2004; B. Draganski & May, 2008; Hanggi et al., 2010). The results of our study suggest, that balance training leads to an increasing number of fiber crossing between cortical regions, associated with the processing of balance. Stronger connections between different sensory cortices indicate a stronger extent of interaction between the sensory systems. The increase in fiber crossings between frontal motor cortices and posterior sensory cortices on the other hand, suggests an improved sensorimotor transformation. We thus concluded, that balance training leads in both groups, i.e. independent of the existence of vestibular input, to an increase in multisensory interaction and an improvement of cortical sensorimotor transformation (Hummel et al., 2014).

Taken together, the studies described in this thesis illustrate the ability of the human brain to adapt to changes in our environment during self-motion

perception. Immediate changes are reflected and measurable in our behavior, but over longer time also lead to modifications in cortex connectivity.

5.2 Estimating the direction of self-motion from optic flow: Performance and cortical processing

In this second chapter of the discussion, I would like to focus on one specific task of self-motion perception: Our ability to estimate the direction of our self-motion, i.e. our heading direction. We need this ability continuously during everyday motion and it also provides the basis for our ability to orient in a complex environment and to navigate. Although visual, vestibular and proprioceptive systems interact strongly during this process, the input of one sensory system is usually sufficient for an accurate estimate of our heading direction (Ohmi, 1996; Telford et al., 1995; Warren & Hannon, 1988). In this part of the discussion, I would like to summarize the contribution of the research presented in this thesis, regarding the performance and the cortical processes during heading estimation based on a self-motion consistent optic flow.

5.2.1 Behavioral evidence on visual heading perception

We described human performance in heading estimation and discrimination tasks for different sensory systems, body positions, motion planes, and heading directions. Independent of all these factors we can say that best performance could be observed for 0° and 180°. For more lateral heading estimates, subjects showed systematic biases towards, or away from, 0° and 180°. Surprisingly, however, although these biases can produce estimation errors of up to 50°, the precision of the visual estimates is considerably higher than, for example, for vestibular estimates.

Systematic biases in visual heading perception have been described before (Crane, 2012, 2014; Cuturi & MacNeilage, 2013). They have been argued with the specific tunings of neuronal populations in cortical regions of self-motion processing in order to maximally discriminate straight ahead from other motion

directions, at the cost of biased estimates for oblique directions (Crane, 2012, 2014; Cuturi & MacNeilage, 2013; Gu et al., 2010). In general, it has been suggested that humans and other primates show a higher sensitivity towards radial flow stimuli, compared to other flow types (Beardsley & Vaina, 2005; Burr et al., 1998), because this kind of flow pattern is most common during everyday motion. It was further suggested that cortical looming detectors exist, neurons that specifically respond to radial attributes, like the vector pattern and the change in object size (Regan & Beverley, 1978), and neuronal abilities of discriminating expansion from contraction or other types of complex object motion have been reported for a number of brain regions (Albright, 1989; Bremmer, Duhamel, et al., 2002; Duffy & Wurtz, 1991a; Steinmetz et al., 1987; Xiao et al., 2006). These explanations would be consistent with our findings of superior performance for radial flow directions.

5.2.2 Cortical processing of visual heading perception

In the fMRI study described in Chapter 3, we looked at cortical activation patterns during a heading discrimination task, with the goal to understand the processes that allow us to evaluate at any given time point, to which direction we are currently moving. Here, I would like to discuss, in how far this study helped us to identify which brain regions are involved in the process of self-motion direction estimation and what their respective tasks might be.

Using the method of multivariate pattern classification (MVPA, (Haxby et al., 2001), we were able to determine from activation patterns throughout all stages of visual processing, and also in frontal and cingulate regions of motor control and cognition, which of eight transverse motion directions was being presented. Our results suggest, that not the mere level of activation, but subtle patterns of activation need to be considered to reveal higher cortical sensitivities for the direction of a self-motion. They further indicate, that heading discrimination is a task of high cognitive demand. First, the visual input has to be evaluated, on low-level, but also on higher-level visual motion processing stages, including the spatial association of objects relative to each other and relative to the observer and the evaluation of temporal sequences. Then, two successive stimulus intervals have to be compared, a process that requires memory

performance on the one hand and decision making on the other hand - tasks of the frontal and cingulate cortices.

