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Meta-analytical definition and functional connectivity of the human vestibular cortex

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ABSTRACT

Contrary to most other sensory systems, no consensus has been reached within the scientific community about the exact locations and functions of human cortical areas processing vestibular information. Metaanalytical modelling using activation likelihood estimation (ALE) for the integration of neuroimaging results has already been successfully applied to several distinct tasks, thereby revealing the cortical localization of cognitive functions. We used the same algorithm and technique with all available and suitable PET and fMRI studies employing a vestibular stimulus. Most consistently across 28 experiments vestibular stimuli evoked activity in the right hemispheric parietal opercular area OP 2 implicating it as the core region for vestibular processing. Furthermore, we took our primary results as a seeding point and fed them into a functional connectivity analysis based on resting-state oscillations in 100 healthy subjects. This subsequent calculation confirmed direct connections of the area OP 2 with every other region found in the meta-analysis, in particular temporo-parietal regions, premotor cortex, and the midcingulate gyrus. Thus revealing a joint vestibular network in accordance with a concept from animal literature termed the *inner vestibular circle*. Moreover, there was also a significant vestibular connectivity overlap with frontal but not parietal cortical centres responsible for the generation of saccadic eye movements, likely to be involved in nystagmus fast phase generation. This was shown in an additional ocular motor meta-analysis.

We conclude that the cytoarchitectonic area OP 2 in the parietal operculum, embedded in a joint vestibular network, should be the primary candidate for the human vestibular cortex. This area may represent the human homologue to the vestibular area *PIVC* as proposed by Guldin and Grüsser in non-human primates.

Introduction

Human equilibrium and our physical ability to navigate strongly depend on the processing of vestibular information. Although Aristotle did not include balance in his list of essential senses, we probably would not have evolved into upright stance and bipedal locomotion without permanent central nervous computation and representation of signals delivered by our peripheral vestibular organs. All other sensory systems have long been localized to specific areas within the human brain. The exact whereabouts of a well-defined vestibular cortex in man though is still very much in contention. This is in contrast to the undisputed human vestibular anatomy of the brain stem and its multisensory interconnections. During the course of time, four out of five brain lobes have been considered to "harbour" the cortical vestibular system (the exception being the occipital lobe) (Duque-Parra, 2004), thus showing the level of uncertainty as well as the possibly distributed nature of the vestibular network.

Animal literature

Studies employing neuron recordings and tracer injections in rats, squirrels, java monkeys and macaques have focused on several separate structures in the frontal, temporal and parietal cortex that undoubtedly receive vestibular input: the area 2v at the tip of the intraparietal sulcus, the area 3aV (a vestibular region within area 3a representing neck and trunk) in the central sulcus and an area called the parieto-insular vestibular cortex (PIVC) located posterior to the dorsal end of the insula. Area 2v in the parietal cortex was the first definite cortical vestibular area found in primates. It was initially thought to represent the vestibular area anterior to the suprasylvian sulcus (ASSS) found in the cat (Fredrickson et al., 1966). The ASSS had been the first cortical vestibular projection demonstrated in mammals. As early as 1973, Pandya and Sanides had already stressed in their findings that there is a distinctive cytoarchitectonic analogy between the retroinsular parietal cortex in primates and ASSS (Pandya and Sanides, 1973). The PIVC as the correlate for this retroinsular region was then discovered by Grüsser and his group in the Java monkey and later also confirmed in the squirrel and marmoset monkey (Grusser et al., 1990). It seemed more likely to represent ASSS in non-human primates than area 2v.

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Among the regions that have also been shown to receive vestibular information in the monkey are the ventral intraparietal area (VIP), area 7 in caudal inferior parietal lobe, the primary motor cortex (area 4) and the premotor cortex (area 6). A distinct vestibular cingulate region has been termed though it seems to only receive preprocessed vestibular information from the aforementioned areas 3aV and PIVC (for a more detailed comparative anatomy of the cortical vestibular representations in animals and humans see Lopez and Blanke, 2011) (Lopez and Blanke, 2011).

The aim of the present study was to pinpoint and segregate vestibular representations in the human cortex through means of a quantitative meta-analytical approach. We wanted to follow up on the quest for a unique vestibular cortex (Guldin and Grüsser, 1998). The use of a wide variety of stimuli (warm and cold caloric irrigation, galvanic vestibular stimulation, short tone bursts as an otolith impulse) as well as multiple imaging modalities (H_2O_2- and FDG-PET, electrical source and dipole reconstruction in EEG, and fMRI) in the last 30 years of human vestibular research has led to a variegated and still inhomogeneous level of knowledge about the cortical vestibular network. With our analysis, we hoped to condense and streamline the heterogeneous literature in this aspect of vestibular research. Based on previous hypotheses on laterality and interhemispheric dominance within the vestibular system, we anticipated to find lateralized cortical areas responding to a strictly unilateral side of stimulation as well as central nodes activated by all vestibular stimuli alike. Furthermore, it was our aim to look for unique patterns in vestibular activations with respect to the different subtypes of vestibular excitation (galvanic, caloric or otolith). Finally, we intended to gain knowledge about a cortical vestibular network by means of integrating our meta-analysis findings with a separate subsequent functional connectivity approach.

