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Transcranial Magnetic Stimulation (TMS) of the Supramarginal Gyrus: A Window to Perception of Upright

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Although the pull of gravity, primarily detected by the labyrinth, is the fundamental input for our sense of upright, vision and proprioception must also be integrated with vestibular information into a coherent perception of spatial orientation. Here, we used transcranial magnetic stimulation (TMS) to probe the role of the cortex at the temporal parietal junction (TPJ) of the right cerebral hemisphere in the perception of upright. We measured the perceived vertical orientation of a visual line; that is, the subjective visual vertical (SVV), after a short period of continuous theta burst stimulation (cTBS) with the head upright. cTBS over the posterior aspect of the supramarginal gyrus (SMGp) in 8 right-handed subjects consistently tilted the perception of upright when tested with the head tilted 20° to either shoulder (right: 3.6°, left: 2.7°). The tilt of SVV was always in the direction opposite to the head tilt. On the other hand, there was no significant tilt after sham stimulation or after cTBS of nearby areas. These findings suggest that a small area of cerebral cortex—SMGp—has a role in processing information from different sensory modalities into an accurate perception of upright.

Keywords: cortex, perception, SVV, TMS, vestibular

Introduction

Vestibular information is crucial for the cognitive processing that underlies spatial orientation and navigation in the environment. A widely distributed cortical network receives and processes information from the vestibular system. Vestibular signals, unlike those from other sensory systems, do not usually reach consciousness unless there is a pathological disturbance. They are incorporated to self and extrapersonal spatial perception and serve in many high-level cognitive and motor functions (e.g., Angelaki and Cullen 2008). Different areas of the cerebral cortex are involved in processing and integrating information from vestibular, visual, and somatosensory systems to construct a coherent spatial orientation. Based on human and animal studies, posterior insular cortex, inferior parietal lobule (angular and supramarginal gyrus [SMG]), and superior temporal gyrus are key cortical areas that receive, process, and integrate vestibular inputs with other sensory information (Guldin and Grüsser 1998; Angelaki and Cullen 2008; Lopez and Blanke 2011; Chen et al. 2011a). In humans, most evidence comes from functional neuroimaging studies with vestibular stimulation, direct stimulation of the cerebral cortex, and behavior analysis after cortical lesions (Brandt et al. 1994; Kahane et al. 2003; Seemungal et al. 2009; Baier et al. 2012; Lopez et al. 2012). Nevertheless, we do not know 1) the precise functional role of these cortical areas, 2) how information is processed within and between these regions, and 3) how disruption in one sensory modality can affect integration of different sensory inputs and overall perception of spatial orientation.

As an individual interacts with the surrounding environment, the projection of the scene onto the retina continuously changes due to eye movements, head movements, and changes in body orientation. Despite these changes, “orientation constancy” is maintained and the percept of the scene as a whole remains stable along an axis called earth-vertical, a static upright reference that indicates the orientation of the head and body. This internal reference—that is, perception of upright—is generated by integration of different sensory inputs including those from the labyrinths (vestibular system), proprioception (somatosensory system), and vision (Beh et al. 1971; Dieterich and Brandt 1993; Borel et al. 2008; Barra et al. 2010).

Experimentally, the perception of upright is often judged by aligning an illuminated line in an otherwise dark room with the subject’s perceived vertical called the subjective visual vertical (SVV). Normal individuals can position a visual line in an otherwise completely dark room within 2° of true vertical, whereas lesions in different parts of vestibular pathways including the cerebral cortex can produce pathological tilts of the SVV (Howard 1982; Brandt and Dieterich 2004; De Vrijer et al. 2009). With cerebral cortical lesions, the altered perception of upright reflects a disruption in higher level cognitive processing and multisensory integration of vestibular, visual, and somatosensory inputs (Angelaki et al. 2009a; Angelaki et al. 2009b).

In this study, we addressed directly the functional role of the right temporal parietal junction (TPJ) in perception of upright using transcranial magnetic stimulation (TMS). TMS has been a useful tool to link the function of a particular cortical region to behavioral measures (e.g., Hallett 2000). Our specific probe was a short period of continuous theta burst stimulation (cTBS), which can transiently disrupt cortical activity (Huang et al. 2005; Cárdenas-Morales et al. 2010). We asked whether the disruptive effect of the cTBS over the right TPJ in healthy subjects could alter the SVV. The TPJ was chosen for magnetic stimulation based on its location within the nexus of vestibular projections to the cerebral cortex and the overall putative role of the parietal lobe in spatial orientation (e.g., Andersen and Cui 2009; Lopez and Blanke 2011). The right hemisphere in particular was chosen as there is ample evidence for specialization of the right hemisphere in spatial localization (Vallar 2001; Dieterich et al. 2003; Fink et al. 2003; Balslev et al. 2005). Our findings confirmed our more general hypothesis about the role of parietal cortex in spatial orientation and furthermore suggested a specific way in which a restricted portion of parietal cortex influences the perception of upright.

