

Scientific Report

VESTIBULAR CONTRIBUTIONS TO SELF-AWARENESS

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The vestibular system is essential for almost all successful interactions between the body and the external environment. Crucially, our ability to acquire a sense of direction and orientation in external space depends on the capacity of our brain to integrate vestibular inputs arising from the otolith organs and semicircular canals with other sensory signals. Thus, the vestibular system may influence bodily self-awareness in at least three ways: (1) modulating the representation of the body as a spatially extended volumetric object, (2) influencing the mechanism for maintaining the differentiation between the self and the world, and (3) affecting the balance between the exploration and the exploitation in the external environment. In this project, the vestibular organs of healthy volunteers were non-invasively artificially stimulated. Participants made judgements about sensory stimuli, bodily sensation, and the relation between the body and the environment both under vestibular stimulation, and under control conditions.

Here we report the results from the experiments completed during the project.

Session 1. Modulation of low-level somatosensation

Experiment A: Effects of vestibular stimulation on nociceptive laser evoked potentials.

No unimodal vestibular cortex has been identified in the mammalian brain, yet vestibular input projects to several cortical areas. Therefore vestibular input could influence processing in other sensory modalities. We recently observed that caloric vestibular stimulation (CVS) decreases perceptual thresholds for touch, but increases thresholds for pain, thus suggesting a direct role of vestibular inputs in multisensory interactions with pain. The neural mechanisms of such vestibular-induced analgesia remain unclear. To address this issue we delivered nociceptive laser stimuli to the dorsum of the left hand before and immediately after left CVS, and recorded the corresponding brain responses (nociceptive laser-evoked potentials, LEPs) together with the single-trial ratings of subjective pain intensity.

Participants

Ten right-handed healthy volunteers (3 females, age 26.7 ± 4.4 yr, mean \pm SD) participated in the study. Exclusion criteria included any history of motor, somatosensory, vestibular or auditory disorders. All participants gave their written informed consent and were paid for their participation. The study conformed to the standards required by the Declaration of Helsinki and was approved by the local ethics committee.

Methods

Our interest focused on specific changes in LEPs between two experimental conditions: one before CVS (Pre-CVS) and one immediately after CVS (CVS). To control for non-specific effects, as time-dependent habituation, laser evoked potentials were also recorded one hour after CVS (Post-CVS). CVS was performed by slowly pouring 30 ml of cold (iced) water into the external left auditory canal close to the tympanic membrane using a 50 ml syringe with a short piece of elastic tubing attached. The participant's head was positioned 30° backward from the horizontal plane, placing the lateral semicircular canal in the vertical orientation, and 30° toward the right. The duration of the stimulation was 30s. To reduce discomfort, participants were asked to close their eyes during the stimulation. After CVS, the participant's head was positioned in the upright position to check the presence of caloric horizontal nystagmus. Care was taken to ensure the electrophysiological recording was completed within fifteen minutes following CVS, since CVS effects on the vestibular system are limited.

Noxious radiant stimuli were generated by an infrared neodymium yttrium aluminum perovskite (Nd:YAP) laser with a wavelength of $1.34 \mu\text{m}$ (Electronical Engineering, Florence, Italy). Laser pulses were directed at the dorsum of the left hand, on an area defined prior to the beginning of the experimental session. The laser pulse was transmitted via an optic fiber and its diameter was set at approximately 8 mm ($\sim 50 \text{mm}^2$) by focusing lenses. The duration of the laser pulses was 4

ms. The energy of the laser stimulus was fixed at 3.5 J in each participant. At this energy laser pulses elicited a clear pinprick pain, related to the activation of A δ fibers (Treede et al. 1995). After each stimulus, the laser beam target was shifted by approximately 1 cm in a random direction, to avoid nociceptor fatigue or sensitization. We delivered two block of nociceptive stimulation in each experimental condition. In each block we delivered 30 laser pulses, using an inter-stimulus interval (ISI) ranging between 6 and 8 s. At the end of each stimulus, participants were asked to rate the intensity of the painful sensation elicited by the laser stimulus ranging from 0 (not painful) to 10 (extremely painful).

The EEG was recorded using 32 Ag–AgCl electrodes, placed on the scalp according to the International 10–20 system and referenced to the nose. The electro-oculogram (EOG) was recorded using two surface electrodes, one placed over the right lower eyelid, the other placed lateral to the outer canthus of the right eye. Acoustic isolation was ensured using headphones. Signals were amplified and digitized at a sampling rate of 1024 Hz.

Data analysis and results

EEG data were preprocessed and analysed using Letswave (<http://amouraux.webnode.com>) and EEGLAB (Delorme and Makeig 2004). EEG epochs were extracted using a window analysis time of 1500 ms (500 ms pre-stimulus and 1000 ms post-stimulus) and baseline corrected using the pre-stimulus interval. Trials contaminated by eye-blinks and movements were corrected using an Independent Component Analysis (ICA) algorithm (Delorme and Makeig, 2004).

In each participant, epochs belonging to the same experimental condition were averaged, time-locked to the onset of the stimulus. Thus, three average waveforms were obtained, i.e. one waveform for each experimental condition: Pre-CVS, CVS and Post-CVS. Single-subject average waveforms were subsequently averaged to obtain group-level average waveforms.

Scalp topographies were plotted at the peak latency of the N2 and P2 LEP waves, measured at the vertex (Cz). The N2 wave was defined as the most negative deflection after stimulus onset. The P2 wave was defined as the most positive deflection after stimulus onset. N1 peaks were identified using the C4–Fz montage. For this reason, scalp topographies capturing the N1 activity were plotted, in steps of 10 ms, for the time preceding the N2 peak. This approach allowed defining better the N1 activity across time in each experimental condition.

