OUT OF BALANCE! OUT OF ORDER?

A MULTIMODAL APPROACH ON THE CONSEQUENCES OF CHRONIC STRUCTURAL AND FUNCTIONAL VESTIBULAR SYNDROMES ON COGNITIVE FUNCTION, NEURAL PROCESSING, AND BRAIN STRUCTURE.

Pauline Popp

Graduate School of
Systemic Neurosciences

LMU Munich

Dissertation at the
Graduate School of Systemic Neurosciences
Ludwig-Maximilians-Universität München

July, 2018

First reviewer (Supervisor)
Prof. Dr. Marianne Dieterich

Second reviewer:
Prof. Dr. Paul Sauseng

Date of submission:
03.07.2018

Date of oral examination:
25.09.2018

"I've heard an idea I've proposed, I've no idea how seriously to account for the sensation of vertigo. It's an idea that I instinctively liked and it goes like this.

The dizzy sensation we experience when standing in high places is not simply a fear of falling. It's often the case that the only thing likely to make us fall is the actual dizziness itself, so it is, at best, an extremely irrational, even self-fulfilling fear.

However, in the distant past of our evolutionary journey toward our current state, we lived in tress. We leapt from tree to tree. There are even those who speculate we might have something birdlike in our ancestral line. In which case, there may be some part of our mind that, when confronted with a void, expects to be able to leap out into it and even urges us to do so. So what you end up with is a conflict between a primitive, atavistic part of your mind which is saying "Jump!" and the more modern, rational part of your mind, which is saying "For Christ's sake, don't!"
In fact, vertigo is explained by some not as the fear of falling, but as the temptation to jump."

Douglas Adams, Last chance to see

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Summary

Dizziness and vertigo are common and incapacitating symptoms in the population that significantly affect patients in their everyday life and wellbeing. The most obvious consequences of chronic vertiginous diseases are the impairments of gait and posture. However, the functions of the vestibular system are manifold, and vestibular input is essential for many different processes, such as the perception of self-motion, navigation, and bodily self-consciousness. A defective vestibular input or processing can thus lead to repercussions beyond the apparent perceptual and postural disabilities. As the prevalence of vestibular syndromes increases in an aging society, the understanding of the implications and underlying disease mechanisms is crucial for early diagnosis, prevention of manifestation, and treatment.

This PhD-work investigated the consequences of chronic structural and functional vestibular syndromes by using two different approaches. The first study was directed towards the consequences of a structural vestibular failure on non-spatial cognitive abilities. In the second study the disease-specific underlying brain mechanisms in functional dizziness, i.e., phobic postural vertigo (PPV), were examined.

Study 1: Behavioral studies have demonstrated spatial memory and navigation deficits in animals and humans with bilateral vestibular failure (BVF). The aim of this study was therefore to explore the functional consequences of a chronic unilateral vestibular failure (UVF) or BVF on the four cognitive domains, namely short-term memory, processing speed, executive function, and visuospatial abilities, using various neuropsychological tests. Data analysis revealed that BVF patients were significantly impaired in all of the examined cognitive

domains, whereas UVF patients exhibited significant impairments in their visuospatial abilities and processing speed compared to age-matched healthy controls. Moreover, the degree of vestibular dysfunction positively correlated with some of the cognitive scores. These results corroborate that vestibular failure can lead to cognitive impairments beyond spatial navigation deficits. As the deficits are more severe in BVF, it appears that one intact peripheral vestibular organ can to some extent compensate for the missing contralateral vestibular input. Given the multi-faceted consequences of vestibular failure, patients would likely benefit from individualized cognitive training in addition to vestibular rehabilitation therapy.

Study 2: Functional dizziness is the second most common diagnosis in patients with chronic dizziness, but the neural characteristics of the syndrome are largely unknown. The aim of this multimodal neuroimaging study was to pin-point disease-specific brain changes by measuring brain morphology, task response, and functional connectivity in PPV patients using a visual motion stimulation. The results suggest that the underlying mechanisms of PPV are rooted in networks and brain areas involved in emotional regulation, interoception, cognitive motor control, and fear generalization. These brain areas are commonly also altered in anxiety and depressive disorders. On the contrary, no alterations were detected in primary visual or vestibular areas. Thus, PPV could be regarded as a specific type of mood disorder with the key symptoms of subjective instability and fear of falling.

In summary, this thesis substantiates the evidence that the sensory conflict that arises in vestibular syndromes compromises processes beyond postural balance. Healthy vestibular input and processing essentially contribute to various aspects of attention, memory, executive

control, interoception, and emotional regulation. This should be considered in the therapeutic approach of chronic vestibular syndromes.

Abbreviations

BDI	Beck depression index
BVP	Bilateral vestibulopathy
BVF	Bilateral vestibular failure
CSD	Chronic subjective dizziness
fMRI	Functional magnetic resonance imaging
MAE	Motion aftereffect
PPPD	Persistent postural-perceptual dizziness
PPV	Phobic postural vertigo
SBM	Surface-based morphometry
UVF	Unilateral vestibular failure
VBM	Voxel-based morphometry
VF	Vestibular failure
vHI	Visual height intolerance
VN	Vestibular neuritis
VOR	Vestibulo-ocular reflex
VRT	Vestibular rehabilitation therapy
VSR	Vestibulospinal reflex

1. Introduction

Dizziness and vertigo are highly prevalent (15-30%) symptoms in the population that cause significant distress and disability; they strongly affect patients in their everyday life and well-being (Yardley 2002, Neuhauser et al., 2007, Neuhauser et al., 2008, Weidt et al., 2014). Vertigo is aside from headaches and back pain among the main reasons why patients seek medical help (Brandt, 1996). This incapacitating sensation is usually caused by a mismatch in the perception of the different sensory systems (visual, vestibular, somatosensory, acoustic) or a dysfunction within the peripheral or central vestibular system.

Even though the vestibular system normally operates unnoticed in the back of our consciousness, it is essential for maintaining balance and stable vision while moving (Goldberg et al., 2012). To this end, it works in close collaboration with the visual and somatosensory system on several levels of the central nervous system. Its crucial role in our everyday life is often only recognized and appreciated when a dysfunction occurs (Dieterich and Brandt, 2008).

Apart from reflexive control of gaze and posture, the functions of the vestibular system are manifold, and vestibular input essentially influences many different processes such as the perception of self motion, the cognitive control of movement, spatial navigation, and bodily self-consciousness (Straube and Brandt, 1987, Blanke et al., 2002, Angelaki et al., 2004, Lopez et al., 2008, Dieterich and Brandt, 2015). A defective vestibular input or processing can, thus, lead to consequences far more severe than the apparent perceptual and postural disabilities.

This chapter outlines the structure and function of the vestibular system, the general symptoms of vestibular dysfunction, and the specific syndromes that were investigated in this thesis: peripheral vestibular failure (VF) and functional phobic postural vertigo (PPV).

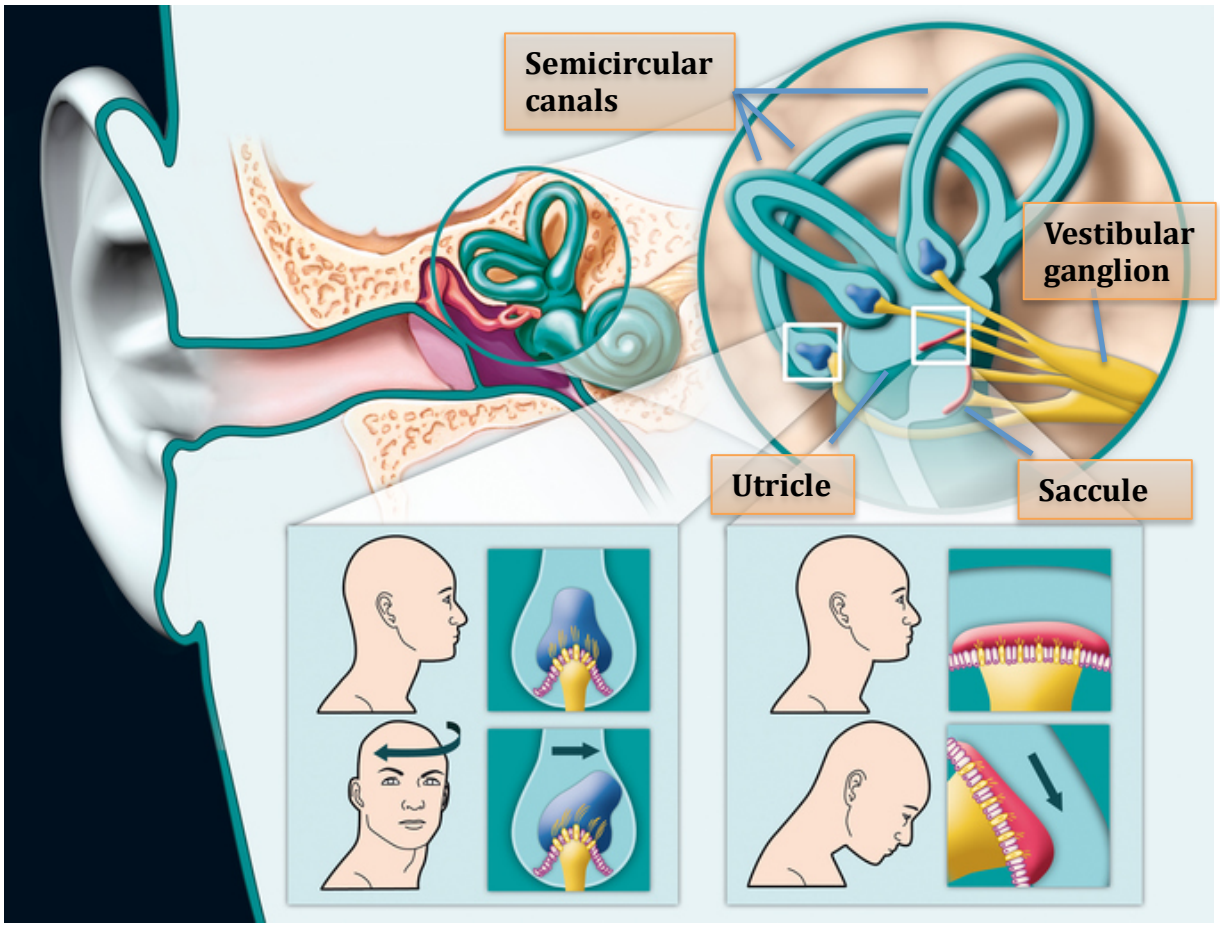
1.1. **The vestibular system – from the ear to the cortex**

The peripheral vestibular system is involved in the reflexive control of balance and gaze during head and body movements, whereas the central vestibular system is processing motion perception and higher vestibular functions like navigation and multisensory integration.

The peripheral part in the inner ears detects active and passive acceleration as well as gravity and sends the information to the central vestibular nervous system. It consists of the bilateral, mirror-symmetric labyrinths and the vestibular nerves. Each labyrinth comprises of five receptor organs to measure acceleration (figure 1). Linear accelerations and gravity are discerned by the utricle and saccule (the otolith organs), whereas the three semicircular canals detect angular accelerations (Goldberg et al, 2012).

The hair cells in the labyrinths are deflected by head accelerations, leading to a change in their membrane potential. This causes a shift in the discharge pattern of the connected vestibular neurons. As the semicircular canals work as antagonists, head acceleration towards one direction activates the ipsilateral and inhibits the contralateral canals. The neurons transport the information about head velocity and acceleration via the vestibular nerve to the vestibular nuclei in the brainstem. Here, information from both ears is integrated (Angelaki and Cullen, 2008).

Figure 1: The peripheral vestibular system



The labyrinth in the inner ear comprising of the three semicircular canals that detect angular acceleration and the otolith organs – utricle and saccule – that detect linear acceleration and gravity. Both are innervated by neurons that converge in the vestibular nerve. Source and permissions from istockphoto.com

On the level of the brainstem, the vestibular system is involved in several crucial reflexes. The vestibulospinal reflex (VSR) secures upright postural stability, whereas the vestibulo-ocular reflex (VOR) compensates for head movement to ensure stable vision (Goldberg et al., 2012). Importantly, the vestibular, visual, and somatosensory modalities work closely together to ensure and maintain a stable gaze, an upright posture, and the orientation in space (Cullen and Sadeghi, 2008).

The vestibular nerves project to the four major vestibular nuclei in the dorsal part of the pons and the medulla, which integrate information from the labyrinths with signals from the visual system, the spinal cord,

and the cerebellum. The information is then transferred to the upper brainstem, the thalamus, the cerebellum, and the cortex via several bilateral pathways with multiple crossings (Lopez and Blanke 2011, Goldberg et al., 2012, Dieterich and Brandt 2015, Kirsch et al., 2016).

Imaging studies in humans using caloric irrigation and galvanic or otolith stimulation have identified multiple multisensory cortical areas, all of which jointly constitute the "vestibular cortex". The main regions are the temporo-parieto-insular and retroinsular cortex, the inferior parietal cortex, the cingulate cortex, and the thalamus, basal ganglia, and cerebellum (Bense et al., 2001, Fink et al., 2003, Stephan et al., 2005, Miyamoto et al., 2007, Dieterich and Brandt 2008, Schlindwein et al., 2008, zu Eulenburg et al., 2012, Lopez et al., 2012, Kirsch et al., 2016). Although there is no distinct primary unimodal cortex, as in other sensory modalities, recent studies suggest that the opercular area 2, posterior insula and retroinsular cortex most likely represent the core vestibular cortex. It has the most connections with the other areas and responds most consistently to vestibular stimulation (Dieterich and Brandt 2008, zu Eulenburg et al., 2012, Lopez et al., 2012, Kirsch et al., 2016, 2018). Moreover, the central vestibular cortex exhibits a lateralization of functions (dominance) ipsilateral to the dominant hand (Dieterich et al., 2003, Bense et al., 2003, Janzen et al., 2008, Dieterich et al., 2017, Kirsch et al., 2018).

The visual, somatosensory, and vestibular information is converged in the cortex to represent a proper understanding of the questions "where am I?" and "where am I going?". This integration is very complex and necessitates high accuracy. Accordingly, a reciprocal inhibitory interaction between the visual and vestibular modalities had been identified that functions to avoid a potential perceptive mismatch (Brandt et al., 1998, Bense et al., 2001, Wenzel et al., 1996, Deutschländer

et al., 2002, Stephan et al., 2005, Dieterich et al., 2003, Kikuchi et al., 2009). As a result, the weighting of the different sensory inputs is shifted to the more reliable source. Similar patterns of an increase or decrease in interaction have also been observed between the somatosensory, nociceptive and visual systems (Bense et al., 2001, Laurientini et al., 2002; Maihöfner et al., 2006, Merabet et al., 2007). The clinical relevance becomes visible, for example, in patients with peripheral vestibular failure (Dieterich and Brandt, 2008) (see chapter 1.2.1.).

Since the vestibular system can only detect acceleration and gravity, it cannot, on its own, give information on relative position and self-motion. This is probably why there is no unimodal primary vestibular cortex. Hence, the system usually acts unnoticed in the background and is only brought to the fore in pathology or abnormal stimulation. The symptoms and consequences of a dysfunction within the vestibular system will be discussed in the following chapter.

1.2. **Vestibular syndromes and the symptoms**

Vestibular syndromes exhibit various symptoms resulting from a disturbance and imbalance of the visuo-vestibulo-somatosensory interactions on the level of the peripheral or central vestibular system. In addition to a mismatch in perception, i.e., dizziness and vertigo, vestibular syndromes are typically accompanied by difficulties in gaze stabilization (which affect the interaction with the visual system), nausea and vomiting (autonomic nervous system), and postural difficulties, i.e., ataxia (which affect the interaction with the somatosensory and proprioceptive system).

The vestibular syndromes can be classified into peripheral and central vestibular syndromes that cause vertigo and dizziness disorders. These can be classified on the basis of the duration of symptoms (acute, episodic or chronic), the type of dizziness (rotational vertigo or postural vertigo/dizziness), and the accompanying symptoms (e.g., ear signs, headache). Furthermore, they can be categorized as structural vestibular, organic non-vestibular, psychiatric or functional disorders (Bisdorff et al., 2015).

For this thesis two different patient groups with vestibular syndromes were investigated: patients with a peripheral vestibular failure (study 1) and patients with functional phobic postural vertigo (study 2). In the following section these syndromes will be further defined.

1.2.1. Failure of the peripheral vestibular system

A peripheral vestibular failure can occur bi- or unilaterally and usually has different etiologies. **Bilateral vestibulopathy (BVP)** develops from a failure of the vestibular hair cells in the labyrinth or the vestibulocochlear nerve (Brandt 2003). It was first described in 1941 in a study with patients who had undergone bilateral vestibular neurectomy and developed BVP after the operation (Dandy 1941). The main symptoms of BVP are unsteadiness of stance and gait and blurred vision that worsen in darkness, on uneven ground or during head movements, i.e., when somatosensory or visual feedback is reduced. The symptoms usually do not occur when sitting or lying down (Brandt 2003, Strupp et al., 2016, 2017). It is a severe chronic disorder with various etiologies. Common causes are ototoxical drugs, bilateral Menières disease or

vestibular neuritis, autoimmune diseases of the inner ear, or bilateral vestibular schwannoma, but in many cases BVP remains unexplained (Rinne et al., 1998, Zingler et al., 2009). The postural instability is owed to an abnormal processing of the vestibular labyrinth (the semicircular canals and/or the otolith organs) or the vestibular nerve (Brandt 2003, Agrawal et al., 2013). In most cases, there is no or insufficient regeneration of the vestibular function.