Materials and Methods

Subjects

Eight right-handed volunteers (5 males and 3 females; aged 22–72 years) were studied after giving written consent. All were in good health without vestibular, neurologic, or psychiatric illness. The inclusion criteria were based on the consensus guidelines for the use of TMS in research (Rossi et al. 2009). All experimental procedures were approved by Johns Hopkins Institutional Review Board.

SVV paradigm

Subjects sat on a chair with their head immobilized by a molded bite bar. A red laser line (length: 34.5 cm, width: 2 mm), covering 15° of the binocular visual field, was back-projected on a semitransparent screen 135 cm away in front of the subject. The center of rotation was at the bottom of the laser line which was marked by a red dot (diameter: 3 mm), positioned at eye level. Subjects were instructed to look at the red dot while estimating the orientation of the line. SVV was measured in a completely dark room using a forced-choice paradigm consisting of 2 consecutive blocks each lasting about 4 min (Fig. 1*A*). The blocks were displayed 5 min apart in a randomized order between different recording sessions and a dim light was turned on in between blocks. Subjects were placed in the dark for 30 s before each block was recorded. In block 1, the line started at a roll orientation of −16° (counterclockwise or leftward tilt from true vertical) and moved in 2° steps to a roll orientation of +16° (clockwise or rightward tilt from true vertical). At each line projection, subjects rotated a potentiometer with their right hand to 3 different positions to indicate their perception of line tilt as: tilted to the left, upright, or tilted to the right. A button was used to confirm selections with the left hand. In order to reduce second guessing, subjects had 5 s to respond. After each confirmation, the line was turned off for 1 s before the next line appeared. Block 2 was similar to block 1 except that the line started at +16° and moved to −16°. In both blocks, the series of line projections between ±16° was repeated 8 times. The results from blocks 1 and 2 were combined to calculate SVV. The successive stimuli in each block—as opposed to a randomized design—was to avoid the arbitrary drift of estimates of the SVV that can occur with random stimulus presentation because of a "tilt after effect," a form of hysteresis in which perception of the line orientation is biased by the previous line orientation (Pagarkar et al. 2008; Tarnutzer et al. 2012).

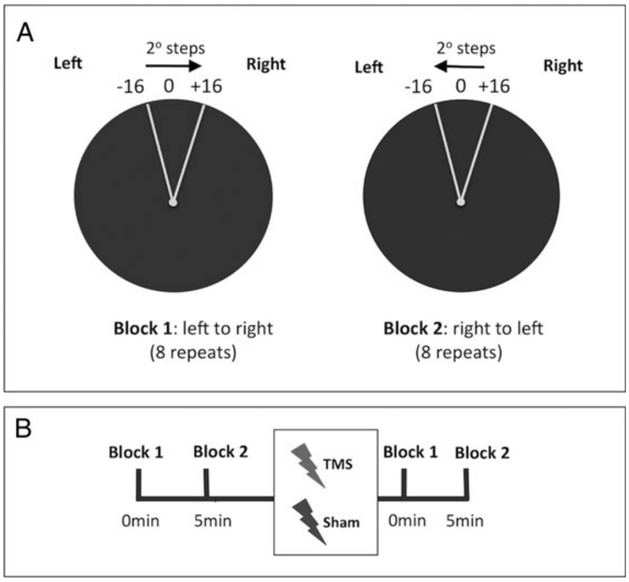

Figure 1. (*A*) The SVV was measured using a forced-choice paradigm consisting of 2 consecutive blocks. In block 1, a line was projected starting at the roll orientation of −16° and moved clockwise in steps of 2° to the roll orientation of +16°. At each line projection, the perceived line orientation was recorded using 3 alternative choices: left tilt, upright, or right tilt. Block 2 was similar except that the line orientation started at +16° and moved counterclockwise to −16°. In both blocks, the series of line projections between ±16° was repeated 8 times. (*B*) Block 2 started 5 min after the start of block 1. In each experiment, both blocks were recorded before and after TMS or sham stimulation (within 2 min of completion of stimulation).

