NeuroImage: Clinical 14 (2017) 538–545

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Altered functional brain connectivity in patients with visually induced dizziness

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ARTICLE INFO

Article history:
Received 1 December 2016
Received in revised form 6 February 2017
Accepted 24 February 2017
Available online 28 February 2017

Keywords:
rsfMRI
Visually induced dizziness
VID
Functional connectivity
Vertigo
Vestibular

ABSTRACT

Background: Vestibular patients occasionally report aggravation or triggering of their symptoms by visual stimuli, which is called visually induced dizziness (VID). These patients therefore experience dizziness, discomfort, disorientation and postural unsteadiness. The underlying pathophysiology of VID is still poorly understood.
Objective: The aim of the current explorative study was to gain a first insight in the underlying neural aspects of VID.
Methods: We included 10 VID patients and 10 healthy matched controls, all of which underwent a resting state fMRI scan session. Changes in functional connectivity were explored by means of the intrinsic connectivity contrast (ICC). Seed-based analysis was subsequently performed in visual and vestibular seeds.
Results: We found a decreased functional connectivity in the right central operculum (superior temporal gyrus), as well as increased functional connectivity in the occipital pole in VID patients as compared to controls in a hypothesis-free analysis. A weaker functional connectivity between the thalamus and most of the right putamen was measured in VID patients in comparison to controls in a seed-based analysis. Furthermore, also by means of a seed-based analysis, a decreased functional connectivity between the visual associative area and the left parahippocampal gyrus was found in VID patients. Additionally, we found increased functional connectivity between thalamus and occipital and cerebellar areas in the VID patients, as well as between the associative visual cortex and both middle frontal gyrus and precuneus.
Conclusions: We found alterations in the visual and vestibular cortical network in VID patients that could underlie the typical VID symptoms such as a worsening of their vestibular symptoms when being exposed to challenging visual stimuli. These preliminary findings provide the first insights into the underlying functional brain connectivity in VID patients. Future studies should extend these findings by employing larger sample sizes, by investigating specific task-based paradigms in these patients and by exploring the implications for treatment.

1. Introduction

A fundamental characteristic of mammals and humans is the ability to maintain gaze stabilization and postural control in normal circumstances (Goldberg et al., 2012). In order to do so, the human brain integrates visual, somatosensory and vestibular input (Goldberg et al., 2012). Depending on the circumstances and therefore the most relevant input, a central weighting favors one system more than the other (Peterka, 2002). In darkness for example, vestibular and somatosensory cues will dominate the less accurate visual information. This reweighting is done automatically and does not constitute problems, unless there is an underlying visual, vestibular or proprioceptive deficit (Peterka, 2002). In the latter, this might lead to dizziness, imbalance and

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http://dx.doi.org/10.1016/j.nicl.2017.02.020

falls. In the case of a peripheral vestibular lesion, some patients even develop an overreliance on visual cues, which might lead to visually induced dizziness.

Visual induced dizziness (VID) is characterized by the occurrence of vestibular symptoms as a result of complex or moving visual triggers, such as encountered during walking down supermarket aisles or the moving surroundings during driving (Page and Gresty, 1985; Jacob et al., 1989; Bronstein, 1995a, 1995b). VID is a term first implemented by the international classification committee of vestibular disorders (Bisdorff et al., 2009), but is also known as visual vertigo (Bronstein, 1995a, 1995b) or visual vestibular mismatch (Longridge et al., 2002). VID is a chronic disorder, often triggered by an acute vestibular disorder, during which these visual stimuli trigger or aggravate vestibular symptoms (Guerraz et al., 2001; Pavlou et al., 2006). Chronic vestibular symptoms triggered by an acute vestibular disorder can also manifest as chronic subjective dizziness (CSD) (Staab et al., 2004; Staab and Ruckenstein, 2005) or phobic postural vertigo (PPV) (Brandt, 1996; Kapfhammer et al., 1997), of which the former is also characterized by increased sensitivity to visual motion (Staab and Ruckenstein, 2005). When a group of 21 patients with VID were assessed for changes in postural sway and SVV in the presence of a tilted visual frame or a rotating visual disc, they displayed increased sway and poorer accuracy in estimating the gravitational vertical compared to controls - suggesting an influence of (moving) visual surroundings on vestibular processing (Guerraz et al., 2001). Later, a study by Pavlou and co-workers also reported that patients with VID show increased postural sway and worse results on the situational characteristics questionnaire (SCQ) when confronted with conflicting visual stimuli (Pavlou et al., 2006). Recently, our research group showed that visual roll motion is a crucial factor in provoking VID symptoms, which was also assessed by means of postural sway and questionnaires (Van Ombergen et al., 2016). The studies by Pavlou and Van Ombergen did not observe changes in SVV in challenging visual environments, whereas Guerraz and colleagues did. This discrepancy is most likely the result of a methodological difference and of inter-individual variability.