BVP is a disease that especially occurs in the elderly and commonly develops gradually. Patients do not exhibit acute rotational vertigo or spontaneous nystagmus and many of their symptoms, such as insecurity in stance and gait, are frequent in many other vestibular syndromes (Brandt 2003). As a result, in initial routine neurological examinations (without neuro-otological bedside tests) it is often misdiagnosed as functional dizziness. The reduced excitability of the labyrinth, i.e., the organic deficit, can only be disclosed by neuro-otological examinations. Specifically the head-impulse test to examine the sensitivity of the semicircular canals at higher frequencies and the caloric irrigation for the function at lower frequencies are useful (Halmagyi and Curthoys, 1988, Jorns-Häderli et al., 2007, Zingler et al., 2009, Fujimoto et al., 2009).

A **unilateral vestibular failure (UVF)** develops after an acute vestibular disorder like vestibular neuritis or Menières disease, trauma, or after unilateral labyrinthectomy or neurectomy (Curthoys 2000).

All patients who were examined in the present study developed a chronic UVF due to insufficient rehabilitation after a vestibular neuritis (VN). This chronification occurs in about 30% of VN patients (Godemann et al., 2005). VN is believed to be an inflammation of the vestibular nerve, probably due to a viral infection (Arbusow et al., 1999, Himmelein et al., 2017). In the acute phase of VN, patients suffer from severe vestibular symptoms such as rotational vertigo, spontaneous nystagmus, and

lateropulsion (Brandt and Dieterich, 2017). However, the symptoms usually are mitigated after some days or weeks, even when the vestibular deficit remains. This is the result of a process of central cortical and subcortical compensation for the missing unilateral vestibular input (Curthoys and Halmagyi, 1995, Bense et al., 2004, zu Eulenburg et al., 2010, Helmchen et al., 2011, Becker-Bense et al., 2014, Zwergal et al., 2014). Since an inadequate VOR (Halmagyi and Curthoys, 1988) cannot be fully compensated by the central mechanisms, some residual constraints may remain, such as instable visual scenes during rapid head movement or while running (Brandt et al., 2012).

Even bilateral vestibular failure (BVF) patients who lack any intact vestibular input can, to some extent, compensate for the missing information in the low frequency range. Therefore, some non-vestibular mechanisms have been proposed to counterbalance complete vestibular failure. These encompass visual substitution and adaptations in visual cortical areas (Dieterich et al., 2007) or a pronounced interaction between the processing of visual and proprioceptive input (Cutfield et al., 2014, Sprenger et al., 2017).

Furthermore, insufficient vestibular information seems to lead to repercussions beyond instability of gaze and posture. There is accumulating evidence that a lack of vestibular input elicits all sorts of deficits involving functional self-referential processing, spatial memory, and navigation (Brandt et al., 2005, Smith and Zheng, 2013, Besnard et al., 2015). In light of these findings, the consequences of a vestibular failure on non-spatial cognitive processes have been investigated in study 1 (Popp et al., 2017) and will be summarized in chapter 2.1.

1.2.2. Functional phobic postural vertigo, a subtype of functional dizziness

Patients experiencing vertigo, sensitivity to motion stimuli, various forms of anxiety, and discomfort in open space (agoraphobia) were characterized as early as the 19th century (Kuch and Swinson, 1992). However, it was over a century later that this entity became more prominent again in research. Functional dizziness is the second most common diagnosis in individuals with vertigo and dizziness (Brandt et al., Obermann et al., 2015, Brandt and Dieterich, 2017) and was first characterized in the 1980s as phobic postural vertigo, PPV (Brandt and Dieterich, 1986). Other functional dizziness syndromes have also been described, such as chronic subjective dizziness, CSD (Staab and Ruckenstein 2007), visual vertigo (Bronstein, 1995), and space and motion discomfort (Jacob et al., 1993). Therefore, the Committee for Classification of Vestibular Disorders of the International Society for Neurootology – the Bárány Society - recently reevaluated the existing data of the earlier mentioned syndromes and suggested a new superordinate syndrome named persistent postural-perceptual dizziness (PPPD) (Staab et al., 2016, Staab and Dieterich, 2016), which was introduced into the new international classification of disorders (WHO, 2015). Here, CSD and PPV represent synonyms.

As the experiments for the current study commenced before the introduction of PPPD, the patients included were evaluated using the original PPV criteria. Thus, the focus lies on the entity of functional phobic postural vertigo, one well-described subtype of functional dizziness (Dieterich and Staab, 2016).

PPV is characterized by symptoms of subjective postural imbalance and attacks of vertigo and dizziness, despite clinically inconspicuous neuro-otological test results (Brandt, 1996). Contrary to organic vestibular syndromes, symptoms are less severe in the morning and increase over day (Feuerecker et al., 2015).

The main symptoms are similar to a BVF. During history taking, however, the diagnosis of PPV is less ambiguous as PPV patients demonstrate typical vegetative and anxiety symptoms (Brandt, 1996). PPV can be preceded by a vestibular dysfunction or other physical illnesses – named secondary somatoform (now defined as functional) - or can be provoked by a major psychological stressor – named primary somatoform (Dieterich, 2000, Huppert et al., 2005).

Even though it is a predominant fear in the patients, the subjective instability does not lead to an increase in falls (Brandt, 1996, Schlick et al., 2016). Indeed, in the analyses of stance and gait (by posturography or gait analysis) patients display different postural control strategies compared to their healthy counterparts. In a quiet upright standing position, body sway is increased in a fashion similar to healthy subjects that perform a difficult postural task like walking on ice (Holmberg et al., 2003, Krafczyk et al., 1999). In contrast, during difficult tasks, such as tandem stance with eyes closed, postural behavior is normalized comparable to healthy controls (Querner et al., 2000). Moreover, patients display reduced gait speed and altered rhythm of gait, suggesting that they require more attentional control and, as is the case for BVP patients, they heavily rely on visual input (Schniepp et al., 2014).

The subjective postural instability appears to be a result of a vicious cycle of self-enforcing symptoms. Fearing the next dizziness sensation, patients are constantly preoccupied with monitoring and controlling their balance (Krafczyk et al., 1999) and, consequently, constantly co-contract their

anti-gravity muscles (Wuehr et al., 2013). The mismatch between anticipated and actual motion leads to further tension and dizziness (Brandt 1996, Querner et al., 2002, Holmberg et al., 2003; Staab 2012). Similar patterns of conscious over-compensation have also been observed in specific phobias, such as fear of heights (Brandt et al., 2015, Wuehr et al., 2014). Accordingly, when PPV patients perform cognitive tasks during walking (dual task paradigms) the inadequate strategy of balance control and muscle co-contraction improves and normalizes comparable to that of healthy controls (Wühr et al., 2016). The cognitive task possibly withdraws the attentional focus from the posture, leading to a more natural postural control.

Furthermore, patients often report a particular increase in unsteadiness when looking at a moving visual scene, such as traffic or a moving crowd, and in response to intense sensory stimuli (Dieterich 2000, Querner et al., 2002). These symptoms are frequently accompanied by depressive symptoms, an obsessive-compulsive personality, and anxiety. Patients tend to generalize the distressing stimuli and, thus, typically develop some kind of avoidance behavior (Dieterich 2000). Moreover, anxiety and the resulting avoidance behavior can exacerbate and maintain dizziness, leading to a general manifestation of disorientation and distress (Yardley 2000).

PPV and CSV have been well defined using posturographic and psychological measures (Dieterich and Staab, 2016). However, little is known about the underlying disease-specific cortical mechanisms, e.g., the changes in brain activity during visual stimulation. They have been investigated in study 2 (Popp et al., 2018), which is presented in chapter 2.2.

2. Cumulative thesis

This cumulative thesis presents two peer-reviewed articles that analyzed different aspects of chronic postural dizziness, the possibility of cognitive deficits in patients with chronic bilateral vestibular failure and the brain activity and connectivity in patients with functional phobic postural vertigo. The original manuscripts can be found in the appendix. This chapter will give a short overview and summary of the two studies.

2.1. Study 1: Cognitive deficits in patients with a chronic vestibular disorder

The clinical consequences of a vestibular failure have been described in chapter 1.2.1. Beyond that, there is strong evidence that the vestibular system is not only involved in perception, ocular motor, and postural control, but also influences higher spatial cognitive functions, such as multisensory motion detection, spatial navigation, and memory (Smith et al., 2010, Smith and Zheng, 2013, Mast et al., 2014, Besnard et al., 2015). These insights are derived from behavioral studies in both rodents (Baek et al., 2010, Besnard et al., 2012) and patients with vestibular failure, VF (Glasauer et al., 2002, Schautzer et al., 2003, Péruch et al., 2005, Brandt et al., 2005, Guidetti et al., 2008).

So far, very few studies have empirically elucidated the involvement of the vestibular system in non-spatial cognitive processes, such as working memory or executive function, even though complaints about difficulties to focus attention are quite common in VF patients (Yardley 1998, Jauregui-Renaud et al., 2008) and quality of life is strongly reduced

(Guinand et al., 2012). Notably, problems frequently persist even after the alleviation of the main symptoms due to central compensation.

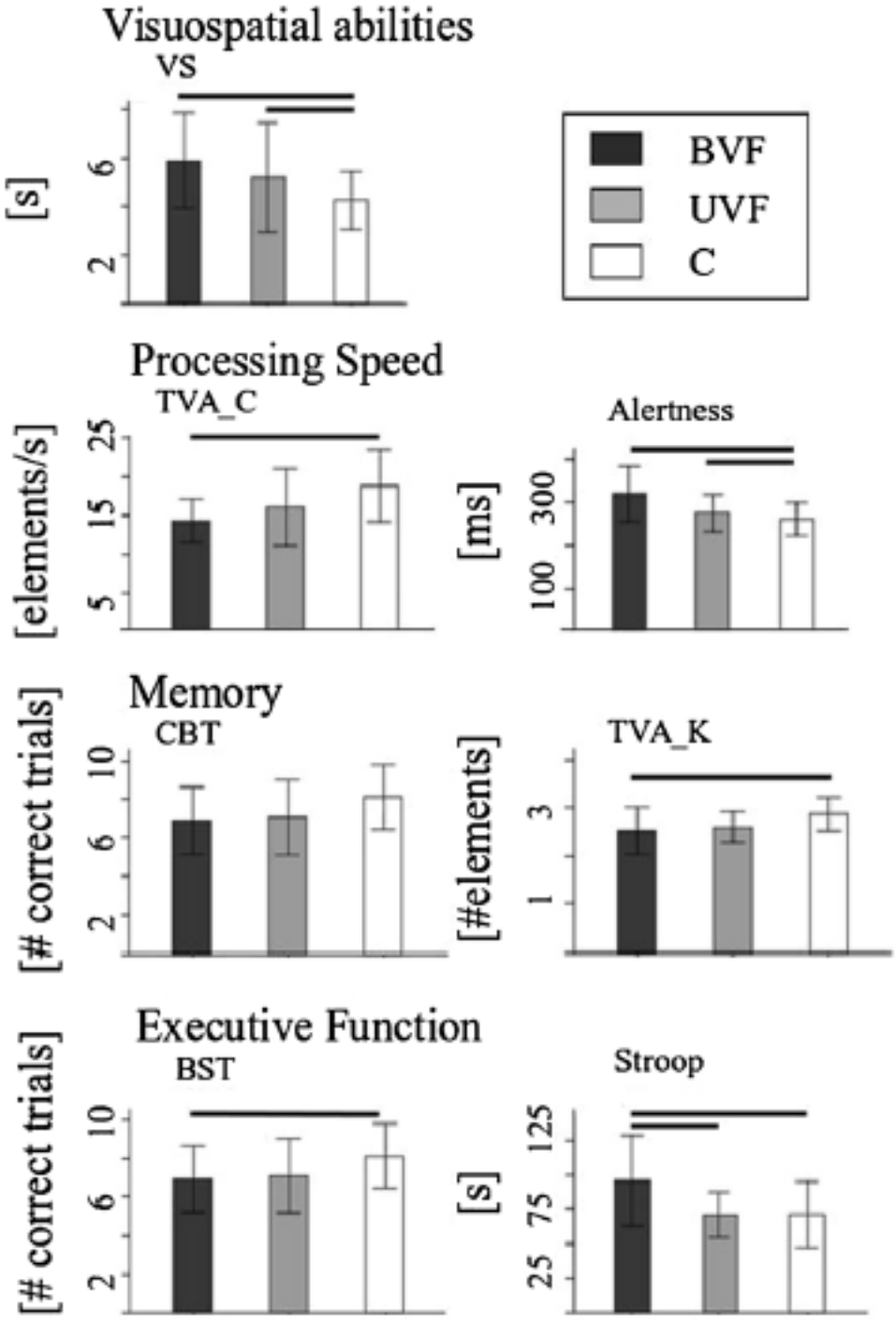
The aim of this prospective study was therefore to ascertain if the cognitive impairments in patients with a unilateral or bilateral vestibular loss reach beyond spatial cognitive categories, i.e., affect non-spatial cognitive domains.

Thus, a variety of neuro-psychological tests (see figure 2) were applied to examine some of the core neurocognitive domains: memory, processing speed (complex attention), executive function (combines several abilities), and visuo-spatial abilities (American Psychiatric Association, 2013, Sachdev et al., 2014).

Sixteen patients with unilateral vestibular failure (UVF), 18 patients with bilateral vestibular failure (BVF), and 17 age- and gender-matched healthy controls participated in the study. The cognitive performance was correlated with the degree of vestibular dysfunction as well as disease duration. A detailed description of the experimental, analytical, and statistical methods is provided in the attached original article (Popp et al., 2017).

The results offer first evidence that a lack of vestibular input, in fact, leads to deficits in non-spatial cognitive processes. They further corroborate that vestibular failure adversely affects spatial cognition. BVF leads to unequivocal deficits in all cognitive domains, whereas the consequences of UVF are more subtle and complex. Overall, there appears to be a gradual increase in the level of impairment from controls over unilateral failure to bilateral vestibular failure (figure 2).

Figure 2: Graphical overview of mean performances in tested cognitive domains and applied cognitive tests. Statistically significant differences highlighted with lines.



Abbreviations*: BVF* bilateral vestibular failure, *UVF* unilateral vestibular failure, *C* healthy controls, *VS* visual scanning, *TVA C* cognitive processing speed, *TVA k* visual short-term capacity, *CBT* Corsi Block Tapping, *BST* backwards Corsi Block Tapping. From Popp et al., 2017. With permissions from Springer Nature.

These observations are in line with findings of other studies investigating spatial cognitive abilities (Brandt et al., 2005, Hüfner et al., 2009, Smith and Zheng, 2013 for a review, Kremmyda et al., 2016). One intact labyrinth seems to be sufficient to partially compensate for a lack of vestibular information from the other labyrinth.

Moreover, when correlated with the degree of vestibular dysfunction (=responsiveness of the labyrinth), significant effects for some of the cognitive scores were detected in BVF and UVF patients. Thus, a reduction of vestibular input seems to increase cognitive impairment.

These findings complement results from imaging studies. Complete bilateral vestibular deafferentiation resulted in a striking hippocampal atrophy of 16% (Brandt et al., 2005). Structural brain analyses in incomplete bilateral lesions revealed less distinctive hippocampal atrophy (Kremmyda et al., 2016, Göttlich et al., 2016). The hippocampus plays an important role in memory formation and spatial navigation (Hitier et al., 2014). Even patients with a unilateral vestibular failure due to compensated vestibular neuritis that presented with a persistent caloric unresponsiveness developed two years after disease onset a significant atrophy in the left posterior hippocampus (zu Eulenburg et al., 2012). The brain changes in function and structure after a peripheral vestibular failure might not only be the result of compensation, but could also be in part caused by the lack of vestibular input.

Imaging studies in vestibular failure further disclosed functional (Bense et al., 2004, Dieterich et al., 2007, Deutschländer et al., 2008, Becker-Bense et al., 2013, Helmchen et al., 2013, Göttlich et al., 2014) and structural (Hüfner et al., 2007, Hüfner et al., 2009, zu Eulenburg et al., 2010, Helmchen et al., 2011, Hong et al., 2014) changes in several brain areas, such as the superior temporal gyrus, the anterior cingulate cortex, the insular cortex, and the superior parietal cortex. Some of these areas

like the superior temporal gyrus, are also involved in non-spatial cognitive processes (Gottlieb and Snyder, 2010, Shomstein and Gottlieb, 2016). The disease related cortical changes could, thus, reflect some of the deficits in both spatial and non-spatial cognitive abilities.

In conclusion, the results of this study confirm the hypothesis that a missing vestibular input can lead to impairments in cognitive abilities without mere spatial references, such as complex attention and executive function.

The possible implications for the treatment and therapy of patients are discussed in section 3.1.

2.2. **Study 2: Cortical alterations in phobic postural vertigo – a multimodal imaging approach**

Even though PPV patients can be distinctly diagnosed in a specialized vertigo center, as they show typical pathognomic posturography results, diagnosis and treatment is often difficult and inefficient. When reassessed three years after the initial specialized examination, 63% of patients with primary PPV displayed continuing symptoms (Tschan et al., 2013). Moreover, functional dizziness patients are more hampered in their professional and daily activities than patients with organic forms of dizziness (Eckhart-Henn et al., 2003; Yardley 2000).

Possibly, a better understanding of the neural circuits involved in PPV may contribute to a more efficient therapeutic approach.

Even to date, only a handful of imaging studies have investigated functional dizziness by means of resting state functional connectivity (van Ombergen et al., 2017, Lee et al., 2018), voxel-based morphometry, VBM (Wurthmann et al., 2017), fMRI with sound-evoked vestibular

stimulation imaging (Indovina et al., 2015), and fMRI with visual stimulation (Ricelli et al., 2017).