Localization of Brain Sites

Prior to the experiment, each subject underwent a T_1-weighted, high-resolution MRI using a 3T scanner (Phillips). We used a frameless neuronavigation system (Brainsight, Rogue Research, Inc., Montreal, Canada) to create a 3D surface model of the subject's brain and provide an interactive navigational guide to track the trajectory of the TMS coil in real time and place the coil over a cortical area of interest. With this method, a series of scalp landmarks were identified and co-registered with corresponding points on the subject's head.

TMS Protocol

Subjects sat in the light with their head fixed in the upright position with a molded bite bar. A train of 200 bursts was given at 5 Hz (interburst interval of 200 ms) for 40 s. Each burst consisted of 3 pulses repeating at 50 Hz, for 600 pulses total. Magnetic pulses were generated using a MagStim Rapid2 stimulator and 70 mm figure-of-eight coil. The TMS coil was held tangential to the surface of the scalp by an articulated coil stand (MagStim). The coil handle was parallel to the Sylvian fissure and pointed backward. The stimulation locus (i.e., center of the coil) was continuously monitored using the navigation system to ensure it was over the site of interest. This stimulation locus has an estimated spatial resolution of 1–2 cm with a penetration depth of ~2 cm below the scalp (Brasil-Neto et al. 1992; Rudiak and Marg 1994).

Measurement of motor threshold is the classical method of individualizing magnetic stimulation intensity. However, it may not represent the excitability of nonmotor areas of the brain (Robertson et al. 2003). Therefore, fixed stimulation intensity has been used in TMS studies of parietal cortex (Vesia et al. 2010; Lewald et al. 2002). Here, we stimulated at 55% of maximum output. The range of active motor threshold was 48–55% across subjects. The frequency, intensity, and duration of the cTBS were within safe limits (Rossi et al. 2009). Subjects wore ear plugs to damp the noise from the coil discharge. There were no side effects from stimulation.

Data Acquisition and Analysis

The data collected from blocks 1 and 2 were processed offline using interactive programs written in Matlab (The MathWorks 2008). Each block consisted of 136 trials (8 data points at 17 angles, spaced at 2° within ±16°). The results from both blocks were combined to calculate cumulative probabilities of the responses at each angle as a tilt index (left = 0, upright = 0.5, and right = 1). A logistic regression curve was then calculated by averaging 2 nominal fits between left/upright and right/upright response probabilities (multinomial logistic regression). The SVV was determined as the angle with cumulative probability of 0.5 on the logistic regression curve (i.e., the center of the curve or the value on the curve with the tilt index of 0.5; Fig. 2).

Experimental Procedure

Subjects were initially familiarized with the testing paradigm using a practice session (without TMS) equivalent to one experimental block. The first task was to find an area in the parietal cortex that might modify SVV when stimulated and then verify the effect of TMS over this specific area in a group of subjects. To this end, we explored various locations within the right TPJ by placing a virtual grid over this cortical region in one subject. TMS sessions for different target locations were at least 48 h apart. In each session, the SVV paradigm was recorded before and within 2 min after applying cTBS at one target location (see Fig. 1*B*). The subject's head was in the upright position during SVV measurement. Figure 2 shows the result at 4 target locations in this subject. At targets 1 and 2, the tilt of SVV after TMS was small (0.6° and 0.1°) and the median angles with the tilt index of 0.5 before and after TMS were 4° ($P = 0.25$ and 0.95) (Mann–Whitney