Together with the existing literature, I will now attempt to create a general concept about the stages of visual processing of a heading direction throughout the cortex.

Stage 1: Primary visual cortex (V1)

Neurons in V1 are oriented in systematic columns and maps, according to their preferred orientations and motion directions, respectively (Hubel & Wiesel, 1974; Weliky et al., 1996). They have small receptive fields and are unlikely to extract the global optic flow pattern. However, it has been shown that the direction of planar object motion can be decoded from activation patterns in V1 (and also in other early visual regions and MT+), and this has been explained by firing preferences of neuronal populations to specific motion directions (Kamitani & Tong, 2006). The differences across the eight flow directions, that we find in this region, on the level of single-voxel activities and on the level of multi-voxel patterns, are thus very likely based on the differences between single object motion directions.

Figure 2 illustrates a hypothetical approach to an explanation of these findings. Assuming that the smallness of the receptive fields leads to a dominance of one motion direction in a neuron's receptive field, and that neurons in V1 are sorted in mosaic-like maps of direction preference (Weliky et al., 1996), it is likely that the different distributions of object motion directions in the optic flow fields of different self-motion directions cause different activation patterns across these maps: In a radial flow pattern, all object motion directions are represented. This means neurons of all directional preferences will fire, however, only if their preferred motion direction is dominant in their receptive field. For planar flow, the same motion direction (90° or -90°) is present in every receptive field. All neurons preferring this motion direction will fire. In mixed flow patterns, different motion directions are present, but they are biased towards a certain lateral orientation. This means neurons of specific motion direction preferences will fire. The different distribution of neurons firing across the direction preference maps might thus lead to different patterns of activation

that can be measured on the voxel-level. This approach is consistent with the conclusions of Kamitani and Tong (Kamitani & Tong, 2006).
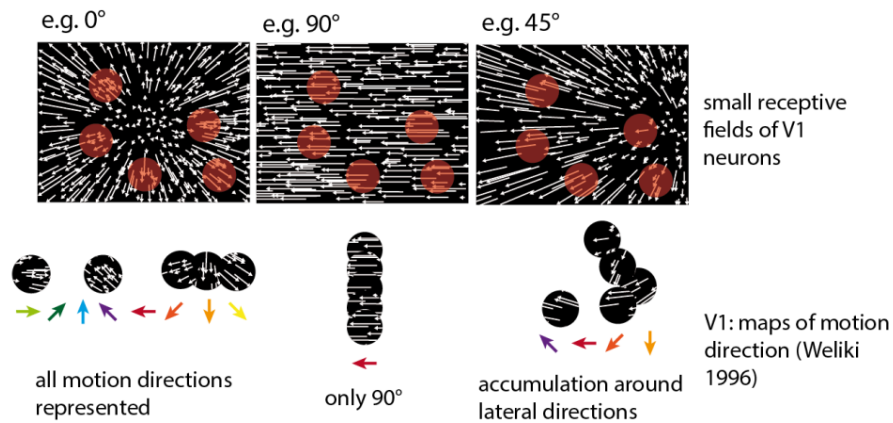
Figure. 2. Heading direction sensitivity in V1. Hypothetical explanation of why we find differences in the activation patterns on voxel-level across different heading directions. Neurons in V1 have small receptive fields. It is thus likely that within one receptive field only one dominant motion direction is present. The motion direction of a stimulus is represented in maps in V1. While a radial stimulus contains many different motion directions, a planar stimulus consists of only one motion direction, and a mixed stimulus is biased towards one motion direction. This might explain why we find differences in the activation patterns across different heading directions in V1.

Stage 2: Visual association cortices of the dorsal & ventral streams

The ventral visual stream was originally proposed to process mechanisms like object recognition and form representation (Goodale & Milner, 1992). Later its role in the temporal processing of visual motion has been described. For example, the fusiform gyrus responds specifically to successive, in contrast to simultaneous, visual motion stimuli (Cornette et al., 1998; Orban et al., 1998), and, together with the lingual gyrus, can discriminate walking from not-walking (Vaina et al., 2001).