Material and methods

Study selection criteria

Functional neuroimaging studies were retrieved via searches in Pubmed, ISI Web of Knowledge and Scopus databases as well as identified by reference tracing and through reviews. Experiments reported in these papers that corresponded to the contrast of a vestibular stimulation against a resting baseline or a somatosensory control condition were included in the meta-analysis if they fulfilled the following criteria (cf. Table 1):

Analyses must be computed across the whole brain and not restricted by partial coverage or regions of interest analyses. Coordinates must be reported in an XYZ format, either in MNI or Talairach space with the latter being transformed into MNI co-ordinates using the Lancaster transform (Lancaster et al., 2007). Only experiments that investigated differences between stimulation conditions in healthy control populations were included. Experiments focusing on between-group differences, 'group x condition' interactions or the effects of experimental manipulation other than vestibular stimulation, e.g., attention or pharamacology, were excluded. All studies were obtained from peer-reviewed journals.

Table 1
Overview on the regions showing a significant convergence of coordinates over all functional neuroimaging experiments assessing the neural effects of vestibular stimulation. ALE activations over all vestibular studies.

Macroanatomical location	Peak coordinates			Cytoarchitectonic allocation
	X	Y	Z	
Central Insula	−36	0	−4	N/A
Parietal operculum	−52	2	2	OP 4
Parietal operculum	−46	−14	12	OP 1
Parietal operculum	−38	−20	16	OP 2
Inferior parietal cortex	−46	−32	22	PFcm
Posterior Insula	−40	−16	14	Ig2
Central Insula	42	4	−8	N/A
Parietal operculum	48	−12	12	OP 4
Parietal operculum	50	−32	18	OP 1 / OP 2
Inferior parietal cortex	66	−26	20	PF
Posterior Insula	38	−18	6	Ig2
Premotor cortex	48	4	50	BA 6
Medial premotor cortex	4	4	54	BA 6

Activation likelihood estimation (ALE) algorithm

Meta-analysis was carried out using a revised version (Eickhoff et al., 2009) of the ALE approach (Laird et al., 2005; Turkeltaub et al., 2002) implemented in MATLAB (The MathWorks Inc., Natick, USA). This algorithm aims to identify areas showing a convergence of findings across experiments, which is higher than expected under a spatially random spatial association. The key idea behind ALE is to treat the reported foci as centers of 3D Gaussian probability distributions reflecting the spatial uncertainty associated with each reported set of coordinates. The probabilities of all foci reported in a given experiment were then combined for each voxel, resulting in a modeled activation (MA) map. Taking the union across these yielded voxel-wise ALE scores describing the convergence of results at each particular location of the brain. To distinguish 'true' convergence between studies from random convergence, i.e., noise, ALE scores were compared to an empirical null-distribution reflecting a random spatial association between experiments. Hereby, a random-effects inference is invoked, focusing on inference on the above-chance convergence between studies, not clustering of foci within a particular study. Computationally, deriving this null-hypothesis involved sampling a voxel at random from each of the MA maps and taking the union of these values in the same manner as done for the (spatially contingent) voxels in the true analysis. The p-value of a 'true' ALE was then given by the proportion of equal or higher values obtained under the null-distribution. The resulting non-parametric p-values for each meta-analysis were then thresholded at a cluster level threshold of $p<0.05$ and transformed into Z-scores for display.

Conjunction analyses aim at identifying those voxels in which a significant effect was present in two separate analyses. To compute the conjunction between two ALE analyses, we used the conservative minimum statistic (Nichols et al., 2005), which is equivalent to identifying the intersection between the two cluster-level corrected results (Caspers et al., 2010). In order to exclude smaller regions of presumably incidental overlap, an additional extend-threshold of 15 voxels was applied.

Differences between conditions were tested by first performing an ALE analysis separately for each condition and computing the voxel-wise difference between the ensuing ALE maps (Eickhoff et al., 2011). All experiments contributing to either analysis were then pooled and randomly divided into two groups of the same size as the two original sets of experiments reflecting the contrasted ALE analyses. ALE-scores for these two randomly assembled groups were calculated and the difference between these ALE-scores was recorded for each voxel in the brain. Repeating this process 10,000 times yielded voxel-specific null-distribution of differences in ALE-scores between the two conditions. The differences in ALE scores were then compared against the permutation distribution and only those voxels which had a post-hoc probability pf $P>0.95$ for representing true differences were retained. Moreover, effects were inclusively masked by the respective main effects, i.e., the significant effects of the ALE analysis for the particular condition (Bzdok et al., 2011).

