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DISSOCIABLE CEREBELLAR ACTIVITY DURING SPATIAL NAVIGATION AND VISUAL MEMORY IN BILATERAL VESTIBULAR FAILURE

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Abstract—*Objective:* Spatial orientation and navigation depends on information from the vestibular system. Previous work suggested impaired spatial navigation in patients with bilateral vestibular failure (BVF). The aim of this study was to investigate event-related brain activity functional magnetic resonance imaging (fMRI) during spatial navigation and visual memory tasks in BVF patients. *Methods:* Twenty-three BVF patients and healthy age-and gender matched control subjects performed learning sessions of spatial navigation by watching short films taking them through various streets from a driver's perspective along a route to the Cathedral of Cologne using virtual reality videos (adopted and modified from Google Earth®). In the magnetic resonance imaging (MRI) scanner, participants were asked to respond to questions testing for visual memory or spatial navigation while they viewed short video clips. From a similar but not identical perspective depicted video frames of routes were displayed which they had previously seen or which were completely novel to them. *Results:* Compared with controls, posterior cerebellar activity in BVF patients was higher during spatial navigation than during visual memory tasks, in the absence of performance differences. This cerebellar activity correlated with disease duration. *Conclusions:* Cerebellar activity during spatial navigation in BVF patients may reflect increased non-vestibular efforts to counteract the development of spatial navigation deficits in BVF. Conceivably, cerebellar activity indicates a change in navigational strategy of BVF patients, i.e. from a more allocentric, landmark or place-based strategy (hippocampus) to a more sequence-based strategy. This interpretation would be in accord with recent evidence for a cerebellar role in sequence-based navigation.

Key words: bilateral vestibular failure, navigation, visual memory, cerebellum.

INTRODUCTION

Spatial orientation and navigation relies on information from the visual and vestibular system (Stackman et al., 2002; Brandt et al., 2005; Aronov and Tank, 2014). Both sensory systems provide information for a mental spatial representation of the external world. Experimental navigation tasks employ either place-based navigation strategies which rely on allocentric (world-centered) representations of locations or sequence-based navigation, which relies on sequential egocentric representations. Both navigation strategies engage the hippocampus but at different body sites (Iaria et al., 2003; Igloi et al., 2010) supporting its crucial role in spatial memory and navigation (Morris et al., 1982). In humans, the entorhinal-hippocampal circuit, as well as inferior and medial parietal cortical regions are activated during navigation tasks implicating involvement of encoding where places are located and how they are regionally related to navigate between them (Maguire et al., 1998). In addition, dorsal striatum and the cerebellum have been implicated in human navigation (Maguire et al., 1998), e.g. by showing task-related activity during mental rotation tasks (Stoodley et al., 2012).

Neural substrates for navigation have been identified in the animal hippocampus model by place cells in the hippocampus coding the animal's location and head direction cells coding for its orientation (Taube et al., 1990). Place cells receive cortical inputs from medial entorhinal grid cells, which define a hexagonal array across the full extent of space available to the animal. This provides the grounds for a path-integration-based spatial map in which the animal's position can be constantly updated with its own movements. It remains an open question whether the maturation of this neural representation of spatial maps requires vestibular information (Langston et al., 2010).

Spatial memory processes in the hippocampus largely depend on distal visual and self-motion cues provided by both visual (e.g. optic flow) and vestibular signals which are processed in distinctly different but adjacent parts in

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Abbreviations: BVF, bilateral vestibular failure; CVS, Clinical Vestibular Score; EPI, echo-planar imaging; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; GLM, general linear model; HIT, head impulses; MoCA, Montreal Cognitive Assessment test; qHIT, quantitative head impulse test; ROI, region of interest; SDS, Subjective Dizziness Score; SVV, subjective visual vertical; VEMPs, vestibular evoked potentials; VHQ, Vertigo Handicap Questionnaire; VOR, vestibulo-ocular reflex; VSS, Vertigo Symptom Scale.