This is the first multimodal neuroimaging study elucidating brain morphology, activity, and connectivity, in combination with psychophysical data in functional PPV patients. The aim of this study was to decipher the disease-specific cortical mechanisms of PPV. Relevant questions were: Does the disease originate in the vestibular or visual motion perception networks or is it rooted in networks or areas that are also commonly altered in anxiety or mood disorders? With respect to the available imaging techniques, the following research questions were addressed:

a) Can structural changes in distinct brain regions be detected with **voxel- and surface-based morphometry (VBM/SBM)** that can be related to PPV?

b) Since PPV patients are particularly sensitive toward intense visual stimulation, can changes in brain activity (task responses) be found with **functional magnetic resonance imaging (fMRI)**, using a visual motion stimulus that triggers the motion aftereffect (MAE) (Mather et al., 2008), i.e., a visual motion illusion?

c) Can differences in **functional connectivity** within networks of the most salient regions identified by VBM and fMRI be observed?

Forty-four patients with primary PPV and 44 age- and gender-matched healthy controls participated in the experiment. The structural images for the morphometric analyses were acquired prior to the functional images (visual stimulation paradigm) in the MRI scanner. During the visual stimulation the subjects were exposed to several sequences of coherently moving dots followed by a stationary period and asked to indicate the subjective duration of the MAE. For correlation analyses the

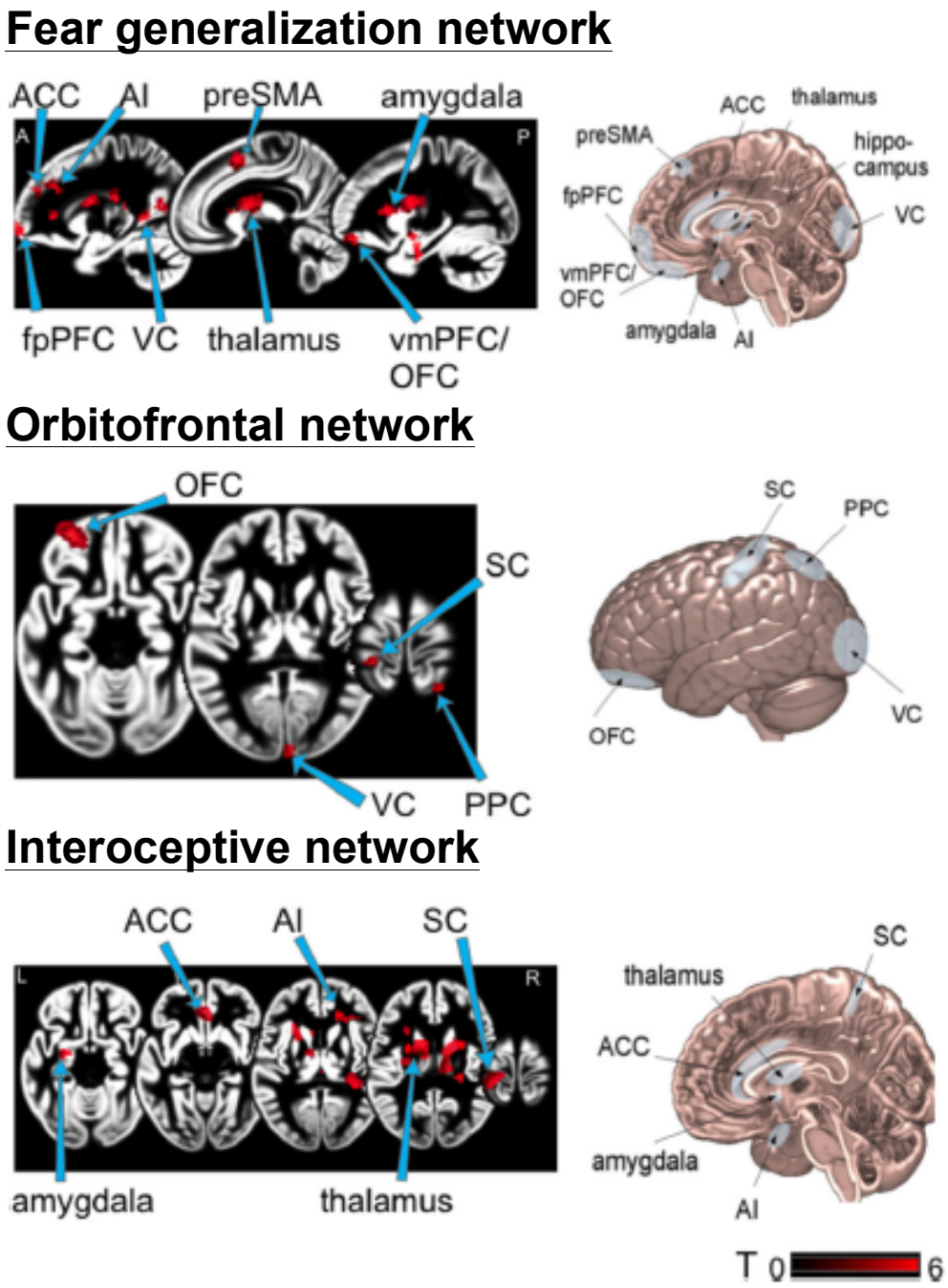
Beck depression index (BDI) was measured. A detailed description of the experiment, the analytical methods, and the results is provided in the attached original article (Popp et al., 2018).
Overall, the results imply that PPV's disease-specific mechanisms are related to aberrant structure and function of networks and brain regions involved in emotional regulation, fear generalization, interoception, and cognitive motor control.

Surprisingly, the volume analyses revealed no structural alterations in primary visual and vestibular cortical areas. The visual stimulation triggered a typical bilateral activation-deactivation pattern in visual and vestibular cortical areas (Bense et al., 2006, Stefanova et al., 2013) that did not differ between patients and controls. The patients, however, demonstrated an increased task-dependent activity in the anterior cingulate cortex, a region involved in emotion and fear processing (Palermo-Gallagher et al., 2014), which is not expected to be activated during a rather neutral visual stimulation. Furthermore, the subjective duration of the MAE was significantly longer in patients than in controls. This might be an effect of the reported sensitivity toward intense sensory stimuli in PPV patients (Dieterich 2000).
Figure 3 depicts three networks with significantly increased task-dependent functional connectivity in PPV patients. The fear-generalization network is involved in mood-regulation (Price and Drevets, 2010), the interoceptive network mediates afferent visceral and vestibular information (Khalsa et al., 2009), and the orbitofrontal network merges sensory and affective information to create cognitive maps (Schuck et al., 2016). Similarly, in a resting state study, PPPD patients exhibited increased connectivity in networks integrating visual and emotional processing (Lee at al., 2018).

Furthermore, the morphological analyses revealed an increase in regions of the prefrontal cortex and the associated thalamic projection zones in PPV compared to controls. Structural increases in various prefrontal areas involved in mood regulation (medial and orbital prefrontal areas)(Etkin et al., 2011, Bludau et al., 2014) and cognitive control (lateral prefrontal areas) (Corbetta and Shulman, 2002, Comte et al., 2016) in patients correlated positively with disease duration and BDI.
Additionally, increases in the primary motor cortex structure and connectivity with prefrontal areas and decreases in cerebellar regions and fronto-cerebellar connections were observed in patients. These alterations might reflect the predominant compulsive control of stance and gait.

These findings nicely complement the clinical characteristics of the PPV patients and the observations from posturographic and psychological studies, such as excessive self-referential appraisal, a constant anxious monitoring and obsessive controlling of gait and posture (Querner et al,. 2002, Eckhardt-Henn et al., 2003, Yardley 2000, Wuehr et al., 2015, 2017). The symptoms in PPV deteriorate with disease duration (Brandt et al., 1994), which is reflected by the detected structural changes.
Most of the affected brain areas and networks observed in the current study of PPV patients are also altered in patients with mood disorders (Phillips et al., 2003, Liao et al., 2010, Gimenez 2012, Heitmann et al., 2016, Feldker et al., 2016). There seems to exist a close connection between emotional modulation and vestibular symptoms (Balaban et al., 2011). In light of these results and the potential implications, this link deserves further discussion, which is initiated in section 3.3.

Figure 3: Altered functional connectivity networks in phobic postural vertigo patients (PPV) compared to healthy controls (HC) with schematic illustrations



Statistically significant regions superimposed on a publicly available template from 555 healthy subjects (http//brain development.org/ixi-dataset/). P<0.05 was set after FDR correction, with a critical cluster size of 50.

Abbreviations: ACC anterior cingulate cortex, AI anterior insula, fpPFC frontopolar prefrontal cortex, l left, OFC orbitofrontal cortex, PMC primary motor cortex, PPC posterior parietal cortex, preSMA pre-supplementary motor area, r right, SC somatosensory cortex, VC visual cortex, ventromedial prefrontal cortex. (Popp et al., 2018)

An additional interesting finding in PPV was a task-dependent **decrease** in the connectivity of networks that are typically highly connected during the processing of visual motion (Deutschländer et al., 2004). In contrast to normal subjects, functional connectivity between frontal and visual cortex areas was increased in PPV patients. Posturographic studies have shown that patients with functional dizziness rely eminently on visual input while standing, walking, and navigating (Cousins et al., 2014, Schniepp et al., 2014). Recently published studies in PPPD (Ricelli et al., 2017, Lee et al., 2017, Wurthmann et al., 2017) and visually induced dizziness patients (van Ombergen et al., 2017) have, similarly, observed an increased involvement of visual cortical areas and decreased connectivity between areas of multisensory vestibular processing. As they may mistrust the vestibular information, PPV patients seem to shift their sensorial weight towards mere visual input. In parallel, patients with anxiety disorders also rely predominantly on visual information (Viaud-Delmon et al., 2002, Redfern et al., 2007, Liao et al., 2011, Gimenez et al., 2012). As a result, multisensory integration is hindered. Intriguingly, a significant atrophy of the left supramarginal gyrus – a multisensory integration area (zu Eulenburg et al., 2012) - was detected in the current study.

The initial main interest of this study was to investigate potential changes in visual-vestibular interaction and activity of visual and vestibular areas. Therefore, the examination concentrated on neurootological testing and as a psychometric measure only the depression index BDI was included. Given these results, it would be very promising for future studies to further investigate the interconnections between psychiatric disorders and functional dizziness using magnetic resonance imaging.

In summary, the combination of morphometric, functional, and psychophysical data provide first evidence that the disease-specific underlying mechanisms of PPV are related to the networks and areas involved in emotional regulation, interoception, cognitive motor control, and fear generalization. Surprisingly, no changes were detected in primary visual or vestibular cortex areas. Future research should further decipher the connection between PPV and emotional disorders by employing more psychological measures.

3. General discussion

Vestibular disorders evoke vertigo or dizziness due to a sensory conflict between the different sensory systems and imbalance of stance and gait. Depending on the origin of the disease, the instability has different causes. In case of a peripheral vestibular failure, the instability derives from a bottom-up perceptual incoherence due to deficient vestibular input. In functional dizziness syndromes the subjective imbalance stems from a top-down compulsive postural control and disturbed self-perception, while there is no organic deficit. Nevertheless, the sensory conflict in both syndromes can compromise processes beyond the postural balance.

This thesis investigated the consequences of chronic structural and functional vestibular syndromes by using two different approaches.
In the first study, a detailed examination of the cognitive abilities in patients with a peripheral vestibular deficit revealed that vestibular failure could indeed lead to cognitive impairments beyond the spatial navigation deficits described in earlier studies. The second study could disambiguate that the disease-specific neural correlates in PPV, a subtype of functional dizziness, are related to areas and networks involved in mood regulation, fear generalization, interoception, and cognitive control but not to vestibular or visual cortex areas.
Potential implications and future research questions will be addressed in the following sections.

3.1. **Study 1: Implications and future outlook**

The lack of vestibular input – especially in bilateral vestibular failure - can have severe consequences for higher-order cognitive processing. This raises the question: What are the possible implications and consequences for an aging society?

Conventional treatment in patients with vestibular failure includes vestibular rehabilitation therapy (VRT) and balance training (Brown et al., 2001, Deveze et al., 2014, Hall et al., 2016). Even though VRT alleviates symptoms like postural instability in BVP patients, recovery often remains incomplete (Hain et al., 2013). Therefore, based on the results in this study, detailed cognitive testing during the first examinations of patients is suggested. The aim should be to determine if and to what extent cognitive impairments exist and identify the cognitive domains that are affected. This would allow the detection of the subtle cognitive impairments present in patients with unilateral vestibular failure and even more of those in patients with bilateral vestibular loss. Based on these observations, specific individualized cognitive training and therapy could be implemented, complementary to VRT (Andersson et al., 2006).

In combination with modern VRT techniques, such as interactive virtual technology (Bergeron et al., 2015, Jahn et al., 2018), cognitive training could be a promising tool to recover the multisensory abilities, self-motion perception (Ellis et al., 2018), cognitive abilities and, most importantly, self-confidence.

3.2. **Objective deficits and subjective symptom severity**

Vestibular failure patients often develop secondary functional vertigo and dizziness or a psychiatric disorder, such as anxiety and depression (Eagger et al., 1992, Huppert et al., 1995, Eckhardt-Henn et al., 2003, Godemann et al., 2005, Best et al., 2009, Brandt 2012).

Self-confidence, resilience, a sense of coherence, and general satisfaction with life reduce the risk of the development of secondary functional dizziness after an acute vestibular failure *(*Tschan et al., 2011). In contrast, an introverted, dependent, and anxious personality is a potential risk factor for the development and negative course of functional dizziness (Kopfhammer et al., 1997, Staab et al., 2014).

Interestingly, the manifestation of functional dizziness does not depend on the objective degree of vestibular dysfunction derived from neurootological examinations, but rather on subjective symptom severity and handicap (Best et al., 2009). Recent observations regarding visual height intolerance (vHI) in vestibular patients (Brandt et al., 2018) give a percentage of vHI in BVF similar to that of the general population (27%), whereas it exits in 64% of PPV, the patient group with the highest co-morbid anxiety. This implies that the development of the fear of heights is not attributed to the objective postural instability but to the subjective fear of falling and instability.

These observations further support the need for early screening of cognitive deficits and potentially psychological traits like anxiousness to improve the quality of life and to avoid a manifestation of chronic dizziness and distress.

3.3. **Study 2: Implications and future outlook**

The results of study 2 clearly demonstrate that the cortical brain areas that are structurally and functionally affected in PPV are mainly involved in interoception, emotion regulation, fear generalization, and cognitive control. As these brain areas are also commonly altered in patients with depression and anxiety, PPV can be interpreted as one special type of mood disorder with the key symptoms of subjective unsteadiness of stance and gait and fear of falling.

The close mutual connections between dizziness and mood regulation are well documented (Hallpike et al., 1951, Simon et al., 1998, Balaban and Jacob, 2001, Staab and Ruckenstein, 2005, Jacob et al., 2009, Balaban et al., 2011, Goto et al., 2011). Rates of anxiety are 5 to 15 times higher in patients with dizziness than in the general population (Simon et al., 1998, Wiltink et al., 2009). Especially PPV patients have a high prevalence of a psychiatric disorder (Schmid et al., 2011, Lahmann et al., 2015). Reciprocally, a disturbed balance control and dizziness are very common in anxiety and mood disorders (Jacob and Turner, 1996, Jacob et al., 2009, Balaban et al., 2011, Feldker et al., 2016).

Certain common networks and pathways are hypothesized to explain the link between balance and emotional modulation (Balaban et al., 2011, Gurvich et al., 2013). They are generally involved in cognitive, sensorimotor, and interoceptive regulation. In line with these data, the same processes were affected in the PPV patients of the current study. The cerebral cortical network, for example, including the insula, orbitofrontal cortex, and anterior cingulate cortex regulates vestibular and interoceptive processing. In the raphe nuclear-vestibular network, the neurons of the dorsal raphe nucleus in the brainstem (releases serotonin) are bi-directionally connected with the amygdala (fear

processing) and the vestibular nuclei (Halberstadt and Balaban, 2006). This could explain how emotional modulation can influence vestibular processing and, reciprocally, how a deficient vestibular integration can affect emotional processing. The strong coupling between mood and balance control is additionally substantiated by means of these imaging results.

Future studies should intend to further link the neural correlates to psychological traits by employing more detailed psychometric measures to establish a more profound understanding of the cortical mechanisms underlying functional dizziness.

Furthermore, future research and development of therapeutic approaches should take the results of this study into account and focus more on the treatment of the affective impairments.

Conventional treatment includes education about the mechanisms behind the symptoms, a self-controlled desensitization, vestibular rehabilitation, and physical exercise (Brandt et al., 1994, Yardley et al., 1998, Dieterich at al., 2016). These methods are supposed to help patients to regain trust in their postural mechanisms and delineate real postural threat from self-induced instability. However, many, functional dizziness patients are still strongly impaired in their professional and daily activities and complain about ongoing symptoms even after several years of treatment (Yardley 2000, Eckhart-Henn et al., 2003, 2009).

Cognitive-behavioral therapy (CBT) might produce short-term improvements of dizziness and disability (Holmberg et al., 2006, Schmidt et al., 2011, Edelmann et al., 2012). Several months after the treatment, however, anxiety was still high (Mahoney et al., 2013) and dizziness-related symptoms had returned (Holmberg et al., 2007). This could be due to the fact that the CBT approach had no particular focus on

overcoming anxiety (Mahoney et al., 2013). Hence, a standardized treatment with long-term improvements is still lacking.

Recent studies indicate that a combination of psychoeducation, balance training, exposition to dizziness inducing situations, and learning of coping strategies can improve postural strategies and reduce psychological distress (Best et al., 2015, Schaaf et al., 2015). Accordingly, a long-term, multidisciplinary approach that includes CBT and, importantly, specific anxiety and depression therapy may provide a permanent alleviation of the symptoms and may break the vicious cycle of subjective instability and reinforcing fear. This needs to be examined in future research.

