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Complete List of Authors:	Smith, Andy; Royal Holloway, University of London, Psychology Wall, Matthew B; Royal Holloway University of London, Psychology Thilo, Kai V; Royal Holloway University of London, Psychology
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Vestibular inputs to human motion-sensitive visual cortex

Andrew T Smith, Matthew B Wall* and Kai V Thilo

Department of Psychology, Royal Holloway, University of London, Egham, Surrey TW20 0EX, UK

*Current address of MBW:

Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square House, Queen Square, London WC1N 3BG, UK

Corresponding author:

Andy Smith
email: a.t.smith@rhul.ac.uk
FAX +44 1784 434347

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ABSTRACT

Two crucial sources of information available to an organism when moving through an environment are visual and vestibular stimuli. Macaque cortical area MSTd processes visual motion, including cues to self-motion arising from optic flow, and also receives information about self-motion from the vestibular system. In humans, whether MST (hMST) receives vestibular afferents is unknown. We have combined two techniques, galvanic vestibular stimulation (GVS) and functional MRI, to show that hMST is strongly activated by vestibular stimulation in darkness, whereas adjacent area MT is unaffected. The activity cannot be explained in terms of somatosensory stimulation at the electrode site. Vestibular input appears to be confined to the anterior portion of hMST, suggesting that hMST as conventionally defined may contain two sub-regions. Vestibular activity was also seen in another area previously implicated in processing visual cues to self-motion, namely CSv, but not in V6. The results suggest that cross-modal convergence of cues to self-motion occurs in both hMST and CSv.

INTRODUCTION

In both human and non-human primates, a major cortical brain center for processing image motion is the MT complex. In macaque MSTd, a sub-region of this complex, most neurons are strongly responsive to visual motion and many are tuned for specific patterns of retinal motion associated with movement of the head through a static world (Tanaka and Saito, 1989; Duffy and Wurtz, 1991). MSTd cells that are responsive to expansion are often sensitive to the location of the center of expansion (Duffy and Wurtz, 1995; Page and Duffy, 1999). This suggests that they encode direction of heading during self-motion, an idea supported by the demonstration that micro-stimulation in MSTd can influence heading judgements (Britten and van Wezel, 1998).

Many macaque MSTd neurons also respond to vestibular stimulation arising from actual forward motion (Bremmer et al., 1999; Gu et al., 2006; Fetsch et al., 2007) and there is evidence that these signals feed into heading perception (Gu et al., 2007; Gu et al., 2008). In some cases MSTd neurons show the same tuning for direction of motion in both modalities, suggesting multisensory co-operation in encoding heading. Other cells show opposite tuning, suggesting antagonism. Similarly, many MSTd neurons respond to visual rotation of the type generated during roll movements, and these often respond also to real roll in darkness. Here, antagonism is the norm (Takahashi et al., 2007). In contrast, area MT appears not to receive vestibular afferents (Chowdhury et al., 2009). Such results have led to speculation (e.g. Fetsch et al., 2009) that MSTd may be a primary locus for visual/vestibular integration.

The ventral intraparietal area, VIP (Colby et al, 1993) is also strongly implicated. Macaque VIP neurons are sensitive to visual heading direction and a wide range of headings are covered by the neural population (Bremmer et al., 2002b), Indeed, VIP and MSTd have similar selectivity for optic flow and similar resilience to pursuit eye movements (Zhang and Britten, 2010; Maciokus and Britten, 2010). Macaque VIP also receives vestibular afferents (Klam and Graf, 2003) and, as in MSTd, these may be congruent or incongruent. Thus VIP constitutes another strong candidate for encoding self-motion. However, the existence of motion-sensitive somatosensory

inputs, sometimes matched in head-centered space to visual receptive fields, has led to the suggestion (Colby et al, 1993) that VIP may be specialized for detecting approaching objects in near space.

Human MT and MST (hMT and hMST) have been identified with fMRI, as have several other areas that may also be involved in processing egomotion. These include VIP, CSv and V6. Human VIP (Bremmer et al., 2001), located in the anterior intraparietal sulcus, is polysensory, has many properties in common with macaque VIP and is a self-motion candidate for the same reasons. It is known to process somatosensory and auditory stimuli but whether it receives vestibular afferents, as might be expected based on macaque VIP, is unknown. CSv is located in the cingulate sulcus and has strong sensitivity to optic flow patterns that are consistent with self-motion, while coherent motion that is incompatible with self-motion elicits almost no response (Wall and Smith, 2008). This property is also apparent in human VIP, but the difference is much less marked. Human V6 is located in the dorsal part of the parieto-occipital sulcus, is strongly sensitive to optic flow (Pitzalis et al., 2010) and again shows differential sensitivity to optic flow that could have arisen from self-motion (Cardin and Smith, 2010). It has much in common with macaque V6 (Galletti et al., 1991), from which it takes its name.

Whether any of these areas of the human brain are responsive to vestibular stimuli is unknown. Natural vestibular stimulation is not possible during fMRI but vestibular sensations can be induced artificially with caloric stimulation, in which one ear canal is irrigated with warm or cold water, or galvanic vestibular stimulation (GVS) in which a controlled electric current is passed between two electrodes attached to the mastoid processes. It is known from fMRI studies with GVS (Bucher et al., 1998; Lobel et al., 1998; Bense et al., 2001; Stephan et al., 2005) and caloric stimulation (Suzuki et al., 2001; Fasold et al., 2002) that several cortical regions including the parieto-insular vestibular cortex (PIVC) are consistently active during the resulting sensations of movement or tilt. Two reports (Bense et al., 2001; Fasold et al., 2002) show vestibular activation in the hMT complex, but neither attempted to distinguish hMT from hMST. Moreover, the other studies cited above do not list the MT complex among areas active during vestibular stimulation, leaving considerable uncertainty concerning the vestibular status of the human MT complex. Here we use

fMRI in combination with GVS to quantify vestibular sensitivity in several human cortical visual areas, including MT and MST, V6, CSv and VIP, that were independently defined with visual localizers.

MATERIALS AND METHODS

Participants

Nine healthy volunteers (4 male, 5 female; mean age 30 years) participated. All had normal or corrected-to-normal vision and were screened according to standard MRI exclusion criteria. Written informed consent was obtained. All participants took part in Experiment 1; subsets later took part in Experiments 2 and 3.

Data Acquisition

MRI images were obtained with a 3-Tesla Siemens Magnetom Trio scanner and either a standard Siemens 8-channel array head coil (Experiments 1 and 2 and anatomical scans) or a custom 8-channel posterior-head array coil (Stark Contrast, Erlangen, Germany) that gives improved SNR in occipital cortex at the expense of anterior regions (Experiment 3). For each participant, a high-resolution T1-weighted 3D anatomical image was acquired (modified driven-equilibrium Fourier transform, MDEFT (Deichmann et al., 2004), 176 axial slices, in-plane resolution 256 x 256, 1 mm isotropic voxels, TR = 7.92 ms, TE = 2.45 ms, flip angle = 16, bandwidth = 195 Hz/pixel). MDEFT was chosen in place of standard 3D anatomical sequences because of its improved contrast between grey matter and white matter, which is beneficial for segmentation and flattening. This anatomical image was used as a reference to which all the functional images from all experiments were co-registered. The functional data were acquired with a gradient echo, echoplanar sequence (Experiments 1 and 2: TR = 3000ms, 42 contiguous axial slices covering the cerebral cortex, interleaved acquisition order, 3 mm isotropic voxels, FoV 192x192 mm, flip angle = 90°, TE = 31 ms, bandwidth = 1396 Hz/pixel; Experiment 3: TR = 1500ms, 14 axial slices including the MT complex and surrounding cortex, interleaved acquisition order, 2 mm isotropic voxels, FoV 128x128 mm with phase over-

sampling, flip angle = 75°, TE = 45 ms, bandwidth = 1396 Hz/pixel). Each scan consisted of 203 (Experiments 1 and 2) or 406 (Experiment 3) acquisition volumes and lasted 10 minutes 9 seconds.