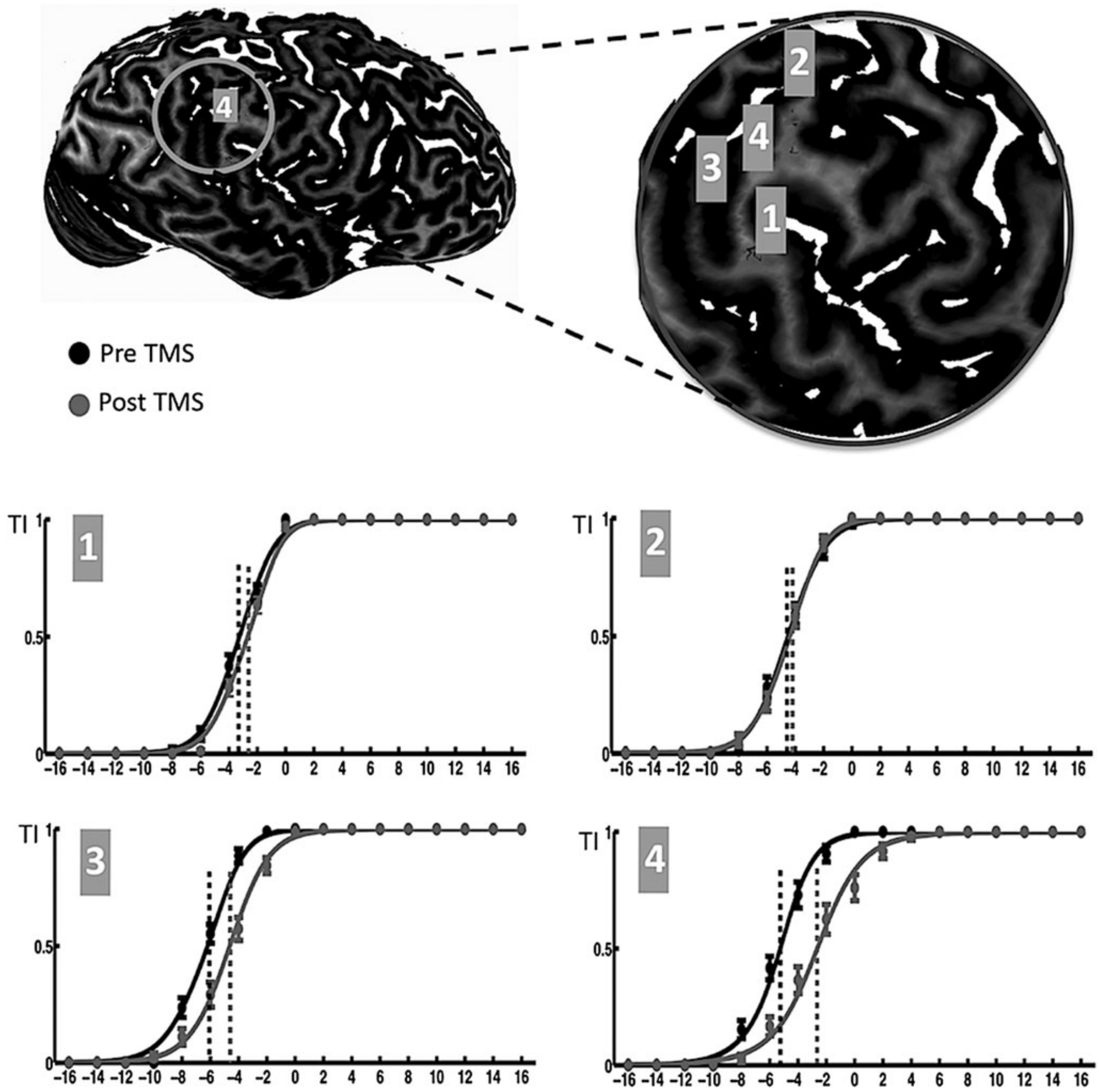

Figure 2. TMS sessions at 4 target locations within the right TPJ in 1 subject. The SVV was recorded with the head upright. Each point on the graphs represents the average tilt index (TI) and the error bars show standard error of mean. The result before TMS is shown in black and after TMS in grey. The SVV calculated as the angle value at the center of the logistic fits (dotted lines). The maximum tilt of SVV after TMS was at target location 4 (i.e., SMGp).

test). At target 3, the tilt of SVV after TMS was 1.6° and the median angle with the tilt index of 0.5 was larger than before TMS (−4° and −6°, $P < 0.0001$). There was a marked tilt of SVV (2.6°) after TMS at target 4. The median angle value with tilt index of 0.5 was larger after TMS than before TMS (−4° and −6°, $P < 0.0001$). The maximum tilt of SVV measured with the head upright was therefore about 2°. Target 4 was localized at the posterior aspect of the SMGp at the border with the angular gyrus (AG) (Fig. 2).

