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

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

based on metaanalytic results (Laird et al., 2009; Lopez et al., 2012; Niendam et al., 2012).

2.5. Connectivity analysis

The average time course over all voxels that were associated with the respective RSN was estimated. If one voxel was associated with two RSNs, it was excluded from the estimation of the connectivity. Then, we estimated differences in the functional connectivity between different networks between the first measurement (acute state of vestibular neuritis), the follow-up measurement as well as between the first measurement and healthy controls as follows:

1. The Pearson's correlation coefficients were computed between a selected pair of brain regions for each subject.
2. Each correlation coefficient was converted to a z-value by the Fisher r-to-z transformation ($z = 0.5 * \log[(1 + r) / (1 − r)]$) to improve the normality of the correlation coefficients.
3. The z-value matrices were compared between the measurements (patient acute vs. patient follow up, patient acute vs. healthy subject). To reduce the variance we age- and gender matched two healthy subjects for each patient (28 healthy control subjects). The corresponding two z-value matrices of the matched healthy subjects were averaged prior to the statistical testing.

These values were tested for significant differences between the DMN and the other selected RSNs with a paired t-test (acute patient vs. follow up and acute patient vs. healthy controls). Findings were considered to be significant at $P < 0.05$ (Bonferroni-corrected). The current method for estimating the functional connectivity among spatially independent resting state networks was previously used and validated (Jafri et al., 2008).

2.6. Vestibular testing

Vestibular testing was performed using infrared videonystagmography (VNG; Hortmann Video CNG Analyser, GN Otometrics) and a thermal stimulation unit (Variotherm, ATMOS MedizinTechnik GmbH & Co. KG, Lenzkirch, Germany). In all subjects, vestibular testing was performed on the day of the initial MRI and during the follow-up visit. Goggles were placed securely on the patient's head to eliminate light from entering in. Saccadic eye movements, smooth pursuit, optokinetic nystagmus, and any spontaneous and positional nystagmus were recorded. Bithermal caloric testing was also performed with suppression fixation. Saccades were tested for accuracy, velocity, and latency. Smooth-pursuit and optokinetic tracking were analyzed for symmetry and gain. The gaze test was performed by recording eye movements as the patient gazed 30° eccentrically in four directions (right, left, up, and down). Each position was held for at least 20 s to allow for adequate recording of eye movements. Spontaneous nystagmus was examined while the patient was in the supine position and her/his eyes were in the neutral position. Positional and positioning (Dix–Hallpike) tests were performed to determine if the vestibular system responded normally and symmetrically to changes in head position. Findings for spontaneous and positional nystagmus were considered abnormal if the slow phase velocity (SPV) was >5°/s. Caloric irrigation was performed to evaluate the response of the lateral semicircular canals. The produced caloric nystagmus was analyzed for presence and symmetry. According to Honrubia, vestibular paresis was defined as more than 25% asymmetry between the right-sided and the left-sided responses. This asymmetry was calculated with Jongkees' formula from the slow-phase velocity (SPV): [(R 33° + R 44°) − (L 30° + L 44°)] / (R 30° + R 44° + L 30° + L 44°) * 100.

3. Results

3.1. ICA

To investigate the variability between different functional systems, we first performed an ICA to identify important functional systems.

We selected eight ICs from the group ICA. The selection of the ICs based on prior anatomical and functional knowledge and our hypothesis (see Materials and methods section for details). The corresponding IC maps were corrected for multiple comparisons at a significance level of $P < 0.05$ (Bonferroni-corrected). The spatial maps of these eight resting state networks (RSNs) are illustrated in Fig. 1. The following networks were identified: default mode network (130 cm³), left and right frontoparietal network (142, 88 cm³), occipital cortex (127 cm³), cerebellar cortex (85 cm³), auditory/vestibular/insular cortices (92 cm³), primary somatosensory cortex (64 cm³), primary and secondary motor cortex (93 cm³).