Stimuli and design

Vestibular stimuli were generated by a specialist current-limited stimulator (Digitimer, UK; model DS5), located outside the scan room, under computer control. The output of this device is fully isolated to prevent dangerous electric shock. Two gold electrodes (diameter 1cm) were attached to the skin, one over each mastoid process, and filled with conducting jelly. These were connected to the stimulator with a screened low-voltage cable that passed out of the MRI examination room through a waveguide. Radio frequency (RF) filters were used to prevent RF interference in the MR images. The system was tested to ensure that there was no significant heating of the electrodes from RF energy emitted by the scanner.

All experiments employed an event-related design. Each vestibular event lasted for 2s and consisted of two cycles of a low-frequency (1 Hz) sinusoidal AC current passed between the two mastoid electrodes (see Figure 1a). The current had a mean of 0mA and an amplitude that varied across experiments and conditions but never exceeded ±3mA. It was presented in sine phase to avoid sharp transients at onset and offset. This typically gave rise to a sensation of sinusoidal roll, each cycle being experienced as the head (and sometimes body) tilting a few degrees first to one side then the other. Some participants experienced motion that also had a yaw component but all experienced roll. Stimulation events were separated by inter-trial intervals (ITI) that varied between 2 sec and 10 sec with a Poisson probability distribution (mean 5.5 sec) arranged in a pseudo-random sequence. Each scan run contained 80 events.

The vestibular sensation was accompanied by a tactile sensation at the electrode site. Such effects have also been noted by others (Lobel et al., 1998; Stephan et al., 2005). Tactile sensation is experienced mainly at the cathode so alternating current caused the sensation to be felt alternately at the right and left electrode. In Experiment 2, control stimuli were used in which the same 2s stimulus current was passed between

the mastoid and an additional electrode on the ipsilateral earlobe. The tactile sensation of the main experiment was created, without any vestibular sensation, by stimulating each side in turn with a half-wave-rectified sinusoid (see Figure 1b).

The experiments were conducted in total darkness. All light was excluded from the scan room and, as an additional precaution, participants were asked to close their eyes. This ensured that any activity seen in visual cortical areas during vestibular stimulation was not related to visual stimulation. There was no task; although a task is generally desirable to control attention and hence reduce BOLD variability, we wished to avoid stimuli that might cause confounds and it is difficult to introduce a task without introducing visual or auditory stimuli. Participants were asked to confirm at the end of the scan that they experienced a vestibular sensation but no subjective estimates of its magnitude were obtained.

Three experiments and several localiser scans were conducted:

Localisers for MT and MST

In either the same or a separate scan from the main experiments, hMST was identified in all hemispheres on the basis of the presence of ipsilateral visual activity, which is essentially absent in hMT (Dukelow et al., 2001; Huk et al., 2002; Smith et al., 2006). Standard methods were used to allow comparability with previous studies. Visual stimuli were presented via an LCD projector, back-projected onto a screen mounted into the rear of the scanner bore, and viewed through a mirror mounted on the head coil. Pairs of 4-min scans were acquired employing a block design in which dot motion (optic flow, alternately expanding and contracting) was presented for 15s, followed by static dots for 15s. The stimulus had a diameter of 15 deg and was presented at an eccentricity of 17.5 deg, to the right of fixation in one scan and to the left in the other. At least two such pairs of scans were acquired for each participant and the results averaged.

Localisers for VIP, CSv and V6

To localise visual areas VIP, CSv and V6 as defined in our previous work (Wall and Smith, 2008; Cardin and Smith, 2010), at least two further 4-min scans were conducted in which a large (approximately 20 deg.), centrally fixated, time-varying

optic flow field was presented, alternated with a 3x3 array of 9 flow patches, in a block design with 15s blocks. A statistical contrast was used to find voxels that were significantly more active in response to one flow patch than nine. Within the resulting map, clusters were sought at the expected locations for the three areas.

*Experiment 1: low-resolution whole-head sca*n

An initial experiment was performed to examine whether vestibular inputs to hMT+ exist and, more broadly, to identify the range of cortical regions that are activated by GVS. In this experiment, 42 axial slices were used to cover most of the brain and images were acquired with a standard headcoil to give even coverage. Each scan lasted for 10 min (80 events) and two scans were conducted with a short rest break between scans, giving a total of 160 vestibular events.

Experiment 2: control for somatosensory responses

In this experiment, the procedure was similar to Experiment 1 but one scan run employed tactile stimulation only (see Fig 1b), simulating the tactile sensation of the GVS stimuli without vestibular sensation. All participants confirmed that the tactile control procedure was effective. However, although it provided a fair match in terms of qualitative sensation, we found that the relationship between stimulation current and subjective intensity was different. Subjective intensity was greater, for a given current, in the somatosensory control condition, perhaps because the two electrodes were closer. Because it is difficult to know whether the control should be matched to GVS in subjective terms or in terms of current, we did both. The tactile control run was conducted at a stimulation level judged by the participant to be strong but not unpleasant. To permit a direct comparison to be made under identical circumstances, two additional scan runs were conducted employing vestibular stimulation similar to that in Experiment 1. One such GVS run was conducted with the same current and another with a matched tactile sensation as reported by the participant. The order of the three scans was randomised. Four of the original 9 participants took part. These were selected for strong vestibular activity in Experiment 1, minimal head motion and willingness to undertake a longer experiment. All scans were again conducted in darkness and the acquisition protocol was similar to Experiment 1.

Experiment 3: high-resolution occipital scan

Following identification of vestibular activity in hMT+ in Experiment 1 (see Results), further scans were conducted aimed at identifying the precise location of this activity within hMT+. Five of the original participants took part. To increase precision, smaller voxels were used (2mm isotropic). To compensate for the consequent reduction in signal-to-noise (SNR), several manipulations were applied. Firstly, a custom array coil was used for image acquisition. This gives an SNR improvement of about 3X on the occipital cortical surface, at the expense of sensitivity in deeper and more anterior locations. Secondly, the TR was reduced to 1.5s (and the acquisition volume reduced accordingly) to increase sampling frequency. 14 axial slices covering hMT+ were used. Thirdly, each participant was scanned twice on different days and the results averaged. In each session, three 10-min scans were performed, giving 6 in total. All involved GVS and were conducted in darkness. The GVS stimulus protocol was the same as in Experiments 1 and 2.

Precise localization of vestibular activity is only useful in relation to similarly precise, well-registered localization of MT and MST. To ensure accuracy, we conducted MST localisers (method as in Experiment 1) in the same scan sessions as the GVS scans, once at the beginning of the scan and once at the end, i.e. before and after the GVS scans, giving 4 repetitions in total (2 on each day). The averaged results across all 4 pairs of localiser scans were used to define the MT and MST regions of interest (ROI). This procedure (i) ensured that any errors of co-registration across days (due, for example, to slightly different EPI distortion) affected visual and vestibular localizers equally and (ii) gave us a check on the reliability of visual localizers across scans.

Data Analysis

All pre-processing and analyses were performed with BrainVoyager QX (version 1.9; Brain Innovation, Inc, The Netherlands). Functional data were pre-processed to correct for head-motion and slice-timing, and filtered with a temporal high-pass filter of 0.014Hz. The data from each participant were analysed separately. Time-series were analysed by fitting a regressor formed by convolving the event time-course with a standard haemodynamic response function (HRF). Six regressors taken from the head-motion correction were also included as regressors of no interest. No spatial

smoothing was applied. Correction for the effects of serial autocorrelations (which we regard as essential in single-subject analyses – see Smith et al., 2007) was applied using the AR(1) method. The analyses used were a hypothesis-driven combination of whole-brain contrasts and more focussed ROI-based analyses using the pre-defined visual areas. Activation was displayed as an overlay on a segmented and inflated or flattened representation of each hemisphere based on the MDEFT anatomical scan. Activation maps were thresholded at $p < 0.001$ (uncorrected), which is conventional for single-subject analyses.

RESULTS

Experiment 1: low-resolution whole-head scan

Considering first the activation maps for each subject, vestibular responses were observed in several cortical areas. All regions of activation are shown for a typical participant in Figure 2B. In most hemispheres, activity was seen in the parieto-insular vestibular cortex (PIVC) and in some, putative vestibular areas 2v and/or 3aNv were also active. These results are consistent with a vestibular origin and are in line with previous reports (Bucher et al., 1998; Lobel et al., 1998; Bense et al., 2001; Stephan et al., 2005; Eickhoff et al., 2006). Also evident on the medial surface is activity in the supplementary motor area (SMA), which has also previously been noted (e.g. Stephan et al, 2005). These areas are not discussed further here.