Structure-function analysis

Results were then anatomically assigned to probabilistic cytoartchitectonic maps of the human brain in MNI space (Eickhoff et al., 2007b). Details of the cytoarchitecture, inter-subject variability

and location of areas' borders employed in the present study are referenced in papers (Amunts et al., 1999, 2005; Caspers et al., 2008; Eickhoff et al., 2006b; Geyer et al., 1996; Grefkes et al., 2001; Scheperjans et al., 2008).

Resting-state data: imaging and pre-processing

In order to also delineate the functional connectivity of vestibular core regions, resting state fMRI images were acquired in 100 healthy volunteers (mean age 48.7 years) without any record of neurological or psychiatric disorders. Subjects gave written consent to participate in the study as approved by the ethics committee of the University of Bonn. They were instructed to keep their eyes closed and let their mind wander but not to fall asleep which was confirmed by post-scan debriefing. For each subject 300 resting state EPI images were acquired using blood-oxygen-level-dependent (BOLD) contrast [gradient-echo EPI pulse sequence, TR = 2.2 s, TE = 30 ms, flip angle = 90°, in-plane resolution = 3.1 × 3.1 mm, 36 axial slices (3.1 mm thickness) covering the entire brain]. Image acquisition was preceded by four dummy images allowing for magnetic field saturation which were discharged prior to further processing using SPM8 (www.fil.ion.ucl.ac.uk/spm). The EPI images were first corrected for head movement by affine registration using a two-pass procedure. The mean EPI image for each subject was then spatially normalized to the MNI single subject template using the "unified segmentation" approach(Ashburner and Friston, 2005) and the ensuing deformation was applied to the individual EPI volumes. Finally, images were smoothed by a 5-mm FWHM Gaussian to meet requirements of the general linear model and compensate for residual anatomical variations.

Resting-state data: functional connectivity analysis

Functional connectivity analyses may be influenced by several confounds such as physiological processes, e.g., fluctuations related to cardiac and respiratory cycles, and in particular motion-related effects (Bandettini and Bullmore, 2008; Fox et al., 2009). In order to reduce spurious correlations, variance that could be explained by the following nuisance variables was removed from the time series of each voxel's time series (Bzdok et al., 2011): i) the six motion parameters derived from the image realignment ii) their first derivative iii) mean grey, white matter and CSF signal intensity iv) coherent signal changes across the whole brain reflected by the first five components of a PCA decomposition. All nuisance variables entered the model as first and all but the PCA components also as second order terms. Following confound removal, data was band pass filtered preserving frequencies between 0.01 and 0.08 Hz (Biswal et al., 1995; Fox and Raichle, 2007; Greicius et al., 2003). The time course of the vestibular cortex area OP 2 was then extracted for each subject as the first eigenvariate of all grey-matter voxels located within 5 mm of the peak coordinate.

For each subject we computed linear (Pearson) correlation coefficients between the time series extracted for the vestibular cortex and any other grey matter voxel in the brain. These voxel-wise correlation coefficients were then transformed into Fisher's z scores. Group analysis was then performed on these scores by means of mass-univariate analysis (one sample *T*-test) across subjects. The results of this random-effects analysis were regarded as significant if they passed a threshold of $p<0.05$, cluster-level corrected for multiple comparisons (Eickhoff et al., 2011).

Meta-analysis of saccadic eye movements

For comparison, we performed an additional meta-analysis over functional neuroimaging experiments on saccadic eye movements. Using the BrainMap database (Laird et al., 2009) (www.brainmap.org), we extracted those experiments which reported stereotaxic coordinates from normal mapping studies (no interventions, no group comparison) in healthy subjects using either fMRI or PET. Only experiments that contrasted saccadic eye movements with a resting or control condition were retained while contrasts between different saccade conditions, e.g., anti- vs. pro-saccades, were excluded (Suppl. Data 2). Meta-analysis was performed over the retrieved experiments using the same approach as for the meta-analysis on vestibular processing detailed above.

Results

Meta-analysis of all vestibular activations

Activation likelihood (ALE) meta-analysis over the foci reported in all 28 suitable neuroimaging experiments (cf. Table 1) yielded significant convergence bilaterally in the peri-sylvian cortex (Fig. 1a, all overlays done with MRIcroGL by Chris Rorden). The extended clusters in both hemispheres included the posterior parietal operculum, the secondary somatosensory cortex, the inferior parietal cortex as well as the middle and posterior insula (Fig. 1b). Further significant convergence across experiments was found in the right lateral premotor cortex and the medial premotor cortex (supplementary motor area SMA).

