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Altered resting-state functional connectivity in patients with chronic bilateral vestibular failure

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ABSTRACT

Patients with bilateral vestibular failure (BVF) suffer from gait unsteadiness, oscillopsia and impaired spatial orientation. Brain imaging studies applying caloric irrigation to patients with BVF have shown altered neural activity of cortical visual–vestibular interaction: decreased bilateral neural activity in the posterior insula and parietal operculum and decreased deactivations in the visual cortex. It is unknown how this affects functional connectivity in the resting brain and how changes in connectivity are related to vestibular impairment.

We applied a novel data driven approach based on graph theory to investigate altered whole-brain resting-state functional connectivity in BVF patients (n= 22) compared to age- and gender-matched healthy controls (n= 25) using resting-state fMRI. Changes in functional connectivity were related to subjective (vestibular scores) and objective functional parameters of vestibular impairment, specifically, the adaptive changes during active (self-guided) and passive (investigator driven) head impulse test (HIT) which reflects the integrity of the vestibulo-ocular reflex (VOR).

BVF patients showed lower bilateral connectivity in the posterior insula and parietal operculum but higher connectivity in the posterior cerebellum compared to controls. Seed-based analysis revealed stronger connectivity from the right posterior insula to the precuneus, anterior insula, anterior cingulate cortex and the middle frontal gyrus. Excitingly, functional connectivity in the supramarginal gyrus (SMG) of the inferior parietal lobe and posterior cerebellum correlated with the increase of VOR gain during active as compared to passive HIT, i.e., the larger the adaptive VOR changes the larger was the increase in regional functional connectivity.

Using whole brain resting-state connectivity analysis in BVF patients we show that enduring bilateral deficient or missing vestibular input leads to changes in resting-state connectivity of the brain. These changes in the resting brain are robust and task-independent as they were found in the absence of sensory stimulation and without a region-related a priori hypothesis. Therefore they may indicate a fundamental disease-related change in the resting brain. They may account for the patients' persistent deficits in visuo-spatial attention, spatial orientation and unsteadiness. The relation of increasing connectivity in the inferior parietal lobe, specifically SMG, to improvement of VOR during active head movements reflects cortical plasticity in BVF and may play a clinical role in vestibular rehabilitation.

1. Introduction

Bilateral vestibular failure (BVF) is a severe chronic disorder of the labyrinth or the eighth cranial nerve characterized by unsteadiness of gait and oscillopsia during head movements (Brandt, 1996). BVF has a wide spectrum of etiologies (Zingler et al., 2007). The most common cause of BVF is vestibulotoxicity of ototoxic drugs (specifically aminoglycosides). New technical improvements allowing precise and easy assessment of vestibular function by videooculography have shown that BVF is much more common as previously believed but etiology often remains unknown, i.e., idiopathic BVF (Machner et al., 2013). Clinical signs and prognosis of BVF are different from those of unilateral vestibular failure (UVF). Vestibular neuritis patients complain about acute vertigo and show spontaneous nystagmus and lateropulsion in the acute phase. They have a fairly good recovery although a third of all patients do not show peripheral regeneration. This has partly been attributed to cortical and subcortical mechanisms of compensation which have been studied by various brain imaging techniques, using PET (Becker-Bense et al., 2013; Bense et al., 2004a), voxel based morphometry (Helmchen et al., 2009; Helmchen et al., 2011; Zu Eulenburg et al., 2010) and functional imaging of resting-state connectivity

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(Helmchen et al., 2013).

The characteristic symptoms of BVF patients, oscillopsia and blurred vision during head movements and locomotion, result from a deficient vestibulo-ocular reflex (VOR) which normally stabilizes gaze during rapid head movements. Gait unsteadiness in BVF is often not attributed to a deficient VOR and therefore misdiagnosed. Unfortunately, about 80% of BVF patients do not recover which may be due to brain mechanisms which are entirely different from UVF (Dieterich and Brandt, 2008a). While partial or complete peripheral vestibular nerve regeneration (Palla and Straumann, 2004; Schmid-Priscoveanu et al., 2001) and central, presumably compensatory, mechanisms contribute to vestibular rehabilitation in vestibular neuritis (Alessandrini et al., 2009; Becker-Bense et al., 2013; Bense et al., 2004a; Helmchen et al., 2009; Helmchen et al., 2013; Zu Eulenburg et al., 2010) peripheral nerve dysfunction and dizziness in BVF are often permanent (Zingler et al., 2008). As the contralesional vestibular input subserving cortical vestibular processing is missing, other non-vestibular mechanisms have been suggested to provide central vestibular compensation in BVF, e.g., substitution by changing the gain in the somatosensory (Strupp et al., 1998) or visual system (Dieterich et al., 2007a). Recently, a possibly adaptive mechanism of enhanced proprioceptive signal interaction with cortical visual processing has been found in BVF patients presumably subserving proprioceptive substitution of vestibular function (Cutfield et al., 2014).