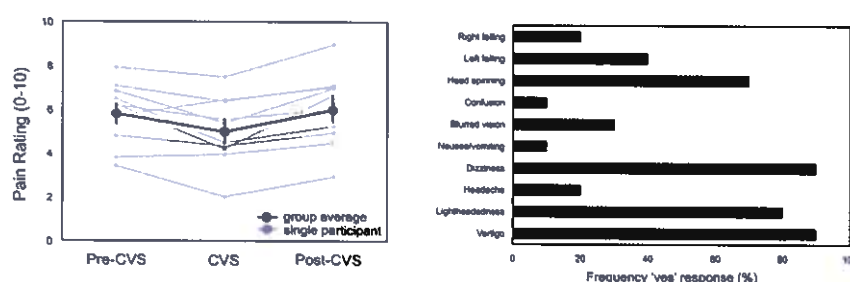


Figure 1. Left panel: CVS significantly induced an analgesic effect in the subjective judgement of pain intensity. Right panel: More than 80% of participants felt vertigo and dizziness immediately after CVS.

In all participants, laser stimuli elicited a clear pinprick sensation, related to the activation of A δ fibers (Bromm and Treede 1984). CVS induced a significant analgesic effect (Figure 1), with lower pain ratings in CVS condition compared to both Pre-CVS ($t_{(9)}=2.914$, $p=0.017$) and Post-CVS ($t_{(9)}=-4.987$, $p=0.001$) conditions. No differences in pain ratings between Pre-CVS and Post-CVS ($p>0.05$) were found.

CVS reduced the amplitude of standard LEP peak in the early time-window of the N1 wave (Pre-CVS vs CVS: $t_{(9)}=-3.535$, $p=0.006$). Similarly, comparison between CVS and Post-CVS conditions revealed a significant reduction of N1 amplitude ($t_{(9)}=3.157$, $p=0.012$). On the contrary, Pre-CVS and Post-CVS conditions were not different ($p>0.05$). Later time components were similarly affected by CVS. Both N2 and P2 waves showed significant reduction of the amplitude contrasting Pre-CVS and CVS conditions ($t_{(9)}=-4.13$, $p=0.003$ and $t_{(9)}=3.377$, $p=0.008$, respectively). A significant difference emerged in the contrast between CVS and Post-CVS conditions in both N2 ($t_{(9)}=3.892$, $p=0.004$) and P2 ($t_{(9)}=-2.78$, $p=0.021$) waves. There were trends for habituation of the N2 and P2 peaks between Pre-CVS and Post-CVS conditions (both $p>0.05$).

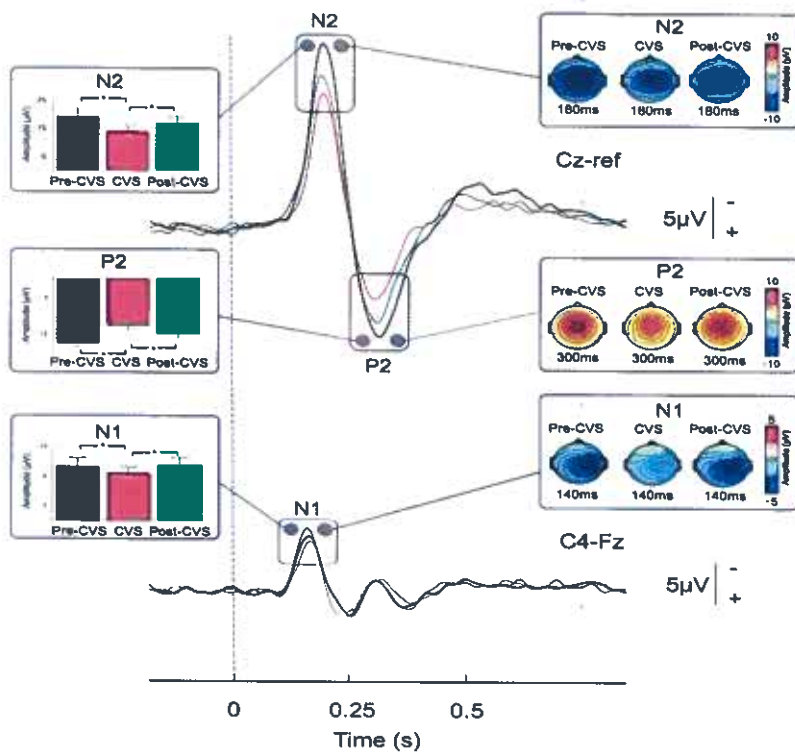


Figure 2. LEPs results.

Scalp topographies were plotted at the peak latency of the N2 and P2 LEP waves measured at the vertex (Cz) and N1 wave measured using the C4-Fz montage. The N2 wave was defined as the most negative deflection after stimulus onset. The P2 wave was defined as the most positive deflection after stimulus onset. CVS reduced the amplitude of standard LEP peak in both early time-window of the N1 wave and later time window of N2 and P2 waves.

Conclusion

These results provide that an analgesic effect is induced by caloric vestibular stimulation. Furthermore, CVS virtually modulates all cortical responses (N1, N2, and P2 waves) elicited by nociceptive stimuli. Although N2 and P2 waves showed trends for habituation between

experimental conditions, the observed reduction of N1 amplitude is purely induced by CVS. The N1 wave of the LEPs has been recently demonstrated to represent somatosensory specific activities maximally reflecting the magnitude of the incoming nociceptive input rather than the magnitude of pain perception (Lee et al., 2009). Thus, the most striking effect of the CVS was a strong reduction of cortical responses to nociceptive laser stimulation, including components localised to the primary somatosensory cortex (Lee et al., 2009).

Session 2. Modulation of body distances

Experiment B. Effect of vestibular stimulation on tactile localization.

Some evidence highlighted a vestibular-induced modulation in the primary processing of somatic stimuli. However, the vestibular contribution to other aspects of body models is not yet clear. Clinical observations suggested that vestibular signals are essential to compute body representations. For instance, caloric vestibular stimulation (CVS) positively modifies bodily disorders of neurological origin, as the disownership for body parts (somatoparaphrenia), somatoagnosia (Rode et al., 2012) and anosognosia (Rode et al., 1992). Additionally, CVS modifies or restores phantom limbs sensations in both paraplegic (Le Chapelain et al., 2001) and amputee patients (André et al., 2001). In this experiment we investigated whether vestibular inputs influence the recognition of the location of a stimulus on the skin surface. The ability to localise stimuli on the skin is subserved by a cognitive representation of the body surface, namely the superficial schema. Here we directly tested the hypothesis of general shrinkage of the body.