In addition, three other active regions were commonly observed. First, activity was observed in MT+. This region, normally thought of as a visual motion complex, has been documented in many previous fMRI studies (e.g. Tootell et al., 1995; Sunaert et al., 1999; Huk et al., 2001; Goossens et al., 2006).

Second, in a rather more anterior location, between MT+ and PIVC, in or near the superior temporal sulcus (STS), an active region was commonly identified at a location that has been identified in connection with visual and auditory processing (Beauchamp et al., 2004b; Beauchamp et al., 2004a; van Atteveldt et al., 2007) and is also responsive to touch (Beauchamp et al., 2008). It may be homologous with the

macaque superior temporal polysensory area (STP) but we refer to it here as STSms, after Beauchamp et al. (2004a).

The third active region is in the cingulate sulcus. Several previous reports (Cornette et al., 1998; Braddick et al., 2001; Antal et al., 2008; Wall and Smith, 2008) show an isolated patch of visual activity at the location shown in Fig. 2 and we refer to this region as area CSv, after Wall and Smith (2008). The location of the GVS activation corresponded closely with the location of CSv as defined by the visual localiser, confirming that it is the same functional region. The mean Talairach coordinates for the GVS cluster were -8 -26 42 (left) and 11 -28 42 (right) and for visually defined CSv were -10 -26 39 (left) and 11 -27 40 (right). Unlike MST or STSms, area CSv showed strongly ($p<0.05$ FDR corrected) in a random effects group analysis (see supplementary material). Although the sample size (n=9) is too small to expect all active areas to emerge in such an analysis, the appearance of CSv may suggest either that vestibular activity is particularly strong in CSv, or that its location is particularly consistent across individuals. CSv was the only visual area to show in this analysis. the only two other active regions being vestibular areas PIVC and 3aNv.

Occasionally, activity was seen at a location consistent with putative VIP (Bremmer et al., 2001) in the fundus of the anterior portion of the intraparietal sulcus (not evident in the case shown in Fig. 2b). In macaques, VIP is responsive to both visual and vestibular activity (Bremmer et al., 2002b) and so vestibular activity might be expected in our experiments. Surprisingly, perhaps, vestibular activity occurred only weakly in this region. GVS-related activity has been noted previously in the vicinity of the IPS (Bense et al., 2001; Stephan et al., 2002) but was described as in inferior parietal cortex and may or may not reflect the same functional region. Similarly, there are several visual regions in this vicinity (Orban et al., 2006; Hagler et al., 2007; Silver et al., 2007; Swisher et al., 2007) and it is not clear which, if any, was active in our study.

Vestibular activity was not seen in the final visual area examined: V6, in the parieto-occipital sulcus (POS). Human V6 is a visual area that has been described by Pitzalis et al. (2006) and is thought to be homologous with macaque V6. It has recently been shown to be sensitive to optic flow structure (Pitzalis et al., 2010; Cardin and Smith,

2010) and could therefore be a candidate for vestibular input. However, we did not see consistent vestibular activity at this location.

Activity related to GVS was quantified in each of the visual areas that were defined with an independent localizer. MT+ was divided into two components, MT and MST based on separate localiser scans (see Methods). Figure 3 shows the results. Significant activity is present in MST in total darkness ($t(17) = 2.74$, $p < 0.02$), whereas activity in MT is absent. Inspection of the inflated brains showed that in many cases, activity within MST appeared to be confined to the anterior portion of MST. We return to this observation in Experiment 3. Like MT, activity in V6 was not significantly different from zero. In VIP, weak activity is evident (marginally significant: $t(17) = 2.05$, $p = 0.056$). By far the strongest activity among the visual areas localized independently is seen in CSv ($t(17) = 8.23$, $p < 0.001$). The right-hand panel of Figure 3 shows the activity obtained in STSms. This is substantial and statistically significant ($t(15) = 8.09$, $p < 0.001$). STSms is shown separately because it was not defined with an independent localiser. It was evident in some hemispheres with the visual localizers but did not appear sufficiently reliably to permit definition of the region in this way across participants. Instead it was defined on the basis of the GVS-related activity itself: a cluster was identified in posterior STS within the activation map obtained from the contrast between GVS events and baseline. Consequently the magnitude of activity may be over-estimated relative to the other cortical areas in the figure. For comparison, GVS-related activity in MST defined in the same way is shown alongside that for STSms, based on 14 hemispheres, the remaining 4 having no detectable activity in the vicinity at standard thresholds. This activity estimate is much larger than the MST estimate in the left panel. The difference may partly reflect bias from the use of a non-independent localizer, but likely arises mainly from the fact that the posterior part of MST is typically not active during GVS, so that the independent MST ROI includes tissue that is not responsive during GVS as well as a sub-region that is.

In summary, the results of Experiment 1 suggest that human MST, CSv, STSms and possibly VIP receive vestibular input but that MT and V6 probably do not.

Experiment 2: control for somatosensory responses

The galvanic stimulation used in Experiment 1 always caused noticeable skin sensations at the electrode site. It is therefore possible that some of the cortical activations seen in Experiments 1 reflect somatosensory responses rather than vestibular responses. We conducted another experiment to test this possibility by generating the tactile sensation without the vestibular sensation (see Materials and Methods). A 10-min scan run was conducted at a stimulation level judged by the participant to be strong but not unpleasant. One GVS run was conducted with the same current and another with a matched sensation as reported by the participant.

The results are shown in Figure 4. On the left are results for the three areas identified in Experiment 1 that were defined by independent localizers and showed vestibular activity in darkness, namely MST, VIP and CSv. The ROIs used for the analysis were the same as in Experiment 1. In area MST, significant activity is seen in the GVS conditions relative to the control condition, whether matched in terms of subjective sensation ($t(7) = 4.27$, $p < 0.005$) or stimulation current ($t(7) = 6.43$, $p < 0.001$). MST appears to be sensitive to the stimulation strength, being weaker in the "matched current" condition (although still highly significantly different from the control condition), where the current is typically somewhat lower. In the control condition there is no activity (if anything there is suppression, but this is non-significant), suggesting that there is no significant somatosensory response to GVS in MST and that the activity seen here and in Experiment 1 can be attributed to vestibular input to MST. Area VIP shows a different pattern of results. As in Experiment 1, activity is weaker in VIP than MST, and in this instance (with a smaller sample than in Experiment 1) is not significantly different from the control conditions ($p > 0.1$ in both cases). Unlike MST, it shows no sign of dependence on the matching procedure. The response in the control condition is around 50% of the GVS response, suggesting that both vestibular and somatosensory responses may contribute to the GVS response in VIP, but in view of the lack of statistical significance, this is uncertain. Finally, area CSv also shows no dependence on the matching procedure and also shows some response in the control condition. However, in this case, the GVS response is clearly much larger (and significantly different from control; $t(7) = 2.41$, $p < 0.05$ for the subjectively matched condition

and $t(7) = 4.26$, $p < 0.005$ for the current matched condition), suggesting that it primarily reflects vestibular activity.

On the right-hand side of Figure 4, corresponding results are shown for two areas (STSms and PIVC) which were not independently defined in terms of their visual responses. Here, the ROI consists of the cluster of activity obtained with GVS in Experiment 1. In STSms, the pattern of results appears quite similar to MST, with no significant control response, suggesting predominantly vestibular activity. PIVC is not of particular interest here but is shown for comparison. It has a large vestibular response that is current-dependent and also gives a response in the control condition, suggesting somatosensory as well as vestibular input.

It is noteworthy that varying the GVS stimulation current does not affect all areas equally. MST, PIVC and STSms show clear increases in activation with a higher current, mirroring the increased subjective sensation, but VIP and CSv do not. The reason for this is unclear but it suggests that activity in VIP and CSv may be less closely related to subjective vestibular sensation.

Experiment 3: high-resolution occipital scan

Several of the activity maps obtained in Experiment 1 suggested that GVS activity in MST is confined to the anterior portion of MST, which would indicate that human MST has at least two subdivisions, only one of which receives vestibular input. The purpose of Experiment 3 was to investigate this further and with greater anatomical precision.

