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Effects of Cortical Processing of Vestibular Mismatch Information on the Generation of Nystagmus and Vertigo

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Abstract

Objective: Here, we investigate whether vertigo and nystagmus is generated at the first stage of vestibular processing in the parieto-insular vestibular cortex (PIVC).

Background: It is believed that the PIVC is the first and most important hub for the cortical processing of vestibular information. In this region of the brain, vestibular information from both hemispheres is integrated with somatosensory and visual information. Mismatches among these inputs have been consistently demonstrated to activate the PIVC and the widespread vestibular network. Such mismatches also cause behavioral responses, such as vertigo and nystagmus. However, the role of the PIVC in the generation of these symptoms remains elusive, particularly because behavioral and cortical responses have been found to follow very different time-courses. It therefore remains unclear at which level of information processing vertigo and nystagmus are generated.

Methods: We performed functional magnetic resonance imaging (fMRI) on 20 healthy subjects during caloric stimulation at different temperatures. We were particularly interested in the changes in the strengths of PIVC activity under these stimulus conditions.

Results: By using a non-inferiority analysis, we demonstrate that activity in the PIVC did not increase with the occurence of vertigo and nystagmus.

Conclusions: The current data suggest that perceptions of vertigo and nystagmus are not generated at the first integrative stage in the PIVC. We further speculate that nystagmus originates *via* a direct interaction of vestibular signals with somatosensory and visual information at a subcortical level.

Keywords: Vertigo; fMRI; Mismatch information; PIVC; Vestibular cortex

Introduction

In most mammals, posture and gaze are controlled by the complex integration of vestibular, visual and proprioceptive information. This redundancy allows for compensation in the absence of one of these sensory inputs. The downside of this sophisticated and fine-tuned integrative system is that problems arise if the information gathered from different systems or sides of the body is not consistent. Typical examples include reading a book while riding in a car or the dysfunction of one of the vestibular organs. These events sometimes lead to unique feelings that are termed "vertigo" and that are often difficult for patients to describe. The phenomenon of vertigo is difficult to grasp not only for patients but also for neuroscientists. Although the last two decades have greatly improved our understanding of the processing of vestibular information within the brain, our understanding of the perception of vertigo remains incomplete.

Previous studies have used various types 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 large network of engaged multisensory cortical areas, namely, the parieto-insular vestibular cortex (PIVC), the anterior insula, the inferior/middle frontal gyrus, the operculum, 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 [12].

It has been hypothesized that the perception of vertigo originates from the divergence of sensory information in higher multimodal brain areas [13]. However, there is no direct evidence for this theory. On the contrary, it was shown that the

onset and time course of cortical activation induced by vestibular stimulation differs significantly from that of nystagmus and vertigo [10,11,14,15]. Therefore, the relation between the cerebral activation pattern and the appearance of vertigo and nystagmus remains elusive. One possible method to further explore this problem is to investigate the relationship between cortical activation pattern and vertigo induced by different strengths of vestibular stimuli.

However, there are currently no studies available that focus on the relationship between vestibular mismatch information, behavioral effects and cerebral activity changes. In the current study we compared the cortical activity caused by a caloric vestibular stimulus that elicited nystagmus and vertigo with a caloric stimulus that did not elicit these symptoms. The caloric stimuli differed mainly in the strength of their mismatch to the vestibular information of the contralateral body side and to somatosensory and visual information. The integration of these pieces of information is primarily performed by the PIVC. This area is considered the main hub for the processing of vestibular information and is connected to all other parts of the vestibular network, thus relaying the integrated information throughout the vestibular network [16-19].

We hypothesized that if the feelings of vertigo and nystagmus were produced by the cortical processing of vestibular mismatch information, increased activity in the PIVC as the main area responsible for the integration of vestibular mismatch information would be observed. This hypothesis was investigated in the current study by employing functional magnetic resonance imaging during caloric stimulation using different temperatures and simultaneous electrophysiological recordings of the elicited nystagmus.