Since the error in estimates of the SVV was about 2° with the TMS in the upright head condition, as the next step, we studied the effect of TMS by measuring the SVV only with the head tilted in this subject and in an additional 7 subjects. Based on the known increase in errors in the perception of upright with head tilt in normal subjects, we hypothesized that testing with the head tilted would pose a more demanding challenge to estimate upright and therefore make the SVV more susceptible to the possible effects of magnetic stimulation (Howard 1982; De Vrijer et al. 2009). The SVV was measured using 2 tilt conditions (head on body using a molded bite bar): 20° roll to the left and 20° roll to the right. Eight subjects participated in this experiment and the SVV paradigm was recorded in TMS and sham sessions on separate days (see Fig. 1*B*). Only the right cerebral hemisphere was stimulated in these subjects. In the TMS session, the SVV paradigm was recorded before and within 2 min after applying cTBS. The sham session was similar except that a wooden block was placed between the TMS coil and the subject's scalp. Anatomical landmarks were used on the MRI of each subject to estimate the location of SMGp (similar location as target 4 in Fig. 2) where we would apply TMS. Figure 3 shows the normalized *XYZ* coordinates according to MNI stereotactic space (Montreal Neurological Institute, ICBM 152 template) for the SMGp location in each subject (red marks). In 6 of our subjects, TMS was also applied at other cortical locations near to the SMGp in order to show the specificity of the effect of stimulation. A total of 6 adjacent target locations was explored with the head tilted to the left and 5 target locations with the head tilted to the right (orange marks in Fig. 3).

The tilt of SVV was calculated as a difference between SVV after TMS or sham stimulation and baseline SVV value before stimulation in each recording session. The tilt of SVV with TMS and sham stimulation (group data from all subjects) were compared in each head tilt condition (1-way ANOVA). Also, the average tilt of SVV with TMS

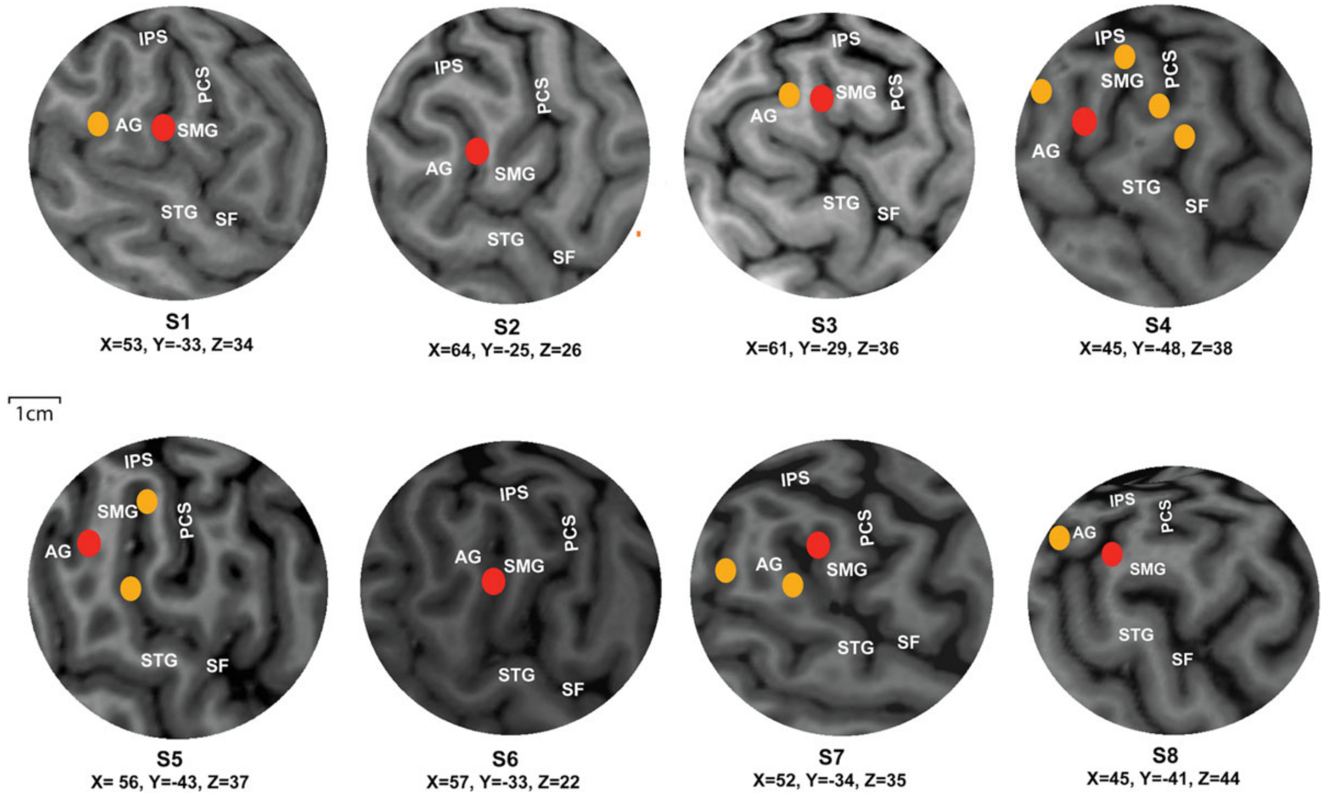

Figure 3. The right TPJ is shown for all subjects with the SMGp (marked in red) identified by anatomical landmarks. See Figure 2, right, for the location of this area in the entire hemisphere. MNI coordinates of the SMGp are provided for each subject. The different SMGp location in each subject is due to anatomical variability among subjects. Also shown are TMS locations within cortical areas near to the SMGp (marked in orange). AG, angular gyrus, IPS, intraparietal sulcus, PCS, postcentral sulcus, SF, Sylvian fissure, SMG, supramarginal gyrus, STG, superior temporal gyrus.