The dorsal visual stream, on the other hand is more associated with spatial processing, evaluating the relation between different objects to each other and to the observer. Areas V3A, MT+ and V6 of the dorsal visual stream have often been discussed regarding their roles in visual motion and self-motion perception. The MT+ complex has been identified early as the 'motion center'

(Zeki et al., 1991), containing a high concentration of direction selective neurons. Area MST, which is part of the MT+ complex, has large receptive fields and seems to be highly selective to self-motion consistent visual and vestibular stimuli (Cardin, Hemsworth, et al., 2012; Duffy & Wurtz, 1995; Komatsu & Wurtz, 1989; Wall & Smith, 2008). We observed relatively little overlap of heading direction sensitive regions with area MT+. It is, however likely that differences in heading sensitivity between areas MT/V5 and MST exist that we could not separate from our MT+ mask. A suitable functional localizer to distinguish between subregions MT/V5 and MST could answer this question (Dukelow et al., 2001). The roles of areas V3A and V6 in the evaluation of global flow patterns have only been investigated more recently. Both areas have large receptive fields and show abilities to extract self-motion relevant information from the global flow pattern (Cardin, Hemsworth, et al., 2012; Cardin, Sherrington, et al., 2012; Pitzalis et al., 2010). V6 further shows a sensitivity towards self-motion consistent over self-motion inconsistent optic flow, suggesting that this region plays a particular role regarding the visual perception during self-motion (Cardin, Sherrington, et al., 2012).

The direction of a self-motion in an optic flow stimulus is represented by a certain motion pattern, that is determined by the position of the SoF and the type of motion, and the temporal sequence of object motion. To successfully discriminate different heading directions knowledge about both of these parameters is required. Our results show above chance-level classifications across eight different heading directions, and suggest the ability to distinguish different motion patterns and different temporal sequences, across the ventral and dorsal visual association areas. Consistent with earlier reports, the ventral regions seem to be specifically involved in the temporal analysis of flow patterns, rather than evaluating the global flow pattern itself, while dorsal regions show higher sensitivities to the pattern of the global flow. As V3A, V6 and the posterior parietal cortex are hierarchically connected along the dorsal visual stream, it seems plausible to conclude a hierarchical processing of the flow pattern information: V3A evaluates the global flow pattern, V6 creates associations regarding self-motion consistency, and then forwards this information to the posterior parietal cortex.

Stage 3: The posterior parietal cortex (PPC)

The PPC is a higher association area, that combines input from different sensory systems, and is involved in a multitude of functions, like attention, spatial perception, working memory, eye movements and action guidance (for a review see Culham & Kanwisher, 2001). It is part of neural network between visual areas of the occipital cortex and frontal motor areas (Rizzolatti et al., 1998), and thus a mediator to serve 'vision for action' (Goodale & Milner, 1992). A variety of regions along the intraparietal sulcus (IPS) has been mentioned in the regard to visual motion and self-motion perception: Parieto-occipital (POIPS), anterior dorsal (DIPSA), medial dorsal (DIPSM) and lateral dorsal (DIPSL), as well as a ventral (VIP) area and the medial precuneus (PcM) (Cardin & Smith, 2010; Kovacs et al., 2008; Sunaert et al., 1999). In particular VIP seems to be a promising candidate of self-motion processing. It distinguishes self motion consistent and inconsistent optic flow (Wall & Smith, 2008), responds to the position of the SoF (Bremmer, Duhamel, et al., 2002; Furlan et al., 2014), and integrates visual, vestibular and somatosensory inputs (Bremmer, Klam, et al., 2002), but the other regions seem also involved (see Table 1 in Chapter 1 - Introduction). We observe above chance-level direction classification accuracies all along the IPS and extending also to the inferior and superior parietal lobules. This suggests an important role of the PPC during heading estimation. Not only is it possible to differentiate between different optic flow patterns in this area, but we also report evidence for a sensitivity specifically to object looming. The existence of cortical looming detectors has been postulated, as forwards motion produces radial looming patterns of optic flow and behavioral experiments indicated a superior performance for this kind of stimuli (Regan & Beverley, 1978). A number of regions, including MT, MST, PPC, and FEF, has previously been suggested from electrophysiological recordings to respond specifically to this type of stimuli (Albright, 1989; Saito et al., 1986; Steinmetz et al., 1987; Xiao et al., 2006). Our results are consistent with these reports and show that this preference for looming stimuli might also be apparent on a larger scale of neuronal activity.