3.2. Inter-network functional connectivity

The differences in functional connectivity were estimated between selected RSNs according to our hypotheses. First, we tested whether there was an overall disturbed connectivity between the DMN and all other investigated networks. Therefore, we estimated the correlation coefficient between the DMN and each other IC. The resulting seven r-values were transformed to z-values and were then averaged for each subject. Then we tested these averaged z-values for differences between groups. We found a decreased inter-network connectivity (DMN vs. all other selected ICs) in the first measurement (acute state of vestibular neuritis) compared to the second measurement (after complete clinical remission of symptoms) (Fig. 1, $P < 0.05$, Bonferroni-corrected). We further tested each of the selected networks whether the connectivity was decreased to the DMN. Decreased functional connectivity was found between the DMN and multiple other networks namely the somatosensory cortex, the auditory/vestibular/insular cortex, the motor cortex, the occipital cortex, the LFPC and the RFPC in the first measurement (acute state) compared to the follow-up measurement (after complete clinical remission of symptoms) (Fig. 1, $P < 0.05$, Bonferroni-corrected). By comparing the first measurement (acute state) with the group of healthy control subjects, the same areas (except the occipital cortex) showed a decreased connectedness to the DMN (Fig. 1).

3.3. Correlation between caloric and reduced sonnectivity

The videonystagmography showed a spontaneous nystagmus in darkness in 12/14 patients. The caloric testing results demonstrated a vestibular paresis in all subjects, with an averaged hyporesponsiveness of the affected side of 53.2% ($\pm$ 25.0%) compared to the unaffected side. All subjects showed reduced asymmetry of the caloric responsiveness in the follow-up investigation (20.8% $\pm$ 24.1%) compared to the acute/subacute stage. The severity of the impaired vestibular function measured by the caloric test was tested for correlations with changes of the functional connectivity but did not reveal any significant results.

4. Discussion

In the present study, we used fMRI to investigate the effects of an acute unilateral vestibular deficit on the functional connectivity between different brain networks. Multiple studies have demonstrated a tight correlation between behavioral performance and the strength of the functional connectivity, suggesting altered information transfer of the corresponding networks (Lowe et al., 2002; Sorg et al., 2007; Sun et al., 2007; Damoiseaux et al., 2008; Abutalebi et al., 2009; Albert et al., 2009; Mintzopoulos et al., 2009). Based on these results, our current findings of reduced internetwork functional connectivity of the DMN indicate that disturbed cerebral information transfer of the DMN is connected to the underlying symptoms in the early stage of a vestibular deficit.

