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Research report

Components of vestibular cortical function

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HIGHLIGHTS

- Model-free investigation of the hemodynamic components during vestibular stimulation.
- Cortical response comprises multiple different independent components (ICs).
- ICs showed significant differences in their time courses.

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ABSTRACT

It is known that the functional response (e.g., nystagmus) to caloric vestibular stimulation is delayed and prolonged compared with the stimulus-response timing of other sensory systems. Imaging studies have used different models to predict cortical responses and to determine the areas of the brain that are involved. These studies have revealed a widespread network of vestibular brain regions. However, there is some disagreement regarding the brain areas involved, which may partly be caused by differences in the models used. This disagreement indicates the possible existence of multiple cortical components with different temporal characteristics that underlie cortical vestibular processing. However, data-driven methods have yet to be used to analyze the underlying hemodynamic components during and after vestibular stimulation. We performed functional magnetic resonance imaging (fMRI) on 12 healthy subjects during caloric stimulation and analyzed these data using a model-free analysis method (ICA). We found seven independent stimulus-induced components that outline a robust pattern of cortical activation and deactivation. These independent components demonstrated significant differences in their time courses. No single-modeled response function was able to cover the entire range of these independent components. The response functions determined in the present study should improve model-based studies investigating vestibular cortical processing.

1. Introduction

The capacity to sense one's spatial orientation and body acceleration is shared by most complex animals. In most mammals, the vestibular system provides an important contribution. These vestibular inputs are integrated with visual and proprioceptive information. Posture and gaze are thus controlled by complex multisensory integration.

To investigate the cortical brain regions involved in the processing of vestibular information, imaging studies have used various kinds of vestibular stimulation methods, such as saccular tone burst stimulation [1–3], galvanic vestibular stimulation [4–7] and caloric irrigation [8–11]. These studies have revealed a network of engaged multisensory cortical areas, namely the posterior insula and retroinsular regions, the anterior insula and the inferior/middle frontal gyrus, the superior temporal gyrus, the temporoparietal cortex, the pre- and postcentral gyrus, the basal ganglia, the anterior cingulate gyrus, the precuneus, the parahippocampal gyrus and hippocampus, the occipital lobe, the supplementary motor area (SMA) and the cerebellum.

All of these studies have used model-based designs to analyze the regional signal changes associated with vestibular stimulation. Although model-based methods are widely used, they require prior knowledge of the time course of the induced signal changes.

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Normally, the stimulation period is convolved with a hemodynamic response function and is used as a model. In the case of caloric vestibular stimulation, the model used is controversial because the induced nystagmus and the perceived body rotation peak after a significant delay following the stimulus [9]. One study has analyzed vestibular cortical function by recording and modeling the time of subjective rotational feeling after caloric stimulation [11]. Another study has excluded the stimulation period from the statistical analysis because of possible non-vestibular influences such as somatosensory and auditory stimuli [9]. A more recent study included different hemodynamic delays in its design matrix demonstrating a different temporal activation profile in the brainstem compared with the cortex [10]. However, despite the given uncertainty regarding the modeling of vestibular processing in response to caloric stimulation, no data-driven analysis methods have yet been applied to investigate cortical vestibular function.

Therefore, the main objective of this study was to investigate the underlying hemodynamic components during and after caloric vestibular stimulation using a model-free analysis method. We investigate whether the cortical regions that are involved in vestibular processing are composed of multiple components with differences in their hemodynamic time courses. We further aim to investigate the correlation of these independent components (ICs) with the stimulation period and the time course of the elicited nystagmus. Moreover, we are interested in determining whether certain aspects, such as the direction of the nystagmus, are accessible by different independent components. We analyzed these hypotheses in the present study by employing functional magnetic resonance imaging (fMRI) during caloric vestibular stimulation and using an independent component analysis.

2. Materials and methods

2.1. Subjects

Twelve healthy volunteers (mean age: 35.2 ± 13 years, range: 22–56 years) without any history of neurological, otolaryngologic, or psychiatric diseases participated in this study. All subjects were right-handed according to the Edinburgh Handedness Inventory [12]. The study was approved by the local ethics committee, and all subjects gave their written informed consent according to the Declaration of Helsinki.

2.2. Caloric irrigation and electrooculography

Vestibular stimulation was performed by irrigating the ear canals with 150 ml of warm (44 °C) or cold (30 °C) water for 30 s according to the standard recommendations for caloric testing. Thin silicone tubes were placed in each outer ear canal. Outside the MRI chamber, a constant flow of water was heated by a commercially available thermal stimulus unit (Variotherm, ATMOS MedizinTechnik GmbH & Co. KG, Lenzkirch, Germany). Isolated water pipes and pneumatically controlled valves were used to precisely regulate the inflow of water into the external auditory meatus and guarantee a predefined water temperature. The head was slightly elevated (30°) for optimal stimulation of the horizontal canal. A horizontal DC electrooculogram (EOG) was recorded from two electrodes placed at the lateral canthi of each eye (ground electrode over the glabella) using the Brain Amp MRplus amplifier (Brain Products GmbH, Munich, Germany). The subjects kept their eyes closed during and after caloric irrigation. The EOG was cleared of MR artifacts with the MR artifact correction method implemented in the BrainVision Analyzer software (http://www.brainproducts.com). After artifact correction, the number of nystagmus beats per minute was counted.