and sham stimulation was compared with zero (1-sample *t*-test). All the results were considered statistically significant at $P < 0.05$ (uncorrected).

Results

In each head tilt condition, the SVV was measured before and after TMS and sham stimulations. The tilt of SVV with TMS (at the SMGp or adjacent cortical locations) and from sham sessions are shown for all subjects in Figure 4. In the left head tilt condition, the average tilt of SVV with TMS at the SMGp (2.7°) was significantly different from TMS at adjacent locations (0.2) and sham stimulation (−0.9°) ($P = 0.02$) (Fig. 4*A*). The average tilt of SVV with TMS at SMGp was larger than zero ($P = 0.04$) whereas the average tilt of SVV with sham stimulation was minimal and not significantly different from zero ($P = 0.3$). In the right head tilt condition, the average tilt of SVV with TMS at the SMGp (−3.6°) was significantly different from TMS at adjacent locations (−0.6°) and sham stimulation (−0.8°) ($P = 0.004$) (Fig. 4*B*). The average tilt of SVV with TMS at SMGP was larger than zero ($P = 0.002$) whereas the average tilt of SVV with sham stimulation was minimal and not significantly different from zero ($P = 0.2$). Figure 5*A* illustrates representative results of TMS at the SMGp and sham stimulation for both head tilt conditions in one subject. The tilt of SVV with TMS at the SMGp and the sham session are shown for each subject in Figure 5*B*. In both head tilt conditions and in all subjects, with TMS at the SMGP, the tilt of SVV was "always away from the head tilt" relative to sham stimulation (Figs 4 and 5*B*): leftward tilt of SVV with the head tilted right and rightward tilt of SVV with the head tilted left (sign test $P = 0.0039$).

Discussion

Here, using the effect of TMS in the cerebral cortex of normal human subjects, we can now suggest a specific and immediate functional role for a small region of the right parietal cortex in the perception of upright. Following a short period of continuous theta burst stimulation over the posterior aspect of the right SMGp, in every subject, the SVV was tilted and always opposite to the direction of the head tilt. Mapping studies of patients with structural lesions have shown tilt of the SVV with general involvement of the posterior insula and peri-insular regions within the temporal and parietal cortex (Brandt et al. 1994; Yelnik et al. 2002; Barra et al. 2010; Baier et al. 2012). However, the exclusive role of a more focal area in perception of upright has not been previously described. Here, the tilt of SVV after TMS at the SMGp suggests a specific and immediate role for this small area in the perception of upright. This novel observation can have important implications for understanding how the brain and especially "vestibular cortex" creates a veridical perception of uprightness.

Both animal and human studies show that vestibular information is processed in a widely distributed multisensory cortical network predominantly in the temporoinsular and temporoparietal cortex (reviewed in Lopez and Blanke 2011). This is not surprising considering how vital it is for us to know the body orientation relative to the ground when any motor action is contemplated. In nonhuman primates, the parietoinsular vestibular cortex, located in the posterior insula is strongly activated by vestibular stimulation with motion in any direction but not during static tilts from the upright or during optic flow (Guldin and Grüsser 1998; Chen et al. 2010; Lopez et al. 2012). In line with these findings, patients with ischemic lesions restricted to the posterior insula do not exhibit significant tilt of SVV, which suggests that the posterior insula is not the primary area for the neural basis of multimodal sensory integration (Baier et al. 2013). The vestibular cortex also extends to the superior temporal gyrus, the TPJ, and the intraparietal sulcus (Guldin and Grüsser 1998; Lopez and Blanke 2011; Chen et al. 2011a; Lopez et al., 2012). Electrophysiological recordings have shown that activity in single neurons in various parts of vestibular cortex responds to different sensory stimuli, and that vestibular inputs typically converge with those from other sensory modalities (Guldin and Grüsser 1998; Chen et al. 2008, 2011a, 2011b, 2011c). For example, extrastriate areas, including the dorsal portion of the medial superior temporal area and ventral intraparietal area contain robust neural representations of self-motion based on both visual and vestibular cue integration (Fetsch et al. 2007; Chen et al. 2008, 2011c). Moreover, from a functional perspective, the perception of the position of the body depends on processing and integration of vestibular, visual, and somatosensory information (Balslev et al. 2005; Borel et al. 2008; Osler and Reynolds 2012). In the process of multisensory integration, the vestibular cortex must solve the problem of the different reference frames in which sensory information is encoded. Generally, the parietal cortex faces a similar task for other sensorimotor behaviors that require coordinate transformations (e.g., Andersen and Cui 2009). Information from different sensory modalities must therefore be transformed into a common reference frame to generate a coherent and veridical perception of spatial orientation. The difficulty of this task is reflected in the systematic errors in estimations of upright at different head tilt angles in normal subjects, with underestimation of the true vertical orientation for tilts >70° (known as the A-effect) and tendency for overestimation at smaller head tilt angles (known as