Materials and Methods

Subjects

Twenty healthy volunteers without any history of neurological, otolaryngologic, or psychiatric diseases participated in this study. All subjects were right-handed according to the Edinburgh Handedness Inventory [20]. One subject revealed movement artefacts during the MRI acquisition of more than 3 mm and was therefore excluded from further analyses, resulting in a final group size of 19 subjects (mean age: 28.7 ± 8 years, range: 21-55 years). The study was approved by the local ethics committee, and all subjects gave their written informed consent according to the Declaration of Helsinki.

Caloric irrigation and electrooculography

Vestibular stimulation was performed by irrigating the ear canal with 150 ml of 44°C water or 37°C water for 30 s according to the standard recommendations for caloric testing. Thin silicone tubes were placed in each outer ear canal for applying the water deep into the external auditory meatus. 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 entire assembly and particularly the exact temperature was tested multiple times ensuring an temperature deviation from the target value within the ear channel of less than ± 0.5°C. 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 using 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. To enable a better inter-individual comparison, the maximum number of nystagmus (beats per minute) was normalized to a value of one in each subject, and the group nystagmus time course was estimated by averaging across all subjects. 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 415 EPI volumes. The first 15 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.

Stimulation procedure

Caloric irrigation was applied to each subject four times in the following order: right ear canal 37°C, left ear canal 37°C, left ear canal 44°C, and right ear canal 44°C. The duration of each stimulus was 30 s. The inter-stimulus interval was 300 s (100 scans). The experimental design is shown schematically in Figure 1.

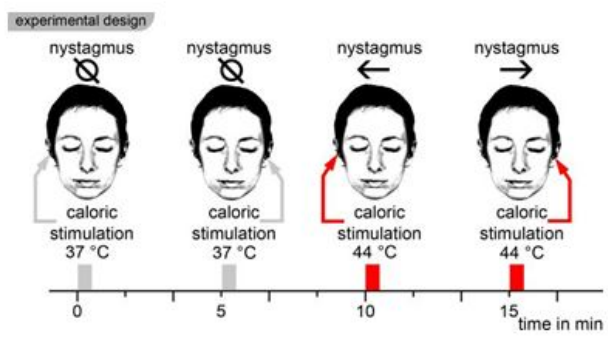

Figure 1: Experimental design. The study setup for caloric irrigation during the fMRI experiment.

Data analysis

The data analysis was performed on a workstation using MATLAB (Mathworks, Natick, MA, USA) with SPM12 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. All images were corrected for differences in the image acquisition time between slices. The images were co-registered with the subject's corresponding anatomical (T1-weighted) images, normalized to the Montreal Neurological Institute (MNI) standard brain [21] to report MNI coordinates, smoothed using a 6-mm full width at half maximum Gaussian kernel and low-pass filtered (<0.1 Hz).

Statistical analyses were performed using a general linear model to obtain statistical parametric maps by performing a multiple regression analysis. Functional MRI signal time courses were high-pass filtered at 1/128 Hz to remove low frequency confounds; serial correlations were handled with an AR(1) model. Each experimental condition was analyzed using a finite impulse response function to allow for a more flexible model. The GLM design matrix included 10 hemodynamic delays, thus allowing for a linear deconvolution of each voxel-time series within the first 100 s of the post-stimulus response. The individual maps were used to perform a random-effect analysis to obtain consistent group activation patterns. The resulting group statistical maps were thresholded by the false discovery rate Genovese et al.

Hemodynamic response function (HRF) analysis

We were interested in the strength of blood-oxygen-level-dependent (BOLD) signal responses in the PIVC. We extracted the peristimulus time course of the 40 voxels surrounding the point of maximum activation in each area (group level SPM analysis) from the preprocessed (normalized and smoothed) images. For each of the four stimulus conditions, we performed a least-squares fit of the experimental signal time courses of each subject with a double gamma-variate function, as previously described.

The following initial values were selected: a=7, b=0.9, d=6.3, a'=14, b'=0.9, d'=12.6, c=0.35, and E=0.05. These fitted time courses were used to calculate the amplitude of the BOLD response for each subject. A one-way analysis of variance (ANOVA) for the correlated samples was used to identify differences in the values induced by the experimental conditions (R37°C, L37°C, R44°C, and L44°C). According to our hypotheses, we tested for differences between the 37°C (37°C) and the 44°C (44°C) stimuli in the PIVC on each side.

