

DIRECTION-DEPENDENT ACTIVATION OF THE INSULAR CORTEX DURING VERTICAL AND HORIZONTAL HAND MOVEMENTS

C. ROUSSEAU,^{a,b} L. FAUTRELLE,^{f,g}
C. PAPAXANTHIS,^{a,b,*} L. FADIGA,^{d,e} T. POZZO^{a,b,c,d} AND
O. WHITE^{a,b}

^a Université de Bourgogne Franche-Comté (UBFC), Cognition Action et Plasticité Sensorimotrice (CAPS) UMR1093, F-21078 Dijon, France

^b Institut National de Santé et de Recherche Médicale (INSERM U1093), Cognition Action et Plasticité Sensorimotrice (CAPS) UMR1093, BP 27877, F-21078 Dijon, France

^c Institut Universitaire de France (IUF), Paris, France

^d IIT@UNIFE Center for Translational Neurophysiology, Istituto Italiano di Tecnologia, Italy

^e Section of Human Physiology, Università di Ferrara, Ferrara 44121, Italy

^f EA 2931, Centre de Recherches sur le Sport et le Mouvement, Campus Universitaire Paris Ouest Nanterre La Défense, UFR STAPS Bât S., 200 avenue de la République, 92000 Nanterre, France

^g Université de Paris Ouest Nanterre la Défense, UFR STAPS, 92000 Nanterre, France

Abstract—The planning of any motor action requires a complex multisensory processing by the brain. Gravity – immutable on Earth – has been shown to be a key input to these mechanisms. Seminal fMRI studies performed during visual perception of falling objects and self-motion demonstrated that humans represent the action of gravity in parts of the cortical vestibular system; in particular, the insular cortex and the cerebellum. However, little is known as to whether a specific neural network is engaged when processing non-visual signals relevant to gravity. We asked participants to perform vertical and horizontal hand movements without visual control, while lying in a 3T-MRI scanner. We highlighted brain regions activated in the processing of vertical movements, for which the effects of gravity changed during execution. Precisely, the left insula was activated in vertical movements and not in horizontal movements. Moreover, the network identified by contrasting vertical and horizontal movements overlapped with neural correlates previously associated to the processing of simulated self-motion and visual perception of the vertical direction. Interestingly, we found that the insular cortex activity is direction-dependent which suggests that this brain region processes the effects of gravity on the moving limbs through

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Key words: fMRI, gravitational force, hand movements, insular cortex, internal model.

INTRODUCTION

Gravity fundamentally affects the dynamics of all our everyday movements. Living beings have learned to live with gravity since time immemorial. Therefore, the CNS (Central Nervous System) has developed neural mechanisms to process gravitational acceleration in order to refine motor control and planning.

Biological sensors provide complementary signals that allow the brain to form an internal representation of gravity. Otoliths – which are linear accelerometers – respond identically during translational motion and gravitational acceleration. Remarkably, Angelaki and colleagues highlighted populations of neurons in monkeys which reflect the computations necessary to encode the physics of the external world (as gravity) in vestibular nuclei and cerebellar neurons. In particular, the neural activities of cells of the rostral vestibular nuclei and the fastigial nucleus of the cerebellum revealed processed rather than sensory-like, motion information (Angelaki et al., 1999, 2004; Angelaki and Dickman, 2000). This provides clear evidence that the action of gravity on otoliths allows the CNS to define the vertical direction on body–limb joints prior to engage any action. Previous investigations showed that the mechanical effects of gravity on body motion are well anticipated, suggesting that humans optimize the effects of gravitational force on subsequent actions in a predictive, feedforward manner (Pozzo et al., 1998; Augurelle et al., 2003; Zago et al., 2005; Gentili et al., 2007; White et al., 2008; Gaveau et al., 2014). This strategy allows circumvent the incompressible delays of feedback.

Vertical upward and downward limb movements show robust kinematic asymmetries (Papaxanthis et al., 1998a, 2005; Gentili et al., 2007; Gaveau and Papaxanthis, 2011). Bell-shaped velocity profiles reach their peak sooner in upward movements and later in downward movements, while the acceleration and deceleration phases have the same duration for movements performed in the horizontal plane. Further, these asymmetries appear as early as 200 ms after movement onset

*Correspondence to: C. Papaxanthis, Université de Bourgogne, UFR STAPS, F-21078 Dijon, France. Tel: +33-380396757.