Figure 5 shows patches of flattened grey matter covering MT+ from all 10 hemispheres, with vestibular activity superimposed as a color overlay. The boundaries of MT and MST are also shown, in green and pink respectively. These are based on the high-resolution localisers obtained as part of Experiment 3 and may differ subtly from those obtained with 3mm voxels used for analysis in Experiments 1 and 2. All ten hemispheres showed at least some statistically significant vestibular activity in MST, although in some cases it was minimal. There was considerable variability in the extent of activity but in all cases, activity was largely confined to

the anterior portion of MST. This suggests that vestibular afferents do not exist throughout hMST but only in an anterior sub-region. Several hemispheres also show vestibular activity in nearby STSms. In about half of cases this activity is more extensive than that in MST. One subject (S2) shows strong asymmetry of MST results between hemispheres but the others show good symmetry and there is no reason to conclude that there are any reliable hemispheric differences.

Mean activations for MT and MST, based on the independent visual localiser, are shown in Figure 6. They are in line with those of the two previous experiments and they confirm that vestibular activity is present in MST but not in MT.

In summary, Experiment 3 confirms the presence of vestibular activity in MST and STSms and it suggests that the activity in MST is confined to the anterior portion of MST.

DISCUSSION

The results show that at least two cortical areas previously implicated in processing visual self-motion information (hMST and CSv) are also activated by vestibular stimuli. They also suggest that the same may be true of VIP. The results also show that a region thought to correspond to STSms, an area known to have polysensory inputs including vision but not strongly associated with self-motion, has vestibular afferents. Finally, selective vestibular activity in the MT complex is confined to the anterior portion of hMST, which may represent a new functional subdivision of the MT complex.

Visual area V6, which has recently been shown to be strongly sensitive to visual cues to egomotion, does not appear to have vestibular inputs. However a lack of activity during GVS does not necessarily indicate that a particular region is uninfluenced by vestibular stimuli. First, vestibular signals are widely integrated with signals from other sense systems, particularly the visual system. There may be brain regions in which vestibular signals act as a modulator of visual signals and do not generate excitation in darkness. Second, the rotational perceptual response to GVS probably

reflects induced neural activity that is interpreted mainly as originating in the semicircular canals. Translational egomotion sensitivity is associated more with otolithic activity. Opposite otolithic signals are expected largely to cancel during GVS (Fitzpatrick and Day, 2004) and indeed, GVS does not induce sensations of translation. There may be cortical regions that are concerned purely with translational egomotion and are little affected by GVS despite receiving otolithic signals. Third, of course, the vestibular sensation induced by GVS is relatively weak and it may be that some brain regions are not stimulated strongly enough to permit detection in a noisy system.

In the following sections, the results are discussed for each visual area in which vestibular activity was found.

Vestibular activity in hMST

We have shown clearly that hMST responds to vestibular stimulation as well as to visual motion stimuli. We have ruled out (Experiment 2) an explanation in terms of somatosensory activation. Another possibility to be considered is that the response might relate to eye movement signals of vestibular origin. During head motion, compensatory eye movements often occur that are driven by vestibular signals (the vestibulo-ocular reflex, VOR). It is known that such eye movements can occur during GVS (Courjon et al., 1987; Zink et al., 1998) as well as during natural vestibular stimulation. Macaque MSTd is known to have neurons that are active during smooth pursuit (Newsome and Wurtz, 1988) and appears to use pursuit signals to compensate for eye movements when encoding direction of heading (Komatsu and Wurtz, 1988; Page and Duffy, 1999). Is it possible that MSTd, and hMST, also receive information about eye movements associated with VOR? If so, our hMST activity might reflect this signal. The distinction may be a fine one, because any such VOR signal would have a vestibular origin and would be highly correlated with the vestibular information that drives it; it is nonetheless a meaningful one. We know of no evidence for the presence of a VOR-related signal in macaque MSTd. VOR involves reflexive eye movements and has a different origin from smooth pursuit, which is voluntary. Although it cannot be ruled out, it should not be assumed that VOR involves MSTd simply because pursuit does. Also VOR

eye movements elicited by GVS stimuli of the kind we used are very small (2-3 deg of torsion at 3mA; Zink et al., 1998). Pending further evidence, we therefore favour the interpretation that our hMST response reflects the vestibular information itself rather than the reflexive eye movements it generates.

Within MST, the tissue that shows vestibular activity is consistently confined to the anterior portion of hMST (Figure 5), suggesting that hMST has at least two sub-regions. The vestibular region does not share a border with hMT, but is separated from it by a more posterior zone, still within hMST, that can readily be activated by both contralateral and ipsilateral visual motion stimuli but not by galvanic vestibular stimulation. We refer here to the two sub-regions as hMSTa and hMSTp (anterior and posterior). One previous human fMRI study (Dukelow et al., 2001) has claimed the existence of sub-regions within hMST.

In macaque, the portion of MST that receives vestibular input is the dorsal portion, MSTd (Bremmer et al., 1999; Gu et al., 2006; Fetsch et al., 2007). If hMSTa corresponds directly to one sub-region of macaque MST (which cannot be assumed), then this is expected to be MSTd. Macaque MSTd is located in the anterior/dorsal bank of the superior temporal sulcus (STS). Traditionally, it is regarded as extending into the fundus of STS and having a border with MT, which is located in the posterior bank (Desimone and Ungerleider, 1986; Komatsu and Wurtz, 1988; Tanaka et al., 1993). Thus, if our vestibular area hMSTa corresponded to MSTd then it would be expected to abut hMT, which it does not. However, the definition of macaque MSTd and other MST sub-regions (MSTl/MSTv) has always varied somewhat among studies. Moreover, recent macaque fMRI studies (Nelissen et al., 2006; Kolster et al 2009) show MSTd confined to the anterior bank of STS and non-adjacent to MT. On this view, our hMSTa might correspond to MSTd proper and hMSTp to a distinct intermediate region. This interpretation, which assumes that there are no species differences, is strengthened by the fact that a recent human fMRI study (Kolster et al 2010) identifies strong similarities of organisation between human and macaque in the vicinity of MT when both species are examined with fMRI.

It may be that attempts to map human MT+ areas onto the macaque MT complex are misguided and that such parallels cannot be made because of species differences (see Orban et al., 2004 for a discussion). In macaque, there is no evidence for a vestibular-free portion of MST adjacent to MT: even the fundus of the STS (the portion of MST immediately adjacent to MT) contains neurons with vestibular sensitivity (Gu and Angelaki, personal communication). Thus, the overall organization of the human MT complex, and how closely it resembles other primates, remains unclear.

Area STSms

We observed strong vestibular activity in a region of the superior temporal sulcus that we refer to as STSms, after Beauchamp et al. (2004a). Vestibular activity tended to be stronger here than in MSTd, although this was somewhat variable from subject to subject. In many cases, visual responses were observed in STSms during localiser scans; these occurred in response to ipsilateral as well as contralateral motion stimuli but on average they appeared weaker than the vestibular responses elicited in the same area and were more often absent (undetectable). Our impression is that whereas hMST is readily activated by visual stimuli and more weakly so by vestibular stimuli, the reverse is true in STSms.

There seems little doubt that our STSms is the same as that reported previously (Beauchamp et al., 2004b; Beauchamp et al., 2004a; van Atteveldt et al., 2007; Beauchamp et al., 2008). Previous fMRI studies show that STSms responds to visual, auditory and somatosensory stimuli. To this list, we add vestibular stimuli. STSms may be homologous with the macaque superior temporal polysensory area (STP). Certainly there are striking similarities. One is their location on the grey-matter sheet, more anterior than MSTd and separated from it by a seemingly unresponsive region. Macaque STP neurons have very large visual receptive fields that commonly include ipsilateral space and many neurons are polysensory (Bruce et al., 1981). Some cells respond to specific types of global motion including full-field motion consistent with egomotion (Bruce et al., 1981; Hietanen and Perrett, 1997; Anderson and Siegel, 1999). STP has connections with MST (Boussaoud et al., 1990) and so MST may be the origin of its visual and/or vestibular afferents. Like MST, STP may

have subdivisions (Hikosaka et al., 1988; Cusick et al., 1995). Macaque STP has also been identified with fMRI (Nelissen et al., 2006) and this method confirms that it has similar response characteristics to MSTd. Thus, the human superior temporal sulcus contains an area that may be homologous with STP, is certainly polysensory, responds to vestibular stimuli and has much in common with hMSTa in terms of response properties.