If no differences were found, we further tested for the non-inferiority of the 37°C stimulus compared to the 44°C stimulus [4]. Please note that this testing procedure can be considered as "closed testing" and did not require a statistical penalty for multiple testing, as we examining a single confidence interval that controlled for the overall Type I error rate of the two tests [4].

Table 1: MNI coordinates of activation maxima with corresponding t-value in response to caloric stimulation (BA brodmann area; l left; r right;, ACC anterior cingulate cortex, PIVC parieto-insular vestibular cortex).

		SPM-group analysis							
Area	Side of stimulation	44°C				37°C			
		X	Y	Z	t-value	X	Y	Z	t-value
Cerebellum r	R	30	-52	-32	5.0	33	-55	-35	6.8
Cerebellum l	L	-18	-49	-32	8.1	-24	-46	-38	7.9
Temporal r	R	42	-10	-35	4.5	45	11	-41	5.5
Temporal l	L	-36	-1	-38	6.2	-39	8	-35	6.3
Ant. Insular l	R	-36	11	13	5.2	-30	17	4	6.0
Ant. Insula r	L	30	17	10	4.1	36	20	4	4.5
Thalamus l	R	-15	-16	1	4.3	-15	-7	-2	5.6
Thalamus r	L	15	-13	-2	5.4	18	-13	-5	7.1
PIVC l	R	-54	-31	13	4.7	-54	-34	25	7.4
PIVC r	L	51	-28	15	5.2	48	-31	22	6.9

Results

Caloric stimulation of both ears at both temperatures evoked highly significant activations (P<0.05, FDR corrected) in the SPM random-effect group analysis (Figure 2).

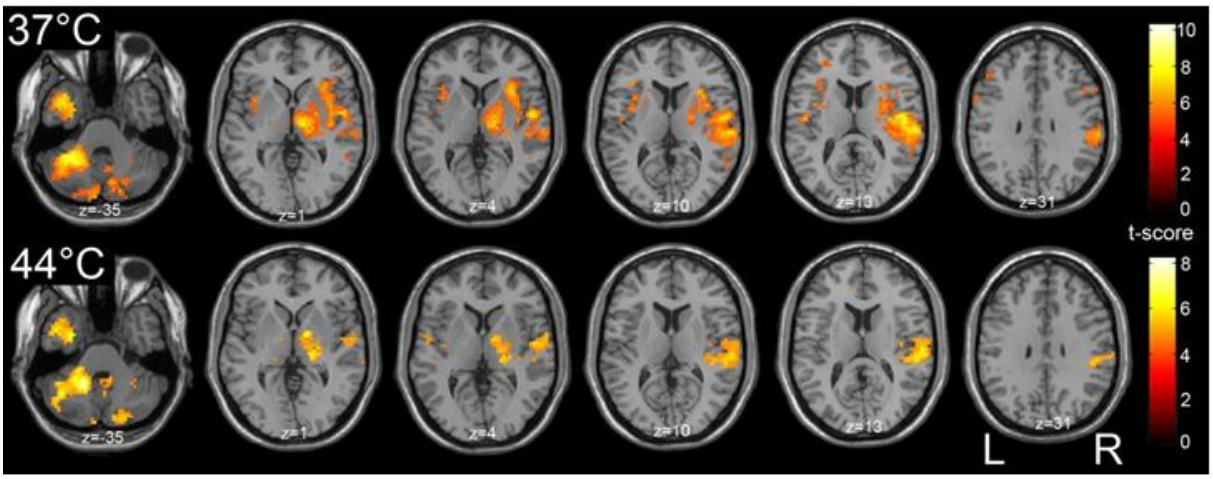

Figure 2: SPM random-effect group (n=19) analysis. Activations (P<0.05, FDR corrected) in response to a 37°C (upper part) and a 44°C (lower part) caloric stimulation of the left ear. The stimulation of the right ear revealed comparable activation maps (see also Table 1). The results are shown superimposed on an individual T1

Table 1 summarizes the MNI coordinates and the t-values corresponding to the peak activation for both 44°C stimuli. These activations were located in the ipsilateral cerebellum, the ipsilateral temporal lobe, the contralateral thalamus, the contralateral PIVC and the contralateral anterior insula.