E-mail address: charalambos.papaxanthis@u-bourgogne.fr (C. Papaxanthis).

Abbreviations: BOLD, blood oxygenation level-dependent; CNS, Central Nervous System; GLM, General Linear Model; HL, Horizontal movement with additional load; MNI, Montreal Neurological Institute; VL, Vertical movement with additional load.

which clearly indicates feedforward control (Gaveau and Papaxanthis, 2011). As shown in altered gravity experiments, exposure in microgravity modifies this directional asymmetry which clearly confirmed a central integration of gravity effects in the dynamic planning process (Papaxanthis et al., 2005; Crevecoeur et al., 2009a, 2009b; White, 2015). The same authors also proposed that the CNS is able to control independently inertial and gravitational forces to optimize movement. Recently, it has been demonstrated that the specific temporal pattern of vertical limb and body displacements is the result of direction-dependent planning processes that minimize energy expenditure on Earth (Berret et al., 2008; Gaveau et al., 2014).

Besides these behavioral results, we still lack a general understanding of neural mechanisms that encode the interaction of our movements with the external environment. Recent seminal investigations showed that the visual processing of gravity activates in particular the insular cortex and the temporo-parietal junction (Indovina et al., 2005). These experiments demonstrated that the processing of visual motion of an object along the vertical direction depends on the expected effects of gravitational acceleration, i.e., the activation of an internal model of gravity, on massive bodies (McIntyre et al., 2001; Zago et al., 2009; Moscatelli and Lacquaniti, 2011).

Most previous investigations addressed the complex question of the internal representation of gravity through visual stimuli presentation (Lacquaniti and Maioli, 1989; McIntyre et al., 2001; Zago et al., 2004, 2009; Indovina et al., 2005; Zago and Lacquaniti, 2005). Whether this is the case, however, during arm movements remains still an open question. Is the insular cortex engaged during the performance of arm movements without visual control? Here, we specifically test how non-visual information contributes to the processing of an internal model of gravity through the activation of the insular cortex. Because gravity influences differently the dynamics of movements in vertical and horizontal directions, we asked participants to perform hand movements in both directions while lying in an MRI scanner. We predict the existence of areas dedicated to the processing of non-visual information when gravity affects the way the task is achieved. By contrasting brain activation in vertical vs. horizontal conditions, we expect to highlight direction-dependent brain activity dedicated to the non-visual processing of gravity.

EXPERIMENTAL PROCEDURES

Participants

Nineteen healthy participants (all males, 29.1 ± 5.8 years old, from 22 to 50 years, 180.7 ± 5.6 cm, and 76.5 ± 7.6 kg) volunteered for the experiment. None of them had history of neuromuscular or neurological disorders or any indication against an MRI examination. All were right handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). All experimental acquisitions were conducted during the same time slots between 8 pm and midnight. The entire experiment conformed to the Declaration of Helsinki and informed

consent was obtained from all participants. The protocol was approved by the clinical Ethics Committee of the University Hospital of Dijon (registered number 2009-A00646-51).

Data acquisition

Data were acquired using a 3T Magnetom Trio system (Siemens AG, Munich, Germany), equipped with a standard head coil configuration. We used standard single shot echo planar (EPI) T2*-weighted sequence in order to measure blood oxygenation level-dependent (BOLD) contrast. The whole brain was covered in 40 adjacent interlaced axial slices (3 mm thickness, TR = 3050 ms, TE = 45 ms, flip angle = 90°), each of which was acquired within a 64×64 Matrix (FOV was 20×20 cm), resulting in a voxel size of 3.125×3.125 mm.