Most authors suggest that VID is the result of a defect in central reweighting of multisensory inputs (Bronstein, 1995a, 1995b; Guerraz et al., 2001), which is the phenomenon of adjusting the weight of different sensory modalities aiding in vestibular functions (e.g., postural control (Hwang et al., 2014)). In the case of VID patients, this means that the weight of visual input is too high, making these individuals strongly dependent on vision (Bronstein, 1995a, 1995b; Guerraz et al., 2001; Pavlou et al., 2006; Cousins et al., 2014; Van Ombergen et al., 2016). Indeed, this has been observed in patients with chronic vestibular symptoms after an acute vestibular neuritis, where symptom severity was associated with higher visual dependency (Cousins et al., 2014). However, it remains unclear whether these individuals acquired an increased visual dependency secondary to the vestibular insult or whether this was pre-existing, since it is a normally distributed trait in the general population (Witkin and Asch, 1948; Witkin, 1959). The former option would indicate a deficient sensory reweighting, where the visual system will account for the loss of vestibular function (Dieterich et al., 2007; Zu Eulenburg et al., 2010; Hong et al., 2014).

A recent structural MRI study of VID patients reported significantly more white matter abnormalities compared to dizzy controls without VID symptoms (Pollak et al., 2015). However, these changes were non-specific, therefore it is unclear where the white matter abnormalities were located and which white matter pathways they impinged upon. A separate study using fMRI with vestibular stimulation reported localized hypofunction and decreased connectivity between several brain regions including the superior temporal gyrus, anterior insula/inferior frontal gyrus, middle occipital gyrus and hippocampus in patients with chronic subjective dizziness (CSD) compared to controls (Indovina et al., 2015). The authors suggested that the VID symptoms, often present in CSD patients (Staab and Ruckenstein, 2005), might be related to the decreased connectivity between anterior insula and middle occipital gyrus together with the decreased activity in anterior insula, anterior cingulate cortex and hippocampus.

The current gaps in knowledge on the etiology and pathophysiology of VID highlight the need for further in-depth studies. We performed an explorative study, implementing resting-state fMRI analysis to study the brain's functional organization in rest. Resting-state fMRI has the advantage of reflecting the disease state more naturally, as opposed to task fMRI, where results are influenced by the choice of stimulus (e.g. Göttlich et al., 2014). We assessed differences in functional connectivity (i.e., the temporal correlation of the spontaneous BOLD response between spatially distant areas) between healthy control subjects and patients with VID using both hypothesis free and hypothesis-driven methods. For the latter, seeds belonging to the vestibular and visual networks were used.

2. Material and methods

2.1. Participants

Patients were recruited from the Department of Otorhinolaryngology at the Antwerp University Hospital. All patients underwent routine ear, nose, throat, and neuro-otological examinations, followed by specific audio-vestibular investigations when required. A detailed and systematic history was taken for each patient using the SO STONED questionnaire (Wuyts et al., 2016). Patients were included when showing a clear pattern of VID symptoms and triggers, based upon the questionnaire proposed by Mallinson for visual vestibular mismatch (Mallinson, 2011). Exclusion criteria were: 1) other medical conditions in the acute phase e.g. orthopedic injury, 2) fluctuating symptoms caused by episodic vestibular disorders (e.g. Meniere's disease) and 3) vestibular migraine. In addition, patients and control subjects were excluded if there were any contra-indications for the MRI examination.

In total, 10 VID patients were recruited (3 males, mean age (SD) 50.5 (8.3) years). As age- and gender-matched controls, 10 healthy participants (3 males, mean age (SD) 49.7 (6.1) years) were included. All participants were right-handed. Based on the history and/or results from the audio-vestibular test battery, a peripheral vestibular disorder was identified as the likely explanation for symptom onset in 9 out of 10 patients. In total, 5 patients presented with a unilateral vestibular hypofunction (two left, three right) and one patient presented with a bilateral areflexia. One patient presented with a unilateral vestibular hyperfunction left. One patient presented with abnormal low gain and phase for the vestibulo-ocular reflex. Two patients presented with an otolith dysfunction: one bilateral (concomitant with a unilateral horizontal semicircular canal hypofunction), one unilateral right. For three of the patients with a unilateral vestibular hypofunction, vestibular neuritis was identified as the specific etiologic diagnosis. For the other patients, a specific diagnosis could not be made since all of them were already in a chronic phase. Patients had persistent VID symptoms for 5.0 (3.1) years (mean duration (SD)), ranging from 1.2 to 9.9 years. None of the patients were assessed in an acute phase. For an overview, see Table 1.

Ethical approval was provided by the local Ethics Committee of the University Hospital Antwerp (IRB number 13/38/357). Each participant provided a signed informed consent. All investigations have been conducted according to the principles expressed in the Declaration of Helsinki.

2.2. Data acquisition and analysis

Data was acquired on a 3 T scanner (Magnetom Trio Tim, Siemens AG, Siemens Medical Solutions, Erlangen, Germany) using a 32-channel head coil. The examination was performed with the patient in the following position: head first – supine. Earplugs were given to each subject and the head was stabilized with cushions to minimize head movement. The head was elevated 30° above horizontal to minimize the magnetic