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Disrupted functional connectivity of the default mode network due to acute vestibular deficit

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ABSTRACT

Vestibular neuritis is defined as a sudden unilateral partial failure of the vestibular nerve that impairs the forwarding of vestibular information from the labyrinth. The patient suffers from vertigo, horizontal nystagmus and postural instability with a tendency toward ipsilesional falls. Although vestibular neuritis is a common disease, the central mechanisms to compensate for the loss of precise vestibular information remain poorly understood. It was hypothesized that symptoms following acute vestibular neuritis originate from difficulties in the processing of diverging sensory information between the responsible brain networks. Accordingly an altered resting activity was shown in multiple brain areas of the task-positive network. Because of the known balance between the task-positive and task-negative networks (default mode network; DMN) we hypothesize that also the DMN is involved.

Here, we employ functional magnetic resonance imaging (fMRI) in the resting state to investigate changes in the functional connectivity between the DMN and task-positive networks, in a longitudinal design combined with measurements of caloric function. We demonstrate an initially disturbed connectedness of the DMN after vestibular neuritis. We hypothesize that the disturbed connectivity between the default mode network and particular parts of the task-positive network might be related to a sustained utilization of processing capacity by diverging sensory information. The current results provide some insights into mechanisms of central compensation following an acute vestibular deficit and the importance of the DMN in this disease.

1. Introduction

Vestibular neuritis is defined as a sudden unilateral partial failure of the vestibular nerve that impairs the forwarding of vestibular information from the labyrinth. Because normal vestibular function depends on continuous bilateral input, a unilateral failure leads to an immediate direction-specific imbalance of the bilateral vestibular tone. The patient suffers from vertigo, horizontal nystagmus and postural instability with a tendency toward ipsilesional falls. Most patients experience a quick recovery that seems to be independent from the function of the affected vestibular nerve but is caused by a compensatory adaptation of central vestibular information processing (Strupp et al., 1998).

The great majority of our current knowledge about the cortical processing of vestibular information in the human brain is derived from brain activation studies in healthy subjects that used PET and fMRI during various kinds of vestibular stimulation methods, such as vestibular evoked myogenic potentials (Miyamoto et al., 2007; Janzen et al., 2008; Schlindwein et al., 2008), galvanic vestibular stimulation (Lobel et al., 1998; Bense et al., 2001; Stephan et al., 2005; Stephan et al., 2009) and caloric irrigation (Suzuki et al., 2001; Fasold et al., 2002; Dieterich et al., 2003; Marcelli et al., 2009). Although still debated, some authors have suggested that there is no primary vestibular cortex that obtains projections exclusively from vestibular afferents (Guldin and Grüsser, 1998). Instead, several separate and distinct cortical areas have been identified that integrate vestibular, visual and somatosensory information (Faugier-Grimaud and Ventre, 1989; Fredrickson et al., 1966; Guldin and Grüsser, 1998; Odkvist et al., 1974). These multimodel areas include the temporo-parietal vestibular cortex, retroinsular areas, the superior temporal gyrus and the inferior parietal lobule (for review see Lackner and DiZio, 2005; Dieterich and Brandt, 2008). It was shown that unilateral vestibular stimulation increases the activity in these multimodal areas, while the activity in the visual cortex, the somatosensory cortex and the default mode network decreased (Klingner et al., 2013b).

The impact of vestibular neuritis on cortical processing has been less thoroughly investigated. However, a PET study showed that areas responsible for multisensory integration revealed an increased glucose metabolism, while a decreased metabolism was found in the visual cortex, the somatosensory cortex and parts of the auditory cortex (Bense et al., 2004). A further study showed that vestibular failure suppresses

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cortical visual motion processing (Deutschlander et al., 2002). These studies support the view that vertigo and dizziness following an acute vestibular neuritis originate from the conflicting information between sensory sources and an altered activity state of different sensory sources.

Because of the known balance between the task-positive and task-negative networks (default mode network; DMN) we hypothesize that the DMN is also involved. Such an impaired balance might explain findings such as difficulties with reading, arithmetic and concentration (Hanes and McCollum, 2006). We further hypothesize that such an impaired balance between these networks should be measurable by an altered coupling. Based on studies which demonstrated a tight coupling between behavioral changes and changes of the functional connectivity (Hampson et al., 2006; Albert et al., 2009; Barnes et al., 2009; Lewis et al., 2009; Zhu et al., 2011), we hypothesize that symptoms following unilateral vestibular neuritis are reflected in changes in the functional connectivity between the involved networks.

The identification of these networks and their disturbed connectedness are important pieces of information that can be used to deduce the pathophysiologic mechanism that underlies symptoms following vestibular neuritis. However, no analyses of the relevant functional connectivity that further investigate these assumptions are currently available for this disease.

Here we investigate the effects of unilateral vestibular neuritis on the functional connectivity between the default mode network and other particular task positive networks in the brain. We hypothesize an initially decreased connectivity between the DMN and task positive networks.