Experimental design and fMRI paradigm

We adopted a block design paradigm that alternated periods of rest (10 scans) and periods of hand movements (10 scans) in two different conditions. Participants were lying on their back in the MRI scanner with their upper right limb elevated by 5 cm with small cushions. This prevented the right hand to become in contact with surrounding objects during hand movement recording sessions. In addition, the experiment was realized in the darkness to avoid particular visual stimulation. During the rest period, participants were instructed to remain quiet, still, and to keep their eyes open without thinking of anything in particular. Participants were carefully observed during this period to ensure that no movement was performed. During the task blocks, participants moved their hand either vertically or horizontally. We repeated rest and hand movements blocks four times in one recording session. Therefore, a total of 80 scans in each experimental condition realized during one session (4×10 scans at rest and 4×10 scans of hand movements) were recorded per participant. The order of sessions was counterbalanced across participants.

In a first session (Vertical condition), participants were instructed to perform hand flexions and extensions in the sagittal plane at comfortable pace. Their hand was in supine position (palm up) and their fingers released (Fig. 1A). In a second session, participants performed the same movements in the horizontal plane (Horizontal condition), palm inward (Fig. 1B). Importantly, both movements involved the same flexor and extensor muscles of the hand, which allowed us to rule out any biomechanical effect of muscle activity on the BOLD signal (Mendell and Florence, 1990; Hislop and Montgomery, 2002). On average, participants realized 9 (± 1.2) movements per block, which resulted in 36 movements for each experimental condition. The number of movements performed in the Vertical condition and in the Horizontal condition was not statistically different ($t_{18} = 0.396$; $p = 0.697$), eliminating any possible effect linked to the amount of motion.

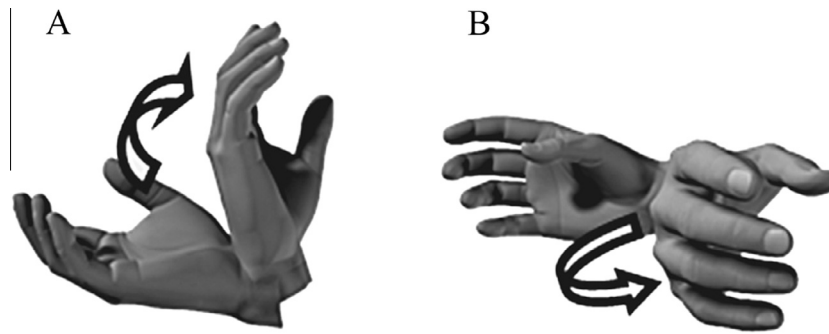


Fig. 1. Experimental task. Hand movements were realized by participant along the vertical direction with palm up (A) and along horizontal direction with palm inward (B). Both movements involved the same muscles and were equivalent in joint coordinates but not in the Euclidian space.

Hand movements were performed along with or orthogonal to gravity, and the relatively small biomechanical differences between these two directions concern the force required to perform the movement. Indeed, torques and inertial forces are dependent on the mass of the system being accelerated, but are low in the case of the hand. To enhance the contrast between the two directions, we added an off-center mass on the participants' hand, which increased more than twice the gravitational torque. This still resulted in small movement amplitudes but amplified the differences to control horizontal and vertical movements. In horizontal movements, the resultant of the weight (vertical) and the inertial forces due to movement onset and offset (horizontal) varies in direction and amplitude in the vertical plane because of motion kinematics. In vertical movements, the effect of mass and inertia are much more important because weight and inertia vectors are collinear. Fourteen participants (six females, 24.8 ± 3.9 years old, from 21 to 35 years, 2 from the main experiment) were equipped with a latex glove attached to a cylinder (25-cm length, 4.2-cm diameter, 35.17 g) placed along the hand axis and loaded with a non-ferromagnetic load at its end (94.57 g). Participants realized the same hand flexion and extension as before in the sagittal plane (Vertical Loaded condition) and in the horizontal plane (Horizontal Loaded condition) but with the additional load. This simple design allowed participants to keep the same hand configuration as in the main experiment, namely palm up or palm inward with fingers released, while increasing the torque at rest from 0.21 Nm to 0.50 Nm (considering a hand mass of 0.42 kg).