Area VIP

Vestibular activity in the intraparietal sulcus was surprisingly elusive, given strong evidence for (i) vestibular input to macaque VIP (Bremmer et al., 2002b; Klam and Graf, 2003) and (ii) visual sensitivity to egomotion-related optic flow in both macaque and human VIP (Bremmer et al., 2001; Bremmer et al., 2002a; Wall and Smith, 2008). Commonly, vestibular activity was not statistically detectable in a standard voxel-wise analysis. It narrowly fails to reach significance when GVS-related activity was averaged across voxels in an independently defined VIP region of interest (see Fig 3). The label 'VIP' originates in the macaque literature and is used here loosely because, since the original demonstration of polysensory activity in the region of the human IPS referred to as VIP by Bremmer et al. (2001), it has become clear that there are multiple visual areas in the vicinity (Orban et al., 2006; Hagler et al., 2007; Silver et al., 2007; Swisher et al., 2007) and it is not known which, if any, corresponds to macaque VIP. Nonetheless, its location suggests that our VIP is the same as that of Bremmer et al. (2001), which is known to respond to visual, auditory and somatosensory stimuli. Our data raise the possibility that vestibular stimuli can be added to this list, but they do not show clearly that this is the case. As with V6, it should be noted that weak or absent vestibular responses in VIP do not necessarily indicate that VIP does not receive vestibular input. All in all, the vestibular status of human VIP remains uncertain.

Area CSv

The area in the cingulate sulcus that we term CSv shows strong and reliable vestibular activity. This is consistent with the hypothesis (Wall and Smith, 2008; Cardin and Smith, 2010) that CSv is closely involved in encoding egomotion. This

hypothesis is based on evidence that CSv is strongly responsive to coherent optic flow that is consistent with egomotion but unresponsive to an array of similar coherent optic flow patches. There are several other references to visual motion sensitivity in this vicinity (Cornette et al., 1998; Braddick et al., 2001; Antal et al., 2008). Antal et al. (2008) have shown that responses to coherent flow are stronger than to motion noise and that sensitivity to rotation is greater than for translation. Other than this, little further is known about CSv. Whatever its function and its relation to hMST, STSms and VIP, we show clearly that it receives vestibular input. Several previous studies have reported activity in nearby parts of the cingulate sulcus and cingulate gyrus following caloric vestibular stimulation (Suzuki et al., 2001; Fasold et al., 2002) and GVS (Stephan et al., 2005). It is likely, though not certain, that the location of this activity corresponds to CSv. One fMRI study with actual head motion (Petit and Beauchamp, 2003) found activity in the paracentral lobule at a location (Talairach co-ordinates 4 -17 55) that is only about 15mm from the location of CSv.

CSv has no clear counterpart in macaque, although there is a visually responsive region in posterior cingulate gyrus (Dean et al., 2004) that might have related functions. In light of our discovery of vestibular input, a possible homologue is a region in the cingulate sulcus identified by Akbarian et al. (1994) as projecting to the brainstem vestibular nuclei. This region, labelled area 23cv, has a plausible location in comparison to CSv.

Conclusion

We have shown that the vestibular system provides afferents to two cortical areas (hMST, CSv) that have previously been identified as central to the processing of visual information related to self-motion. We have also shown that area hMST appears to consist of two functional subdivisions, referred to here as hMSTa (which has vestibular sensitivity) and hMSTp (which, in common with MT and V6, does not). Some of the areas with vestibular sensitivity may represent the sites at which visual and vestibular information are integrated. Area CSv is a strong candidate, being both strongly responsive to vestibular stimulation and also very specifically responsive to egomotion-compatible visual stimuli.

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FIGURE LEGENDS

Figure 1.

Diagram showing the galvanic stimulation procedure. **A**. Vestibular stimulation. A current that varies sinusoidally about zero is passed between two active electrodes, causing a sensation of back and forth body motion. It also causes a tactile sensation at the cathode, which alternates between left and right. **B** Somatosensory control. A half-wave-rectified sinusoidal current is passed between one of the electrodes used for vestibular stimulation and a reference electrode on the ipsilateral ear, to reproduce the somatosensory sensation experienced in the vestibular condition. The two sides of the head are stimulated in anti-phase to create the somatosensory alternation between left and right that is experienced in the vestibular condition.

Figure 2.

Images from the brain of one participant showing the key results. **(a)** Regions of interest (MT, MST, CSv, VIP and V6) derived from independent visual localizers are shown as solid colors overlaid on an inflated representation of the cortex. Activity elicited by the one-patch flow stimulus (see text) is shown for each area in slice view; colors represent *t* values (see key) and the activation maps are thresholded at $p < 0.001$ (uncorrected). **(b)** Results of Experiment 1 for the same participant, shown in the form of activation maps superimposed on the inflated cortex. Colors again represent *t* values thresholded at $p < 0.001$ (unc.). Various regions referred to in the text are identified. **(c)** Results for the same participant from Experiment 2 (somatosensory control). Activations obtained in the GVS conditions (both included) and the somatosensory control were each thresholded at $p < 0.001$ (unc.) and colored red and yellow respectively (see key), before being superimposed transparently on the inflated brain.

Figure 3.

Results of the ROI-analyses from Experiment 1, averaged across all participants. The bars in the left panel show mean vestibular activity in several regions of interest defined with independent visual localisers (see text). On the right are results for STSms, which was defined on the basis of the vestibular activity itself, and for the vestibular part of MST when defined in the same way. Error bars show the standard error of the mean.

Figure 4.

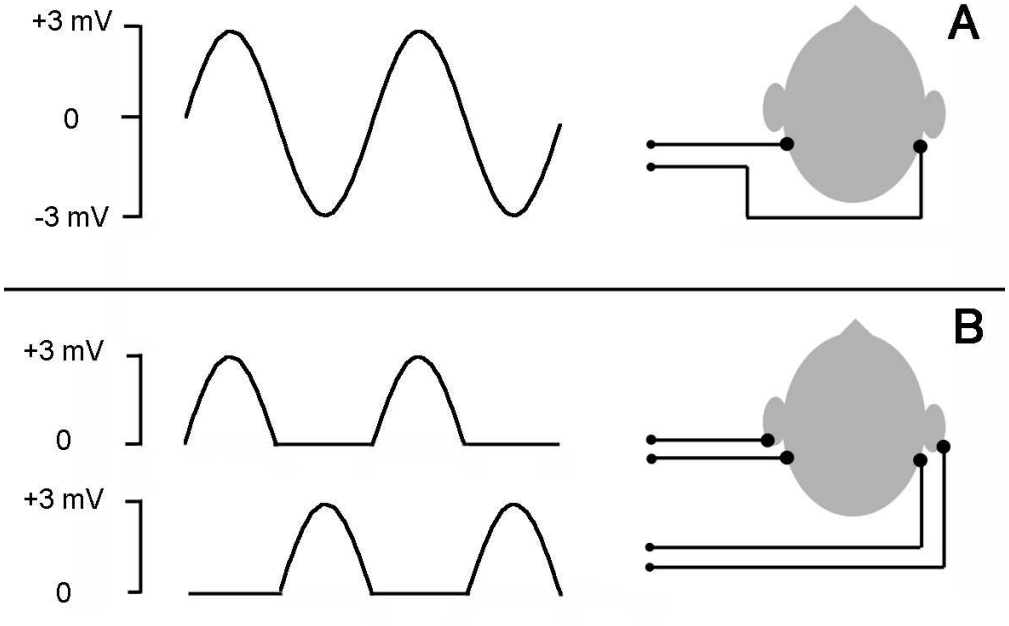
Results from Experiment 2 (somatosensory control experiment). Histograms show activations averaged across all voxels in a region of interest, defined independently with a visual localiser in the case of areas in the left panel and on the basis of GVS-evoked activity in areas on the right. Key: '=sub' subjectively matched. '=mA' matched current. * significant at $p < 0.05$. ** significant at $p < 0.005$. All significance tests were performed on GVS conditions relative to control condition, to indicate the significance of the vestibular component of the response. Error bars show the standard error of the mean.