3.4. **Conclusion**

The vestibular system and its influence is largely underestimated. The consequences of a deficient vestibular system or dysfunctional vestibular processing, however, reach far beyond the obvious impairments in gaze, posture, and gait. Historically, the vestibular system is not counted as traditional sense, probably because of its multisensory nature. On the other hand, the multimodality and widespread cortical vestibular connections could reflect its role as an important modulator in the processing of other sensory modalities and even emotions.

Even in situations without a conscious vestibular perception (e.g., sitting stationary on a chair in front of a display), there is unequivocal evidence for a contribution of the vestibular system to the human consciousness (e.g., otolith input for upright body position). Vestibular input and a healthy vestibular processing are crucial for various aspects of attention, memory, executive control, emotional regulation, interoception, and spatial cognition.

So, apart from answering the questions “Where am I?” and “Which way is up?”, the vestibular system might even contribute to answering other vital and fundamental questions, such as “Where am I going?” and “How does it feel?”.

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Appendix

- Original research article 1
- Original research article 2
- Acknowledgements
- List of publications
- Affidavit
- Declaration of authorship

Research article 1

Cognitive deficits in patients with a chronic vestibular failure

Pauline Popp[1,2], Melanie Wulff [1,2], Kathrin Finke[2,3], Maxine Rühl[1,4], Thomas Brandt[4,5], Marianne Dieterich[1,2,4,6]

[1] Department of Neurology, Ludwig-Maximilians-Universität, München, Marchioninistraße 15, 81377 Munich, Germany

[2] Graduate School of Systemic Neurosciences, Ludwig-Maximilians-Universität München, Germany

[3] Department of Psychology, Ludwig-Maximilians-Universität München, Germany

[4] German Center for Vertigo and Balance Disorders, Ludwig-Maximilians-Universität München, Germany

[5] Clinical Neurosciences, Ludwig-Maximilians-Universität München, Germany

[6] SyNergy, Munich Cluster of Systems Neurology, Munich, Germany

J Neurol (2017) 264:554–563
DOI 10.1007/s00415-016-8386-7

ORIGINAL COMMUNICATION

Cognitive deficits in patients with a chronic vestibular failure

Pauline Popp[1,2] · Melanie Wulff[1,2] · Kathrin Finke[2,3] · Maxine Rühl[1,4] · Thomas Brandt[4,5] · Marianne Dieterich[1,2,4,6]

Received: 7 September 2016 / Revised: 23 December 2016 / Accepted: 25 December 2016 / Published online: 10 January 2017

Abstract Behavioral studies in rodents and humans have demonstrated deficits of spatial memory and orientation in bilateral vestibular failure (BVF). Our aim was to explore the functional consequences of chronic vestibular failure on different cognitive domains including spatial as well as non-spatial cognitive abilities. Sixteen patients with a unilateral vestibular failure (UVF), 18 patients with a BVF, and 17 healthy controls (HC) participated in the study. To assess the cognitive domains of short-term memory, executive function, processing speed and visuospatial abilities the following tests were used: Theory of Visual Attention (TVA), TAP Alertness and Visual Scanning, the Stroop Color-Word, and the Corsi Block Tapping Test. The cognitive scores were correlated with the degree of vestibular dysfunction and the duration of the disease, respectively. Groups did not differ significantly in age, sex, or handedness. BVF patients were significantly impaired in all of the examined cognitive domains but not in all tests of the particular domain, whereas UVF patients exhibited significant impairments in their visuospatial abilities and in one of the two processing speed tasks when compared independently with HC. The degree of vestibular dysfunction significantly correlated with some of the cognitive scores. Neither the side of the lesion nor the duration of disease influenced cognitive performance. The results demonstrate that vestibular failure can lead to cognitive impairments beyond the spatial navigation deficits described earlier. These cognitive impairments are more significant in BVF patients, suggesting that the input from one labyrinth which is distributed into bilateral vestibular circuits is sufficient to maintain most of the cognitive functions. These results raise the question whether BVF patients may profit from specific cognitive training in addition to physiotherapy.

Keywords Vertigo · Cognition · Vestibular failure · Vestibular rehabilitation · Attention · Memory

✉ Marianne Dieterich
marianne.dieterich@med.uni-muenchen.de

1 Department of Neurology, Ludwig-Maximilians University, Klinikum Grosshadern, Marchioninistrasse 15, 81377 Munich, Germany

2 Graduate School of Systemic Neurosciences, Ludwig-Maximilians University, Munich, Germany

3 Department of Psychology, Ludwig-Maximilians University, Munich, Germany

4 German Center for Vertigo and Balance Disorders, Ludwig-Maximilians University, Munich, Germany

5 Clinical Neuroscience, Ludwig-Maximilians University, Munich, Germany

6 SyNergy, Munich Cluster of Systems Neurology, Munich, Germany

Introduction

The vestibular system maintains balance with the eyes, head, and body in the upright position and keeps the gaze in space constant during locomotion. The most obvious effects of an acute unilateral vestibular failure (UVF) are direction-specific vertigo, nystagmus, and instability of stance and gait. Evidence has been increasing that vestibular input also essentially contributes to higher cortical (cognitive) functions such as spatial memory and orientation, multisensory motion perception, and navigation [1, 2].

Several behavioral studies in rodents [3, 4] and humans [5] have demonstrated that visuospatial memory and

cognition depend on vestibular function. Moreover, some patients with a vestibular disorder complain of a loss of memory and attentional focus [6–8]. These handicaps persisted when postural and ocular motor functions were restored by compensatory processes. To date, only a few studies have examined the extent of the vestibular system's influence on cognitive domains like memory and executive functions that do not focus on spatial memory and orientation. Some cognitive studies using the Wechsler Memory test in full on patients with vestibular failure have suggested that general memory and attention are not significantly affected [5]; in contrast, others have reported cognitive impairments such as dyscalculia, decelerated reaction time, or reduced visual short-term memory [9, 10]. These impairments seemed to be more severe in bilaterally affected patients (BVF), although very few studies directly compared the cognitive performance of patients with UVF and those with BVF [11–13]. Hence, the general effects of vestibular disorders on non-spatial cognitive performance are still being debated.

The aim of this group study was to ascertain whether the four main domains of cognition, i.e., executive function, working memory, processing speed, and visuospatial abilities, are impaired in chronic vestibular dysfunction and, if so, to what extent. Six cognitive tests were administered to patients with UVF or BVF and to healthy controls. The following questions were also addressed: (1) Is there a correlation between the degree of cognitive impairment and the severity of vestibular failure or time since disease onset? (2) Does the side of lesion in UVF patients cause a difference in cognitive performance? This is interesting because of the dominance of the right hemisphere and the ipsilateral right-sided pathways for cortical processing of vestibular information in right-handers [14, 15].

Methods

Patients and controls

Sixteen patients with a chronic UVF [mean age (SD) = 56 (10) years, 9 females, 7 with a left-sided lesion, 14 right-handers]; 18 patients with a BVF [mean (SD) = 57 (13) years, 9 females, 16 right-handers]; and 17 healthy controls [HC, mean age (SD) = 52 (14) years, 9 females, 16 right-handers] participated in the study (Table 1).

Patients were recruited from the German Center for Vertigo and Balance Disorders, Ludwig-Maximilians University, Munich, Germany, between January 2010 and December 2013. All patients were assessed neurologically and neuro-otologically on site (Table 2); tests included electronystagmography (ENG) with bithermal caloric testing, neuroorthoptic analysis by experienced orthopticians including the clinical head impulse test (HIT) and measurements of the subjective visual vertical (SVV). Caloric parameters represent low-frequency vestibular function, whereas the HIT represents high-frequency function. Inclusion criteria for the patients were a chronic disease lasting at least 6 months, no spontaneous nystagmus, and no tilts of SVV, which is indicative for an acute vestibular imbalance. The mean disease duration was 43 ± 29 months in BVF patients and 16 ± 10 months in UVF patients. BVF was characterized by the typical symptoms of gait imbalance in darkness and on uneven ground and one of the following responses consistent with prior findings [16, 17]: (1) bilateral pathological HIT and calorically elicited nystagmus with a mean peak slow phase velocity of $<5°/s$ for each caloric irrigation on both ears; (2) bilateral pathological HIT and caloric responses $>5°/s$ on one or both sides; or (3) normal HIT and loss of bilateral responses or reduced responses $<5°/s$ to caloric irrigation on both sides. UVF was defined by the typical history of an acute onset of sustained vertigo with gait deviation and postural imbalance for several days that occurred at least 6 months before the examination and one of the following conditions: (1) pathological HIT and a reduction of the caloric response of the same affected ear compared to the unaffected ear (relative vestibular reduction, RVR) of $>25\%$, (2) normal HIT and a unilateral RVR of $>25\%$, (3) pathological unilateral HIT and RVR of $<25\%$.

HC were recruited by newspaper advertisement and word of mouth. No HC had a history of neurological illness or was on psychopharmacological medication. Neurological and neurootological examinations were normal including tests for spontaneous nystagmus (Frenzel's glasses), gaze-evoked nystagmus, positioning maneuvers, clinical HIT, and tests of stance and gait (Romberg test, Unterberger stepping test), while bithermal caloric testing and measurements of SVV were not performed. The study was approved by the local ethics committee of the Ludwig-Maximilians University, Munich. All subjects gave their informed written consent to participate in the study.

Clinical data for correlation analyses

To determine whether the degree of cognitive impairment correlated with the severity of vestibular dysfunction in BVF patients, the mean peak slow phase velocity (SPV) calculated from the bithermal caloric irrigation of both ears was used as a measure of dysfunction. For UVF patients, the difference of the caloric response between the affected and unaffected ear was used (i.e., relative vestibular reduction, RVR). An asymmetry above 25% was considered pathological according to the Jongkees formula [18, 19]. Caloric parameters represent low-frequency

Table 1 Demographic and examination data of patients with unilateral vestibulopathy (UVF), bilateral vestibulopathy (BVF), and healthy controls (HC)

Group	Age	Gender	Handedness	Education[a]	MMSE[b]
UVF	64	f	r	2	30
	59	m	r	2	28
	34	m	l	3	29
	59	f	r	1	30
	80	m	r	3	29
	59	m	r	2	30
	58	f	r	2	27
	39	m	l	2	28
	58	m	r	1	29
	57	f	r	3	30
	64	f	r	2	29
	46	f	r	3	30
	50	f	r	3	30
	63	f	r	3	29
	50	m	r	3	27
	62	f	r	2	29
BVF	71	m	r	3	29
	63	f	r	3	29
	67	f	r	3	28
	64	m	r	1	30
	59	m	r	3	20
	72	m	l	1	27
	53	f	r	2	28
	47	m	r	2	30
	30	f	r	3	29
	51	m	r	1	30
	70	m	r	2	28
	55	f	r	2	29
	36	f	r	1	30
	48	f	r	2	27
	59	f	l	2	29
	78	m	r	1	28
	45	m	r	3	29
	74	f	r	3	30
HC	71	m	r	3	30
	62	f	r	3	30
	30	f	r	2	29
	47	m	r	2	28
	60	m	l	3	29
	52	m	r	3	30
	60	f	r	2	28
	65	f	r	1	27
	29	m	r	3	30
	67	m	r	2	29
	29	m	r	3	29
	54	f	r	2	28
	44	f	r	2	30
	52	f	r	3	28
	33	f	r	2	29
	72	f	r	1	30

f female, *m* male, *r* right, *l* left, *b* bilateral, *MMSE* Mini-Mental State Examination

[a] Education (1 = Hauptschulabschluss (lowest school degree), 2 = Mittlere Reife (intermediate degree), 3 = Abitur (highest school degree)

[b] Max value = 30. Values 26–30 represent normal global cognition, no mild dementia, and only subjects with values >25 were included in the study

vestibular function, whereas the HIT represents high-frequency function. For the clinical HIT the scaling was 0 = not pathological, 1 = unilateral pathological, 2 = bilateral pathological with one side more pronounced, and 3 = bilateral pathological.

Neuropsychological assessment

Handedness was defined according to the Edinburgh Inventory Laterality Index [20]. Global cognitive function was measured with the Mini-Mental Examination [21], and general intelligence function was assessed using the Multiple Choice Word Fluency Test (MWT-B).

The patients answered the Vertigo Symptom Scale VSS [22], a questionnaire that evaluates the two sub-scales vertigo and related symptoms (VER) as well as somatic anxiety and autonomic arousal (AA).

A battery of well-established neuropsychological tests was used to assess the cognitive domains of processing speed, short-term memory, executive function, and visuospatial abilities:

The Test for Attentional Performance (TAP): *Alertness and Visual Scanning*. A computer-controlled battery of attentional tests consisting of several sub-tests.

Visual Scanning: The subject was asked to quickly push a button when detecting a critical target on a 5 × 5 matrix. The reaction time was a value of visuospatial abilities.

Alertness: When a cross appeared in the middle of the screen, the subject had to push a button as fast as possible. The test measured the alertness and thus cognitive processing speed.

Whole report based on the Theory of Visual Attention (TVA): After a short fixation period, a column of five different, red or green letters appeared on the computer screen to the left or right of the fixation point for variable short exposure times. The task was to report as many letters as possible. Depending on the test person's accuracy in different exposure duration conditions, the parameters visual

Table 2 Clinical data of patients with unilateral vestibulopathy (UVF) and bilateral vestibulopathy (BVF)

Diagnosis	Duration[a]	Lesion	VER	AA[b]	HIT[c]	RW[d]	LW[d]	RC[d]	LC[d]	MCR[e]	RVR[f]
UVF											
PVD	9	l	0.63	0.53	0	21.1	3.7	14.2	3.7		65
PVD	29	r	1.47	1.40	1	1	30	4	25		83
PVD	14	l	0.58	1.33	1	6.8	4.5	10.2	4.4		31
PVD	8	r	0.58	1.87	1	2.2	16	0	12		85
PVD	13	l	1.05	0.27	1	15.8	1.1	26	2.5		84
PVD	36	l	0.58	1.67	1	10.3	3.5	17.6	2.2		66
PVD	8	l	0.74	1.47	1	17.1	3.3	32.8	3		78
PVD	34	l	0.11	0.93	0	11.7	0.9	13.5	1.6		82
PVD	15	r	0.47	1.20	1	7	7.2	6.9	13.6		20
PVD	6	r	0.95	1.87	1	1.3	12.5	0.3	8		86
PVD	16	r	0.16	0.27	1	–	–	–	–		–
PVD	9	r	0.47	1.20	1	2.2	14.8	4	19.3		69
PVD	32	r	0.32	0.47	0	6	8.6	4.9	10		26
PVD	6	r	0.63	1.27	0	5.2	12.8	8	11.4		29
PVD	6	r	0.63	2.00	1	6	15.7	6.1	15.5		44
PVD	12	l	0.42	1.60	1	15.3	11.4	9.8	9.2		10
BVF											
BVP, UE	26	b	1.47	1.67	3	2.7	0.4	0	1.7	1.2	
BVP, UE	69	r > l	0.11	0.00	3	1.2	0.2	0.6	0	0.5	
BVP, MD	48	b	0.47	1.73	3	–	–	–	–	–	
BVP, UE	42	r > l	0.26	1.07	2	3.7	0.5	2.3	3.2	2.4	
BVP, UE	134	b	1.05	1.87	3	4.3	4.2	10.6	4.1	5.8	
BVP, MD	54	l > r	0.16	0.60	3	1.4	3.4	2.1	1.6	2.1	
BVP, UE	27	l > r	0.47	0.80	1	3.7	3.3	2.4	2.3	2.1	
BVP, UE	29	b	0.68	2.00	1	1.1	0.2	1	1.4	0.9	
BVP, VN	20	b	0.21	1.47	3	0	1.2	0.7	1.8	0.9	
BVP, UE	81	b	0.47	1.67	3	2.1	7.6	3	2.9	3.9	
BVP, UE	44	l > r	0.68	2.27	2	2.3	3.9	3.2	3.8	3.3	
BVP, UE	61	b	0.63	1.87	3	1.5	1.1	2.4	2.3	1.8	
BVP, UE	25	b	0.89	1.27	3	3.5	0.6	3.3	2.4	2.5	
BVP, AO	37	r > l	0.58	1.33	0	2.1	2.9	2.3	2.1	2.4	
BVP, UE	29	l > r	0.89	1.53	3	5.5	4.8	4.6	5	5.0	
BVP, UE	48	b	0.79	2.00	1	0	1	1.4	0.8	0.8	
BVP, UE	9	b	1.47	1.33	3	8.3	4.3	5.9	6	6.1	
BVP, UE	6	b	0.26	1.47	0	0	0.2	0	0.3	0.1	

PVD peripheral vestibular deficit after vestibular neuritis, *VN* vestibular neuritis, *BVP* bilateral vestibulopathy, *UE* of unknown etiology, *MD* after Meniere's disease, *AO* of auto-immunological origin, *r* right, *l* left, *b* bilateral, *VER* Vertigo Scale, *AA* autonomic anxiety, *HIT* head impulse test, *RW* right ear, warm water, *LW* left ear, warm water, *RC* right ear, cold water, *LC* left ear, cold water, *MCR* mean caloric response, *RVR* relative vestibular reduction

[a] Duration since onset of disease in months

[b] AA = 0.30 ± 0.40 in controls [22]

[c] 0 = not pathological, 1 = unilaterally pathological, 2 = bilaterally pathological, more pronounced on one side, 3 = bilaterally pathological

[d] Values from caloric irrigation in °/s from both ears with cold water: 30 °C and warm water: 44 °C

[e] Mean caloric irrigation from (RW, RC, LW, LC) in °/s, values <5 considered pathological

[f] In %, Jongkees' formula [18]: values >25 considered pathological

short-term memory capacity *K* (amount of objects in the VSTM) and the visual processing speed *C* (elements/s) were estimated using TVA-based mathematical modeling [23].