Participants

Eleven right-handed healthy participants (6 male, mean age \pm SD: 26 ± 4.32 years) took part in this study. Exclusion criteria included any history of motor, somatosensory, vestibular or auditory disorders. All participants gave their written informed consent and were paid for their participation. The study conformed to the standards required by the Declaration of Helsinki and was approved by the local ethics committee.

Methods

We asked blindfolded participants to sit with their left hand palm down on a table aligned with their body midline. A camera, which captured JPEG images (1.280×960 pixels), was suspended on a tripod directly above the center of the board, pointing straight down (Figure 3a). Participants used a wooden stick, which tapered to a point at the end, to indicate with their right hand the perceived location of touched point on the skin (Figure 3b). Sixteen landmarks were used: six points on the dorsum of the hand and 2 points for each finger (Figure 3c). On each trial, the experimenter touched with a modified von Frey nylon filament at a preselected location. And participants were pointed to this location. GVS was applied in bipolar configuration by a custom-built constant-current stimulator (Good Vibrations Engineering Ltd., Nobleton, Ontario, Canada) used to deliver a square wave pulse of 1 mA. Carbon rubber electrodes (10 cm^2) coated with electrode gel were placed binaurally over the mastoid processes and fixed in place with adhesive tape. According to our convection (Figure 3d), left anodal and right cathodal configuration is named 'LGVS'. The inverse polarity, namely left cathodal and right anodal configuration was named 'RGVS'. LGVS mainly activates vestibular cortical projections in the right hemisphere, conversely RGVS activates

vestibular cortical projections in the left hemisphere. A sham stimulation (PSEUDO-GVS) was applied in which the electrodes were placed on the left and right side of the neck (about 5 cm below the GVS electrodes). Three blocks for each type of stimulation were administered in random order. Each block was composed of 16 trials. The trial lasts for 10s with a total amount of stimulation of 8s.

Data analysis and results

The x–y pixel coordinates of each actual location and pointing location judgment on the images was coded using ImageJ software. Mean coordinates were computed for each landmark. Therefore, two sets of these coordinates were coded in each block, representing the actual and perceived stimulus locations. The two-point registration method developed by Bookstein (1991) was adopted to place the actual and judged locations of two specific landmarks into a common coordinate frame: thus, the knuckle of the little finger was associated to point (0,0) and the knuckle of the index finger as point (1,0). This method defines unit length relative to the size of each participant's hand. Therefore individual differences in overall hand size were removed, allowing averaging across participants.

We then calculated the error in localizing each point as follows. Localization error is considered as the combination of two components. Constant error refers to biases in localisation, and is defined by error vector between the actual location and the average of several attempts to judge its location. Variable error refers to the precision or imprecision of localization, and is defined by the standard deviation of several repeated attempts to judge the location. Notice that constant and variable error are logically independent: for example it is possible to be strongly biased, but highly precise. Here we were focusing on vestibular effects on constant error, given previous findings of spatial biases introduced by vestibular inputs. In order to evaluate the direction of the bias, CE vector was decomposed into two components, one aligned with the proximo-distal axis of the hand and the other aligned with the ulnar–radial axis.

We hypothesized that vestibular stimulation might influence tactile localization of two distinct ways, and we accordingly expressed these hypotheses as planned contrasts. First, any activation of the vestibular system might have a general effect on cognitive processes underlying the localization of touches on the skin surface, independent of the polarity of the stimulation. To test this generic hypothesis, we compared the average of the L-GVS and R-GVS conditions to the PSEUDO-GVS condition. Second, we hypothesized that the effects of vestibular stimulation on tactile localization might be specific to the hemisphere primarily activated by the vestibular stimulation. This specific hypothesis was tested by directly comparing L-GVS and R-GVS.

Investigation of the bias in the proximal-distal axes revealed a significant generic vestibular effect in the localization of tactile stimuli on the dorsum of the hand ($t_{(10)}=2.604$, $p=0.026$). On the contrary, the shift induced in the fingers was not significantly different between conditions ($p>0.05$). We qualitatively explored this bias applying a spatial criterium for grouping touches located in the

same spatial 'row' along the proximal-distal axes. For example, touches on the dorsum were divided in two different sets accordingly whether their location was closer or further to the wrist. This analysis highlighted a spatial gradient in the localisation error, i.e. touches located nearer the wrist are shifted toward the proximal direction, while stimuli located on the finger are shifted toward the distal direction. No generic vestibular effects on the ulnar-radial axes were revealed.

According to the specific hemispheric effect hypothesis, comparison between L-GVS and R-GVS revealed a significant difference in touches located on the dorsum of the hand ($t(10)=-2.596$, $p=0.027$). R-GVS induced a larger displacement toward the proximal axes than L-GVS. No differences were found comparing touches located on the fingers ($p>0.05$).

Investigation of the specific differences between GVS polarities in the ulnar radial axes showed no significant differences in stimuli applied to the dorsum of the hand ($p>0.05$), while touches delivered on the finger were significantly perceived more radial during R-GVS than L-GVS ($p>0.05$).