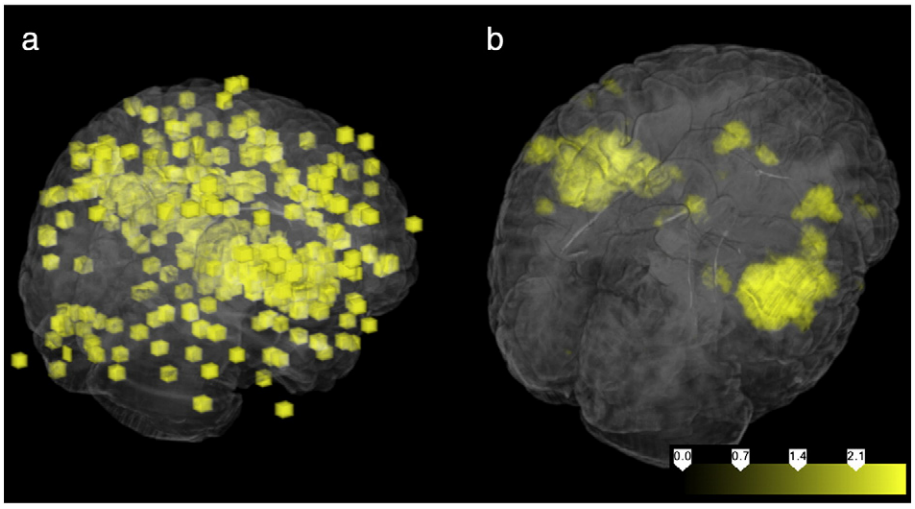

Fig. 1. a) Location of all 414 foci reported in the 28 functional neuroimaging studies on vestibular stimulation on the MNI single subject template. b) Meta-analysis results for all vestibular experiments following statistical comparison against a null-distribution of spatial independence across studies, ALE scores were thresholded at a cluster-level $p<0.05$.

Differentiation of the subtypes of vestibular stimulation

Comparing experiments that employed caloric stimulation (n = 17) against those that used other forms of vestibular stimulation (n = 10) (Fig. 2b) such as galvanic stimuli or otolith stimulation revealed a significantly higher likelihood of evoked activation by the caloric experiments in the right posterior (36/-24/2; Area Ig1) and anterior (34/14/4) insula, parietal operculum (46/-30/12, Area OP 1) and midcingulate cortex (10/14/36) as well as the left central insula (−42/-8/4) (Fig. 2a). In contrast, non-galvanic stimuli evoked more consistent activation in the bilateral dorsal premotor cortex (50/0/44 and −48/2/44; both BA 6). We performed a conjunction analysis testing for significant convergence across the different experiments using caloric stimuli and those using non-caloric stimuli in order to pay tribute to the spectrum of vestibular stimulation and the different characteristics of the vestibular stimuli and to reveal the common denominator. This analysis revealed only a single focus in the right posterior parietal operculum (40/-22/16) that was cytoarchitectonically allocated to area OP 2 (Fig. 3a/c).

Left vs. right sided vestibular stimulation

Of all vestibular stimuli (galvanic, otolith and caloric), caloric stimulation is the most employed, consistent, long lasting and direction-specific throughout all available studies. Effects of unilateral stimulation (left- vs. right-sided) were therefore assessed by testing for significant convergence across those experiments (n = 10) that used unilateral cold caloric stimulation to find the overlap of responses from the two different afferences. While right-sided stimulation evoked significant converging activation on the right posterior parietal operculum (44/-30/16), meta-analysis of experiments using left vestibular stimulation revealed significant bilateral convergence in the posterior parietal operculum (44/-28/16, -48/-26/18) as well as in the right secondary somatosensory cortex (54/-14/8) and the right posterior insula/parietal operculum (42/4/-10). Only the right posterior parietal region survived statistical significance in the direct comparison of left and right stimulation experiments (Fig. 3b/c). Therefore, the only significant convergence in the conjunction between left and right vestibular stimulation was found anew in the right posterior parietal operculum.

Functional connectivity of the PIVC

Our conjunction analyses showed that caloric and non-caloric stimuli as well as left- and right-sided cold caloric stimuli all converged in a single location at the posterior parietal operculum, more precisely in area OP 2 (42/-24/18). We thus propose this location to be the most likely location of the human parietal-insular vestibular cortex. We used it as a seeding point to explore its functional connectivity by correlation analysis of task-free (resting-state) fMRI data. Across a large cohort (100 healthy subjects) covering a broad age range (21–71 years), we found the PIVC to show extended functional connectivity with bilateral peri-sylvian regions (Fig. 4a). Each and every region that was implicated in the meta-analysis across all vestibular stimulation experiments also showed (in this independent dataset and approach) functional connectivity with the right PIVC. Additionally, we found significant "resting-state" connectivity bilaterally with the entire primary sensory-motor cortex (cytoarchitectonic areas 4a, 4p, 3a, 3b, 1, 2) as well as the lateral and medial premotor cortex (area 6). Finally, we found significant functional connectivity with a bilateral region just anterior to the histologically defined V5 (and overlapping with it on the right hemisphere).