The Stroop Color and Word Interference Test: To measure processing speed, the first two conditions required subjects to rapidly read and name a set of words and color bars [24]. In the third interference condition, the subject had to name the color of a word that designated a different color. The main outcome was the time needed to read the text in the interference condition; this measured the executive function.

Corsi Block Tapping Test: forward and backward. Nine blocks were arranged on a small board. Both tasks required the subject to observe the sequence of blocks tapped by the experimenter and then to repeat the sequence in the same order (CBT) or backward (BST). There were two runs, and a maximum of 14 points per task could be achieved. The CBT assessed short-term and working memory; the BST measured executive function [25].

Data analysis

The mean for each task condition was calculated for all three groups. Normal distribution of data were verified with the Shapiro–Wilk test. Where necessary, a log transformation was applied to obtain normality. A simple two-sided *t* test for independent variables was used to examine the differences between the means of UVF vs controls and BVF vs controls in each task. To compensate for alpha inflation, a stepwise Bonferroni–Holm correction was made with an initial *p* level of 0.008. Furthermore, an N-way analysis of variance (ANOVA) was performed to examine the relationship between group and experiment. Subsequently, a one-way ANOVA was conducted to compare the effect of the vestibular dysfunction on the cognitive performance within all three groups. Post hoc comparisons were performed using the Tukey HSD test. The non-parametric Mann–Whitney *U* test was chosen to compare the effect of left- or right-sided lesions in UVF patients. The relationship between severity of vestibular dysfunction or disease duration and task performance was tested with Pearson's correlation for interval scaled values and Kendall-Tau-b correlation for ordinal-scaled values. Statistical analyses were performed with SPSS 22 (SPSS Inc., Chicago, USA).

Results

Groups did not differ significantly in age, sex, or handedness. All subjects performed the experiments properly. None of the participants had a Mini-Mental State Examination (MMSE) or Mehrfach Wortschatz Test (MWT) value below normal. Thus, all 51 subjects were included in the analysis.

UVF patients exhibited an autonomic anxiety (AA) value of 1.2 (0.5) [mean (SD)] and BVF patients, 1.4 (0.5). The scale ranged from 0 to 4, with values of 0.30 (0.40) for controls (18). The vertigo value (VER) was 0.61 (0.32) for UVF and 0.64 (0.39) for BVF patients. This was well below the values of patients with an acute organic vestibular disorder, 1.06 (0.64) [22].

Neuropsychological results

Overall, BVF patients performed significantly worse than HC for at least one of the measures in all of the tested domains (Fig. 1; Table 3). When directly compared to controls, UVF patients performed significantly worse than HC in the alertness and visual scanning test. However, the effect was no longer significant when the performance of

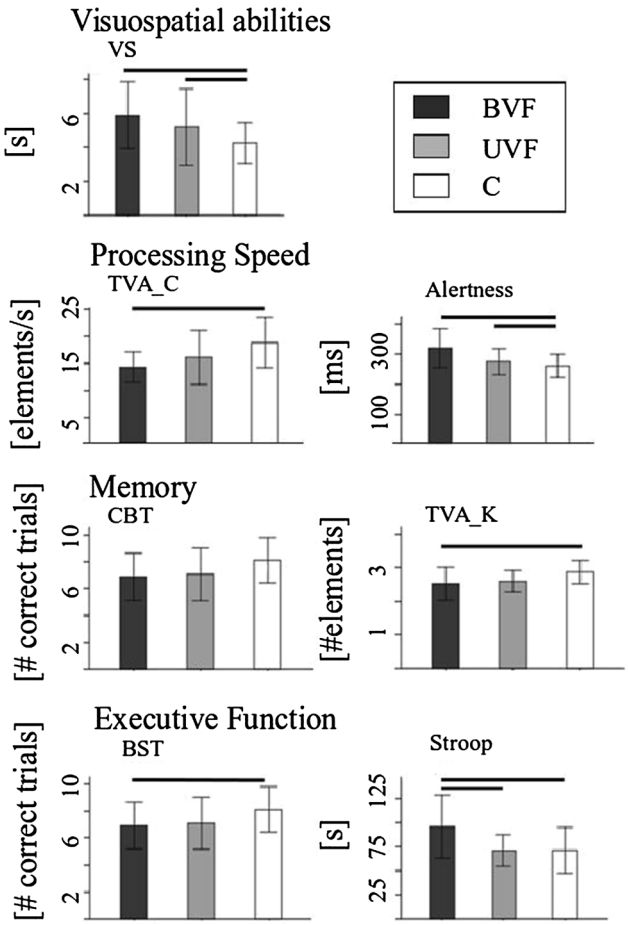

Fig. 1 Graphical overview of mean performances in applied cognitive tests. Statistically significant differences highlighted with lines. *BVF* bilateral vestibular failure, *UVF* unilateral vestibular failure, *C* healthy controls, *VS* visual scanning, *TVA C* cognitive processing speed, *TVA k* visual short-term capacity, *CBT* Corsi Block Tapping

Table 3 Mean performance on applied cognitive tests including standard deviation (SD) and statistical test results

Cognitive domain	Visuospatial abilities	Processing speed		Memory		Executive function	
	VS (s)	Alert (s)	TVA_C[a]	TVA_k[b]	CBT[c]	Stroop (s)	BST[c]
Mean performance							
BVF							
Mean (SD)	5.9 (1.9)	0.32 (0.06)	14.3 (2.7)	2.5 (0.5)	7.4 (1.2)	95.9 (31.8)	6.9 (1.7)
UVF							
Mean (SD)	5.2 (2.2)	0.28 (0.04)	15.1 (6.1)	2.6 (0.3)	7.7 (1.8)	71.0 (16.0)	7.1 (1.9)
HC							
Mean (SD)	4.2 (1.2)	0.26 (0.03)	18.8 (4.4)	2.9 (0.3)	7.5 (1.3)	71.3 (23.1)	8.1(1.6)
T test							
BVF vs HC							
p value	0.003	0.004	0.001	0.02	0.85	0.007	0.04
UVF vs HC							
p value	0.007	0.03	0.98	0.53	0.67	0.48	0.70
ANOVA: *F*(*df*, 2, 49)							
p value	0.05	0.004	0.009	0.03	0.91	0.008	0.11
Post hoc: Tukey HSD							
BVF vs HC							
p value	0.04	0.005	0.007	0.03	0.98	0.01	0.11
UVF vs HC							
p value	0.35	0.72	0.17	0.12	0.96	0.99	0.23
UVF vs BVF							
p value	0.53	0.03	0.43	0.88	0.90	0.02	0.95

UVF unilateral vestibular failure, *BVF* bilateral vestibular failure, *HC* controls, *VS* visual scanning, *Alert* alertness, *TVA C*: cognitive processing speed, *TVA k*: visual short-term capacity, *CBT* Corsi Block Tapping, *BST* Backwards Block Tapping, *df* degrees of freedom

[a] Elements processed per second

[b] Number of elements stored in visual short-term memory

[c] Number of correct trials of a maximum of 12

all groups was compared (ANOVA): The one-way ANOVA revealed that BVF patients differed significantly from UVF patients in the Stroop and the Alertness condition. The results of the N-way ANOVA analysis were not significant considering group ($F = 1.75$, $p = 0.176$, $df = 2$) and experiment ($F = 0.05$, $p = 0.9994$, $df = 6$). However, the interaction between group and experiment was significant ($F = 3.9$, $p = 0$, $df = 12$). Post hoc comparisons, following the one-way ANOVA, using the Tukey HSD test indicated that performance in BVF patients was significantly different from HC in the Alertness, Visual Scanning, Stroop, and TVA whole report and from UVF patients in the Alertness and Stroop test. The Tukey test further revealed no significant differences between UVF patients and HC. The mean performance of BVF was always worse than in UVF. The mean values including standard deviations and results from statistical analysis from all conducted tests are depicted in Table 3. In addition, in visual scanning, the mean of the total number of errors (standard deviation) showed 3.6 (2.2.) errors in HC, 5.3 (6.6) errors in UVF, and 7.6 (5.8) errors in BVF. A two-sided *t* test revealed a significant difference between HC and BVF ($p = 0.02$).

In brief, BVF patients were significantly impaired in all of the examined cognitive domains: visuospatial abilities, processing speed, short-term memory, and executive function. UVF patients exhibited impairments in their visuospatial abilities and in one of the two processing speed tasks.

Unilateral VF: right- vs left-sided lesion

The means of the test performances of UVF patients with a left- ($n = 7$) or a right- ($n = 9$) sided lesion did not significantly differ.

Correlation analysis

The results from caloric stimulation and HIT were correlated with the cognitive scores (Table 4; Fig. 2).

Significant correlations were found for both BVF and UVF patients. BVF patients showed significant correlation for caloric response and performance in the visuospatial task. In UVF patients, the reduction of caloric response (RVR) correlated significantly with one processing speed task, one executive function, and one memory task, while the HIT correlated significantly with one processing speed task, one executive function, and the visuospatial task. There were no correlations between time since disease onset and the cognitive scores (Table 3). This was also the case in the analysis of the subgroup with a similar disease duration (each $n = 9$; BVF 23 ± 9 months; UVF 22 ± 9 months).

Discussion

We explored the functional consequences of vestibular disorders for four cognitive domains: visuospatial abilities, processing speed, short-term memory, and executive function. BVF patients exhibited significant deficits in all four examined domains. UVF patients were affected in their visuospatial abilities and in one of the two processing speed tasks when compared to healthy controls; independently, moreover, they also showed a functional declining trend in the other tests. Thus, our results demonstrate that the cognitive impairments associated with vestibular failure go beyond the domain of spatial cognition, stressing the implications of vestibular failure for non-spatial cognitive processes. Moreover, the UVF patients had considerably better results than the BVF patients, suggesting that one intact labyrinth—the afferent input of which is fed into the bilaterally organized central vestibular system—is sufficient to maintain the measured cognitive functions.

Earlier studies presented evidence that spatial memory and navigation were impaired in patients with vestibular loss. Similarly, animal behavioral studies showed that unilateral [4] and bilateral [3] vestibular deafferentation led to spatial memory deficits. Studies using a virtual version of the Morris Water Task on patients with vestibular failure also demonstrated navigational impairments in complete [5] as well as incomplete BVF [13]. This had been shown earlier in simple path integration tasks [26, 27]. These results may indicate that a lack of vestibular input alters hippocampal functions. Indeed, patients with a chronic complete BVF developed significant atrophy (16%) of the hippocampus relative to controls [5]. Such atrophy of the hippocampal formation was also seen in incomplete BVF [13] and complete UVF [35]. Our current findings add further weight to the view that vestibular function and cognitive visuospatial skills are strongly connected, since visuospatial abilities were impaired in UVF and BVF patients.

It is difficult to compare our data with findings from other studies, most of which only measured the cognitive performance of patients with UVF. One study with BVF patients examined general memory function [5] using the Wechsler Memory Scale; only one of nine patients had an impaired memory index, whereas the Doors test revealed an impaired visual recognition memory in four of the nine patients. The TVA test of the BVF patients in our current study revealed that the visual short-term memory capacity was impaired. However, in contrast to an earlier study with UVF patients [28], we did not find any difference between

Table 4 Correlation coefficients with p values in parentheses

Cognitive domain	Visuospatial abilities	Processing speed		Memory		Executive function	
Test	VS (s)	Alert (s)	TVA_C[a]	TVA_k[b]	CBT[c]	Stroop (s)	BST[c]
HIT[d]	0.31 (0.02)	0.23 (0.93)	−0.07 (0.62)	−0.19 (0.16)	−0.08 (0.58)	0.31 (0.03)	−0.07 (0.61)
RVR[e]	0.27 (0.32)	0.14 (0.60)	−0.53 (0.04)	−0.50 (0.05)	0.00 (0.75)	0.44 (0.00)	−0.55 (0.03)
MCR[f]	0.48 (0.04)	0.14 (0.58)	0.12 (0.63)	−0.42 (0.08)	−0.05 (0.85)	0.17 (0.50)	−0.12 (0.64)
Duration[g]	0.11 (0.52)	0.02 (0.90)	−0.04 (0.84)	0.10 (0.57)	0.12 (0.52)	0.17 (0.34)	−0.09 (0.62)

Cognitive performance correlated with vestibular responsiveness

HIT head impulse test, *RVR* relative vestibular reduction, *MCR* mean caloric response, *VS* visual scanning, *Alert* alertness, *TVA C* cognitive processing speed, *TVA k* visual short-term capacity, *CBT* Corsi Block Tapping, *BST* Backwards Block Tapping

[a] Elements processed per second

[b] Number of elements stored in visual short-term memory

[c] Number of correct trials of a maximum of 12

[d] Including values from unilateral and bilateral vestibular patients (Kendall-Tau-b correlation analysis)

[e] Including values from unilateral vestibular patients only (Pearson's correlation analysis)

[f] Including values from bilateral vestibular patients only (Pearson's correlation analysis)

[g] Duration of disease since onset in unilateral and bilateral vestibular patients (Pearson's correlation analysis)

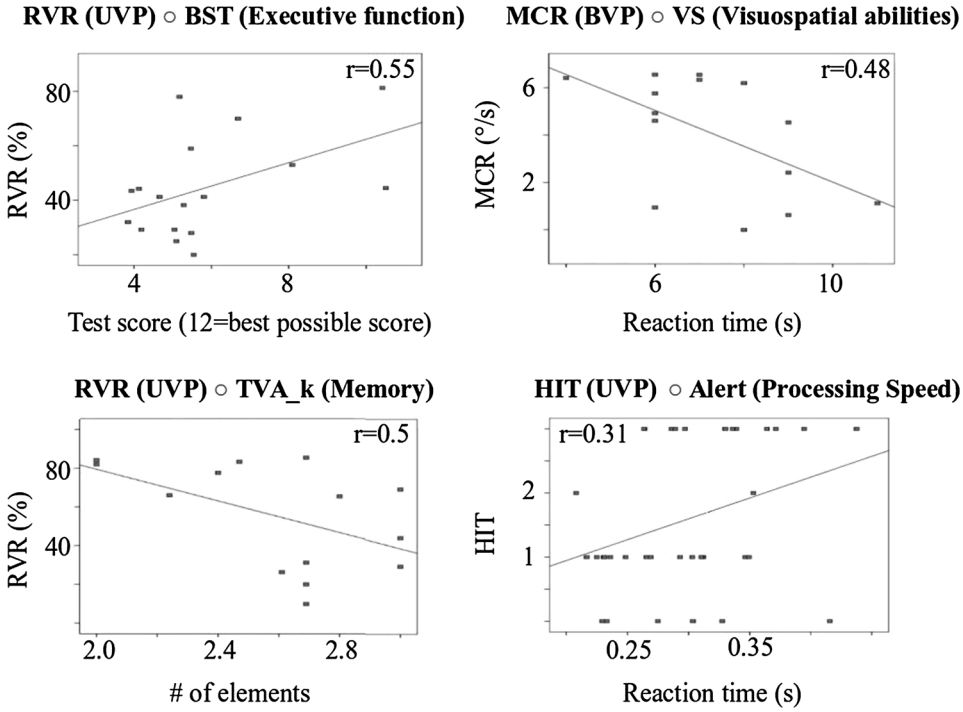

Fig. 2 Scatter plots of selected significant correlation analyses of vestibular responsiveness and cognitive performances including correlation coefficients (*r*). *HIT* head impulse test, *RVR* relative vestibular reduction, *UVP* unilateral patients, *MCR* mean caloric response, *BVP* bilateral patients, *VS* visual scanning, *TVA C* cognitive processing speed, *TVA k* visual short-term capacity, *CBT* Corsi Block Tapping, *BST* Backwards Block Tapping

patients and controls in the forward version of the Corsi Block test. This might indicate that patients in our study were able to use strategies, like verbal rehearsal, to compensate for short-term memory deficits in the task, but it was not possible in the TVA whole report with very short exposure times.

One explanation for our finding of impaired non-spatial cognition may be the changes in functional and structural connectivity that evolve due to missing vestibular input. The vestibular network has widespread cortical areas in the posterior parietal operculum, the insula, the retroinsular cortex, the temporo-parietal junction, the sylvian fissure, and the cingulate cortex [29]. Their functions and the extent to which they are connected to other networks have been only partly elucidated [30]. The temporo-parietal junction, for example, is involved in attentional processes [31]. The vestibular system projects further to many areas besides the parietal cortex and the hippocampus. The vestibular input is also projected to the retrosplenial, entorhinal, and perirhinal cortices, which play an important role in different memory processes [32]. Unilateral and bilateral vestibular damage leads to a complex cascade of neural changes and cortical reorganization due to processes that compensate for the missing vestibular input [13, 33–36].

UVF patients seemed to have less non-spatial cognitive impairments than BVF patients. Although no significant effects were found in the between-group analysis, when independently compared to HC, they performed significantly worse in one of the processing speed tasks (Alertness). Moreover, other cognitive domains seem to be hampered, since their mean performance was worse than that of HC in five of the seven cognitive scores (Fig. 1). This agrees with the findings of a few other studies. In dual-task experiments on postural control during cognitive tasks, UVF patients performed worse on the cognitive tasks than the controls, not only while standing but notably also while seated [10, 37].

The cognitive tasks in the dual-task experiments were reaction time and backward counting tasks. Hence, they examined processing speed and executive control. As the reaction time-based alertness task was the only processing speed measure affected in UVF patients in our study, UFV patients seem to have particular problems with speeded motor responses but not with fast perceptual information uptake as measured in the whole report or the Stroop test.