To draw conclusions from these results with respect to the underlying mechanisms of how an acute vestibular deficit may lead to the associated clinical symptoms, it is necessary to consider the physiologic function of those brain areas that are involved in the measured reduced
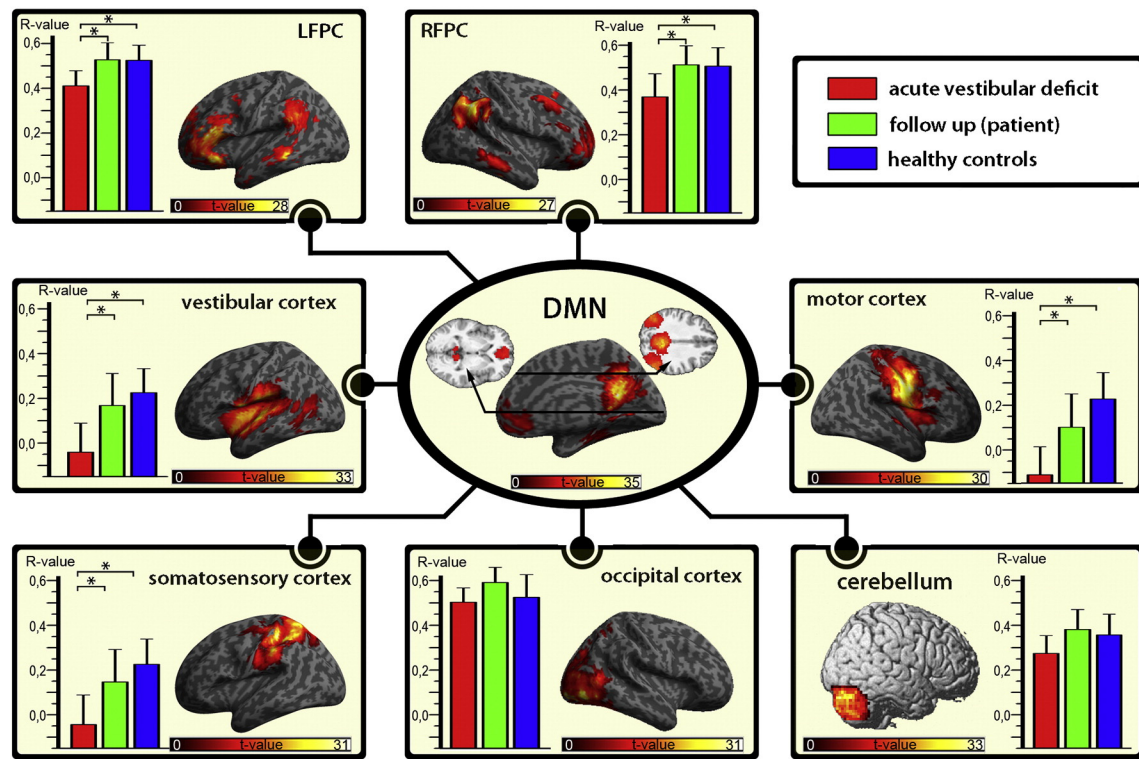
Fig. 1. Changes in the internetwork connectivity to the DMN. The average connectedness between the DMN and each other RSN was estimated and tested for significant differences between the early stage and the follow-up as well as between the early stage and the control group. The figure shows spatial distribution of the 8 identified networks with the corresponding t-values. The column charts next to the spatial distribution of the networks show the strength of the connectedness to the DMN in the early stage (red column), the follow up measurement (green column, same subjects after complete clinical recovery) and the age and gender matched healthy control group (blue column). A large column indicates a high r-value, corresponding to higher connectivity to the DMN. The RSNs are shown superimposed on an inflated brain supplied by the SPM 8 software. Due to the lack of the cerebellum in this brain model, the cerebellar RSN is shown superimposed on slightly other looking brain that is also supplied by the SPM software. Significant differences (P < 0.05, Bonferroni-corrected) are marked by an *.

functional connectivity. It is generally agreed that the brain is composed of two spatially distinct functional networks: the "default-mode" and "task-positive" networks (Corbetta et al., 2002; Fox et al., 2005). During the performance of attention-demanding tasks, prefrontal and parietal structures that comprise the task-positive network are characterized by increased activity; in contrast, the default mode network, including the posterior cingulate and medial prefrontal cortices, is characterized by decreased activity. During wakeful rest, the opposite pattern emerges, with the default mode network becoming more active and the task-positive network less active (Fox et al., 2005; Fox et al., 2009). The default mode network has been hypothesized to generate spontaneous thoughts during mind-wandering and to be an essential component of creativity (Broyd et al., 2009).

After an acute vestibular deficit, we found that the connectivity between these two networks (task-positive and default mode networks) was reduced. We suggest the following mechanism to explain this finding: in the case of an acute vestibular deficit, the imbalance in vestibular tone causes information to diverge from both sides and also a spontaneous nystagmus in the absence of visual fixation. In the resting condition, the diverging vestibular information and also the spontaneous eye movements (nystagmus) are in conflict with information from other sensory modalities. The attempt to integrate this conflicting information requires significantly greater capacity for the processing of information about spatial orientation and brings sensory information processing to our attention, which is normally an automated process that does not require attentional demand. These mechanisms are reflected by increased activity within brain areas responsible for the processing of vestibular information and the integration of multisensory information

(Bense et al., 2004). The sustained increased activity in parts of the task-positive network and the attentional demand reduce the activity within the default mode network. It was shown in healthy subjects that such an activity decrease of the default network is associated with improved performance (McKiernan et al., 2003; Eichele et al., 2008; Singh and Fawcett, 2008; Daselaar et al., 2009). This physiologic mechanism is useful for a short period of time to allocate attentional resources away from intrinsic thoughts and toward difficult extrinsic tasks. This mechanism is also important because the human brain is generally not very efficient at conducting multiple attention-demanding tasks simultaneously. However, in the case of a vestibular neuritis, the attentional demand of diverging sensory information is long-lasting, which greatly limits the ability to focus and process other extrinsic tasks for a long period of time. This phenomenon is reflected by a sustained suppression of the default mode network. The default mode network compensates by decreasing the amount of information that is received from the task-positive network, leading to a decreased connectedness. This involvement of the default mode network in this disease is further supported by findings of difficulties with cognitive skills such as reading, arithmetic and concentration suggesting a decreased ability to engage the task positive networks (Hanes and McCollum, 2006).