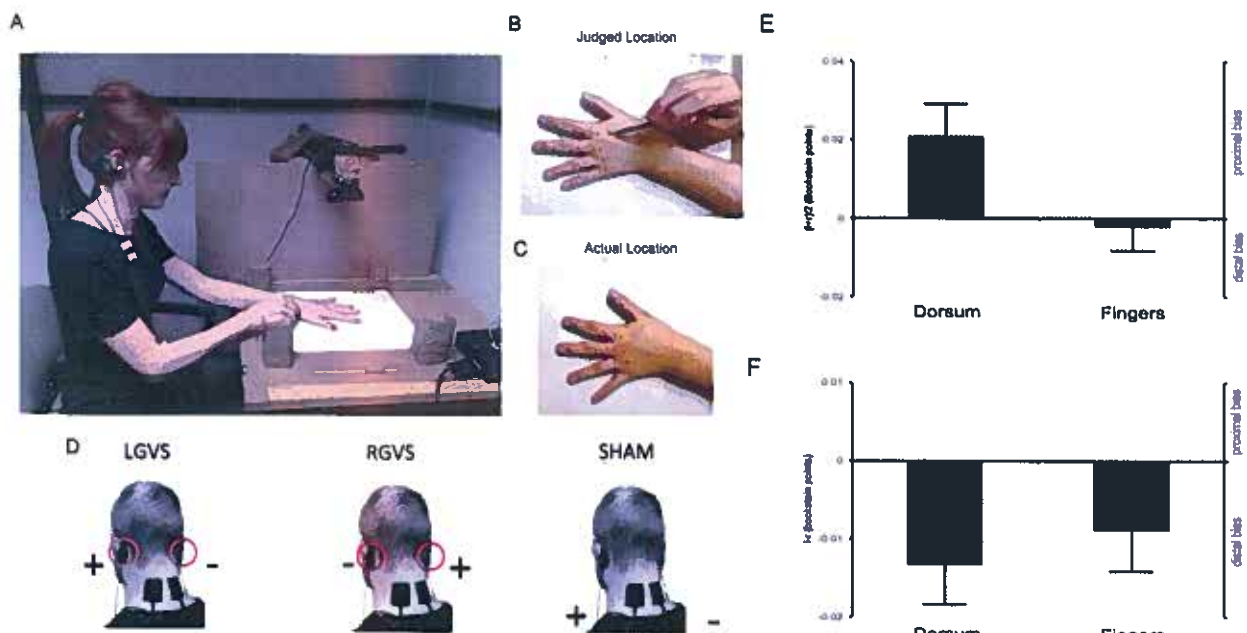


Figure 3. Tactile localization procedure and results. (A) Blindfolded participants sat with their left hand palm down on a table aligned with their body midline. JPEG images are recorded by a camera located on the center of the board. Image are saved for offline coding. (B) Participants used a wooden stick to indicate with their right hand the perceived location of touched point on the skin. (C) Landmarks locations: six points on the dorsum of the hand and two points for each finger. (D) Left anodal and right cathodal configuration is named 'LGVS'. The inverse polarity, was named 'RGVS'. A sham stimulation was applied in which the electrodes were placed on the left and right side of the neck. (E) General vestibular induced localization bias. (F) Polarity specific vestibular induced bias results.

Conclusion

General vestibular signals interfered with the localization of touches on the dorsum of the hand. However, the bias induced by vestibular inputs is selective for the proximal distal axes: stimuli located in the hand are shifted toward the wrist following a gradient with a strong bias in the dorsum and less bias in the fingertips. On the contrary, no significant displacement in the ulnar-radial axes was found. Additionally, specific polarities of vestibular inputs, associated with activation of vestibular projections in each hemisphere separately, had differential effects on localisation of touch. In particular, our data revealed that the proximal shift in tactile localization is stronger during R-GVS than L-GVS.

Hemisphere-specific effects might arise because one polarity of GVS might be stronger than the other. Alternatively, hemisphere-specific effects might be due to the potential hemispheric lateralisation of tactile localization ability. Clinical observations described patients affected by left parietal lesions showing distorted errors of tactile localisation (Rapp et al., 2002). These localisation errors preserved the somatotopic arrangement of the hand, but systematically misplace each point toward the proximal direction (Rapp et al., 2002). Finally, a combination of both these factors cannot be excluded.

Several studies have reported a spatial relation between skin receptors and cortical neurons allows precise perceptual localization. Our data highlighted vestibular-induced systematic errors in tactile localization in the distal-proximal axis, suggesting a spatial shift toward the proximal direction.

Experiment C. Effect of vestibular stimulation on position sense.

No peripheral receptors are directly informative about the size and shape of body parts. Thus the knowledge about these features are linked to a body model of the body's metric properties (Longo and Haggard, 2010). It has recently demonstrated that this body model is rather distorted (Longo and Haggard, 2010). At least for the hand, these distortions included a radial–ulnar gradient of magnification of the digits and shrinkage toward the proximo-distal axis. We assessed whether vestibular inputs interact with this model of body shape.

Participants

Twelve right-handed participants took part in this study (6 male, mean age \pm SD: 26 ± 4.32 years). Exclusion criteria included any history of motor, somatosensory, vestibular or auditory disorders. All participants gave their written informed consent and were paid for their participation. The study conformed to the standards required by the Declaration of Helsinki and was approved by the local ethics committee.

Methods

Participants sat with their left hand palm down on a table aligned with their body midline. An occluding board was placed over the hand, resting on four posts. A camera was suspended on a

tripod directly above the centre of the board, pointing straight down and it captured still JPEG images (1.280 × 960 pixels). Participants used a wooden stick, which tapered to a point at the end, to indicate with their right hand the perceived location of landmarks on their occluded left hand. Ten landmarks were used: the knuckle at the base of each finger and the tip of each finger. On each trial, a recorded voice cued the participant as to which landmark to judge. Participants were instructed to point to the location. GVS was applied in bipolar configuration by a custom-built constant-current stimulator (Good Vibrations Engineering Ltd., Nobleton, Ontario, Canada) used to deliver a square wave pulse of 1 mA. Carbon rubber electrodes (10 cm²) coated with electrode gel were placed binaurally over the mastoid processes and fixed in place with adhesive tape. According to our convention, left anodal and right cathodal configuration is named 'LGVS'. The inverse polarity, namely left cathodal and right anodal configuration was named 'RGVS'. A sham stimulation (PSEUDO-GVS) was applied in which the electrodes were placed on the left and right side of the neck (about 5 cm below the GVS electrodes). Three blocks for each type of stimulation were administered. Each block was composed of 10 trials, one of each landmark, in random order. The trial lasts for 10s; after 1000ms from the beginning of the trials the stimulation starts. Then the recorded voice was played after 1000ms and then 3500ms the pointing 'start' cue was delivered. After 3500ms the trial ended. The total GVS duration was 8 s. Just before each block, a picture was taken without the occluder so that the actual size, shape, and location of the hand could be determined.