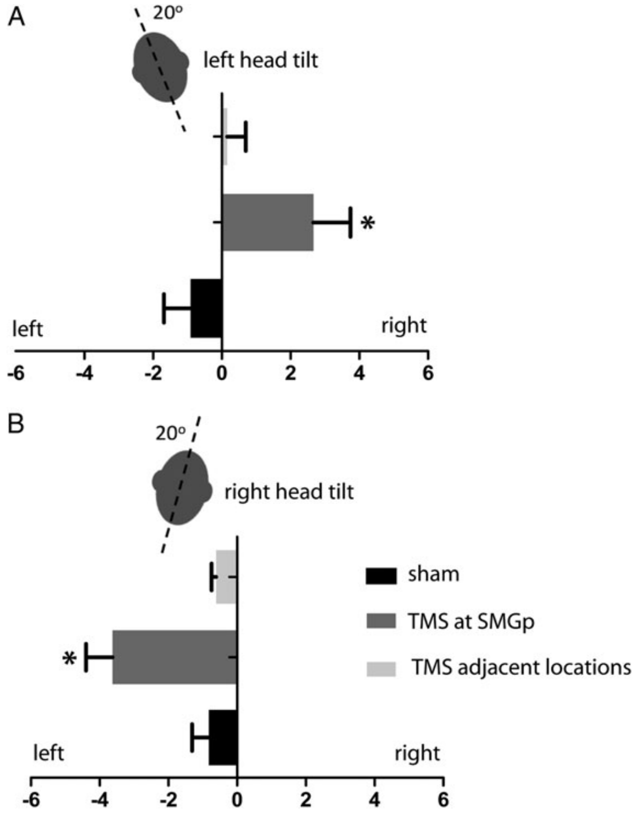

Figure 4. The average tilt of SVV is shown with standard error of mean in TMS and sham sessions for (*A*) left and (*B*) right head tilt conditions. The average tilt of SVV with TMS at the SMGp is significantly different from TMS at adjacent cortical locations and sham stimulation in both head tilt conditions.