In a recent meta-analysis considering 28 PET and fMRI studies employing vestibular stimuli to healthy subjects Zu Eulenburg et al. (2012) suggested the cytoarchitectonic area OP2 (Eickhoff et al., 2005) in the parietal operculum as the primary candidate for the human vestibular cortex. In patients with BVF, PET brain imaging ($H_2{}^{15}O$) during vestibular caloric stimulation revealed decreased bilateral activation in the "parieto-insular vestibular cortex" (PIVC) compared to healthy controls (Bense et al., 2004b). Intersensory cortical processing, specifically reciprocal cortical inhibitory visual–vestibular interaction seemed to be preserved, though at reduced levels, i.e., bilateral deactivation of the visual cortex, which is normally encountered during vestibular stimulation in healthy subjects, was reduced and the posterior insula was less activated bilaterally in BVF patients (Bense et al., 2004b). These data are based on behavioral or event-related brain activation studies. Changes in event-related activation studies can be ambiguous as they may not reflect the underlying pathophysiological mechanisms but only their behavioral consequences. In contrast, looking at the brain's activity at rest (resting-state) might shed more light on fundamental changes of functional connectivity in the brain. Due to the lack of task demands, resting-state fMRI (RS-fMRI) does not require an experimental design, patient's compliance, and training, making it attractive in a clinical environment. However, none of the previous studies looked at resting-state brain activity in BVF patients using fMRI.

Recently, using RS-fMRI, we have shown decreased functional connectivity in the intraparietal sulcus and supramarginal gyrus of patients with unilateral vestibular neuritis which partially reversed over a period of three months when patients had improved. Interestingly, this increase tended to be larger in patients with only little disability in the follow-up examination suggesting a role in vestibular compensation (Helmchen et al., 2013).

In this study we examined brain intrinsic functional connectivity in patients with bilateral vestibular failure (BVF). We used a novel data driven approach based on graph theory to investigate altered whole brain intrinsic functional connectivity in BVF patients as compared to healthy controls. The so-called degree centrality (Bullmore and Sporns, 2009) served as a marker for altered connectivity. In graph theory, the degree of a vertex (node) is defined as the number of links (edges) connected to the node. The degree is thus a measure for the connectedness of a node within a network. Here, voxels serve as nodes and edges are defined by the functional connectivity between voxels. In contrast to network analyses which depend on a given parcellation of the brain, this approach has a higher spatial resolution and is not biased by a priori defined anatomical structures. In previous studies, voxel-based network analyses were performed to investigate topological properties of the brain network (van den Heuvel et al., 2008) and to identify network hubs, i.e., brain regions which show a strong connectivity to the rest of the brain (Buckner et al., 2009; Zuo et al., 2012). Recently, the voxel-degree method was successfully used as a marker for altered resting state functional connectivity in Alzheimer's disease (Buckner et al., 2009), Parkinson's disease (Göttlich et al., 2013), and Obsessive Compulsive Disorder (Beucke et al., 2013).

The aim of our study on BVF patients was therefore to elucidate (i) whether there are changes in functional connectivity in brain areas involved in processing of vestibular information and (ii) whether these changes during resting-state are related to subjective or objective parameters of vestibular impairment. Specifically, we chose the deficient gain of the VOR which can be improved in a behavioral context: UVF patients increase their VOR gain during self-guided, active and thereby predictive head impulse movements as compared to non-predictive, passive head impulses (Black et al., 2005; Sprenger et al., 2006). We hypothesized that BVF patients are also capable of using non-vestibular predictive mechanisms to stabilize images of the visual world on the fovea. Therefore we compared functional connectivity within neural networks in BVF patients with age- and gender matched healthy controls and related the differences in this (active vs. passive) vestibulo-ocular behavior to changes in functional connectivity.

2. Materials and methods

2.1. Participants

Patients with bilateral vestibular failure (BVF) were compared with age and gender matched healthy control subjects. The study was approved by the institutional ethics committee of the University of Lübeck. All participants gave written informed consent before their inclusion into the study. The study was performed in agreement with the Declaration of Helsinki. Participants were recruited from an outpatient neurology clinic in a tertiary care academic medical center at the University of Lübeck (Dizziness Center in Lübeck, Germany). Patients complained about dizziness, gait unsteadiness and oscillopsia during locomotion and head movements. All participants were right-handed and underwent extensive neurologic, neuro-ophthalmologic, and neuro-otologic examinations. BVF patients were on no regular medication known to affect central nervous system processing. None of the patients took any antivertiginous medication during the examination day. Patients were diagnosed to have BVF based on clinical examinations by experienced neurologists and neuro-otologist of the University Dizziness Center in Lübeck and electrophysiological recordings [bithermal cold (27°) and warm (44°) caloric irrigation, quantitative head impulse test] were analyzed by a co-worker with longstanding experience in assessing vestibular function by caloric and quantitative head impulse videooculography who did not know about the history and clinical findings of the patients. Inclusion criteria for BVF were the following: (1) clinical assessment of a bilaterally pathologic HIT (Jorns-Haderli et al., 2007), (2) bilaterally reduced gain of the horizontal VOR (<0.72) assessed by video-HIT (Machner et al., 2013) (3) bilateral caloric hyporesponsiveness (mean peak slow phase velocity (SPV) of $<5°/s$ on both sides), and (4) cranial magnetic resonance imaging without structural brain lesions. Patients with depression (as assessed by the Beck depression score) and dementia (assessed by the MOCA scale) and those with additional evidence of autoimmune and paraneoplastic diseases were excluded from the study. Participants subjectively rated their level of disease-related impairment by the Vertigo Handicap Questionnaire (VHQ) (Tschan et al.,