The few studies that directly compared cognitive performance in UVF and BVF patients are in agreement with our findings of more pronounced impairments in BVF patients [11, 12, 38]. The graduated difference between HC, UVF, and BVF patients suggests that—due to the bilaterally organized vestibular system with several midline crossings in the brainstem and through the splenium of the corpus callosum [39]—one intact labyrinth is able to send sufficient information to both hemispheres and thus supports the maintenance of most functions tested here. One might suspect that the poor performance of BVF patients could be biased by the longer mean disease duration; however, there were no correlations between the degree of cognitive impairment and disease duration and

this was also true for a subgroup analysis with similar disease durations in UVF and BVF patients. This suggests that the impairment occurs early after the breakdown of vestibular function.

Although the Vertigo Scale VER in the VSS of our patients was lower, the autonomic anxiety scale AA was as high as in patients with acute organic vestibular disorders [22]. This finding emphasizes that non-organic impairments persist after postural and oculomotor functions are restored by compensatory processes.

Moreover, the magnitude of cognitive impairment and the vestibular responsiveness significantly correlated in some of our tasks. In BVF patients vestibular caloric responsiveness and cognitive performance significantly correlated in the visuospatial task, whereas in UVF patients it correlated in two processing speed tasks: one executive function and one memory task. Results from the HIT correlated in both patient groups significantly with two processing speed tasks, one executive function and the visuospatial task.

Our data cannot simply be explained by age-related decline of vestibular function in the otherwise healthy elderly, since the test results were compared to age-matched controls. This is important since a study on the elderly reported significant associations between vestibular decline (measured by vestibular-evoked myogenic potentials) and visuospatial, working memory, and attention factor scores [40].

Since the vestibular system exhibits a hemispheric right-sided dominance in right-handers [14], we also tested whether the side of the lesion has an influence on cognitive performance. In some spatial navigation tasks, patients with a right-sided lesion had a tendency to perform worse than patients with a left-sided lesion [12]. Compensated UVF patients had a significant decrease in the volume of the left posterior hippocampus and the right superior temporal gyrus, irrespective of the side of the lesion [35]. In contrast, another study found volume reductions in the superior temporal gyrus in patients with complete unilateral deafferentation ipsilateral to the affected ear [41]. However, the cognitive performance of the UVF patients in our experiments was not influenced by the side of the lesion. This finding may be due to the small number of cases (seven left vs nine right).

A limitation of the study is that the neuropsychological tests preferably included visual measures. To make a stronger case for cognitive impairment, future studies should include non-visual cognitive measures.

Conclusions

In conclusion, our study provides evidence of widespread cognitive impairment after chronic bilateral and even unilateral vestibular failure. Apart from visuospatial abilities, short-term memory, executive function, and attention are significantly impaired when vestibular input is missing. The extent to which these cognitive deficits are relevant for aspects of daily life such as driving a car or working on a computer has up to now been unclear. The current findings may also have implications for the rehabilitation of these patients. They raise the question of whether the treatment of BVF patients should include not only physiotherapy for balance control, but in addition specific cognitive training.

Compliance with ethical standards

Conflicts of interest PP had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and reports no disclosures. MW, KF, MR, TB, and MD report no disclosures.

Ethical statement The study was approved by the local ethics committee of the Ludwig-Maximilians University, Munich. All subjects gave their informed written consent to participate in the study.

Funding This work was supported by funds from the German Research Foundation (GRK Grant Code 1091. to PP, MW, MD), the German Federal Ministry of Education and Research (BMBF Grant Code 01 EO 0901 to MD, TB), the Hertie–Foundation (TB), and the German Foundation for Neurology (MD, MR). The funding sources played no role in the design and performance of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

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Research article 2

Cortical alterations in phobic postural vertigo – a multimodal imaging approach

Pauline Popp [1,2,*], Peter zu Eulenburg [1,2,3*] , Thomas Stephan [1,2,3] , Rainer Bögle [1,2,3] , Maximilian Habs [1,3], Peter Henningsen [3,4] , Regina Feuerecker [1,3] , Marianne Dieterich [1,2,3,5]

[1] Department of Neurology, Ludwig-Maximilians-Universität, München, Marchioninistraße 15, 81377 Munich, Germany

[2] Graduate School of Systemic Neurosciences, Ludwig-Maximilians-Universität München, Germany

[3] German Center for Vertigo and Balance Disorders, Ludwig-Maximilians-Universität München, Germany

[4] Department of Psychosomatic Medicine and Psychotherapy, Technical University, Munich, Germany

[5] SyNergy, Munich Cluster of Systems Neurology, Munich, Germany

* contributed equally to the study

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RESEARCH ARTICLE

Cortical alterations in phobic postural vertigo – a multimodal imaging approach

Pauline Popp[1,2,a], Peter zu Eulenburg[1,2,3,a], Thomas Stephan[1,2,3], Rainer Bögle[1,2,3], Maximilian Habs[1,3], Peter Henningsen[3,4], Regina Feuerecker[1,3] & Marianne Dieterich[1,2,3,5]

[1]Department of Neurology, Ludwig-Maximilians Universität, Munich, Germany
[2]Graduate School of Systemic Neurosciences, Ludwig-Maximilians Universität, Munich, Germany
[3]German Center for Vertigo and Balance Disorders, Ludwig-Maximilians Universität, Munich, Germany
[4]Department of Psychosomatic Medicine and Psychotherapy, Technical University, Munich, Germany
[5]SyNergy, Munich Cluster of Systems Neurology, Munich, Germany

Correspondence
Marianne Dieterich, Department of Neurology, Ludwig-Maximilians-Universität München, Marchioninistraße 15, 81377 Munich, Germany. Tel: 0049-89-4400 72571; E-mail: marianne.dieterich@med.uni-muenchen.de

Funding Information
The work was supported by funds from the German Research Foundation (GRK Grant Code 1091), the German Federal Ministry of Education and Research (BMBF Grant Code 01 EO 0901) and German Foundation for Neurology.

Received: 31 August 2017; Revised: 22 March 2018; Accepted: 22 March 2018

doi: 10.1002/acn3.570

[a]The authors contributed equally to the study.

Abstract

Objective: Functional dizziness syndromes are among the most common diagnoses made in patients with chronic dizziness, but their underlying neural characteristics are largely unknown. The aim of this neuroimaging study was to analyze the disease-specific brain changes in patients with phobic postural vertigo (PPV). **Methods**: We measured brain morphology, task response, and functional connectivity in 44 patients with PPV and 44 healthy controls. **Results**: The analyses revealed a relative structural increase in regions of the prefrontal cortex and the associated thalamic projection zones as well as in the primary motor cortex. Morphological increases in the ventrolateral prefrontal cortex positively correlated with disease duration, whereas increases in dorsolateral, medial, and ventromedial prefrontal areas positively correlated with the Beck depression index. Visual motion stimulation caused an increased task-dependent activity in the subgenual anterior cingulum and a significantly longer duration of the motion aftereffect in the patients. Task-based functional connectivity analyses revealed aberrant involvement of interoceptive, fear generalization, and orbitofrontal networks. **Interpretation**: Our findings agree with some of the typical characteristics of functional dizziness syndromes, for example, excessive self-awareness, anxious appraisal, and obsessive controlling of posture. This first evidence indicates that the disease-specific mechanisms underlying PPV are related to networks involved in mood regulation, fear generalization, interoception, and cognitive control. They do not seem to be the result of aberrant processing in cortical visual, visual motion, or vestibular regions.

Introduction

Functional dizziness syndromes are among the most common diagnoses in chronic vertigo patients.[1] Recently, the Committee for Classification of Vestibular Disorders of the International Society for Neurootology – the Bárány Society – established a definition for functional dizziness syndromes for the disorder "persistent perceptual-postural dizziness" (PPPD)[2,3] based on clinical observations and data on phobic postural vertigo (PPV),[4] chronic subjective dizziness (CSD),[5] visual vertigo,[6] and space and motion discomfort.[7] As PPPD was not yet established at the beginning of this study, the patients included in our study were evaluated according to the initial diagnostic criteria of PPV.[8,9] PPV is defined by symptoms of subjective postural imbalance and dizziness, but objectively normal neuro-otological test results, often accompanied by obsessive-compulsive personality traits, anxious and depressive symptoms. Later posture and gait analyses disclosed typical leg muscle co-activation during stance and gait indicating an anxious behavior.[4,9–11] PPV patients are constantly preoccupied with their balance, anxiously monitoring it.[10–14] Precise posturographic analyses of stance showed that PPV patients increased their postural

sway by co-contracting the flexor and extensor leg muscles during normal stance.[10–12] During difficult balancing tasks, however, their posturographic data did not differ from those in healthy subjects.[15] Furthermore, compared to other types of vertigo the prevalence of psychiatric disorders, typically depression or anxiety is increased in functional dizziness.[16,17] At the beginning, the dizziness in PPV occurs in attacks often induced by typical triggers of phobic syndromes (e.g., bridges, driving a car) or by a moving visual scene[8,9] before it comes to a generalization of dizziness. Consequently, patients show avoidance behavior and a tendency to generalize the provoking stimuli.[18]

Up to now very little is known about how these behavioral consequences are linked to cortical neural networks, especially the visual and vestibular networks during visual stimulation and the emotional network. In a functional magnetic resonance imaging (fMRI) study with sound-evoked vestibular stimulation CSD patients showed reduced activity and altered functional connectivity in vestibular, visual, and prefrontal cortical regions.[19] These findings suggest that the persisting vestibular symptoms may be linked to aberrant activity and connectivity within the vestibular-visual-prefrontal network.

The current multimodal neuroimaging study analyzed brain morphology, activity, and connectivity in patients with PPV to pin-point disease-specific mechanisms, using voxel-based morphometry, functional magnetic resonance imaging, and functional connectivity analyses.

Methods

Participants

Forty-four patients with primary PPV (mean age 44 ± 14 years, 24 females, 42 right-handers) and 44 healthy controls (HC, mean age 43 ± 14, 24 females, 42 right-handers) participated in the study. All patients were recruited from the Department of Neurology and the German Center for Vertigo and Balance Disorders, Ludwig-Maximilians University, Munich, Germany, from January 2010 to December 2015. They underwent a detailed neurological and neuro-otological onsite assessment to exclude possible organic or other somatoform disorders. Vestibular testing of the vestibulo-ocular reflex included bilateral caloric irrigation (30/44°C) for the low-frequency range and a clinical head-impulse test[20] for the high-frequency functions of the semicircular canals, as well as measurements of the subjective visual vertical and ocular torsion for otolith function.

The diagnosis of PPV was based on the following diagnostic criteria: subjective dizziness and/or posture and gait instability, but no pathological findings in neurological and neuro-otological tests, as acknowledged by the Bárány Society.[3,8] The HCs were individually age- and gender-matched to the patients and had no history of psychiatric, neurological, or neuro-otological disorders. Patients and HCs were not allowed to take any psychoactive medication, and should not have a cerebrovascular disorder. All subjects completed the German version of the Beck Depression Inventory, BDI.[21] The study was approved by the local Ethics Committee of the Ludwig-Maximilians-University, Munich, Germany. All subjects gave their informed written consent to participate in the study.

Neuroimaging data acquisition

Structural and functional images were acquired on a clinical 3T scanner (GE, Signa Excite HD, Milwaukee, WI, USA) at the hospital of the Ludwig-Maximilians-University, Munich, using a 12-channel head coil. The functional images were recorded using a T2*-weighted gradient-echo echo-planar imaging sequence sensitive to blood oxygen level dependent (BOLD) contrast (repetition time TR = 2.45 sec, echo time TE=40 msec, flip angle FA=90°, voxel size 3 × 3 × 3 mm, 38 transversal slices). Each of the three consecutive functional runs contained 264 MRI volumes covering the whole brain. Four prior scans to allow for magnetization equilibrium by the scanner were discarded automatically. Slices were measured in an ascending interleaved order. The high-resolution structural T1-weighted image (slice thickness=0.7 mm, matrix 256 × 256, field of view 220 mm, phase encoding direction=anterior/posterior, FA=15 msec, bandwidth=31.25, voxel size: 0.86 × 0.86 × 0.7 mm) was acquired at the start of the MRI session.

Functional neuroimaging

Thirty-four patients (mean age 40 ± 13, 16 females, 32 right-handers) and 37 HCs (mean age 43 ± 26, 18 females, 34 right-handers) participated in the functional neuroimaging experiment.

The subjects were equipped with a Lumina LU400-Pair button response unit (http://cedrus.com/lumina/), earplugs, and sound-isolating headphones. A laptop running MATLAB 8.0 (The MathWorks, Inc., Natick, Massachusetts, US) and the cogent 2000 toolbox (http://www.vislab.ucl.ac.uk/cogent_2000.php) delivered the stimuli. The field of view was restricted to ±24.9° in the horizontal and ±18.9° in the vertical plane.

The stimulation paradigm consisted of subsequent periods of stationary and moving patterns, intended to trigger the visual motion aftereffect (MAE), that is, the illusion that occurs after being exposed to a moving directional stimulus for a prolonged time.[22] The experiment, modeled

in a block-design, comprised three runs (3 × 11 min), each including 12 blocks of moving stimulation (7°/sec), followed by a stationary period of 27.5 sec each. The stimuli consisted of 600 black and white dots (diameter = 0.5°) randomly positioned on a gray background. The subjects were instructed to indicate the end of the experienced MAE using the response unit during the stationary period.

Data analysis

Behavioral data

The behavioral data were analyzed in SPSS 22.0 (SPSS Inc., Chicago, Illinois, US). After testing for normality, two-sample *t*-tests were applied to compare the means of the latencies of the MAE in the different conditions between the two groups. *P* values below a value of 0.05 were considered significant.

Voxel- and surfaced-based morphometry (VBM/SBM)

The CAT12 toolbox Version 1109 (http://dbm.neuro.uni-jena.de/cat/) was used to perform voxel-based morphometry and surface-based cortical thickness analysis. The T1-weighted image was DARTEL-normalized[23] to MNI space, segmented into gray matter, white matter, and cerebrospinal fluid and smoothed with an 8-mm FWHM Gaussian kernel filter. Surface reconstructions of cortical thickness values for each hemisphere were resampled and then smoothed with a 15-mm filter.[24] The modulated normalized volume images were combined in a whole-brain voxelwise statistical analysis (two-sample *t*-test) in the VBM approach and age and total intracranial volume (TIV) were entered as nuisance regressors in each comparison. An association was tested for BDI score and duration of disease and voxelwise gray matter density information in two separate random-effects multiple regression analyses. Activation maps were thresholded at $P < 0.001$ (uncorrected) for cluster definition and considered significant at $P < 0.05$ (FDR corrected) at a cluster level with a minimum cluster size of 10 voxels.[25] The resulting regions were visualized and identified with the anatomy toolbox in SPM12.[26]

Task-based fMRI data analysis

Data processing was performed with MATLAB using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Prior to preprocessing the motion fingerprint algorithm[27] was used to detect head motion larger than 3 mm or 3° in any axis or direction within one session with respect to the first image.

The functional images were slice-time corrected and realigned to the mean image of the respective run. The structural image was coregistered to the mean functional image, followed by segmentation into gray and white matter and DARTEL registration. Subsequently, the functional images were normalized with the DARTEL-derived flow fields[23] using a publicly available template (http://brain-development.org/ixi-dataset/) and spatially smoothed with a 6-mm Gaussian kernel filter.

A general linear model (GLM) assessed the effects of the task parameters on the BOLD activation for each subject using SPM 12. First-level GLMs included the experimental conditions Motion and Aftermotion, convolved with the canonical hemodynamic response function (HRF). Motion was modeled as of fixed duration, whereas the Aftermotion duration was defined by inserting the individually recorded duration of the MAE in the design matrix. The previously acquired realignment parameters were included as additional regressors of no interest. Low frequency signal drift was eliminated using a standard high-pass filter (cut-off, 128s). The contrasts Motion and Aftermotion were defined to compute contrast images.

The contrast images from the first-level analysis were used to employ a random-effects model to examine group differences. Two-sample *t*-tests between healthy subjects and patients as well as linear correlation analyses with behavioral data were performed. Activation maps were thresholded at $P < 0.001$ (uncorrected) for cluster definition and considered significant at $P < 0.05$ (FDR corrected) at a cluster level with a minimum cluster size of 10 voxels.[25] The resulting regions were visualized and identified with the anatomy toolbox (Version 2.2c) in SPM12.[26]

Task-based functional connectivity

Functional connectivity was analyzed using the DPARSFA 4.1 (http://rfmri.org/dpabi) toolkit implemented in SPM 12, using the first run of the functional images. Data were slice-time corrected and realigned for head motion correction. The corrected images were DARTEL-normalized to MNI space,[23] resampled to 2 × 2 × 2 mm^3 and spatially smoothed with a 6-mm FWHM Gaussian kernel filter. Nuisance covariates, including cerebrospinal fluid and white matter signals, were regressed out of the BOLD signals, and band-pass filtering (0.01–0.1 Hz) was applied to reduce noise derived from physiological signals. Based on the results obtained in the VBM analysis and fMRI experiment, regions of interest (ROIs) were defined as follows: frontopolar area (fpPFC), orbitofrontal cortex (OFC), and subgenual anterior cingulate cortex (sACC). Activity within the anatomically defined ROIs was extracted and correlated

Table 1. Demographical, clinical, and psychophysical data in phobic postural vertigo patients (PPV) and healthy controls (HC).