Data pre-processing and analysis

Analysis was performed using SPM 8 (www.fil.ion.ucl.ac.uk/spm). For functional data pre-processing, each volume of both sessions was spatially realigned with the first volume of the first session using a 6-parameter fixed body transformation. Secondly, the T1-weighted anatomical volume was co-registered to mean images created by the realignment procedure and was normalized to the Montreal Neurological Institute (MNI) space resampled to 2 mm isotropic voxel size. The anatomical normalization parameters were subsequently

used for the normalization of functional volumes. Finally, the normalized functional images were spatially smoothed with a $8 \times 8 \times 8 \text{ mm}^3$ full-width at half-maximum isotropic Gaussian kernel. Time series at each voxel for each subject were high-pass filtered at 128 s to remove low-frequency drifts in signal and pre-whitened by means of an autoregressive model AR(1).

Data were subsequently analyzed by applying a General Linear Model (GLM) separately for each participant. The two types of hand movements (Vertical and Horizontal), and rest periods were modeled using a box-car function convolved with the hemodynamic response function (HRF). Movement parameters derived from realignment corrections were also used as regressors of no interest.

At the individual level, we first assessed the whole network of brain areas involved in the processing of the motor task by contrasting hand movement blocks with the rest blocks in each session [$V > \text{rest}$] and [$H > \text{rest}$]. Then we highlighted brain correlates associated with the processing of direction of motion by contrasting [$V\text{-rest} > H\text{-rest}$] conditions. At this level, one participant was excluded because no activation in the motor cortex was found, questioning about the reliability of its data. Similarly, in the control experiment, we assessed brain activity using the same contrasts (VL: Vertical movement with additional load; HL: Horizontal movement with additional load).

We next performed a group analysis and applied one sample t -tests for the three contrasts. Clusters of activated voxels were identified, based on the intensity of the individual response, $p < 0.050$, FWE corrected for multiple comparisons, ($t_{18} > 7.03$) for the two contrasts calculated relatively to the rest period and $p < 0.001$ uncorrected ($t_{18} > 3.61$) for contrasts between conditions of interest [$V\text{-rest} > H\text{-rest}$].

We pushed the analysis one step further and considered insular cortex activity more specifically. We used an anatomical mask of the bilateral insula to perform group analysis and applied one sample t -tests for the [$V\text{-rest} > H\text{-rest}$] and [$VL\text{-rest} > HL\text{-rest}$] contrasts of interest. To investigate brain responses in the insular cortex, we used more sensitive statistics ($p < 0.050$, corrected for multiple comparisons).

Results of brain activations were characterized in terms of their peak height and spatial extent and were

presented in normalized stereotactic space (MNI). Brain responses were identified by means of the anatomic automatic labeling (Tzourio-Mazoyer et al., 2002).

RESULTS

The main objective of this study was to identify the direction-dependent neural network when the CNS processes non-visual information relevant to gravity during the planning and control processes of movement. First, we verified that usual sensorimotor areas were activated for the two motor tasks: that is horizontal and vertical hand movements compared to rest. Then, we concentrated our analyses on differences in brain activity between the two movement directions. Notably, we focused on the insular cortex, which is the core region of the vestibular system related to the visual processing of gravity effects, hence that should be sensitive to direction.

Brain activations associated with motion of the right hand

Table 1 reports brain activities for both contrasts [V > rest] and [H > rest] that were specifically involved in hand movements (both $p < 0.05$, corrected for multiple comparisons). The largest cluster for the vertical hand movements (Fig. 2) was identified in the right cerebellum ($X = 2$, $Y = -52$, $Z = -6$). A smaller cluster was also found in the left cerebellum ($X = -26$, $Y = -64$, $Z = -24$). Brain responses were clearly highlighted in motor areas such as the left primary motor and somatosensory cortices ($X = -34$, $Y = -36$, $Z = 60$). The premotor cortex and, more specifically, the left SMA ($X = -4$, $Y = -8$, $Z = 56$) were also activated during the vertical hand movements. Similarly, the

largest cluster for the horizontal hand movements (Fig. 2) was identified in the right cerebellum ($X = 4$, $Y = -52$, $Z = -2$) with a smaller secondary cluster ($X = 20$, $Y = -46$, $Z = -26$). The left primary motor and somatosensory cortices ($X = -34$, $Y = -22$, $Z = 56$) and the left premotor cortex ($X = -22$, $Y = -16$, $Z = 70$) were also activated during this task.