Figure 5.

Sections of flattened grey matter covering MT+ and the surrounding area from all five subjects that took part in Experiment 3, with GVS-related activity overlaid in an orange-to-yellow scale (thresholded at $p < 0.001$, uncorrected). MT and MST ROIs derived from localizer scans conducted in the same scanning sessions are shown in outline, in green and pink respectively. The superior temporal sulcus (STS) is marked with a white broken line. Orientation markers: A = Anterior, P = Posterior, D = Dorsal, V = Ventral. Vestibular activity in MST is generally confined to the anterior portion, activity in MT is entirely absent. In many cases, activity in a more anterior region (STSms) can clearly be seen.

Figure 6.

Results of the ROI-analysis from Experiment 3 for MT and MST, averaged across all participants. Error bars show the standard error of the mean.



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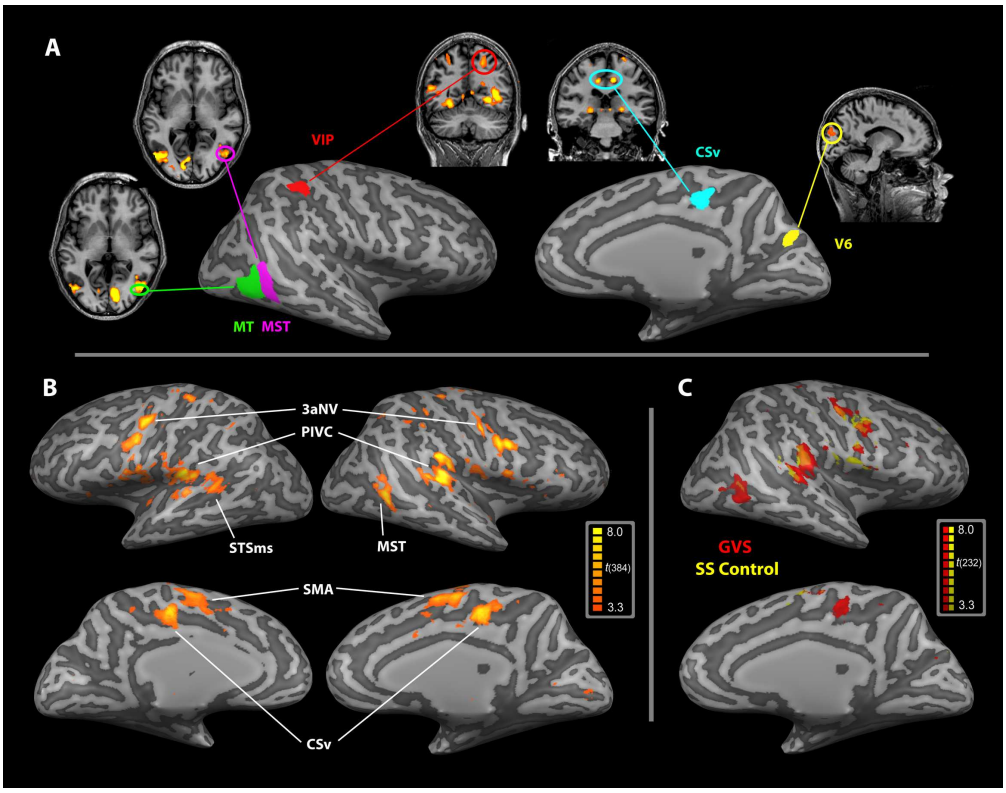

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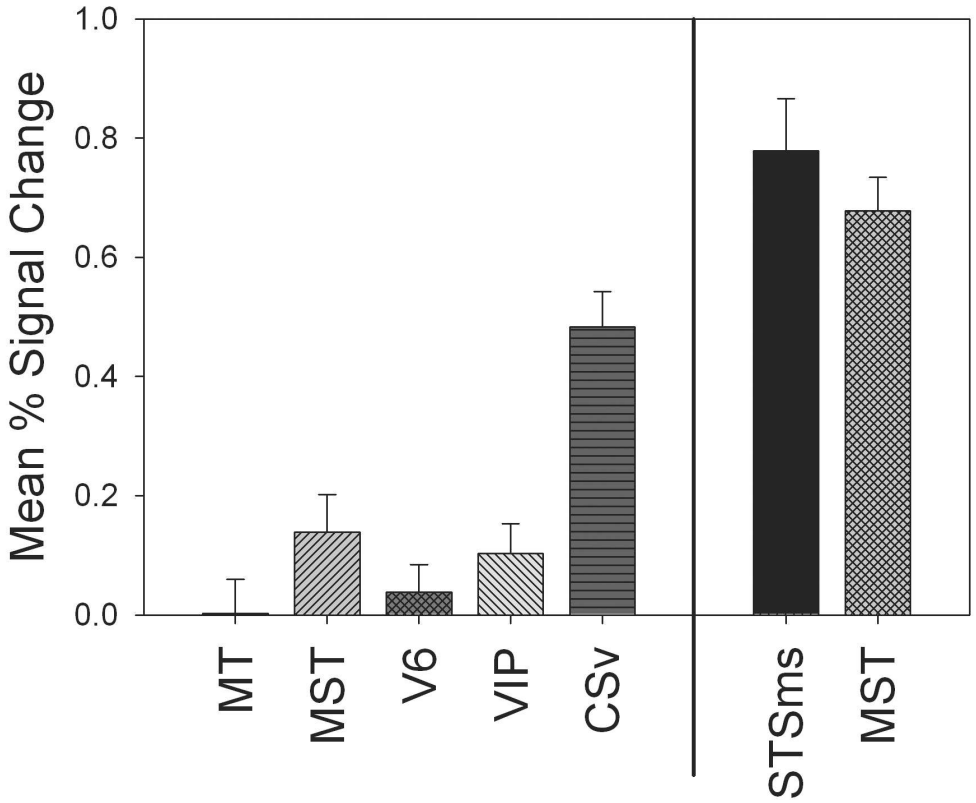

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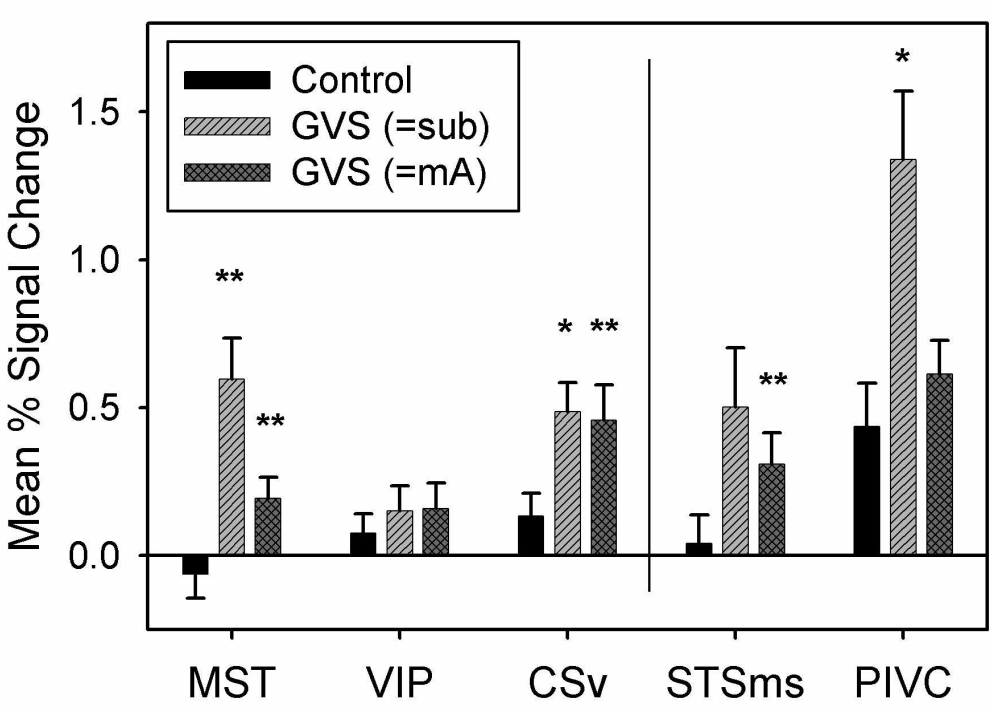