Higher Stages: Frontal regions of motor control and cognition.

Projections from the visual streams, particularly from the PPC, reach the frontal association cortices. These areas control top-down processes necessary to initiate motor responses and cognitive processes like memory and decision making. Previous studies mention a number of frontal regions, that show specific activations during direction discrimination tasks (Cornette et al., 1998; Peuskens et al., 2001). These comprise the frontal operculum and the middle frontal gyrus, which are both mentioned in regard to temporal processing of successive motion intervals (Cornette et al., 1998) and the precentral sulcus, supposedly corresponding to the frontal eye fields (Cornette et al., 1998; Sweeney et al., 1996), associated with premotor processing and the guidance of actions (Wise et al., 1997). In macaques, the frontal eye fields have also been reported to show sensitivity towards looming stimuli (Xiao et al., 2006), to be strongly connected to areas MSTd and VIP and to respond to visual and vestibular heading stimuli (Gu et al., 2015). Frontal activations were observed to be more dominant during active heading tasks, rather than during mere passive viewing or simple direction estimation tasks (Cornette et al., 1998; Peuskens et al., 2001). It has been suggested that these frontal areas represent the final stage of the stimulus processing, where visual stimuli from the PPC are transformed into motor commands (Peuskens et al., 2001) or transferred into working memory (Cornette et al., 1998). Consistent with these previous reports, we observe a sensitivity to the direction of a self-motion in frontal areas. However, the extent that we observe is much greater than previously reported. A large cluster across superior and middle frontal and precentral gyri extending to the frontal pole and the anterior cingulate gyrus shows successful classification results. Differences in activation patterns occur particularly between radial and other flow types. We suggest that these results reveal a unique encoding of radial, in particular of radially expanding, optic flow. This might be a cortical representation of our cognitive prior, i.e. the fact that we are used to forwards heading, and it might partially be caused by eye movements (for radial flow the position of the fixation point and the SoF are identical). Alternatively, the observations in the prefrontal cortex could be a result of the high cognitive load needed to imagine self-motion from object motion, i.e. transforming object motion estimates into self-motion estimates without the multisensory input provided during an actual body-translation.

Towards a general concept of cortical heading processing

Taken together, the pattern of an optic flow, encoding the direction of a self-motion, produces specific activation patterns throughout all stages of cortical processing. Here, I presented a theoretical framework of how direction sensitivity might be represented across these stages: 1) Evaluation of simple object motion in V1 2) Evaluation of the global flow pattern (temporal and pattern factors) in dorsal and ventral visual association cortices 3) Evaluation of the self-motion direction in the PPC and 4) Motor control, memory, decision making and transformation from object to self-motion in frontal regions.

Although this suggests a highly hierarchical processing along stages, observations from brain lesion patients suggest, that different stages might work independent of each other (Vaina, 1998; Vaina & Soloviev, 2004).

5.2.3 Combining behavior and cortical processing

Our performance studies showed us how good we are in estimating or differentiating between different heading directions. Are we able to explain these observations with our findings about cortical activation patterns?