Direction-specific brain activations

Interestingly, only hand movements performed along the vertical direction activated the insular cortex ($X = -44$, $Y = 0$, $Z = 8$). In contrast, we did not obtain brain responses in the insular cortex for hand movements performed along the horizontal direction. We also assessed whether brain activity in the insula was associated to movement direction by contrasting horizontal and vertical movements ([V-rest > H-rest]; p -uncorrected < 0.001 , Fig. 3A). As expected, several clusters in the insular cortex were identified ($X = 34$, $Y = -24$, $Z = 22$; $X = 32$, $Y = 14$, $Z = 14$, $X = -30$, $Y = 10$, $Z = 16$; Table 2). In addition, we obtained brain responses in the bilateral premotor cortex (in particular in the left and right SMA) and the dorso-posterior cingulate cortex. For the same contrast of interest, we also localized brain activity in the bilateral hippocampus, and we found small clusters in the left anterior cerebellum and the left anterior prefrontal cortex. When using an anatomical mask of the bilateral insula for the contrast [V-rest > H-rest], differential activity reached statistical significance at corrected level ($p < 0.050$ corrected for multiple comparisons) in three clusters in the insular cortex ($t = 5.74$; $X = 34$, $Y = -24$, $Z = 22$; $t = 5.73$; $X = 32$, $Y = 14$, $Z = 14$; $t = 4.85$; $X = 32$, $Y = 24$, $Z = 14$). For the sake of completeness, we also tested the contrast [H-rest > V-rest] in order to

Table 1. Significant activations to the contrasts [V > rest] and [H > rest] (p -corrected for multiple comparisons < 0.05). Brain lobe, regions from AAL atlas and coordinates (x , y , z) in the MNI-space are reported. The first region has the highest number of voxels in the cluster and the other regions [between brackets] belong to the cluster with lower number of voxels. The two last columns correspond respectively to the maximum T-value and the number of voxels in the cluster

Lobes	AAL regions	X	Y	Z	T-Value	Voxels in cluster
V > rest						
Anterior and posterior lobe of cerebellum	Right cerebellum (lobules IV and V) [Vermis lobules IV & V] [Right cerebellum (lobule VI)] [Vermis lobule VI]	2	-52	-6	11.25	1005
Parietal and frontal lobe	Left precentral gyrus [Left postcentral gyrus]	-34	-36	60	10.7	678
Posterior lobe of cerebellum	Left cerebellum (lobule VI)	-26	-64	-24	8.51	95
Sub lobar & frontal lobe	Left Rolandic operculum [Left insula]	-44	0	8	8.03	37
Frontal lobe	Left superior motor area	-4	-8	56	7.79	35
H > rest						
Anterior lobe of cerebellum	Right cerebellum (lobules IV and V) [Vermis lobules IV & V]	4	-52	-2	9.51	178
Frontal & parietal lobe	Left precentral gyrus [Left postcentral gyrus]	-34	-22	56	7.43	80
Frontal lobe	Left precentral gyrus	-22	-16	70	7.16	4
Anterior lobe of cerebellum	Right cerebellum (lobules IV and V)	20	-46	-26	6.93	6