Figure 4.
Results from Experiment 2 (somatosensory control experiment). Histograms show activations averaged across all voxels in a region of interest, defined independently with a visual localiser in the case of areas in the left panel and on the basis of GVS-evoked activity in areas on the right. Key: '=sub' subjectively matched. '=mA' matched current. * significant at $p < 0.05$. ** significant at $p < 0.005$. All significance tests were performed on GVS conditions relative to control condition, to indicate the significance of the vestibular component of the response. Error bars show the standard error of the mean.
74x53mm (600 x 600 DPI)

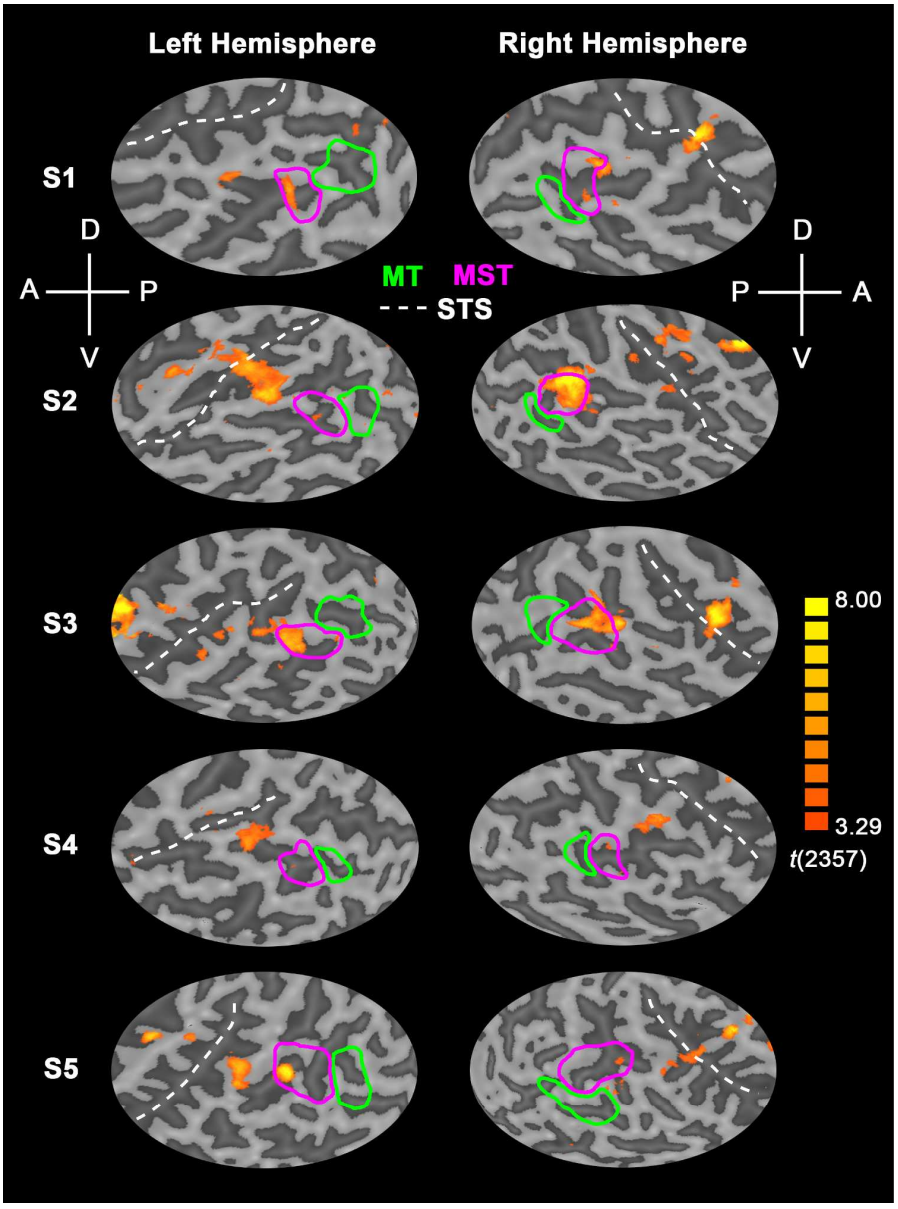

Figure 5.
Sections of flattened grey matter covering MT+ and the surrounding area from all five subjects that took part in Experiment 3, with GVS-related activity overlaid in an orange-to-yellow scale (thresholded at $p < 0.001$, uncorrected). MT and MST ROIs derived from localizer scans conducted in the same scanning sessions are shown in outline, in green and pink respectively. The superior temporal sulcus (STS) is marked with a white broken line. Orientation markers: A = Anterior, P = Posterior, D = Dorsal, V = Ventral. Vestibular activity in MST is generally confined to the anterior portion, activity in MT is entirely absent. In many cases, activity in a more anterior region (STSms) can clearly be seen.
127x170mm (600 x 600 DPI)

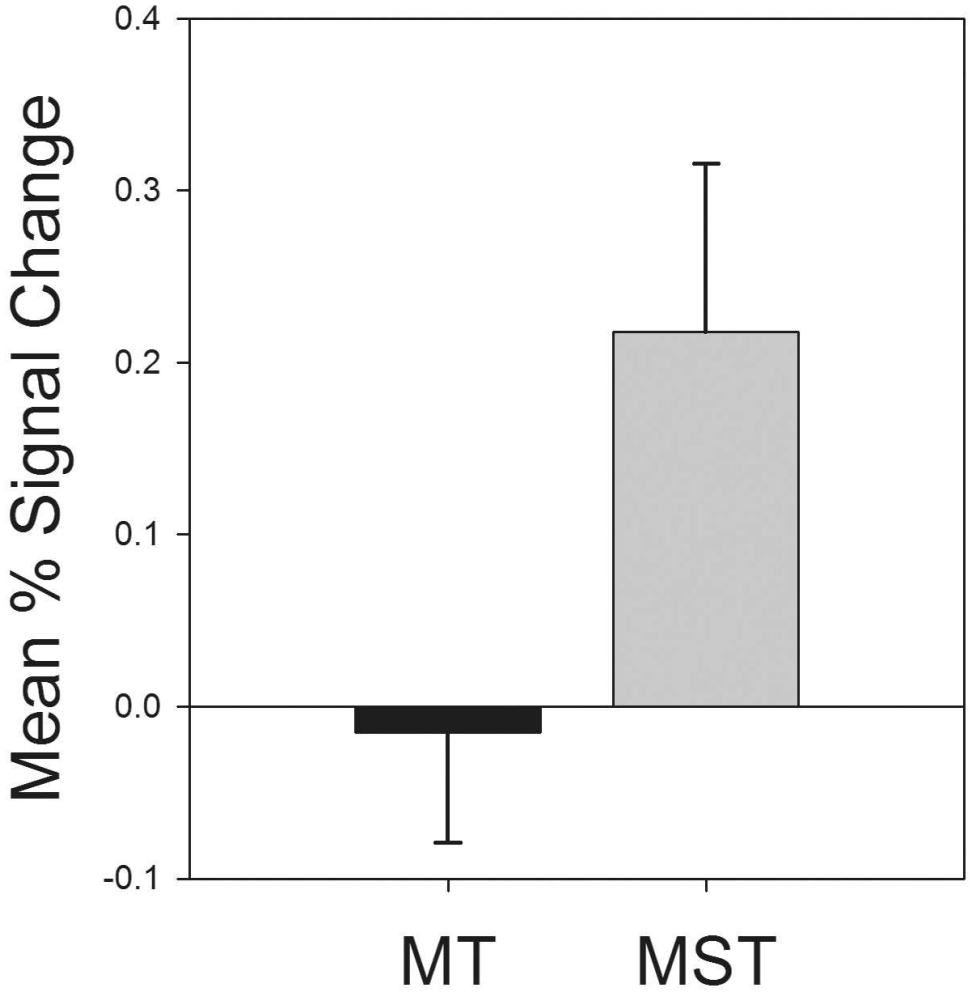

Figure 6.
Results of the ROI-analysis from Experiment 3 for MT and MST, averaged across all participants. Error bars show the standard error of the mean.