Meta-analysis of saccadic eye movements and comparison

ALE meta-analysis of foci reported in neuroimaging experiments (n = 28) that assessed the neural correlates of saccadic eye movements (retrieved via BrainMap; cf. Table 2) yielded significant convergence bilaterally in lateral premotor cortex (presumably corresponding to the frontal eye fields), medial premotor cortex, intraparietal sulcus and adjacent superior parietal lobule as well as the putamen, visual cortex and cerebellum (Fig. 4b).

When computing a conjunction between the functional connectivity map of the PIVC and the meta-analysis on saccadic eye movements, we found converging effects in the right superior temporal gyrus, the medial and bilaterally in the lateral premotor cortex possibly corresponding to the frontal and supplementary eye fields (Fig. 4c). This indicates that these regions are functionally interconnected with the PIVC and may be engaged during the cortical control of saccadic eye movements receiving cortically preprocessed vestibular information.

Discussion

Our analysis showed extended clusters in the temporo-parietal cortex, lateral and medial premotor cortex as well as parts of the insula when looking at the vestibular stimulation studies as a whole. They seem to resemble a network similar to one described by EEG recordings after intraoperative stimulation of the vestibular nerve in patients (de Waele et al., 2001). To find the common denominator for the vastly different kinds of vestibular incitements, we then

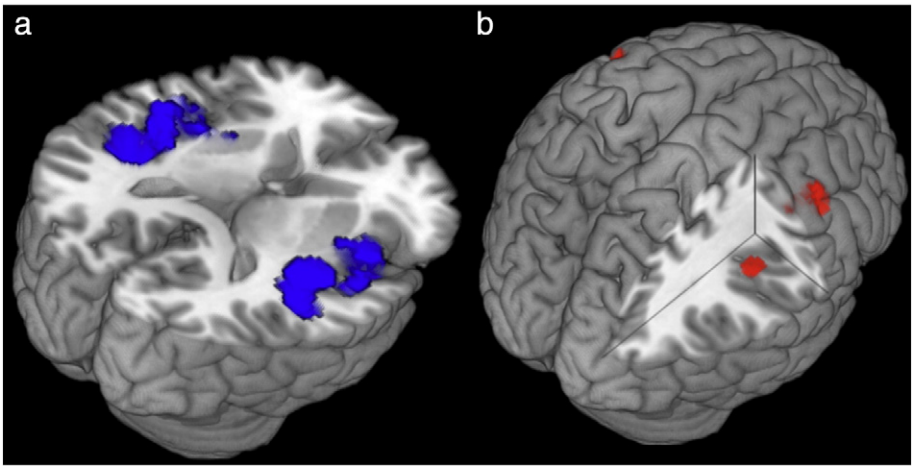

Fig. 2. a) Significant convergence of activation reported in experiments employing caloric vestibular stimulation shown in a transversal view through the insular cortex, thresholded at a cluster-level $p<0.05$. b) Significant convergence of activation reported in experiments employing vestibular stimuli other than caloric irrigation, thresholded at a cluster-level $p<0.05$.