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the hippocampus (Hufner et al., 2011b). Differential effects on this functional and structural (morphological) separation in the hippocampus can be visualized in healthy human subjects by exposure to extensive visual-vestibular stimulation with spatial and non-spatial memory tasks (Hufner et al., 2011a). This has raised the question as to whether deficient or even absent vestibular input alters spatial memory and navigation skills. Lines of evidence have been provided in animal experiments showing disruption of idiothetic navigation or path integration and changing navigational behavior to be critically dependent upon external (i.e. visual) landmarks (Stackman and Herbert, 2002). In humans, patients with complete bilateral vestibular failure (BVF) have been found to show impaired spatial memory and navigation deficits which may be related to morphometric changes in the hippocampus (Brandt et al., 2005). In the rat following bilateral labyrinthectomy, however, spatial memory deficits but no changes in hippocampal volume (Besnard et al., 2012) or the number of hippocampal neurons (Zheng et al., 2012) have been found.

Patients with bilateral vestibulopathy suffer from gait unsteadiness and oscillopsia during head movements and locomotion but usually do not notice difficulties in spatial navigation or spatial memory. This suggests that spatial navigation deficits do not become clinically evident before BVF is complete. Accordingly, morphometric changes in the hippocampus are not (Hufner et al., 2007; Helmchen et al., 2009b) or only sparsely (zu Eulenburg et al., 2010) found in patients with unilateral vestibulopathy. Impaired spatial memory has been visualized in a virtual environment using ambient visual cues similar to the Morris water maze task (Brandt et al., 2005) but it remained unclear to what extent this deficit is related to visual memory deficits.

The aim of this event-related fMRI study was to identify dissociable brain activity in BVF patients and healthy controls while they were exposed to a virtual reality navigation task which called for visual memory and spatial navigation. Virtual reality landscape paradigms have been shown to allow navigation with only distal visual cues, in the absence of significant vestibular or other sensory inputs (Cushman et al., 2013). We hypothesized that BVF would lead to similar navigational deficits as in complete bilateral vestibular loss and that the hippocampus shows reduced activity. We show that posterior cerebellar but not hippocampal activity in BVF patients was higher during spatial navigation than during visual memory tasks. This sheds new light on the role of the cerebellum on human spatial representation during navigation in BVF and may indicate changes in navigational strategies.

EXPERIMENTAL PROCEDURES

Participants

Twenty-three patients (11 women, 12 men; mean ± SD = 65.0 ± 10.4 years, range 43–78 years) with BVF (disease duration: 4.2 ± 4.7 years, range 0.3–20.0 years) were compared with twenty-six age-matched controls (13 women, 13 men; 63.7 ± 9.4 years, range 43–77 years) with no known neurological disease. All patients complained about dizziness, gait unsteadiness and oscillopsia during locomotion and head movements. After having obtained written consent forms from each patient he underwent neurological, neuro-ophthalmological, and neuro-otological examinations (caloric irrigation, quantitative head impulse test (qHIT), vestibular evoked myogenic potentials, subjective visual vertical (SVV)). All participants were right-handed and had normal or corrected-to-normal vision. BVF patients and controls were on no regular medication known to affect central nervous system processing. None of the patients took any antivertiginous medication during the examination day. The study was approved by the Ethics Committee of the University Luebeck. Each participant provided informed oral and written consent in accordance with the revised version (2008 in Seoul) of the Declaration of Helsinki.

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, qHIT] 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 head impulses (HIT) (Jorns-Haderli et al., 2007), (2) bilaterally reduced gain of the horizontal vestibulo-ocular reflex (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 inventory, BDI), dementia and those with additional evidence for autoimmune and paraneoplastic diseases were excluded from the study. General cognitive impairment was evaluated by the Montreal Cognitive Assessment test (MoCA). Participants were scored by neurootological examinations using the Clinical Vestibular Score (CVS) (Helmchen et al., 2009a) and subjectively rated their level of disease-related impairment by the Vertigo Handicap Questionnaire (VHQ), Vertigo Symptom Scale (VSS) (Tschan et al., 2010) and the Subjective Dizziness Score (SDS) (Helmchen et al., 2009a). In all these scores larger values indicate increasing vestibular induced subjective disability (VHQ, VSS, SDS) or objective impairment (CVS). The most common etiology of BVF was antibiotic ototoxicity ($n = 12$) and idiopathic BVF ($n = 8$), followed by sequential vestibular neuritis ($n = 2$), and Meniere's disease ($n = 1$). Apart from clinical signs of BVF and ataxia of stance and gait there were no other neurological signs.

Electrophysiological and psychophysical recordings

All participants were examined by a battery of vestibular investigations. Semicircular canal function was

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