Characteristics	PPV	HC
Participants (total)	44	44
Age (SD) in years	44 (14)	43 (14)
Gender	24 females	24 females
Handedness	42 right-handed	42 right-handed
BDI (SD)	9.3 (6.3)	0.9 (1.1)
Duration of disease (SD) in months	33 (37)	–
Participants fMRI experiment	34	37
Age (SD) in years	40 (13)	43 (26)
Gender	16 females	18 females
Handedness	32 right-handed	34 right-handed
MAE (SD) in seconds	5.70 (1.71)	3.68 (1.17)

SD, standard deviation; BDI, Beck Depression Inventory; MAE, motion aftereffect.

with all other gray matter voxels in the brain. The obtained correlation coefficients were then transformed to Fisher z-scores. To identify differences in the connectivity of the ROIs between patients and controls, a two-sample t-test was carried out. A threshold $P = 0.05$ was set after FDR correction, with a critical cluster size of 50.

Results

The mean BDI score of the patients was 9.3 ± 6.3 SD and 0.9 ± 1.1 SD in controls. Across all runs, the patients had significantly longer ($P < 0.0001$) experiences of the MAE as the HCs (Table 1, Fig. 1).

Voxel-based morphometry

Poor data quality as a result of hardware instabilities of the scanner (spiking) during image acquisition led to the exclusion of seven patients from the study. Therefore, 37 patients and 37 HCs participated in the final VBM/SBM data analyses.

Patients showed increased gray matter volumes (GMV) in the thalamus bilaterally, more specifically, the prefrontal projection zone of the thalamus,[28] precentral gyrus, and primary motor cortical areas and reductions in left supramarginal gyrus (SMG), bilateral cerebellar lobules, and right posterior middle frontal gyrus (Table 2, Fig. 2).

The duration since disease onset was associated with increased GMV in the ventrolateral prefrontal cortex (vlPFC) bilaterally. A negative correlation was found in postcentral gyrus bilaterally, cerebellar vermis, and right SMG. Relatively higher BDI scores were associated with increased GMV in frontopolar PFC (fpPFC), orbitofrontal cortex (OFC), dorsolateral PFC (dlPFC), medial PFC (mPFC) as well as bilateral pre- and right postcentral gyrus and with decreased GMV in right middle occipital gyrus, bilateral cerebellar lobules, and left thalamus. SBM analysis revealed greater values for cortical thickness in HCs for ventromedial prefrontal cortex, the insular sulcus and the lingual gyrus in the left hemisphere and a region bordering the anterior cingulate gyrus and the cuneus in the right hemisphere (Fig. 3).

Functional MRI

To be included in the functional neuroimaging analysis, subjects had to complete at least two runs. The main reason for data exclusion was premature termination of the task-experiment by the subject (overanxiousness). Consequently, 19 patients and 19 matched HCs were included in the final fMRI analysis.

Task-based fMRI

During the visual motion experiment, the response revealed a typical bilateral activation–deactivation pattern in visual and vestibular cortical areas (Fig. 1).[29] Compared to HCs, patients showed increased activations in the subgenual anterior cingulate cortex (sACC). No significant deactivations were found in patients or HCs (Table 3).

Task-based functional connectivity

Patients showed higher functional connectivity than HCs between fpPFC and thalamus, anterior insular, parahippocampal gyrus, ACC, amygdala, and posterior medial frontal gyrus (Table S1, Fig. 4). Furthermore, patients showed lower functional connectivity of the fpPFC with posterior cerebellar lobules, SMG, and middle temporal gyrus areas. In patients the connections were increased between OFC and precentral gyrus, calcarine fissure and superior parietal lobule. Functional connectivity in patients compared to HCs was decreased between OFC and inferior frontal gyrus, cerebellar vermis, and posterior lobules. Stronger connectivity was seen in patients between sACC and left inferior frontal gyrus, fpPFC, lingual gyrus, postcentral gyrus, thalamus, and cerebellar lobule. There was no decreased connectivity with the sACC.

Discussion

In this multimodal imaging study, we analyzed morphological changes and task-based functional activity and connectivity of cortical networks in patients with chronic functional dizziness, in particular the subtype PPV. We found that the PPV patients had an increase in structural parameters and functional connectivity in regions of the

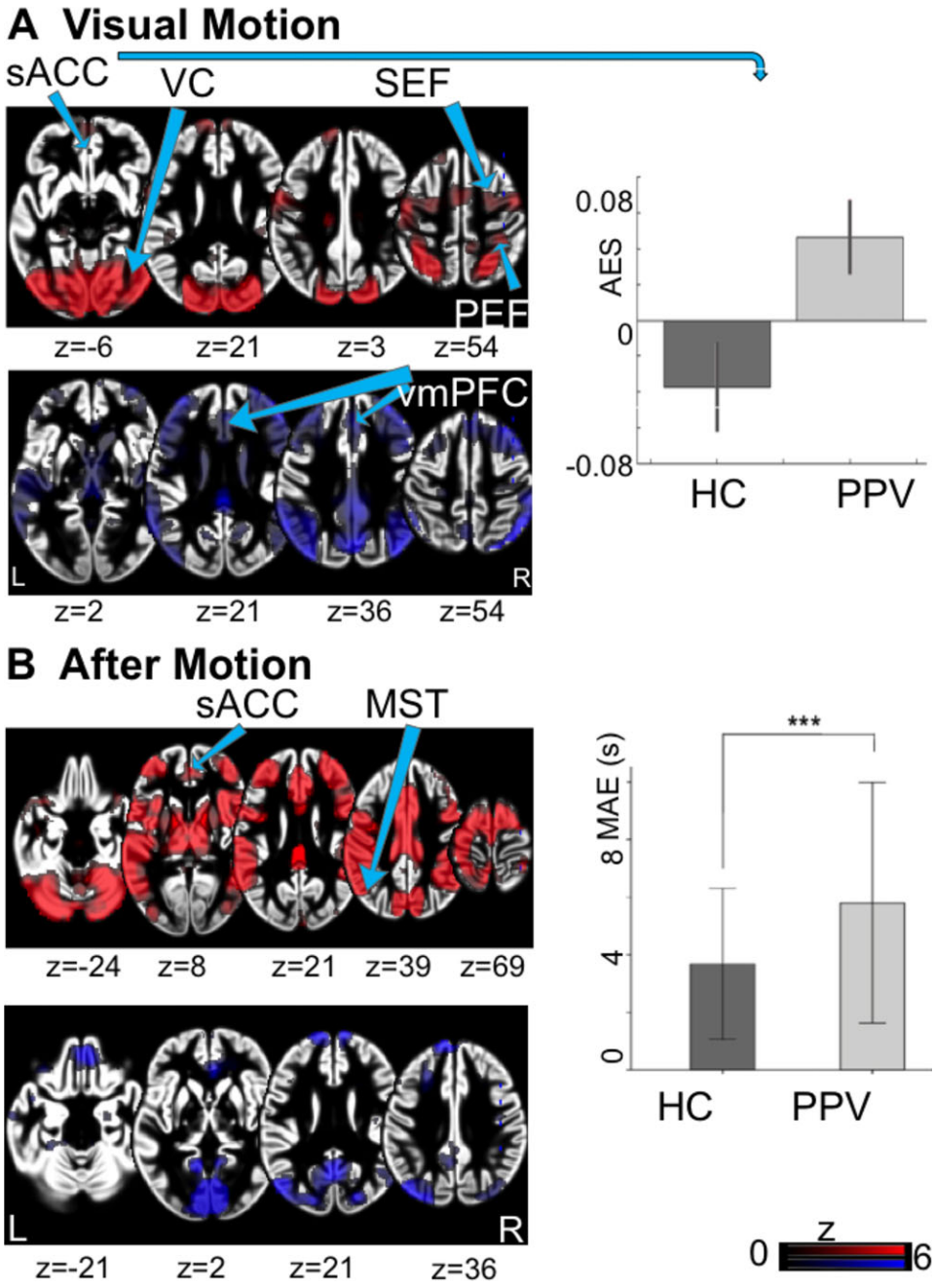

Figure 1. Activation–deactivation pattern during visual motion fMRI experiment and the ensuing motion aftereffect. Statistically significant regions superimposed on a publicly available template from 555 healthy subjects (http//brain-development.org/ixi-dataset/) ($P < 0.0001$, uncorrected, for cluster definition and considered significant at $P < 0.05$ (FDR corrected) at cluster level). Red cluster depict significant activation, blue cluster depict significant deactivations. (A) Activation–deactivation pattern in all subjects during visual motion paradigm. Plot depicts activity extracted from sACC in PPV patients and HC. (B) Activation–deactivation pattern in all subjects during aftermotion paradigm. Plot depicts the duration of the subjective motion aftereffect (MAE) in seconds in PPV and HC. The three asterixes indicate the highly significant ($P < 0.0001$) difference in MAE perception duration between the two groups. AES, arbitrary effect size; FEF, frontal eye fields; L, left; MST, medial superior temporal; PEF, parietal eye fields; R, right; sACC, subgenual anterior cingulate cortex; SEF, supplemental eye fields; VC, visual cortex; vmPFC, ventromedial prefrontal cortex.

Table 2. Gray matter volume in phobic postural vertigo patients (PPV) compared to healthy controls (HC) including covariats.

Brain Region	Hemisphere	Peak *T* value	Voxels	MNI coordinates			Brodmann area
				x	*y*	*z*	
PPV>HC							
Thalamus	r	8.10	5157	3	−21	10	
Thalamus	l	7.48	3862	−17	−32	8	
Paracentral lobule	l	3.83	171	−10	−30	78	BA4
Precentral gyrus	l	3.41	59	−37	−27	69	BA4
Postcentral gyrus	l	3.44	23	−21	−40	73	BA3
PPV<HC							
Supramarginal gyrus	l	4.00	765	−49	−36	31	BA40
Cerebellum, lobule VIIa Crus II	r	3.40	81	11	−87	−29	
Cerebellum, lobule VIIa Crus I	l	3.41	72	−52	−62	−21	
Posterior MFG	r	3.33	36	12	−5	52	BA6
BDI positive correlation							
Precentral gyrus	r	6.34	1570	6	−25	59	BA4
mPFC	r	5.09	430	5	64	−8	BA10
Paracentral lobule	r	4.83	405	10	−28	80	BA4
dlPFC	r	4.26	74	27	36	28	
dlPFC	l	4.19	41	−35	35	43	
vmPFC/OFC	l	3.83	163	−38	50	−17	
Precentral gyrus	l	3.78	149	−36	−21	69	BA4
vmPFC	r	3.76	10	12	31	−11	BA11
Superior occipital gyrus	r	3.74	18	28	−72	40	
Postcentral gyrus	r	3.70	173	46	−32	61	BA1
BDI negative correlation							
Cerebellum, lobule VI	r	4.89	326	29	−48	−37	
Thalamus	l	4.74	239	−13	−15	0	
Middle occipital gyrus	r	4.55	346	51	−76	7	
Cerebellum, lobule IX	l	4.18	158	−12	−47	−45	
Disease duration positive correlation							
vlPFC	l	4.30	501	−55	34	3	BA45
vlPFC	r	3.77	18	52	−2	19	BA44
Disease duration negative correlation							
Postcentral gyrus	r	4.41	539	63	−20	36	BA1
Postcentral gyrus	l	4.05	132	−46	−23	43	BA3
Supramarginal gyrus	r	3.94	284	50	−47	50	
Superior frontal gyrus	r	3.88	72	10	37	57	
Cerebellum, dentate gyrus	r	3.84	357	14	−65	−33	
Cerebellum, vermis	r	3.77	83	3	−55	−28	

DlPFC, dorsolateral prefrontal cortex; l, left; MFG, medial frontal gyrus; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; r, right; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

prefrontal cortex and the associated thalamic projection zones bilaterally, as well as in the primary motor cortex compared to controls. Furthermore, analyses in the patients revealed a decrease in gray matter volume and connectivity in cerebellar regions including the cerebellar vermis and the posterior lobules as well as the supramarginal gyrus. Gray matter volume increases in various prefrontal areas correlated positively with the disease duration and the depression index. These task-based functional activity and connectivity analyses disclosed an aberrant involvement of networks known to be involved in regulating mood, emotion, and interoception as well as motor control. Much to our surprise no significant effects were found in the primary visual and vestibular cortical areas.

Prefrontal cortex and thalamus

PPV patients demonstrated a significant gray matter increase in the "higher-order" thalamus, which projects to the prefrontal cortex[28] and plays a vital role in mood-regulating circuits and enables fast responses to threats.[30] Complementary, task-based functional connectivity analyses revealed a hyperconnectivity between the mPFC, sACC, and the mediodorsal thalamus. Indeed, recent studies

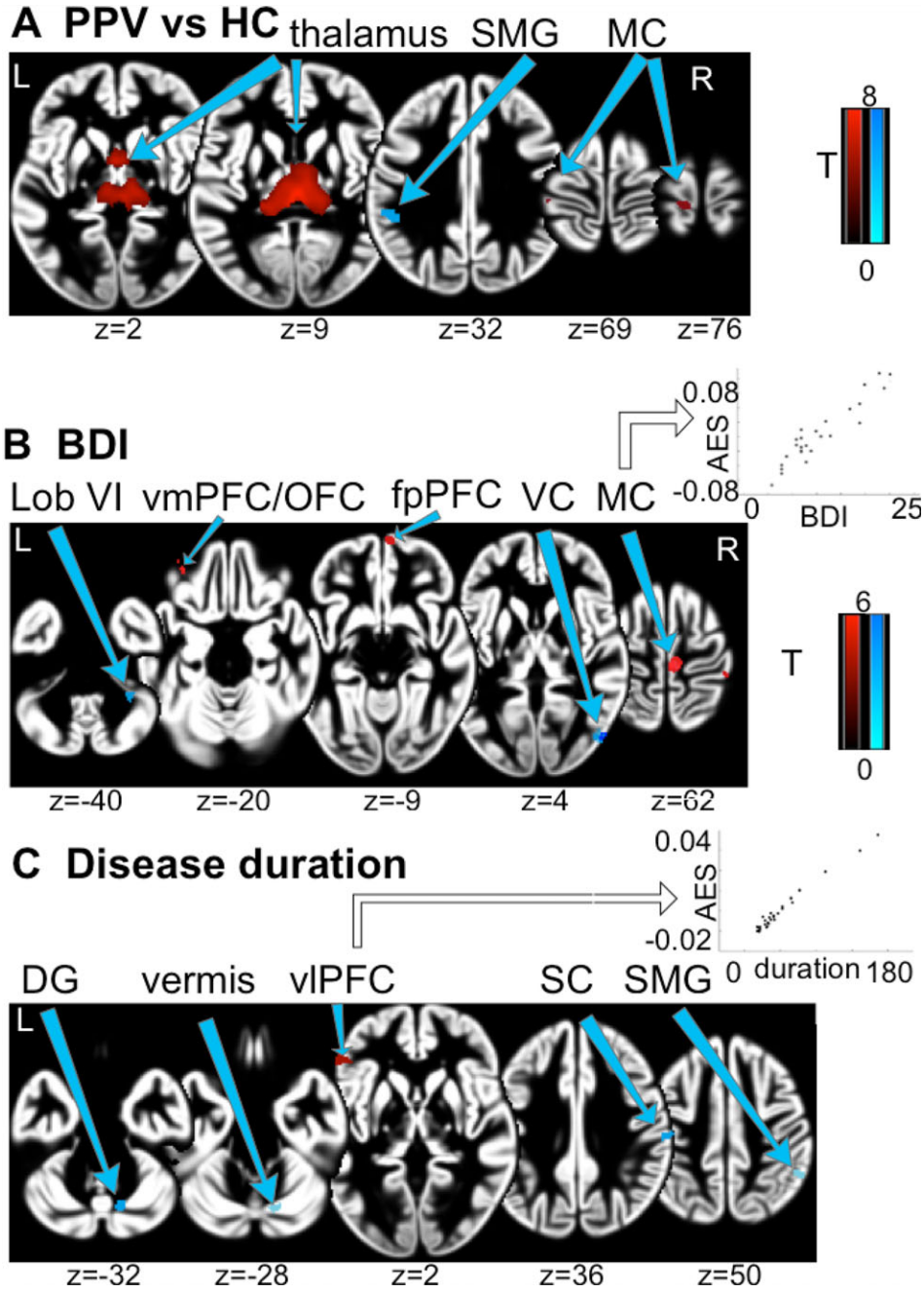

Figure 2. Structural differences found in phobic postural vertigo patients (PPV). Significant VBM results superimposed on a publicly available template from 555 healthy subjects (http//brain-development.org/ixi-dataset/) ($P < 0.0001$ (uncorrected) for cluster definition and considered significant at $P < 0.05$ (FDR corrected at cluster level). Red colored clusters depict gray matter increases, blue cluster depict gray matter decreases. (A) Gray matter volume (GMV) changes in PPV patients compared to healthy controls (HC). (B) GMV changes in PPV patients that correlated positively with the BDI values ($P < 0.001$). The scatter plot depicts the GMV changes for the right paramedian motor cortex (leg region) in the precentral gyrus that showed a positive correlation with the BDI index. (C) GMV changes in PPV patients that correlated with the duration of the disease. The scatter plot depicts the GMV changes for the left vlPFC which correlated with the duration in months. AES, arbitrary effect size; BDI, beck depression index; DG, dentate gyrus; fpPFC; frontopolar prefrontal cortex; L, left; Lob VI, cerebellar lobule VI; MC, motor cortex; OFC, orbitofrontal cortex; R, right, SMG; supramarginal gyrus; VC, visual cortex; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