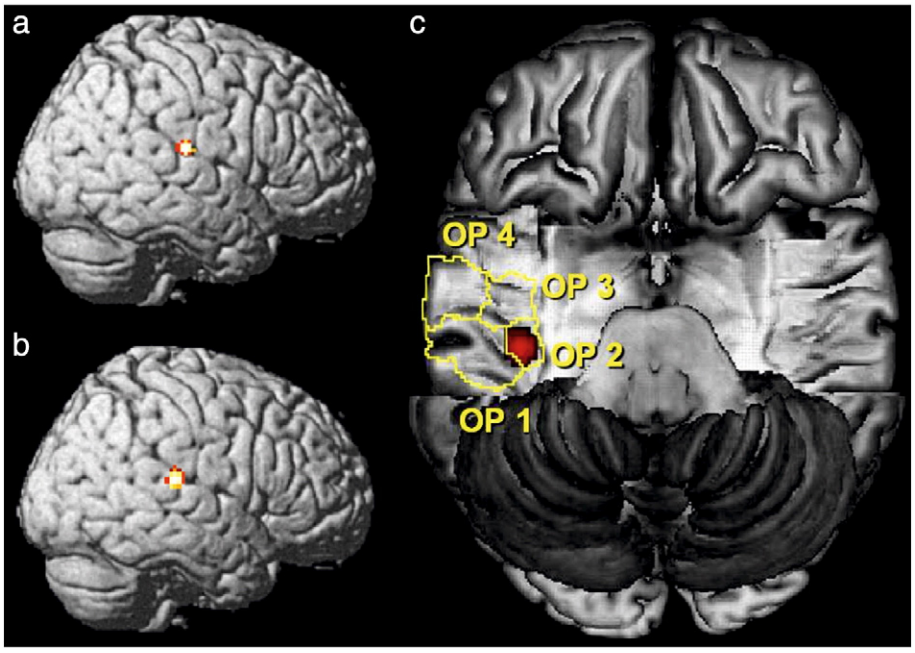

Fig. 3. a) Significant overlap between regions showing convergent activation following caloric and non-caloric stimulation (both thresholded at a cluster-level $p<0.05$) was found only in a single region on the right posterior parietal operculum. The result is shown as a projection onto the surface of the temporo-parietal cortex. b) Significant overlap between regions showing convergent activation following left and right unilateral cold caloric stimulation, respectively, (both thresholded at a cluster-level $p<0.05$) was also found only in a single region on the right posterior parietal operculum. c) Comparison of the region identified in both conjunction analyses with the cytoarchitectonic parcellation of the human parietal operculum in a caudo-cranial view. The most likely location of the human PIVC corresponds to histologically defined area OP 2 (85% volume overlap, probability at local maximum 70%).

differentiated the studies into the respective subtypes of stimulation (galvanic vs. caloric or otolith). After testing for significant convergence across these subtypes in a conjunction analysis, our results boiled down to the histologically defined area OP 2 in the right hemisphere as the key region for vestibular processing. We also found our only statistically significant result in the same region when testing for the different sides of stimulation (left vs. right). The area OP2 in the left hemisphere, on the other hand, only revealed itself in the results of the overall meta-analysis. It may therefore still represent the homologue to PIVC in the left hemisphere and be part of the general vestibular network, but it does not seem to assume the same predominant function as its contralateral right-hemispheric counterpart. For a detailed discussion of the potential roles and interpretations of the obtained activations in the premotor cortices and the midcingulate gyrus we refer to a recent review describing all the cortical vestibular areas in man in question (Lopez and Blanke, 2011). Furthermore we want to focus on our main findings in the parietal operculum and its connectivity.

The "primary" vestibular cortex in humans

The complex topography of human perisylvian cortex has always been challenging for non-invasive electrophysiology and functional neuroimaging (Ozcan et al., 2005). Moreover, discussions on the

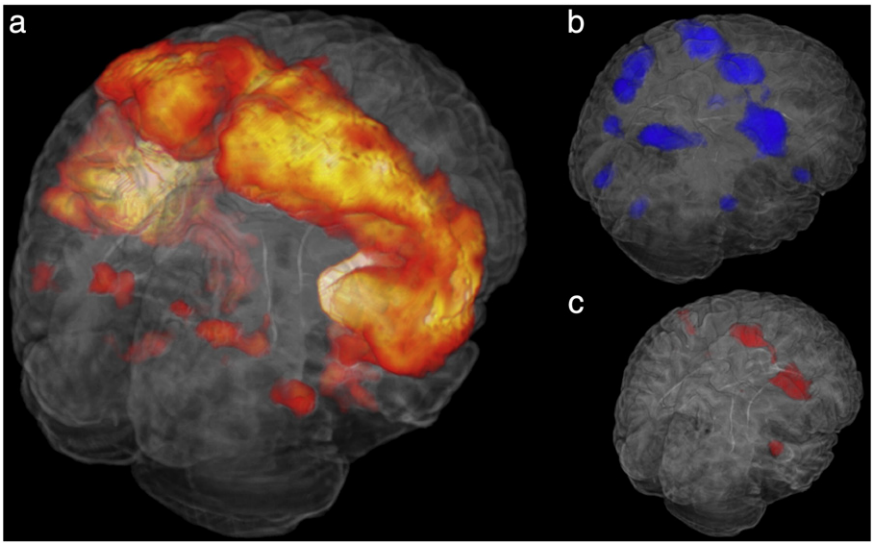

Fig. 4. a) Functional connectivity of the PIVC as indicated by significant (cluster-level $p<0.05$ corrected) correlation in resting state fMRI data. b) Significant convergence of activation reported in experiments that employed saccadic eye movements as retrieved through the *BrainMap* database. c) Conjunction between the functional connectivity of the PIVC and the meta-analysis on saccadic eye movements indicating regions that were significant in both analyses.

Table 2
Overview on the regions showing a significant convergence of coordinates reported in the *BrainMap* database for saccadic eye movement. Results of the *saccade* meta-analysis.