Data analysis and results

X–Y pixel coordinates of each landmark on the images of the actual hand and the corresponding judged locations were coded using ImageJ software. Mean coordinates were computed for each landmark. Therefore, two sets of these coordinates were codified in each block: one representing the actual hand shape, the other reflecting the shape of the hand as represented by the body model. The difference between the two representations was then computed. These values were compared across different stimulation conditions, according to planned comparison (see Experiment B).

We computed a generic vestibular effect, defined as $(L-GVS+R-GVS)/2$, to identify whether generic vestibular input influences the perception of body size. Then we compared it to the PSEUDO-GVS condition. Finger length values did not show any significant difference ($p>0.05$). Similarly, hand width was not different across experimental conditions ($p>0.05$).

Comparison between L-GVS and R-GVS conditions revealed no significant difference in finger length ($p>0.05$) or in finger width ($p>0.05$).

Conclusion

Accordingly to Longo and Haggard results (2010), we found a systematically underestimation of the actual length, computed as distance between the average judged locations of each knuckle

and fingertip. However, no differences between stimulation conditions have been found. An overestimation of knuckle spacing was also observed (Longo and Haggard, 2010). Again, vestibular stimulation did not influence the width component of the hand representation. In conclusion, our data confirmed previous findings that the body model of the hand is massively distorted (Longo and Haggard, 2010), but vestibular inputs might not contribute to these distortions.

Session 3. Modulation of body-to-world distance perception

Experiment D: Effects of vestibular stimulation on distance perception.

Vestibular canal dysfunction leads to disintegration in the normal spatial relation between personal and extrapersonal space (Blanke et al., 2004), confirming the vestibular contribution to the brain's *Global Positioning System*. However, previous studies of vestibular contributions to spatial perception focussed on orienting of gaze (Angelaki et al., 2008), and perception of the subjective visual vertical (Bohmer et al., 1999). These effects on two-dimensional orienting cannot readily explain why vestibular patients also report altered experiences of distance with respect to the environment, notably depersonalisation and derealisation symptoms (Sang et al., 2006). We investigated whether galvanic vestibular stimulation alters distance perception, and thus it influences also the third dimension, i.e. depth, in healthy volunteers.

Experiment D-1: Effects of GVS on visual distance perception.

Participants

Fourteen participants (9 male, mean age \pm SD: 25.1 \pm 5.1 years) took part in this study with ethical committee approval, and on the basis of written informed consent. All participants were right-handed as assessed using the Edinburgh handedness inventory. Exclusion criteria included any history of motor, somatosensory, vestibular or auditory disorders. The experimental protocol was approved by the research ethics committee of University College London. The study adhered to the ethical standards of the Declaration of Helsinki.

Methods

During the experiment participants were asked to lie supine on the floor and to judge the absolute distance between their own body and an object or a mirror held immediately above the centre of the participant's face. Seven distances were used, four distances located in near space (i.e., reachable space, distances: 20cm, 35cm, 50cm, 65cm) and three distances in far space (i.e., non-reachable space, distances: 80cm, 95cm, 110cm).

GVS was applied using a commercial stimulator (Good Vibrations Engineering Ltd., Nobleton, Ontario, Canada) and delivering a boxcar pulse of 1 mA. Carbon rubber electrodes (area 10 cm²) coated with electrode gel were placed binaurally over the mastoid processes and fixed in place with adhesive tape. According to our convention (Figure 4a), left anodal and right cathodal configuration is named 'LGVS', while the inverse polarity, namely left cathodal and right anodal configuration, is named 'RGVS'. Sham stimulation (SHAM) was applied using electrodes on the left and right side of the neck (about 5 cm below the GVS electrodes), using left anodal and right cathodal configuration.

On each trial, the experimenter moved the object/mirror to a pre-indicated distance. Participants were instructed to keep the eyes closed until an acoustic tone indicated them to open the eyes and judge. At the beginning of the task 2 distances slightly under and slightly over the experimental range were presented, their actual distance in cm. was announced, and participants were encouraged to use these as references to calibrate their absolute distance judgements in the experimental trials. A total of twelve blocks were administered, two for each type of stimulation (LGVS, RGVS and SHAM) X type of object (Object and Mirror). Block order was randomized between participants. Each block was composed of 7 trials, one of each distance, in random order. The trial lasted for 8s: first, the participant lay quietly with eyes closed for 4 s. Then, GVS started. One second later an acoustic tone instructed the participant to open his eyes, and judge the distance between his body and the object/mirror by giving a verbal report in cm. The response window was 3 s. At the end of the response window, a further tone instructed the participant to close their eyes and GVS ended. The total duration of stimulation was 4s per trial.

Data analysis and results

A 2 (Object: object/mirror) X 3 (Stimulation: LGVS, RGVS, Sham) X 7 (Distance: (20cm, 35cm, 50cm, 65cm, 80cm, 95cm, 110cm) ANOVA was performed on the absolute distance judgement. Data showed a Main effect of Distance ($p < 0.001$). Additionally, a main effect of Object ($p = 0.001$) was found, with the mirror being judged farther away than the object. Finally, there was a significant interaction between Distance and Stimulation ($p = 0.011$, Figure 4b). Since there were no interactions involving the effect of object, data for judging the mirror and object were collapsed in subsequent analyses. Piecewise linear regressions were used for each subject and condition to identify the transition point between near and far space. We found a significant main effect of stimulation ($p = 0.015$). No differences between LGVS and RGVS ($p = 0.13$), or between RGVS and SHAM ($p = 0.11$) were found (Figure 4c), but LGVS resulted in the transition between near and far space shifting significantly closer to the body than SHAM ($p = 0.01$), implying an increased portion of the environment being subjectively perceived as far space (Figure 4c).

Experiment C-2. Effects of GVS on sound distance perception.

Participants

Fourteen participants (7 male, mean age \pm SD: 25.1 \pm 4.7 years) took part in this study. All participants were right-handed as assessed using the Edinburgh handedness inventory. The experimental protocol was approved by the research ethics committee of University College London.