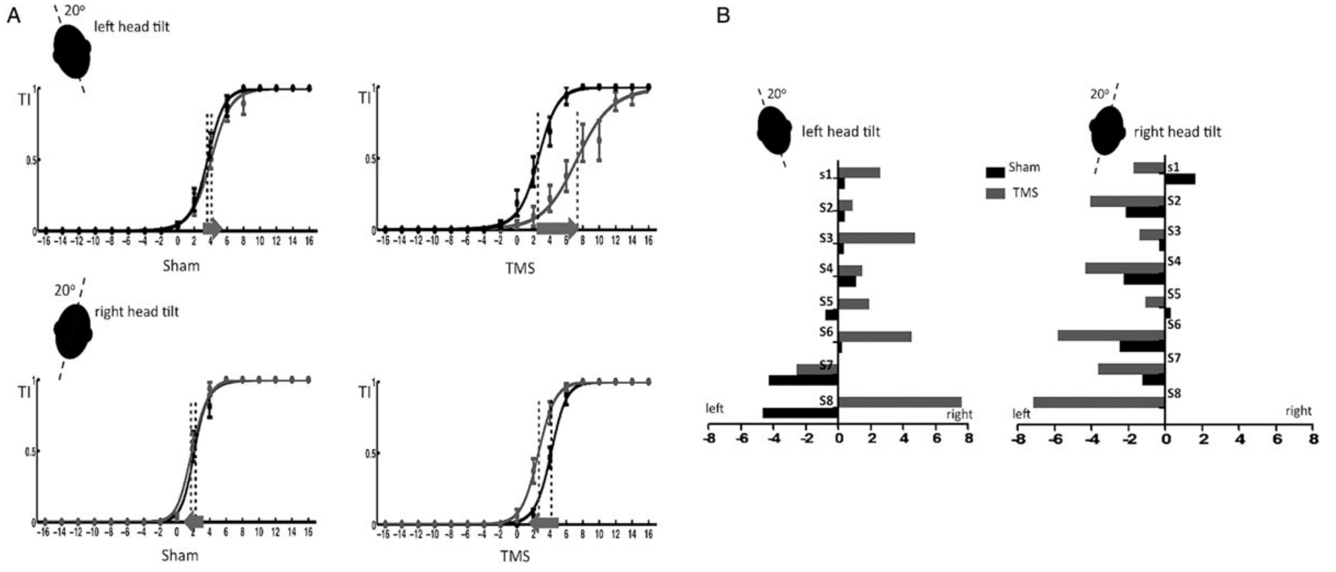

Figure 5. (*A*) Representative TMS at the SMGp and sham stimulation for the left (top) and right (bottom) head tilt conditions (one subject). The points on the graphs show the average tilt index (TI) with standard error of mean. The result before TMS is shown in black and after TMS in grey. The SVV was calculated as the angle value at the center of the logistic fits (dotted lines). Gray arrows show the tilt of SVV in each session. (*B*) The individual tilt of SVV is shown for TMS and sham sessions in both head tilt conditions. The tilt of SVV with TMS relative to sham stimulation is away from the direction of the head tilt.

E-effect) (Howard 1982; Van Beuzekom and Van Gisbergen 2000; Angelaki et al. 2009b; Tarnutzer et al. 2010).

In our study, there was a significant effect of TMS by testing with the head tilted, with alteration of SVV always in the opposite direction to the head tilt. This suggests the SMGp has a role in processing different sensory components for perception of upright including the information about head position relative to gravity, orientation of the eye in the orbit and visual input from the retina. Another way to look at these processes is that they are being integrated into a "common spatial reference frame." For instance, the change in the torsional orientation of the eye (and thus the orientation of the retina in the head) must be taken into account when estimating the SVV (Wade and Curthoys 1997; Betts and Curthoys 1998). When the head is tilted toward one shoulder, the eyes counterroll to a small degree (typically about 10% of the head tilt). Lesions within the central vestibulo-ocular pathways in the brainstem are commonly associated with tilt of SVV and are usually accompanied by a commensurate change in torsion of the eyes (Brandt and Dieterich 2004). It is thus possible that the changes in SVV after TMS were related to an inability of the brain to take into account the change in ocular torsion associated with the head tilt. In favor of this idea is the finding that the tilt of SVV after TMS was opposite to the movement of the head, and roughly in proportion to the degree of expected counterroll from the head tilt. Torsional eye position was not measured in this study, so, while unlikely, we cannot exclude the possibility that there was a direct change in torsion due to the TMS itself. Against this possibility, however, is that changes in torsion are not found in patients with disturbances of the SVV due to lesions in the cerebral cortex (Brandt et al. 1994). Regardless of whether or not there is a direct effect of TMS on torsion, our results show that a focal area of cerebral cortex (SMGp) plays a role in the elaboration of a veridical sense of uprightness.

In all of our subjects, the target cortical areas for magnetic stimulation were within the 2-mm-distance range below the scalp. This is within the expected penetration depth of the magnetic field generated by the TMS coil (Brasil-Neto et al. 1992; Rudiak and Marg 1994). Further anatomical specificity of this hypothetical function for SMGp might be achieved by using a functional mapping with graded TMS stimulation to identify the key areas (e.g., Oliver et al. 2009). The average tilt of SVV after TMS in this study (right: 3.6°, left: 2.7°) is compatible with the amount of tilt reported in patients with cortical lesions though of course those patients had more chronic lesions and could have shown some adaptation (Brandt et al. 1994; Yelnik et al. 2002; Barra et al. 2010; Baier et al. 2012). Finally, our experiments were restricted to stimulating the right cerebral hemisphere. The right TPJ was chosen as our initial target location since there is ample evidence for greater specialization of the nondominant hemisphere in spatial localization and imaging studies show stronger activation in the nondominant hemisphere with vestibular stimulation (Dieterich et al. 2003; Fink et al. 2003). We do not yet know if similar results can be obtained from the left cerebral hemisphere.

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Notes

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