62x64mm (500 x 500 DPI)

Vestibular inputs to human motion-sensitive visual cortex

Smith AT, Wall MB and Thilo KV

SUPPLEMENTARY MATERIAL

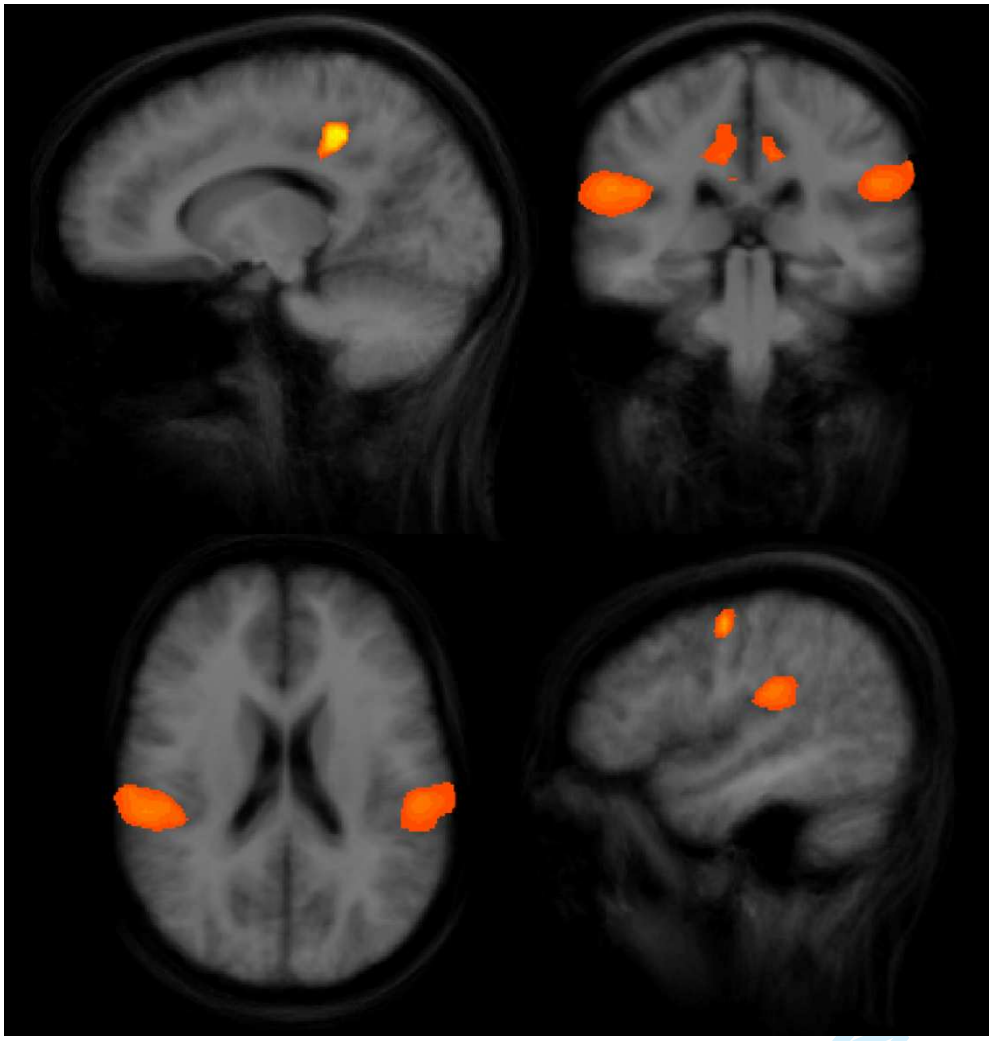

Figure S1
Results of a random effects group analysis performed on the data from Experiment 1. The analysis was performed in *Brain Voyager* using conventional techniques. The data were pre-processed as described in the text, with two additional procedures: spatial smoothing was applied using an 8mm Gaussian kernel, and spatial normalization to a standard template was applied to all brains (n=9). A standard random effects group analysis was then performed, which included AR(1) correction for autocorrelation. Individual voxel *t* thresholds were set at $p < 0.001$, and these maps were subsequently corrected at the cluster level ($k = 8$) in order to yield images conforming to $p < 0.05$ (corrected for multiple comparisons). Significant activity is shown as a color overlay on slices from an averaged brain template. Three significant clusters were obtained, at the expected locations of CSv and vestibular areas PIVC and 3aNv; all appeared bilaterally. The upper left image shows right CSv in a sagittal slice at x=14 (Talairach). CSv is also shown, bilaterally, in the upper right coronal slice at y=-29.. The lateral activations in

the coronal slice are part of PIVC. The lower images show PIVC bilaterally in an axial slice (z=20) and in the right hemisphere in a sagittal slice (x=48). The dorsal activity in the sagittal slice is putative area 3aNv. All images are in radiological orientation. Talairach co-ordinates for the centroids of the three bilateral areas are as follows:
CSv Left [7 -29 38]
CSv Right [9 -36 41]
PIVC Left [-52 -26 23]
PIVC Right [51 -28 21]
3aNv Left [-37 -15 46]
3aNv Right [44 -9 45]

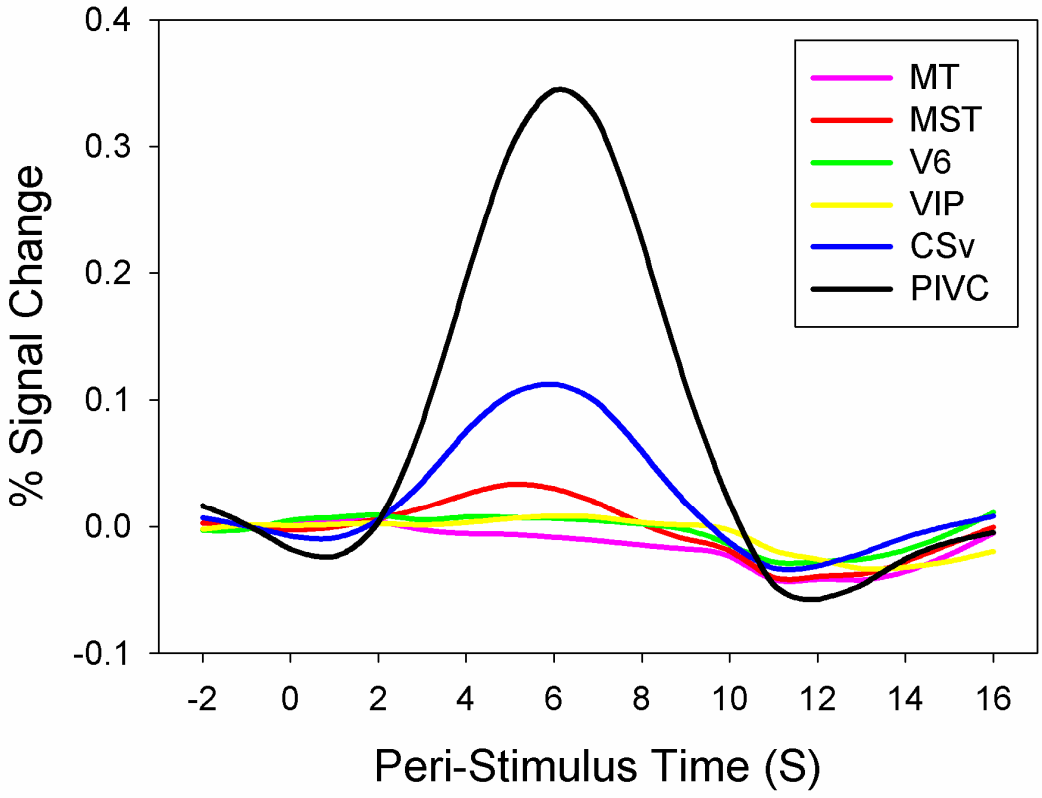

Figure S2
The time-courses of event-related BOLD responses, averaged across trials (using a time-window from -2 to +16 s, relative to trial onset) and subsequently averaged across the 9 participants in experiment 1. The stimulus was present from 0-2s. Time-courses from all independently-defined visual areas are included, as well as from PIVC, for comparison purposes. Note that PIVC was non-independently defined in these data and so the magnitude of the response may be overestimated relative to the visual areas.