Macroanatomical location	Peak coordinates			Cytoarchitectonic allocation
	X	Y	Z	
Left dPMC/FEF	−40	−8	48	BA 6
Right dPMC/FEF	42	−6	48	BA 6
Medial premotor	0	2	52	BA 6
Left IPS / SPL	−34	−52	52	hIP3, PGa, 7PC
Right IPS / SPL	32	−48	52	hIP3, PGa, 7PC
Visual cortex	−12	−88	−6	BA 17 / BA 18
Visual cortex	−14	−80	36	hOC3A
Left Putamen	−20	8	6	
Right Putamen	20	2	8	
Cerebellum	8	−74	−20	Lobule VI

cortical representation of sensory stimulation in the parasylvian cortex were further complicated by longstanding inconsistent labeling of distinct areas in this region. For example, the same stereotactic coordinates are sometimes interpreted as parietal operculum or as insula (compare (Brooks et al., 2002; Chen et al., 2002)). Recent advances in the anatomical parcellation of human parasylvian cortex helped to avoid these ambiguities. The parietal operculum has been divided into four cytoarchitectonic fields (Eickhoff et al., 2006a,b): OP 1 and OP 2 are posterior, and OP 3 and OP 4 anterior. OP 1 and OP 4 each reach the convexity of the brain, whereas OP 2 and OP 3 join the insula at the circular sulcus. While it has been shown by analysis of somatotopic representations and connectivity (Eickhoff et al., 2007a, 2010), that OP 1 and OP 4 are the human homologues of primate somatosensory areas S2 and PV, and area OP 3 has been suggested to correspond to ill-characterized primate area VS, area OP 2 has no homologue in the somatosensory cortex of non-human primates. Our main results in OP 2 may be the human equivalent to a location first described as the retroinsular parietal cortex in rhesus monkeys by Pandya and Sanides (Pandya and Sanides, 1973) and later termed parieto-insular vestibular cortex (PIVC) by Grüsser and coworkers (Grusser et al., 1990). The proximity of OP 2 with SII parallels the findings for PIVC in monkeys (Liu et al., 2011). Since the area of OP 2 lies on the upper bank of the sylvian fissure within in centimeters of the temporo-parietal regions stimulated by Penfield and colleagues, one could speculate that OP2 may have been one of the effector regions in their seminal experiments in 1957. Penfield as well as a follow-up study by Kahane almost 50 years later were able to elicit vestibular sensations after direct electrical stimulation of the temporo-parietal cortex in man (Kahane et al., 2003; Penfield, 1957).

The role of the insula in cortical vestibular processing

It was long thought that the posterior insula might contain primary vestibular cortex (Dieterich and Brandt, 2001; Stephan et al., 2005). Vestibular stimuli seemed to activate the posterior insula, mostly ipsilaterally, and mostly in the right hemisphere (Dieterich et al., 2003). An electrical stimulation study in the insular cortex of 25 epilepsy patients on the other hand could not elicit a single vestibular response (Afif et al., 2011). Kahane and coworkers though were able to elicit distinctive vestibular sensations by means of direct electrical stimulation in epilepsy patients around the temporo-parietal junction in a previous experiment (Kahane et al., 2003). The examined areas were very much in congruence with and in the vicinity of our main result in the parietal operculum.

One of the reasons for the numerous localizations of vestibular responses within the dorsal insula or the retroinsular cortex instead of the parietal operculum aside from the seamless transition between the two neighboring anatomical areas may have been the high spatial uncertainty in early imaging studies (e.g. employment of large smoothing filters, signal source from large draining venules in the sylvian fissure at lower MRI field strengths or slice acquisition with coarse PET scanner resolutions at the time). This rendered the experiments unfit to differentiate between the posterior insula and the parietal operculum. We only found significant activations in the posterior and anterior insula within the selected studies using caloric irrigation as a vestibular stimulus. Caloric irrigation as a method of low frequency modulation of the horizontal semi-circular canal often leads to a strong thermal feeling and an unpleasant, even painful somatosensory stimulation of the exterior auditory canal with a possible vagal arousal as well. Subtraction of all possible coactivations can render it almost impossible to filter out the essence of a vestibular sensation. The insular responses reported in most vestibular studies with caloric stimuli therefore may often be contaminated with multisensory coactivations due to the methodological limitations and side effects of this kind of stimulus.

The exception to the rule could be one of the earliest and most elaborate experiments in the neuroimaging of vestibular responses after caloric irrigation by Friberg and colleagues. They applied the maximum subtraction approach to eliminate possible confounding activations as described above (Friberg et al., 1985). They took to warm water (44°Celsius) for caloric irrigation of the horizontal semi-circular canal to measure the consequential regional cerebral blood flow changes. In their analysis, they then subtracted several separate sessions: the resting state blood flow, possible auditory responses and a caloric irrigation at body temperature without vestibular sensations or nystagmus. Friberg labelled their single remaining activation in the depth of the superior temporal gyrus the vestibular cortex area (VCA). From the figures and drawings provided in the original publication, it may well have been a projection of OP 2 that they found. Unfortunately, no universally valid coordinates of the activations were supplied at the time. Their results though put into perspective the importance and necessity for a uniform cytoarchitectonic mapping and reporting of results in functional neuroimaging today.