Our results indeed suggest that the performance levels that our subjects showed for discriminating or identifying different heading directions are reflected in cortical activation patterns. It has been previously reported that visual cortical processing is highly task-related. In study 2 (Chapter 3) we looked at cortical activation patterns during a cognitively demanding heading discrimination task and indeed we observe a large parietal and frontal network of regions to be involved in an extent that has not been previously reported. These findings suggest, that our subjects did not simply compare patterns of object motion, but that the task indeed involved the imagination of a self-motion and a cognitive comparison of two similar directions of self-motion. We further report unique cortical representations of radial heading directions, i.e. 0° and 180° throughout different cortical processing stages. This cortical uniqueness of processing could be a good explanation for the outstanding performance levels we and others (Beardsley & Vaina, 2005; Burr et al., 1998) observed for these two heading directions. Consistent with previous studies, that report observations of

a bias in the responses to radial orientation and motion across early visual brain regions (Raemaekers et al., 2009; Sasaki et al., 2006), we suggested here, that unique representations of radial optic flow exist in all stages of visual processing, and also in frontal regions of motor control and cognition. Although we could not find significant differences in performance levels between 0° and 180° in our experiments, we found that expanding and contracting optic flow produce different activation patterns in early visual but also in higher visual processing stages of the ventral and dorsal visual stream. Further we found that the patterns evoked by 0° are the most unique across all heading directions. This is a strong support for the hypothesis that our sensory systems adapt to our environment. Straight forwards is our main gaze and motion direction, and it makes sense that our sensory systems are tuned to optimally identify and discriminate this heading direction in particular.

Apart from these findings, we could also show effects of flow laterality in occipital activation patterns. On the behavioral level, we found no differences in performance between left- and rightwards directions. This suggests that the different representations of left- and rightwards optic flow do not lead to differences in the performance, and is consistent with our observation of a hemisphere-specific processing of flow lateralities (see Chapter 3, leftwards self-motion produces higher activation in early visual regions of the right hemisphere and vice versa).

In summary we can say that cortical activation patterns are consistent to what we observe behaviorally. Not only can we differentiate activation patterns between different self-motion directions, we can also explain why we perform better for specific self-motion directions.

5.3 Concluding remarks

Approaches to understand self-motion perception have come from different levels of research. Behavioral evidence, patient observations, electrophysiological recordings, and functional brain imaging all provide valuable information to understand the overall process. Like multisensory self-motion perception, each level has its strengths and weaknesses and only their

combination provides the most precise estimates. In this thesis I discussed behavioral and functional evidence of two different aspects of self-motion perception, that are currently in the focus of research and still not well understood: Multisensory integration and plasticity on the one hand, and the cortical processes underlying self-motion perception on the other hand.

We evaluated intra-modal and cross-modal effects of short-term sensory manipulations and long-term effects of multisensory training, and reported evidence for a strong interplay between task-related, but not necessarily for task-unrelated sensory modalities. Further we provided evidence for the high complexity of cortical processes underlying our ability to estimate a heading direction. The evaluation of a self-motion consistent optic flow stimulus requires recruitment of higher association cortices that suggest complex multisensory association, sensorimotor transformation and cognitive processes that go way beyond the evaluation of simple visual motion. Our results further encourage the investigation of the neuronal basis of human self-motion perception and navigation using virtual visual environments and multivariate analysis methods in fMRI.

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Student researcher and teaching assistent	10 / 2010 - 06 / 2011
Neurocognitive Psychology	

Johann-Wolfgang Goethe University	Frankfurt a.M.
Student researcher	07 - 08 / 2010
Forensics and Entomology	

University of Copenhagen	Copenhagen
Research internship	09 / 2009 - 01 / 2010
Animal Behavior	

PUBLICATIONS

Hummel, N., Cuturi, L. F., MacNeilage, P. R., & Flanagin, V. L. (2016). The effect of supine body position on human heading perception. *J Vis, 16*(3):19.

Hummel N, Hüfner K, Stephan T, Linn J, Kremmyda O, et al. (2014). Vestibular Loss and Balance Training Cause Similar Changes in Human Cerebral White Matter Fractional Anisotropy. PLoS ONE 9(4): e95666. doi:10.1371/journal.pone.0095666

In Preparation

Hummel N. & Flanagin V.L. (in prep.) The neuronal representation of self-motion consistent, visual motion directions.