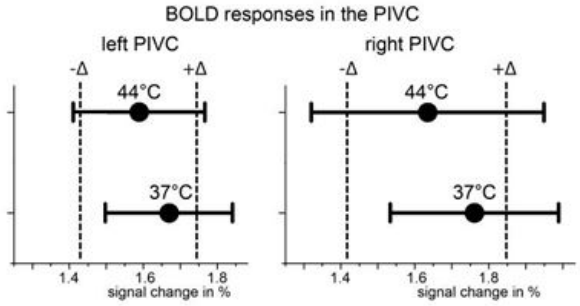

Figure 3: BOLD response of the bilateral PIVC due to the 37°C and 44°C stimuli averaged across all subjects. On the left side are the amplitudes of the BOLD responses of the left PIVC following caloric vestibular stimulation of the right ear. On the right side are the amplitudes of the BOLD response of the right PIVC following caloric vestibular stimulation of the left ear. The dashed lines (- to +Δ) represent the 90% confidence interval of the 44°C stimulus.

Differences between 44°C and 37°C caloric stimuli

The SPM analysis revealed no significant differences between the 44°C and the 37°C caloric stimuli in both hemispheres. According to our primary hypothesis we are particularly interested in whether the PIVC is more active during the 44°C stimulus compared to the 37°C stimulus. We corrected the results at cluster level but did not get any significant results. This lack of significant results can be caused by an difference in the activity of the PIVC that is to small to be detected with the used methods. To investigate whether the PIVC is more active during the 44°C stimulus compared to the 37°C stimulus we performed an analysis of non-inferiority. If the 37°C stimulus is noninferior to the 44°C stimulus than we can rule out the possibility that there is a (hidden and non-significant) stronger activity in the PIVC during the 44°C stimulus. For this aim, we extracted the strength of the BOLD response from the contralateral PIVC and used these data for the non-inferiority analysis. We found that the amplitude of the BOLD response in the PIVC due to a 37°C stimulus was non-inferior to the amplitude of the BOLD response due to a 44°C stimulus (left PIVC p=0.016; right PIVC p=0.004). For visualization, see Figure 3.

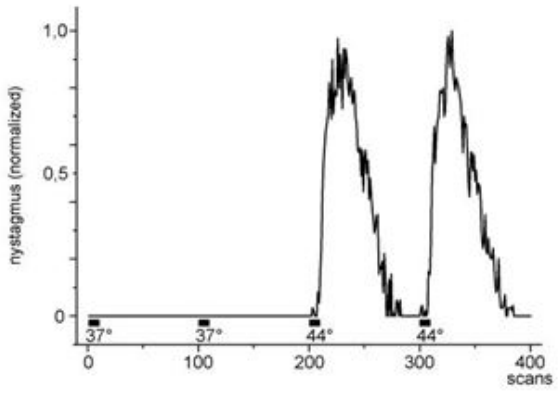

Figure 4: Time course of the recorded nystagmus (normalized); The number of nystagmuses was enumerated in each subject; The maximum number of nystagmuses was normalized to a value of one in each subject, and the group nystagmus time courses were estimated by averaging across all subjects.

Nystagmus and vertigo

Analysis of the electrooculogram that was recorded during the fMRI measurement showed a nystagmus during the 44°C stimuli but not during the 37°C stimuli (Figures 3 and 4). All subjects reported vertigo after the 44°C stimulation, but no subject reported any type of vertigo or dizziness after the 37 Grad stimulus.

Discussion

In the present study, we used fMRI to determine the involvement of the PIVC in the generation of vertigo and nystagmus by investigating the differences between 37°C and 44°C caloric vestibular stimuli. After 44°C caloric stimulation, we identified an activation pattern in line with the existing fMRI studies of vestibular information processing [2,3,5-8,10-12]. We also found a similar activation pattern for the 37°C caloric stimulation. Concerning our primary hypothesis, we demonstrated that the 37°C stimulus elicited an amplitude of the BOLD response in the PIVC that was non-inferior to that of the 44°C stimulus. Further comparisons between the 37°C and the 44°C stimulations did not show any significant differences in the cerebral activity.