Methods

During the task, participants comfortably sat blindfolded and wearing headphones. RoomSim software (Campbell et al., 2005) was used to artificially create a 7x3x3m room with sounds located at different distances (1m, 1.5m, 2m, 2.5m, 3m, 3.5m, 4m) from the listener, and sound loudness and reverberation were manipulated according to distances. At the beginning of each block, 2 distances just above and just below the test range were played, and their distance given, to encourage participants using these as references. On each trial, the test sound was played, and participants judged the absolute distance between their own body and the sound of an object located in different distances of the far space. GVS and sham stimulation were delivered exactly as in Experiment D-1. A total of twelve blocks were administered, four blocks for each type of stimulation (LGVS, RGVS and SHAM). Block order was randomized between participants. Each block was composed of 7 trials, one of each distance, in random order. The trial lasted for 8s; 4s from the beginning of the trial the stimulation started and lasted for 4s.

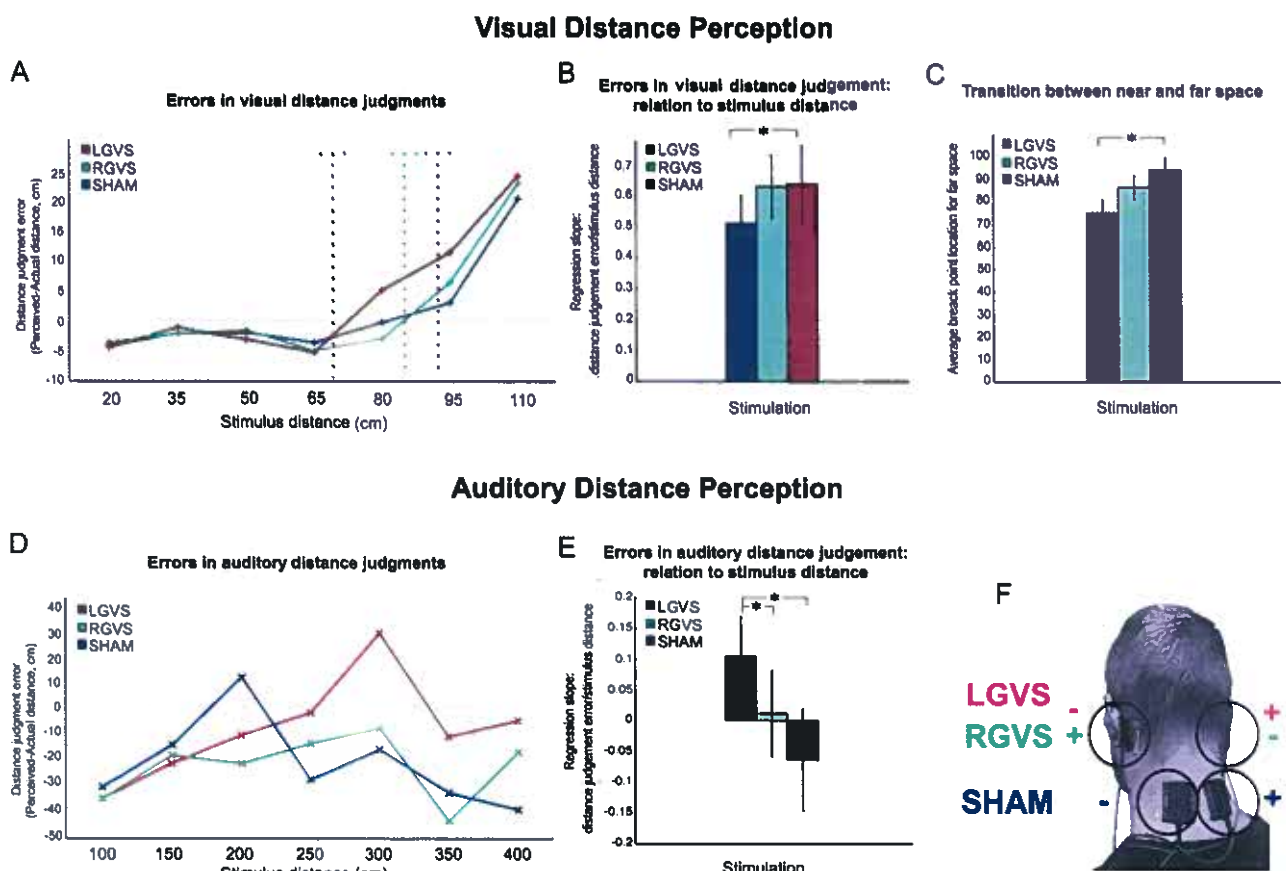


Figure 4. Galvanic vestibular stimulation procedure and results.

(A) Visual distance errors (perceived-actual distance) are represented as a function of stimulus distance. Note minimal errors for objects within reachable space, transitioning to linear relation between error and stimulus distance in far space. Note also overestimation with increasing distance for LGVS. (B) Errors in visual distance judgement as a function of stimulus distance. (C) Transition between near and far space in visual distance judgements results. (D) Auditory distance errors (perceived-actual distance) are represented as a function of stimulus distance. (E) Errors in auditory distance judgement as a function of stimulus distance. The slope of regression lines were calculated for each condition and compared across subjects. (F) GVS condition.

Data analysis and results

Regression lines of judgement error on actual distance were calculated for each condition and subject. Analysis of regression slopes showed a significant effect of stimulation type ($p = 0.005$), driven by a significant difference between LGVS and SHAM ($p = 0.004$) and between LGVS and RGVS ($p = 0.04$) (Figure 4d). In contrast, slopes were similar in RGVS and SHAM conditions ($p = 0.16$).

Conclusion

Vestibular inputs also directly influence the third distance dimension of space perception. Specifically, activating the vestibular network of the right hemisphere caused environmental objects to seem slightly, but consistently, more distant than under sham stimulation. Importantly, this result was consistent across visual and auditory sensory modalities. This makes interpretations based on vestibular-ocular reflexes or visuo-vestibular interactions unlikely. 3D distance is not coded directly by the semicircular canals of the vestibular system, though it could be computed indirectly by integrating otolith translational acceleration signals. However, these results probably do not reflect simple neural integration of GVS-induced firing, for several reasons. First, it is unclear why integrating aggregate otolith signals from artificial stimulation would produce increases in perceived distance, rather than decreases, or no net effect. Second, it is unclear from purely low-level accounts why our effects were specific to objects in far space, and to stimulation of the right-hemisphere vestibular network. Instead, we suggest that distance judgements refer to higher-level neural maps of peripersonal and navigational space, possibly located in parietal and hippocampal regions, which are known to receive vestibular input (Smith, 1997).