Flanagin, V.L., Schoernich S., Schranner M., **Hummel N**., Wallmeier L., Wahlberg M., Stephan T., & Wiegrebe L. (under revision). Human sonar exploration of enclosed spaces

zu Eulenburg P., Treede R.-D., Rupp A., **Hummel N.** & Baumgärtner U. (under revision). Modality-dependent representations of painful sensations: auditory versus aural nociception

Selected conference presentations

Hummel N., Hüfner K, Stephan T, Linn J, Kremmyda O, et al.(2013). Increased and decreased vestibular input show similar effects on white matter diffusivity. *The Vestibular System: A Clinical and Scientific Update. Siena, Italy*

Hummel, N., Cuturi, L. F., MacNeilage, P. R., & Flanagin, V. L.(2013). The impact of posture and stimulus type on human heading perception. *Society for Neuroscience Conference (SfN). San Diego, California, USA*

Hummel, N., Cuturi, L. F., MacNeilage, P. R., & Flanagin, V. L.(2014) The impact of body orientation and plane of movement on human heading perception, *ZüMüLi Okulomotoriktreffen. Zürich, Switzerland*

Hummel, N., Cuturi, L. F., MacNeilage, P. R., & Flanagin, V. L.(2014) Supine position does not affect direction estimation accuracy. *Organization for Human Brain Mapping (OHBM). Hamburg, Germany*

Hummel, N. & Flanagin, V. L.(2015) Direction discrimination of self motion consistent optic flow stimuli in the brain. *Vision Science Society (VSS) Annual Meeting. St. Pete Beach, Florida, USA*

Hummel, N. & Flanagin, V. L.(2016) Decoding cortical activation patterns of self-motion consistent optic flow. *10th FENS forum, Copenhagen, Denmark*

Eidesstattliche Versicherung/Affidavit

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation "Human self-motion perception - sensory processing, adaptation and training" selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation "Human self-motion perception - sensory processing, adaptation and training" is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

München, den 10.06.2016

Nadine Hummel

List of author contributions

Hummel, N., Cuturi, L. F., MacNeilage, P. R., & Flanagin, V. L. (2016). The effect of supine body position on human heading perception. *J Vis, 16*(3):19.

P.R. MacNeilage and V.L. Flanagin conceptualized the study

N. Hummel, L.F. Cuturi, P.R. MacNeilage and V.L. Flanagin designed the study

N. Hummel programmed the visual stimuli

L.F. Cuturi and P.R. MacNeilage programmed the vestibular stimuli

N. Hummel and L.F. Cuturi conducted the experiments

N. Hummel analyzed the data

N. Hummel, P.R. MacNeilage and V.L. Flanagin interpreted the data

N. Hummel wrote the manuscript

L.F. Cuturi, P.R. MacNeilage and V.L. Flanagin critically revised the manuscript

Hummel N. & Flanagin V.L. (in prep.) The neuronal representation of self-motion consistent, visual motion directions.

N. Hummel & V.L. Flanagin conceptualized the study

N. Hummel & V.L. Flanagin designed the study

N. Hummel programmed the stimuli

N. Hummel & V.L. Flanagin conducted the experiments

N. Hummel analyzed the data

N. Hummel & V.L. Flanagin interpreted the data

N. Hummel wrote the manuscript

V.L. Flanagin critically revised the manuscript

Hummel N, Hüfner K, Stephan T, Linn J, Kremmyda O, et al. (2014). Vestibular Loss and Balance Training Cause Similar Changes in Human Cerebral White Matter Fractional Anisotropy. *PLoS ONE 9(4):* e95666. doi:10.1371/journal.pone.0095666

K. Hüfner, O. Kremmyda, and V.L. Flanagin conceptualized the study

K. Hüfner designed the study

O. Kremmyda recruited subjects and conducted behavioral experiments

K. Hüfner and V.L. Flanagin conducted DTI experiment

O. Kremmyda analyzed the behavioral data

N. Hummel, T.Stephan and V.L. Flanagin analyzed the DTI data

N. Hummel, K. Hüfner and V.L. Flanagin interpreted the data

N. Hummel wrote the manuscript

K. Hüfner, T. Stephan, J. Linn, O. Kremmyda, T. Brandt and V.L. Flanagin critically revised the manuscript

München, den 02.09.2016

Dr. Virginia Flanagin   Nadine Hummel