In the following sections, we discuss three important questions resulting from the current findings: 1) Why does a 37°C caloric stimulus elicit a vestibular activation pattern; 2) Why is the activity in the central vestibular hub (PIVC) non-inferior due to the 37°C caloric stimulus compared to the 44°C caloric stimulus; and 3) Why are no significant differences found elsewhere in the brain between both stimuli.

Why does a 37°C caloric stimulus elicit a vestibular activation pattern?

Despite the variety of studies that have investigated cerebral vestibular information processing, no other studies have compared different strengths of caloric vestibular stimuli, and there are no reported studies that have compared a vestibular stimulus with a sham stimulus. Initially, while constructing and testing our experimental setup, we attempted to develop a caloric shame stimulus. However, in all pilot experiments that employed the “sham stimulus”, the subjects showed a cortical activation pattern similar to that known from vestibular studies, and it was not possible to deliver a water temperature that had exactly the same temperature as the inner ear. One might formally argue that the activation pattern due to the 37°C caloric stimulus represents somatosensory and auditory processing and not vestibular information processing. However, the activation pattern due to the 37°C caloric stimulus did not elicit the typical pattern of somatosensory or auditory activation. Particularly, the combination of increased activity in the cerebellum and in the PIVC combined with increased activity in the anterior insula suggest that the 37°C caloric stimulus is not only somatosensory in nature but also delivers vestibular information. A further argument might be the influence of the magnetic field of the MRI. Recent studies have suggested that the pure existence of a strong magnetic field might stimulate rotational sensors of the brain [22]. However, this mechanism explains neither the demonstrated difference between caloric stimulation and rest nor the spatial dependence of activated brain areas from the side of the caloric stimulus. Taken together, these data show that the activity pattern in response to a 37°C caloric stimulation is mainly induced by vestibular information processing, while somatosensory and auditory inputs seem to play a minor role. These results further suggest that caloric stimuli with small temperature discrepancies compared to the temperature of the inner ear activate the cerebral vestibular network.

Why did the activity in the PIVC not increase due to a stronger caloric stimulus?

One might first expect that a 44°C stimulus would lead to stronger activity in the vestibular system, as the 44°C stimulus might be assumed to be the stronger stimulus. This train of thought is based on the assumption that in every other sensory system, the cerebral activation strength depends on the strength of the stimulus. For example, stronger somatosensory stimuli lead to greater changes in cortical activity [23-25]. However, such stimulus-intensity associated dependence of the cortical activity is mainly found in the primary cortices of the corresponding modality. The existence of a similar isolated vestibular cortical representation was questioned for more than a century [19,26,27] and growing evidence supports a lack of a primary cortex in the vestibular domain. Areas of higher cortical processing and particularly areas that integrate information from different modalities did not scale their activity in a linear fashion with the stimulus intensity [24,28,29].

This applies particularly to the PIVC, as this area is considered the main area for the integration of vestibular, somatosensory and visual information [16,17,30,31]. It is therefore in line with the existing knowledge of general sensory information processing that activity of the PIVC is not scaled by the stimulus intensity.

Moreover, it must be questioned whether the temperature of caloric stimuli determine the stimulus strengths in a classical sense. From a behavioral perspective, it is obvious that a 44°C stimulus elicits symptoms that are not present following a 37°C stimulus. At the level of information processing, a deviant vestibular stimulus causes the forwarding of vestibular information that is in mismatch with information from the contralateral vestibular sensor and also in mismatch with somatosensory and visual information. This mismatch increases with the temperature of the stimulus. This mismatch elicits cortical activity patterns and not an increase in vestibular information. Therefore, the temperature of a caloric stimulus indicates the strength of the mismatch but not the stimulus strength per second. However, even if we consider the stimuli not in terms of information strength but in terms of mismatch strength, the question remains why a 37°C caloric stimulus elicits activity in the PIVC that is non-inferior to a 44°C caloric stimulus, when the latter elicits an increased mismatch. To discuss this question, we have to consider the processing of mismatched information by the brain. On the one hand, vestibular information must be extremely precise to perform different sophisticated tasks, such as accelerating our body to catch a ball. On the other hand, it is obvious that we are able to compensate