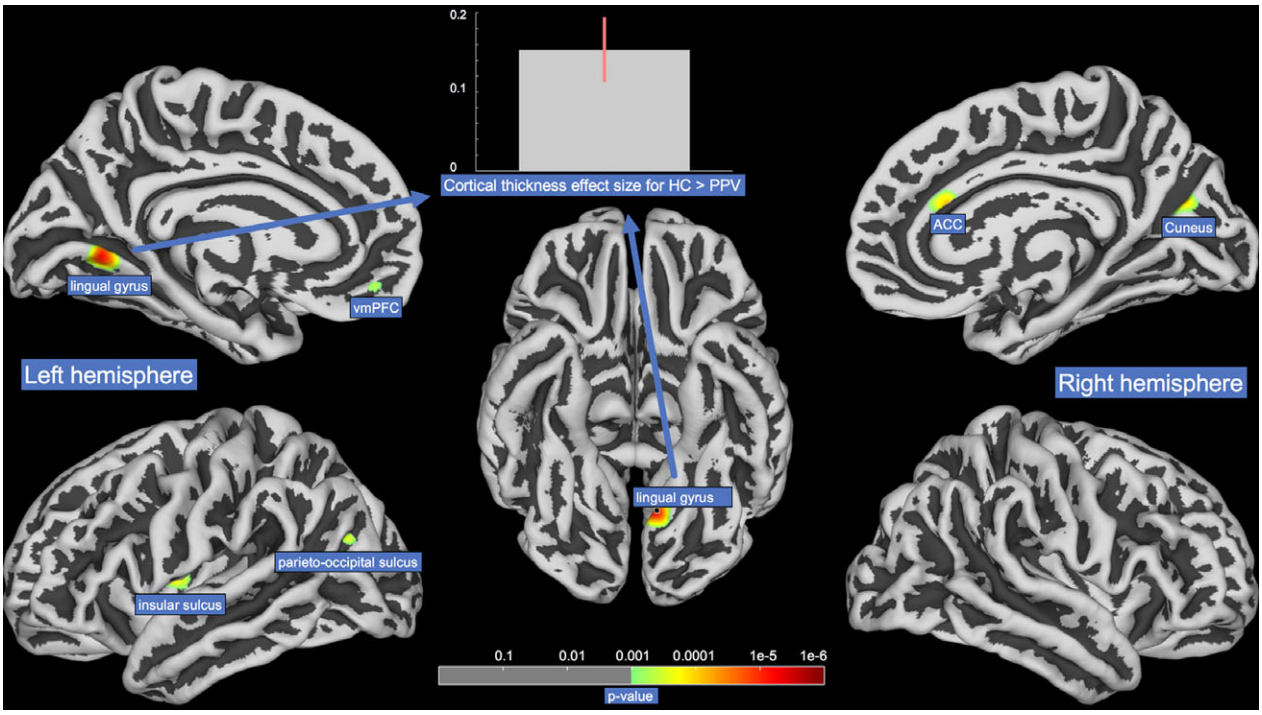

Figure 3. Differences in cortical thickness in phobic postural vertigo patients (PPV) compared to healthy controls (HC). All results shown reflect regions where the PPV patients had a lesser cortical thickness compared to the healthy controls. Exemplary effect size illustrated for the finding in the lingual gyrus of the left hemisphere. For a detailed atlas-based localization of the nodes, please see Table S1. ACC, anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex.

reported increased thalamo-cortical connectivity in various mood disorders during phobic-related threat stimulation.[31] As PPV patients are particularly sensitive to certain sensory stimuli or social situations[3,8] and exhibit a constantly anxious appraisal behavior,[10,11,15] possibly their networks regulating fear responses and emotion might be altered.

Individual disease duration in the patients correlated with volume increase in the vlPFC bilaterally, which is particularly relevant in the cognitive control of motor inhibition and facilitates the capacity to sustain attention.[32,33] PPV patients seem to extensively use these processes, as they are typically constantly occupied with controlling their posture and engaged in intense rumination.[10–12,14,34] Thus, over time the recruitment of additional resources to avoid phobic responses could manifest as a structural volume increase in vlPFC.

Mood disorders are a common comorbidity in PPV[12] and CSD.[5] A positive correlation was observed between BDI and GMV in several prefrontal areas in our patients. A mutual characteristic of depression and PPV is an increased self-focus and excessive self-referential appraisal, mainly regulated by mPFC.[35] The dlPFC is generally associated with attentional top-down control suppression of fear-induced behavior and part of the cognitive control network.[36] Increased GMV in mPFC in more depressive PPV patients might reflect the excessive self-focus and appraisal,[37] whereas an increase in dlPFC may be the result of cognitive control of immoderate fear response[31] to the expected postural threat.

Affective, interoceptive, and orbitofrontal networks

During the visual motion stimulation experiment patients showed significantly increased activation in the sACC, a region involved in emotional processing[38] commonly found to be inactive during visual motion stimulation in healthy subjects.[29] For comparison, CSD patients showed decreased activity in the postero-insular vestibular cortex, hippocampus, and ACC and a disruption of the vestibular-visual-anxiety network when stimulated with loud, short tone bursts to evoke a vestibular-acoustic response.[19] These results during stimulation differ from our findings; however, the stimulation paradigm and targeted sensory modality were not visual but auditory-vestibular. Our findings (during visual stimulation) suggest that the pathophysiology of PPV includes some deficits in fear regulation as the visual stimuli lead to the activation of pathways related to fear. The interaction of

Table 3. Significant hyperactivations during visual stimulation and aftermotion period in phobic postural vertigo (PPV) patients versus healthy controls (HC)

Brain Region	Hemisphere	Peak *T* value	Voxels	MNI coordinates			Cytoarchitectonic area
				x	*y*	*z*	
Visual motion PPV>HC							
Mid orbital gyrus	l	4.52	21	−4	26	−6	s24
Visual motion PPV<HC							
None	–	–	–	–	–	–	–
After motion PPV<HC							
Mid orbital gyrus	l	3.77	15	−4	32	−8	s32
After motion PPV<HC							
None	–	–	–	–	–	–	–

l, left.

emotional disorders and vestibular symptoms has been comprehensively discussed in the literature[39,40]. Although not all PPV patients qualify as having psychiatric disorders, most develop an avoidance behavior.[8] Moreover, an introverted, dependent, and anxious personality is a potential risk factor for the development and negative course of PPV.[41] Patients with a personality of high resilience and optimism are less likely to develop persistent dizziness after an acute vestibular disorder,[42] whereas personality traits such as neuroticism and introversion influence brain responses to vestibular and visual stimuli on visual-vestibular-anxiety systems.[43,44] We found task-dependent hyperconnectivities within brain networks regulating various aspects of emotional behavior and interoceptive pathways in PPV patients (Fig. 4), known to have similarly altered connectivities in patients with mood disorders[45,46]: the fear-generalization network,[47] the interoceptive network,[48] and the orbitofrontal network.[49] The enhanced connectivity within these networks might explain PPV patients' over-generalization and phobic response to certain stimuli or situations, a disturbed self-awareness, and an increased compensatory mechanism for evaluating the specificity of potentially phobic stimuli, respectively.

The networks, which are in healthy controls typically highly connected during visual motion processing, including the precuneus, SMG and MT/V5,[50] appeared to be less connected in PPV patients during our experiment. From posturographic studies and gait analyses it is known that PPV patients exceedingly rely on visual input during standing[51] and walking.[10] Patients with visually induced dizziness, also known as visual vertigo, also show an increased connectivity between thalamus, occipital cortex, and cerebellar areas.[52] Furthermore, during a self-motion simulation in PPPD patients higher dizziness handicap values correlated positively with occipital activity.[53] Thus, it seems possible that PPV patients shift their attentional focus toward mere visual information and as a consequence attenuate secondary visual integrating networks. This might result in the high sensitivity to visual stimuli, which is underpinned by the significantly longer duration of the MAE.

Motor cortex/Cerebellum

We found structural increases in the leg area of the primary motor cortex,[54] which moreover correlated positively with the depression index and functional hyperconnectivity between motor and prefrontal cortex. These findings are complemented by results from posturographic studies and gait analyses in PPV patients, for they show a typical abnormal strategy for postural control of stance and gait.[10,11] The constant co-contraction of the anti-gravity muscles during normal stance in PVV patients seems to be an expression of the irrational fear of imbalance,[11] also observed in specific phobias.[55] It seems likely that the increase in primary motor cortex structure and connectivity with prefrontal areas reflects the predominant cognitive control of stance and gait. On the other hand, the decreases in cerebellar vermis and bilateral cerebellar posterior lobes correlated positively with BDI and disease duration. The cerebellum is important for several aspects of sensorimotor integration such as automatic subconscious motor control.[56] The enhanced use of the primary motor cortex in PPV patients renders the function of subconscious motor control of the cerebellum unnecessary.

Limitations

The limitation of our study is that the only psychiatric measure available was the BDI, as we found these strong similarities in alterations compared to mood disorders. Future studies should further elucidate the relation and influence of factors such as anxiety and depression on functional dizziness. It is also important to note, that a

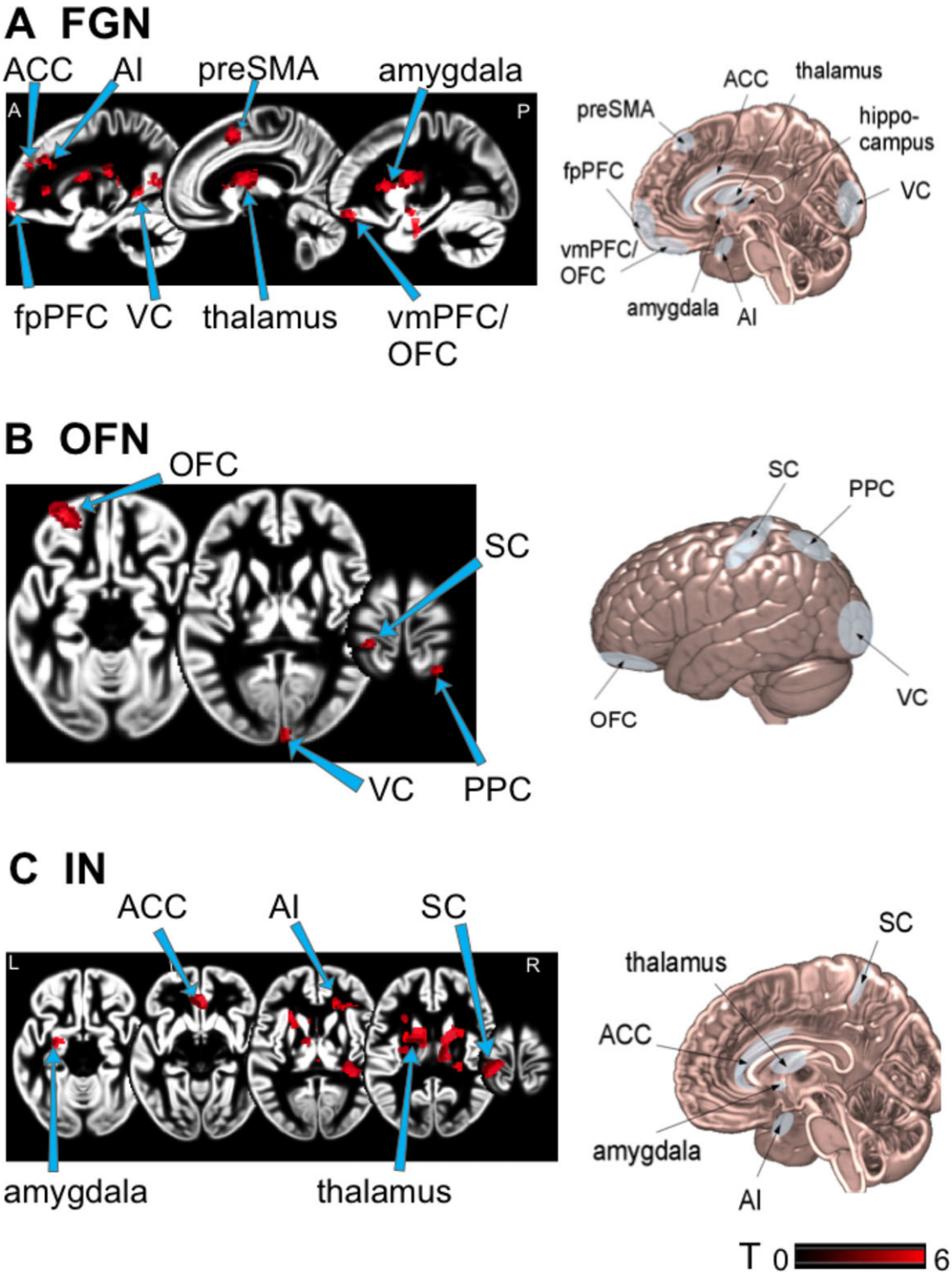

Figure 4. Altered functional connectivity networks in phobic postural vertigo patients (PPV) compared to healthy controls (HC) with schematic illustrations. Statistically significant regions superimposed on a publicly available template from 555 healthy subjects (http//brain-development.org/ixi-dataset/). $P < 0.05$ was set after FDR correction, with a critical cluster size of 50. ACC, anterior cingulate cortex; AI, anterior insula; FGN, fear-generation network; fpPFC, frontopolar prefrontal cortex; IN, interoceptive network; l, left; OFC, orbitofrontal cortex; OFN, orbitofrontal network; PMC, primary motor cortex; PPC, posterior parietal cortex; preSMA, pre-supplementary motor area; r, right; SC, somatosensory cortex; VC, visual cortex; vmPFC, ventromedial prefrontal cortex.

large number of patients were unable to perform the longer lasting visual stimulation part of the study due to high anxiety. This could indicate that our cohort reflects a more "benign anxiety" patient subgroup.

Taken together, first evidence can be provided that patients with PPV, show an aberrant structure and function of networks and brain regions, known to be altered in mood disorders. On the basis of combined morphometric and functional data, we propose that the disease-specific underlying mechanisms in PPV lie within networks and areas involved in mood regulation, fear generalization, interoception, and cognitive control. Intriguingly, they were not a result of structural changes in primary visual or multisensory vestibular cortical areas. This raises the question whether PPV rather lies at the interface between functional and psychiatric disorders.

Acknowledgments

We thank Judy Benson, Ludwig-Maximilians-University, Munich, for copyediting the manuscript and Sabine Eßer, Ludwig-Maximilians-University, Munich, for copyediting the illustrations and all subjects for participating in the study. The work was supported by funds from the German Research Foundation (GRK Grant Code 1091), the German Federal Ministry of Education and Research (BMBF Grant Code 01 EO 0901) and German Foundation for Neurology.

Author Contributions

PP: acquisition and analysis of data, drafting of manuscript and figures. PzE: analysis of data, drafting of manuscript and figures. TS: design of the study, analysis of data. RB, RF, MH, PH: acquisition and analysis of data. MD: conception and design of study, drafting of manuscript.

Conflict of Interest

The authors report no conflicts of interest.

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Supporting Information

Additional supplemental material may be found online in the Supporting Information section at the end of the article:

Table S1. Significant altered functional connectivity of regions of interests (ROI) in phobic postural vertigo patients (PPV) compared to healthy controls (HC)

Acknowledgements

First and foremost, I want to thank my supervisor Prof. Dr. Marianne Dieterich for giving me the opportunity to complete my PhD. I am very grateful for her guidance, advice and patience.

I am very grateful to my thesis advisory committee and thank Dr. Thomas Stephan and Prof. Dr. Peter Falkai for the time they spent to discuss and support my project. I further want to give many thanks to Prof. Dr. Peter zu Eulenburg and Dr. Rainer Bögle for their help and support throughout the process.

Special thanks to the Graduate School of Systemic Neurosciences for their constant support on every level and all the great opportunities they offered me.

Finally, I would like to express my deepest gratitude to my parents for their unconditional love and support not only during these last years but throughout my whole life.

List of publications

Popp P, Wulff M, Finke K, Rühl M, Brandt T, Dieterich M (2017) Cognitive deficits in patients with a chronic vestibular failure. J Neurol 264(3):554-563.

Popp P*, zu Eulenburg P*, Stephan T, Bögle R, Habs M, Henningsen P, Feuerecker R, Dieterich M (2018) Cortical alterations in phobic postural vertigo – a multimodal imaging approach. Ann Clin Transl Neurol 5:717-729.

* equal contribution

Eidesstattliche Versicherung/Affidavit

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation **Out of balance! Out of order? A multimodal approach on the consequences of chronic structural and functional vestibular syndromes on cognitive function, neural processing, and brain structure.** selbstständig angefertigt habe, mich außer der angegebenen keiner weiterer 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 disseration **Out of balance! Out of order? Out of order? A multimodal approach on the consequences of chronic structural and functional vestibular syndromes on cognitive function, neural processing, and brain structure.** is the result of my own work and that I have only used sources or materials listed and specified in the disseratation.

München, den 06.12.2018

Unterschrift
Pauline Popp

Declaration of author contributions

1 Popp P, Wulff M, Finke K, Rühl M, Brandt T, Dieterich M (2017) Cognitive deficits in patients with a chronic vestibular failure. J Neurol 264(3):554-563.

Author contributions: PP: acquisition and analysis of data, drafting manuscript, MW: study concept and design, acquisition and analysis of data, KF: study concept, revising manuscript, MR: acquisition and analysis of data, TB: critical revision of manuscript and intellectual content, MD: study concept and design, study supervision, critical revision of manuscript and intellectual content.

Pauline Popp Prof. Dr. Marianne Dieterich

2 Popp P*, zu Eulenburg P*, Stephan T, Bögle R, Habs M, Henningsen P, Feuerecker R, Dieterich M (2018) Cortical alterations in phobic postural vertigo – a multimodal imaging approach. Ann Clin Transl Neurol 5:717-729.

Author contributions: PP: acquisition and analysis of data, drafting of manuscript and figures, PzE: analysis of data, drafting of manuscript and figures, TS: design of the study, analysis of data, RB,RF,MH,PH: acquisition and analysis of data, MD: conception and design of study, drafting of manuscript. PP and PzE contributed equally to the study.

Pauline Popp Prof. Dr. Peter zu Eulenburg Prof. Dr. Marianne Dieterich