Computing object location from multiple sensory signals is fundamental for effective interaction with the surroundings. Combining vestibular signals with information about current head position relative to gravity would provide sufficient information to map self-motion onto the ground surface, and thus compute distance (Day and Fitzpatrick, 2005). Animal studies confirm that vestibular signals update the hippocampal 'spatial map' (Smith, 1997).

In conclusion, vestibular stimulation made distant environmental objects seem even farther away, suggesting that a function of the normal vestibular input may be to maintain the appropriate linkage between one's own body and the world.

Experiment E. Effects of vestibular stimulation on exploitation and exploration.

Adaptive behaviours in a changing world require the ability to balance exploration and exploitation (Cohen et al. 2007). Exploration involves discovering new possibilities and varying choices, while exploitation involves perseveration and stereotyped behaviour. sOften, both exploration and

exploitation are couched in terms of spatial location and orientation with respect to the external environment. The vestibular system is essential for all the interactions between the organism and the external environment. Therefore, one might expect vestibular inputs contribute to the balance between exploratory and exploitative orienting behaviours. However, a very general distinction, rather similar to the explore/exploit distinction in spatial foraging, can also be identified in strategic control of almost any behaviour. Almost any behaviour or choice can be changed in a novel way (akin to exploration), or repeated in a routine, perseverative or stereotyped way (akin to exploitation). It remains unclear whether the vestibular system could contribute to the balance of behaviour control in such non-spatial, non-navigational contexts. Here we used galvanic vestibular stimulation (GVS) to investigate whether vestibular inputs to each hemisphere contribute to the balancing between novel and stereotyped responses in generating behaviour.

Participants

Twenty-four right-handed paid participants volunteered in the study (14 male, ages mean \pm SD: 24.7 \pm 4.91 years). Subjects with a history of vestibular or auditory disorders were excluded. Informed consent was obtained prior to participation in the experiment. The experimental protocol was approved by University College London research ethics committee. The study was designed according to ethical standards of the Declaration of Helsinki. Data from one subject was discarded due to an inability to correctly follow the instructions

Methods

Bipolar GVS was used to deliver a boxcar pulse of 1 mA with 11 s of duration, via a commercial stimulator (Good Vibrations Engineering Ltd., Nobleton, Ontario, Canada). Carbon rubber electrodes (area 10 cm²) were placed binaurally over the mastoid processes and fixed in place with adhesive tape. According to our convention, left anodal and right cathodal configuration is named 'L-GVS', and predominantly stimulates the right hemisphere. The inverse polarity, namely left cathodal and right anodal configuration, is named 'R-GVS', and predominantly stimulates the left hemisphere. A 'PSEUDO-GVS' stimulation was applied using electrodes on the left and right side of the neck (about 5 cm below the GVS electrodes), with a left anodal and right cathodal configuration.

The random number generation task requires participants to generate a sequence of twenty consecutive digits. In particular, participants were instructed to name the digits from 1 to 9 as random as possible. The generation was paced to the beats at 2 Hz, lasting approximately 10.000 ms. The beginning of each trial (i.e. each sequence) was signalled by some acoustic cues. L-GVS, R-GVS or PSEUDO-GVS was delivered for eleven seconds. Three sequences lasting approximately fourteen seconds for each type of stimulation were repeated in a pseudo-randomized order. The order was different in each participant.

Data analysis and results

The data were analysed by using dependent variables previously established in the random number generation literature, and linked to specific hypothetical cognitive components of random number generation. Analysis of the spatial component in the random number generation task was assessed by calculating the percentage of large digits ('6', '7', '8' and '9') indicating preference for numbers at the right side of the mental number line (Loetscher and Brugger 2007). We also estimated the distribution of first-order differences (FODs) (Towse and Neil 1998), between successive numbers. FODs varied between -8, i.e. response '9' followed by response '1', and +8, i.e. response '1' followed by response '9'. Positive values indicate ascending series, or following a mental number line rightwards, whereas negative values indicate descending series, or following a number line leftwards.

To calculate the quality of the randomness produced in the random number generation task, we calculated the redundancy score (R score) for each sequence. This reflects sampling bias, by calculating deviations from the equiprobability of response alternatives. R score ranges from 0 (all alternatives generated equally frequently) to 100 (one single alternative provided on all trials) (Towse and Neil 1998). We reasoned that low R score values would correspond to exploration or novel behaviour, and high values to exploitation or routine behaviour. Finally, the random number generation index (RNG-I) was applied to assess the degree of equiprobability of pairs of consecutive responses. RNG-I ranges from 0 (all sequential pairs equally frequent) to 1 (perfect predictability of a digit from the preceding digit) (Towse and Neil 1998). Both repetition and counting, for example, would produce high values of RNG-I. An open-source program was used to calculate R score and RNG-I (<http://www.lancs.ac.uk/staff/towse/rgcpage.html>).

Percentages of large digits, FODs, R scores and RNG-I indexes were estimated for each sequence and averaged within each experimental condition, i.e. L-GVS, R-GVS and PSEUDO-GVS. We hypothesized that vestibular stimulation might influence random number generation in either of two distinct ways, and we accordingly expressed these hypotheses as planned contrasts. First, any activation of the vestibular system might have a general effect on cognitive processes underlying random number generation, independent of the polarity of the stimulation, and of any specific hemispheric effects.