2.3. fMRI recordings

All experiments were performed on a 3.0-Tesla MR scanner (Trio, Siemens, Erlangen, Germany) to obtain echo-planar T2*-weighted image volumes (EPI) and transaxial T1-weighted structural images. The functional data consisted of 413 EPI volumes. The first 13 volumes were subsequently discarded due to equilibration effects. One functional image volume comprised 40 transaxial slices including the whole cerebrum and cerebellum (voxel size = 3 mm × 3 mm × 3 mm, repetition time = 3 s, TE 35 ms). The high-resolution T1-weighted structural images had a voxel size of 1 mm × 1 mm × 1 mm to allow for precise anatomical localization.

2.4. Stimulation procedure

Caloric irrigation was applied to each subject four times in the following order: right ear canal warm, left ear canal warm, left ear canal cold, and right ear canal cold. The duration of each stimulus was 30 s. The interstimulus interval was 270 s (90 scans). The experimental design is shown schematically in Fig. 1.

2.5. 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 of the images were realigned to the first volume using six-parameter rigid-body transformations to correct for motion artifacts. The images were co-registered with the subject's corresponding anatomical (T1-weighted) images, normalized to the Montreal Neurological Institute (MNI) standard brain [13] to report MNI coordinates, smoothed using a 6-mm full width at half maximum Gaussian kernel and low-pass filtered (<0.1 Hz). The statistical analysis was performed using an independent component analysis (ICA) with the preprocessed images. Twenty components were estimated using the infomax algorithm implemented in the "gift" toolbox [14,15]. The chosen number of components was the minimum number that was determined in a single dataset and provided a reasonable trade-off between preserving relevant variance in the data while easing the burden of interpretation [16].

2.6. Selection of components

All independent components (ICs) were converted to T-maps and visually investigated. The T-maps were additionally mapped to the segmented high resolution T1 image. The portion of the three segmented tissue classes (gray matter, white matter and liquor space) on the space covered by the T-map of each IC was estimated. All components located more than 50% within the liquor space were discarded. To further assure that the ICs were potentially associated with the caloric stimulation, we estimated the area under the curve between the beginning of two successive caloric stimuli (100 scans/300 s). A BOLD response associated with the stimulus should induce stronger responses in the first 50 scans after stimulation than in the second 50 scans. Components that showed a smaller absolute value of the area under the curve in the first 50 scans than in the second 50 scans were excluded.

According to these criteria, we selected seven ICs. A voxelwise random-effect analysis was performed on the selected component images by entering the single subject component images into a one-sample *t*-test [14,15]. The resulting group statistical maps were thresholded at $P < 0.05$ after correcting for multiple comparisons (familywise error (FEW), as implemented in SPM8).

2.7. Hemodynamic response function (HRF) analysis

We were interested in the properties of the time courses of the selected ICs. We extracted the peristimulus time course of 26 voxels surrounding the point of maximum activation of the group statistical maps in each subject from the preprocessed (normalized and smoothed) images. For each stimulus condition, the averaged BOLD signals within each region of interest (ROI) were estimated separately. We performed a least-squares fit of the experimental signal time courses with a double gamma-variate function as previously described [17,18]. These fitted time courses were used to calculate the time to peak (TTP) and full width at half maximum (FWHM) of the BOLD response for each selected IC and each subject. A one-way analysis of variance for the correlated samples was used to identify differences in the values between the ICs. For comparisons with significant differences ($P < 0.05$, Bonferroni-corrected), a paired *t*-test was performed.

3. Results

We found seven ICs that were affected by the caloric stimulation. These ICs showed highly significant activation and deactivation ($P = 0.05$, FWE corrected) in the random-effect group analysis (Fig. 2). Table 1 summarizes the MNI coordinates and *t*-values of peak activation for the different ICs.

The spatial distribution of the seven ICs can be summarized as follows: IC 1: mainly insular and retroinsular cortex and superior temporal gyrus; IC 2: mainly posterior parietal and frontal cortex; IC 3: left cerebellum and left inferior insula; IC 4: right cerebellum and right inferior insula; IC 5: mainly occipital cortex; IC 6: default mode network particularly precuneus; IC 7: somatomotor cortex (see Table 1 and Fig. 2 for details). ICs 1–4 showed a positive BOLD response to caloric stimulation, whereas ICs 5–7 showed a negative BOLD response (Fig. 2). The time courses of all of the ICs along with the recorded nystagmus frequencies are shown in Fig. 3.