Hemispheric dominance in the processing of vestibular sensations

No animal studies with a focus on the hemispheric dominance in vestibular processing have been published to date. In the current analysis, testing between unilateral stimulations resulted in a significant activation of area OP 2 in the parietal operculum of the right hemisphere. Takeda and coworkers had already proposed a prominent role in the perception of vertigo for the right parieto-temporal cortex as early as 1995 based on their SPECT results in two cerebrovascular patients. They hinted at the possible existence of a human vestibular cortex in this hemisphere in their work (Takeda et al., 1995). Studies carried out by Dieterich and Brandt then propagated a predominance for the cortical processing of vestibular signals in the non-dominant right hemisphere in humans (Dieterich et al., 2003). Most of their reported experiments substantiating and furthering this theory were done with a focus on the unambiguous handedness of their subjects as the decisive covariate. A dexter hemispheric preference for vestibular signal processing as a result of lateralization during evolution also seems plausible in light of a well-documented superiority for visuo-spatial tasks and navigation in the right cerebral cortex (Jager and Postma, 2003). Our primary finding of OP 2 in the right hemisphere as well as the additional results in the same region after testing for unilateral vestibular stimulation clearly support this hypothesis.

The connectivity and multisensory aspects of OP 2

The findings of our functional connectivity analysis confirmed the animal studies in Java and squirrel monkeys by Grüsser and colleagues. They found PIVC to be tightly connected with area 3aV, area 2v and 7 and a so-called visual temporal sylvian area (VTS)

(Grusser et al., 1990; Guldin and Grüsser, 1996; Guldin et al., 1992). The interconnection of the areas 2v, 3aV and PIVC were termed the *inner vestibular circle*. We could demonstrate right-sided OP 2 is strongly coupled with area 3a, all perisylvian regions as well as a location just anterior to MT/V5 which could very well correspond to the area VTS in monkeys. The results in functional connectivity therefore are analogous to the above-mentioned networks previously identified in primate research. In tracer studies, PIVC was the single cortical vestibular hub to receive afferent information from all other cortical areas involved in vestibular processing. This connection pattern also seems to be reproduced in our connectivity findings in humans. The latest neuron recordings in macaques after vestibular stimulation also point to PIVC as the first (chronologically) active cortical representation of vestibular signals (Chen et al., 2011). For the corresponding human area OP 2, there is no published data available for its effective connectivity.

Our functional connectivity analysis also revealed PIVC to be connected with convergent activations in area 6 from a separate meta-analysis on functional imaging studies about the cortical generation of saccadic eye movements. Studies in monkeys by Fukushima and colleagues have repeatedly demonstrated vestibular projections to the frontal eye field in the premotor cortex area 6 (Fukushima et al., 2006). This connection may serve as a cortical loop in the generation of the fast phase ocular motor response during a nystagmus. An activation of human FEF in cortical vestibular processing has also been shown, but its role still remains unclear.

With reference to the long held multisensory history of the vestibular cortex, it is interesting to note that the area found to be most active in our meta-analysis, OP 2, may exclusively process vestibular information and does not represent a multisensory area after all. Thus far, it has not been reported in any study beyond those employing vestibular stimuli. This result would be very much in accordance with the properties of the vast majority of PIVC neurons in macaques, which have just recently been shown to respond only to well-defined vestibular stimuli (translational and rotational) (Chen et al., 2010). Prior to this work, Guldin and Grüsser had reported PIVC neurons responding to optic flow and vestibular stimulation alike (Guldin and Grüsser, 1998). The non-finding of neuroimaging results in OP 2 outside of vestibular research thus far may certainly still be due to the short period of time since its cytoarchitectonical classification in humans. The inferior parietal lobule found in our ALE meta analysis and connectivity study may be the respective cortical multisensory integration area in question. As a potential homologue to monkey area 2v, it may be responsible for self-location (Ionta et al., 2011). But for the majority of our interpretations, we have to always bear in mind that all vestibular stimuli given in the functional neuroimaging experiments of this meta-analysis are artificial in nature and may never perfectly convey the pure vestibular component of a translation, tilt or rotation in isolation, i.e. without concomitant somatosensory activation.

Conclusion

In conclusion, we want to follow-up on the question most prominently posed by Guldin and Grüsser at the end of the 20th century: “Is there a vestibular cortex?” Our results strongly support the existence of such a distinct and unique vestibular cortex in humans with its possible core region in the area OP 2 of the parietal operculum as the homologue to monkey PIVC (Guldin and Grüsser, 1998). Independent separate testing of functional connectivity revealed all other retrieved vestibular regions of our meta-analysis to be strongly coupled with this core region OP 2. We also found further evidence for a predominant role of the right hemisphere in the cortical processing of vestibular afferents. The findings as a whole speak for a primary representation of vestibular signals in OP 2. At this point in neuroimaging research however, we cannot allocate a conclusive order or a hierarchy within the network for the other temporo-parietal, frontal and cingulate cortex areas also involved in the human processing of vestibular information (e.g. secondary or supplementary). Future studies explicitly testing for functional and effective connectivity will have to probe this question in man.

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