The present study investigated this hypothesis by employing functional magnetic resonance imaging (fMRI) in the resting state in a longitudinal design. The individual vestibular function was determined by testing the caloric responsiveness. All patients were investigated in the early stage of vestibular neuritis but after remission of nystagmus during visual fixation. A second scan was performed after complete clinical recovery.

2. Materials and methods

2.1. Subjects

The study population comprised 14 patients (mean age 51.1 ± 10.4 years, range 32–67 years, 6 females, 8 males) and 28 age and gender matched controls (12 females, 16 males) without any history of neurological or psychiatric diseases. Patients were diagnosed with left – (7) or right – (7) sided vestibular neuritis via (1) clinical criteria, (2) caloric hyporesponsiveness with at least 25% canal paresis of the affected side and (3) normal conventional brain imaging (MRI). All patients received an initial fMRI scan at the early stage (mean: 4.9 ± 1.9 days after onset of symptoms). No patient received any sedative medication within 24 h prior to the fMRI session. The patients were recalled at intervals of several months for clinical examination in the outpatient clinic of the department of otorhinolaryngology. A follow-up fMRI was performed when both the physical examination revealed no pathologic findings such as nystagmus or abnormalities in posture or gaze and the patient reported subjective complete remission of symptoms (mean interval to follow-up scan 12 ± 4.6 months). All subjects were right-handed according to the Edinburgh Handedness Inventory, with a laterality quotient greater than +80 (Oldfield, 1971). The study was approved by the local ethics committee and all subjects provided their written informed consent according to the Declaration of Helsinki.

2.2. fMRI recordings

Images were acquired on a 3.0-Tesla MR scanner (Trio, Siemens, Erlangen, Germany) to obtain 203 echo-planar T2* weighted image (EPI) volumes and 192 transaxial T1 weighted structural images. The first three EPI volumes were subsequently discarded due to equilibration effects. A functional-image volume comprised 40 transaxial slices that included the whole cerebrum and cerebellum (voxel size = $3 \times 3 \times 3$ mm, repetition time = 3 s, TE 35 ms). The high-resolution T1 weighted structural images exhibited a voxel size of $1 \times 1 \times 1$ mm to allow for precise anatomical localization and normalization.

2.3. Data analysis

The data analysis was performed on a workstation using MATLAB (Mathworks, Natick, MA, USA) with the "gift" toolbox (http://icatb.sourceforge.net/) and SPM8 software (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). For each subject, all images were realigned to the first volume using six-parameter rigid-body transformation to correct for motion artifacts (Friston et al., 1995). The images were co-registered with the subject's corresponding anatomical (T1-weighted) images, normalized to the Montreal Neurological Institute (MNI) standard brain (Evans et al., 1993) to report MNI coordinates and smoothed using a 6-mm full-width-at-half-maximum Gaussian kernel. Several sources of variance were removed from the data by linear regression: (1) six parameters obtained by rigid body correction of head motion, (2) signals from a ventricular region of interest and (3) signals from a region centered in the white matter (Weissenbacher et al., 2009). All signal intensity time courses were band-pass filtered ($0.01 < f < 0.1$) to reduce the effect of low-frequency drift and high-frequency noise.

2.4. Independent component analysis (ICA)

Statistical analysis was performed by an independent component analysis (ICA) with the pre-processed images (realigned, coregistered, normalized, and smoothed). After preprocessing, single subject data are combined together, followed by the independent component analysis, and finally individual subject maps and time courses are reconstructed. This analysis was carried out using group-ICA toolbox GIFT (Calhoun et al., 2001b; Calhoun et al., 2009). The number of independent components (ICs) was estimated for each subject and ranged from 30 to 39. To ensure that all the ICs were present in each individual, we used the minimum number of components that were determined in a single dataset (30). These 30 components were estimated using the infomax algorithm implemented in the GIFT software (http://icatb.sourceforge.net/) (Calhoun et al., 2001b; Calhoun et al., 2009). The chosen number of components provides a reasonable trade-off between preserving relevant variance in the data while easing the burden of interpretation (Calhoun et al., 2001a).

Next, a voxel-wise random effects analysis was performed on the component image to obtain consistent group activation patterns. The resulting group statistical maps were corrected for multiple comparisons at a significance level of $P < 0.005$ (Bonferroni-corrected). The overlap between each of these group maps and the area of the cerebral spinal fluid was estimated. If we detected an overlap of more than 50%, the group activation map was designated as an artifact and excluded from further analysis. The remaining group activation maps were now used to identify ICs that represent functional networks which were further investigated. We aimed to identify the following networks: default mode network, somatosensory network, vestibular network, motor network, fronto parietal network (FPC), occipital network, cerebellar network. The selection of the ICs was based on prior anatomical and functional knowledge and our hypothesis. We used the anatomy toolbox to identify the somatosensory cortex, the motor cortex, the visual cortex and the cerebellum (Eickhoff et al., 2005). The spatial locations of these areas were determined at a probability of at least 50% (by using the anatomy toolbox). The selection of the IC that best represents the auditory/vestibular/insular cortex, default mode network and the fronto parietal cortex (not included in the anatomy toolbox) was