for small mismatches in vestibular information without any subjective symptoms. If not, no one would appreciate a cold shower in the morning, at least not without earplugs. It has been proposed that in case of a vestibular mismatch signal, the brain is able to decide which vestibular information better matches the other input modalities and use that vestibular information further [14]. If this is true, then the amount of mismatch present may not be important. One could even argue that increased mismatch makes it less cortically demanding to decide which information will be used as the correct one. However, the current results suggest that the cortical processing of mismatched information in the PIVC does not depended only on the strength of the mismatch. The main difference between both stimuli remains that the 44°C stimulus elicits a nystagmus and the very unpleasant feeling of vertigo, while the 37°C caloric stimulus does not. Nystagmus occurs from a breakdown of fixation mechanisms due to the divergent vestibular tone, primarily involving a disturbed vestibulo-ocular reflex. This process takes place mainly at the level of the brainstem nuclei responsible for oculomotor control [32], and these nuclei are also connected to multiple sensory areas [33]. This might indicate that the nystagmus is generated at a subcortical level, which then leads to the feeling of vertigo, while the processing of mismatched information in the PIVC is not mainly involved in the generation of vertigo and nystagmus. This explanation would also clarify why brain lesions that include the PIVC only elicit minor symptoms that are normally not even recognized by the patients [34-36,14].

Finally, we must consider the possible influence of habituation, as the current study used a fixed design, and in this design, the 37°C stimulus preceded the 44°C caloric stimulus. It is therefore well conceivable that the non-inferiority might not have occurred if the order of the experimental stimuli were reversed. However, the effects of habitation did not affect our main research hypothesis, namely the link between activity in the PIVC and the rise in vertigo and nystagmus.

Why are there no significant activity differences found elsewhere in the brain?

The feeling of vertigo that accompanies the nystagmus after the 44°C caloric stimulus clearly affects multiple brain systems. Patients who suffer from a disrupted vestibular tone comparable to that in our experiment but more prolonged (e.g., due to a unilateral vestibular loss) are commonly unable to perform tasks that require any higher degree of attention, and their quality of life is severely affected [37]. Multiple studies have demonstrated that a vestibular failure causes changes in the functional connectivity between different brain areas [38-40]. However, even if nystagmus and vertigo mainly affect the connectivity between brain areas and less on brain activity, a short episode of vertigo and nystagmus should nevertheless elicit some differences in the activity of some brain areas. Particularly, we assume that in the presence of a nystagmus, areas as the frontal eye field should have increased activity compared to the stimulus that did not elicit nystagmus and vertigo [41-43]. We suggest, that our inability to show such differences in the current study is most likely due to the small number of stimulus repetitions and the use of a fixed experimental design. Particularly, the small number of stimulus repetitions is a general problem of caloric stimuli, as their effects are long lasting, and habituational effects are likely substantial. These facts strongly disfavor methods that require a high number of repetitions, such as EEG and MEG, while methods that require few repetitions, such as PET, seem to be well suited for investigating cortical activity patterns underlying the perception of vertigo.

Conclusion

We demonstrated that a vestibular stimulus that did not caused vertigo and nystagmus elicited non-inferior activity in the PIVC compared to a vestibular stimulus that caused nystagmus and vertigo. We therefore suggest that the activity in the PIVC does not determine the generation of nystagmus and vertigo. Moreover, we speculate that a nystagmus is not generated by the cortical processing of vestibular information but is generated at the subcortical level.