In summary, we hypothesize that the measured disconnection of the default mode network is a physiologic mechanism that compensates for the imbalance between both networks by disconnecting the default mode network from the increased amount of information from the task-positive network. It might also be an expression of a sustained, increased utilization of the available processing capacity. The importance of the spontaneous nystagmus in this process remains elusive. This

could be investigated in further studies by comparing a resting state scan with open (without nystagmus) vs. closed (nystagmus) eyes in patients and healthy controls.

The question about the behavioral implications of such a reduced engagement of the default mode network remains. As outlined above, the default mode network is thought to generate spontaneous introspective thoughts during mind wandering. Studies that investigated diseases in which patients particularly indulge in their own thoughts (e.g., schizophrenia, depression) reported predominant hyper-connectivity/activity of the DMN (Broyd et al., 2009; Karbasforoushan and Woodward, 2012; Whitfield-Gabrieli and Ford, 2012).

If hyper-connectivity/activity of the DMN is associated with increased introspective thoughts, it could be hypothesized that a decreased connectivity/activity of the DMN (as found in the current study) is associated with a reduced generation of spontaneous introspective thoughts. We can tentatively speculate whether this inverse effect could modify clinical symptoms (e.g., are depressive symptoms reduced during the acute phase of vestibular neuritis by decreasing the pathologically increased connectivity of the DMN?).

A further point that needs to be discussed is the lack of a significant correlation between changes in the strength of the caloric hyporesponsiveness and changes of the connectivity between the analyzed networks. Correlations between the resting-state functional connectivity and individual task performance have been found for multiple motor, sensory, and cognitive functions as well as during learning (Hampson et al., 2006; Albert et al., 2009; Lewis et al., 2009; Zhu et al., 2011; Klingner et al., 2013a). Therefore it is reasonable to assume, that also behavioral changes due to an improvement of caloric function are associated with changes of the functional connectivity.

However, the question arises whether the caloric function is a suitable parameter for behavioral impairment. Recent studies suggest that it is not and have shown a lack of correlation with the patient's perceived disability (Mandala and Nuti, 2009) or with the functional outcome or the duration of symptoms (Shupak et al., 2008). This might explain the lack of correlation between improvement of caloric function and changes in functional connectivity in the current study. However, it is also possible that caloric function is strongly correlated to the functional connectivity between networks other than the DMN (which are not analyzed in the current study). Particularly one might hypothesize that the connectivity between sensory brain areas of different modalities (e.g., between the visual and vestibular) is more associated with changes in caloric function due to their adjustment of diverging information. In respect to the functional importance of the DMN one might further hypothesize that disturbed connectivity to the DMN is more associated with patient's perceived disability. It further suggests that the time course and severity of the clinical symptoms are mainly dependent on the success of utilizing central mechanisms to adapt and compensate for the diverging sensory information and are less dependent on the strength of the caloric hyporesponsiveness.

Although the mechanisms underlying the emergence and adaptation of motor symptoms due to vestibular neuritis are much better understood than those of dizziness, the question of whether there is a connection between motor symptoms and dizziness remains. It would be interesting to determine whether the same mechanism of a disconnected default mode network could be found in patients without motor symptoms, such as phobic postural vertigo. Therefore, more studies are needed to elucidate the underlying mechanisms of the feeling of dizziness, which are difficult to access but nonetheless significantly affect patients' quality of life.

5. Conclusion

In summary, we found a disturbed connectedness of the default mode network. We hypothesize that the disturbed connectivity is caused by a sustained utilization of processing capacity by diverging sensory information. The reduced connectivity between task-positive and task-negative networks might be related to long lasting symptoms like dizziness or cognitive deficits.

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