To directly investigate whether vestibular stimulation influences random number generation, we computed a generic vestibular effect, defined as $(L-GVS+R-GVS)/2$, and compared this to the PSEUDO-GVS condition, for each dependent variable. Investigation of spatial effects in random number generation did not reveal any differences between vestibular stimulation and pseudo-stimulation. The percentage of 'large' digits generated did not differ between experimental conditions ($p>0.05$) (Figure 5a). These results indicate that vestibular activation did not elicit any general leftward or rightward preference in the generation of number. Similarly, neither the sum of negative FODs (Figure 5b), nor the sum of positive FODs (Figure 5c) differed significantly between experimental conditions, ($p>0.05$). Testing the hypothesis of a generic vestibular effect on

measures of randomness did not reveal differences. No generic vestibular effect was found in the redundancy score (R score) ($p>0.05$) (Figure 5d) or RNG-I index ($p>0.05$) (Figure 5e).

To investigate differences in how vestibular projections in each hemisphere might influence the cognitive processes involved in random number generation, we directly compare L-GVS and R-GVS conditions. No differences were found between experimental conditions in the dependent variables used to investigate spatial effects in random number generation ($p>0.05$). In particular, R-GVS did not decrease the leftward bias, nor did L-GVS decrease the rightward bias, as a hypothesis of spatial attentional shifts induced by GVS might predict.

In contrast, measures of randomness revealed specific differences between GVS polarities. The redundancy score (R score) significantly differed between the two polarities of stimulation ($t(22)=-2.25$, $p=0.035$), because R-GVS increased redundancy relative to L-GVS (Figure 5d). To investigate whether this effect reflected a benefit or a cost, we additionally compared each individual stimulation condition to PSEUDO-GVS. We found that neither mean was significantly different from zero ($p>0.05$), suggesting that the effect lay fundamentally in the balance between the two experimental stimulations, rather than an effect of just one polarity on redundancy. Finally, RNG-I did not show a significant difference between L-GVS and R-GVS ($p>0.05$) (Figure 5e).

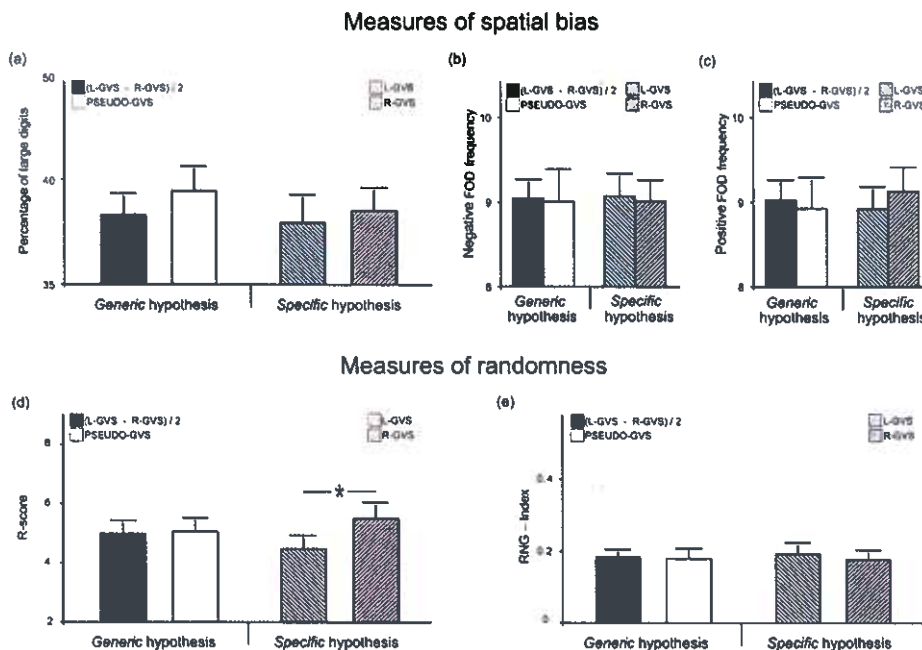


Figure 5. Effects of GVS on spatial bias and randomness.

(a) Preference for large digits as a function of GVS condition. (b) Sum of negative values indicating descending bias and (c) sum of positive values indicating ascending bias in each experimental condition. (d) Redundancy scores in each experimental condition. (e) RNG-I scores in each experimental condition.

Conclusion

Vestibular input, in general, did not interfere with the cognitive processes involved in random number generation. In contrast, specific polarities of vestibular input, associated with activation of vestibular projections in each hemisphere separately, had differential effects on specific aspects of

random number generation behaviour. In particular, our data revealed an hemisphere-specific modulation in the redundancy of behaviour: L-GVS specifically decreased redundancy, or increased randomness, compared to R-GVS which increased redundancy, or decreased randomness. Other dependent variables showed no significant modulation by GVS condition.

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1. Ferrè ER, Bottini G, Haggard P (2012). Vestibular modulation of somatosensory processing. *Brain Struct Funct*. DOI: 10.1007/s00429-012-0404-7
2. Ferrè ER, Bottini G, Iannetti GD, Haggard P(2012). The balance of feelings. Vestibular modulation of bodily sensations. *Cortex*. DOI 10.1016/j.cortex.2012.01.012

Manuscripts submitted and in preparation

1. Ferrè ER, Vagnoni E, Haggard P. Galvanic vestibular stimulation influences randomness of number generation. (Under Review in *Experimental Brain Research*)
2. Ferrè ER, Bottini G, Day B, Haggard P. Vestibular-Somatosensory interaction: a sham-controlled study. (Under Review in *Neuroscience Letters*)
3. Ferrè ER, Fuentes C, Haggard P. Reallocating the world. Vestibular contribution to distance perception. (In preparation)
4. Ferrè ER, Haggard P, Bottini G, Iannetti GD. Vestibular stimulation modulates early cortical responses to nociceptive stimuli. (In preparation).
5. Ferrè ER, Haggard P. Vestibular inputs bias touch localization. (in preparation).

Poster and oral presentations.

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3. Ferrè ER, Haggard P, Bottini G, Iannetti GD. Vestibular stimulation modulates early cortical responses elicited by selective nociceptive stimuli. International Association for the Study of Pain Meeting, Milan 27-31 August 2012.
4. Ferrè ER, Fuentes CT, Haggard P. Reallocating the world. Vestibular contribution to distance perception. Association for scientific study of consciousness ASSC16, Brighton, 2-6 July 2012.
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