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References

1. Janzen J, Schlindwein P, Bense S, Bauermann T, Vucurevic G, et al. (2008) Neural correlates of hemispheric dominance and ipsilaterality within the vestibular system. Neuroimage 42: 1508-1518.
2. Miyamoto T, Fukushima K, Takada T, de Waele C, Vidal PP (2007) Saccular stimulation of the human cortex: a functional magnetic resonance imaging study. Neurosci Lett 423: 68-72.
3. Schlindwein P, Mueller M, Bauermann T, Brandt T, Stoeter P, et al. (2008) Cortical representation of saccular vestibular stimulation: VEMPs in fMRI. Neuroimage 39: 19-31.
4. Schumi J, Wittes JT (2011) Through the looking glass: understanding non-inferiority. Trials 12: 106.
5. Bense S, Stephan T, Yousry TA, Brandt T, Dieterich M (2001) Multisensory cortical signal increases and decreases during vestibular galvanic stimulation (fMRI). J Neurophysiol 85: 886-899.
6. Lobel E, Kleine JF, Bihan DL, Leroy-Willig A, Berthoz A (1998) Functional MRI of galvanic vestibular stimulation. J Neurophysiol 80: 2699-2709.
7. Stephan T, Deutschlander A, Nolte A, Schneider E, Wiesmann M, et al. (2005) Functional MRI of galvanic vestibular stimulation with alternating currents at different frequencies. Neuroimage 26: 721-732.
8. Stephan T, Hufner K, Brandt T (2009) Stimulus profile and modeling of continuous galvanic vestibular stimulation in functional magnetic resonance imaging. Ann N Y Acad Sci 1164: 472-475.
9. Dieterich M, Bense S, Lutz S, Drzezga A, Stephan T, et al. (2003) Dominance for vestibular cortical function in the non-dominant hemisphere. Cereb Cortex 13: 994-1007.

10. Fasold O, von Brevern M, Kuhberg M, Ploner CJ, Villringer A, et al. (2002) Human vestibular cortex as identified with caloric stimulation in functional magnetic resonance imaging. Neuroimage 17: 1384-1393.

11. Marcelli V, Esposito F, Aragri A, Furia T, Riccardi P, et al. (2009) Spatio-temporal pattern of vestibular information processing after brief caloric stimulation. Eur J Radiol 70: 312-316.

12. Suzuki M, Kitano H, Ito R, Kitanishi T, Yazawa Y, et al. (2001) Cortical and subcortical vestibular response to caloric stimulation detected by functional magnetic resonance imaging. Brain Res Cogn Brain Res 12: 441-449.

13. zu Eulenburg P, Muller-Forell W, Dieterich M (2013) On the recall of vestibular sensations. Brain Struct Funct 218: 255-267.

14. Dieterich M, Brandt T (2015) Why acute unilateral vestibular cortex lesions mostly manifest without vertigo. Neurology 84: 1680-1684.

15. Klingner CM, Volk GF, Flatz C, Brodoehl S, Dieterich M, et al. (2012) Components of vestibular cortical function. Behav Brain Res 236: 194-199.

16. de Waele C, Baudonniere PM, Lepecq JC, Tran Ba Huy P, Vidal PP (2001) Vestibular projections in the human cortex. Exp Brain Res 141: 541-551.

17. Guldin WO, Akbarian S, Grusser OJ (1992) Cortico-cortical connections and cytoarchitectonics of the primate vestibular cortex: a study in squirrel monkeys (Saimiri sciureus). J Comp Neurol 326: 375-401.

18. Kirsch V, Keeser D, Hergenroeder T, Erat O, Ertl-Wagner B, et al. (2016) Structural and functional connectivity mapping of the vestibular circuitry from human brainstem to cortex. Brain Struct Funct 221: 1291-1308.

19. Lopez C, Blanke O (2011) The thalamocortical vestibular system in animals and humans. Brain Res Rev 67: 119-146.

20. Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9: 97-113.

21. Evans AC, Collins DL, Mills SR, Brown ED, Kelly RL, et al. (1993) 3D statistical neuroanatomical models from 305 MRI volumes. IEEE Nuclear Science Symposium and Medical Imaging 1813-1817.

22. Roberts DC, Marcelli V, Gillen JS, Carey JP, Della Santina, et al. (2011) MRI magnetic field stimulates rotational sensors of the brain. Curr Biol 21: 1635-1640.

23. Backes WH, Mess WH, van Kranen-Mastenbroek V, Reulen JP (2000) Somatosensory cortex responses to median nerve stimulation: fMRI effects of current amplitude and selective attention. Clin Neurophysiol 111: 1738-1744.

24. Klingner CM, Hasler C, Brodoehl S, Witte OW (2010) Dependence of the negative BOLD response on somatosensory stimulus intensity. Neuroimage 53: 189-195.

25. Zhang N, Gore JC, Chen LM, Avison MJ (2007) Dependence of BOLD signal change on tactile stimulus intensity in SI of primates. Magn Reson Imaging 25: 784-794.

26. Guldin WO, Grusser OJ (1998) Is there a vestibular cortex? Trends Neurosci 21: 254-259.

27. Spitzer A (1924) Anatomie und Physiologie der zentralen Bahnen des Vestibularis., Wien.

28. Ray S, Hsiao SS, Crone NE, Franaszczuk PJ, Niebur E (2008) Effect of stimulus intensity on the spike-local field potential relationship in the secondary somatosensory cortex. J Neurosci 28: 7334-7343.

29. Torquati K, Pizzella V, Della Penna S, Franciotti R, Babiloni C, et al. (2002). Comparison between SI and SII responses as a function of stimulus intensity. Neuroreport 13: 813-819.

30. Grusser OJ, Pause M, Schreiter U (1990) Localization and responses of neurones in the parieto-insular vestibular cortex of awake monkeys (Macaca fascicularis). J Physiol 430: 537-557.

31. Grusser OJ, Pause M, Schreiter U (1990) Vestibular neurones in the parieto-insular cortex of monkeys (Macaca fascicularis): visual and neck receptor responses. J Physiol 430: 559-583.

32. Leigh RJ, Zee DS (2006) The neurology of eye movements (4th edn). New York, Oxford University Press.

33. Dieterich M, Brandt T (2008) Functional brain imaging of peripheral and central vestibular disorders. Brain 131: 2538-2552.

34. Baier B, Conrad J, Zu Eulenburg P, Best C, Muller-Forell W, et al. (2013) Insular strokes cause no vestibular deficits. Stroke 44: 2604-2606.

35. Boegle R, Stephan T, Ertl M, Glasauer S, Dieterich M (2016) Magnetic vestibular stimulation modulates default mode network fluctuations. Neuroimage 127: 409-421.

36. Brandt T, Dieterich M, Danek A (1994) Vestibular cortex lesions affect the perception of verticality. Ann Neurol 35: 403-412.

37. Duracinsky M, Mosnier I, Bouccara D, Sterkers O, Chassany O (2007) Literature review of questionnaires assessing vertigo and dizziness, and their impact on patients' quality of life. Value Health 10: 273-284.

38. Gottlich M, Jandl NM, Wojak JF, Sprenger A, der Gablentz J, et al. (2014) Altered resting-state functional connectivity in patients with chronic bilateral vestibular failure. Neuroimage Clin 4: 488-499.

39. Helmchen C, Ye Z, Sprenger A, Munte TF (2014) Changes in resting-state fMRI in vestibular neuritis. Brain Struct Funct 219: 1889-1900.

40. Klingner CM, Volk GF, Brodoehl S, Witte OW, Guntinas-Lichius O (2014) Disrupted functional connectivity of the default mode network due to acute vestibular deficit. Neuroimage Clin 6: 109-114.

41. Brandt T, Bartenstein P, Janek A, Dieterich M (1998) Reciprocal inhibitory visual-vestibular interaction. Visual motion stimulation deactivates the parieto-insular vestibular cortex. Brain 121: 1749-1758.

42. Klingner CM, Hasler C, Brodoehl S, Witte OW (2012) Excitatory and inhibitory mechanisms underlying somatosensory habituation. Hum Brain Mapp 35: 152-160.

43. Kopietz R, Sakar V, Albrecht J, Kleemann AM, Schopf V (2009) Activation of primary and secondary somatosensory regions following tactile stimulation of the face. Klin Neuroradiol 19: 135-144.