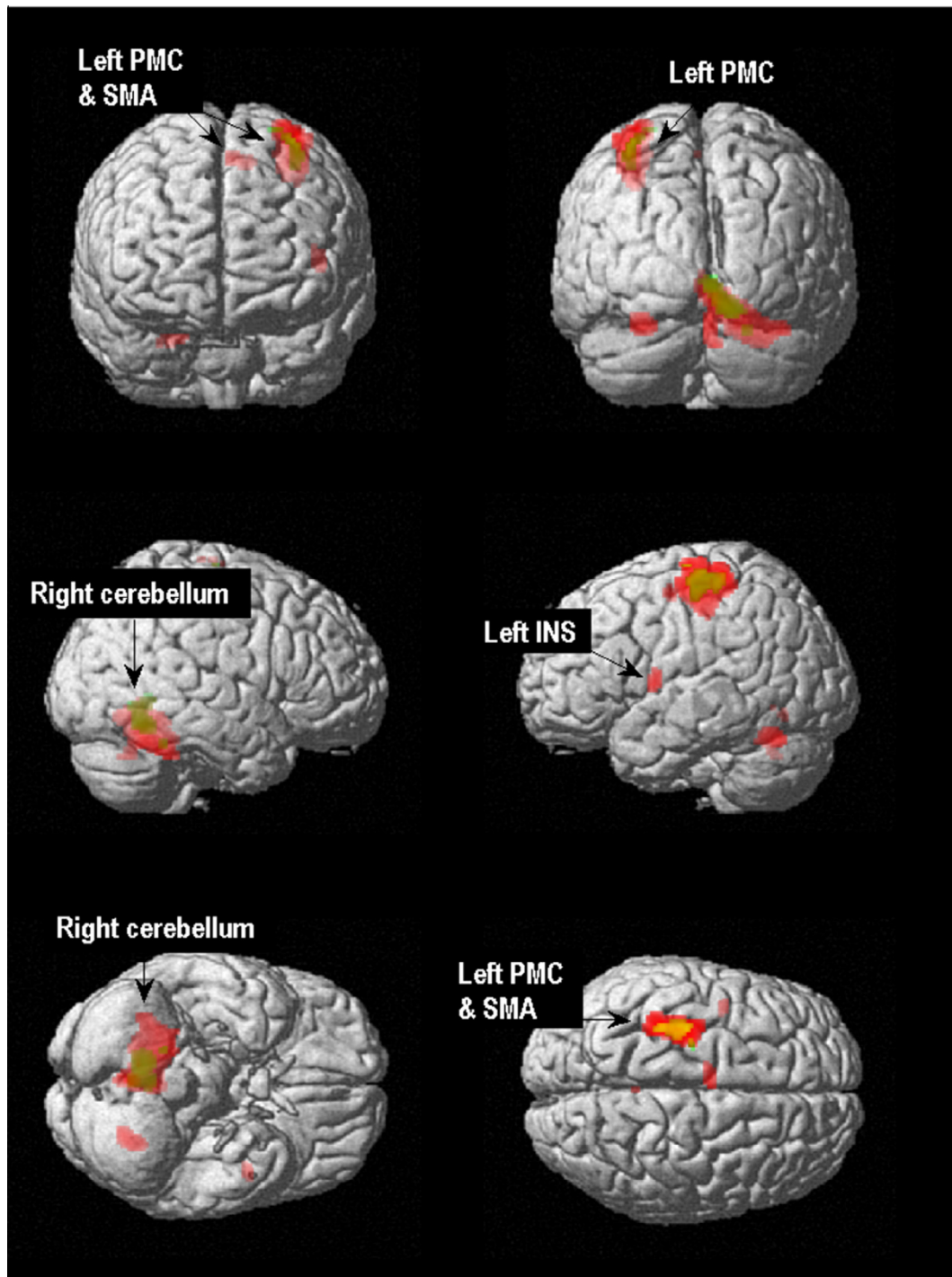


Fig. 2. Brain areas specifically activated for hand movements realized in the vertical direction (in red) and horizontal direction (in green) in contrast with rest period. Brain responses are projected onto the 3D volumetric view of the T1 template of MNI. Views from up to bottom: anterior and posterior, right and left and ventral and dorsal. We highlighted the left primary motor cortex (Left PMC), the left insula (Left INS), the left SMA and premotor cortex (Left SMA) and the right cerebellum (Right cerebellum).

highlight areas more activated in the processing of horizontal than vertical movement. No region reached significant activation (p -uncorrected < 0.001).

The relative biomechanical influence of gravity when performing horizontal and vertical hand movements is small, due to the small mass of the hand. Therefore, we asked 14 participants to realize the same task but in

which the required force increased, hence magnifying the difference between the contribution of gravity in each direction. We expect to identify similar sensorimotor brain areas responsible of the movement's execution and particular insular cortex activity for vertical movements. The brain networks highlighted for hand movements performed with additional load in each

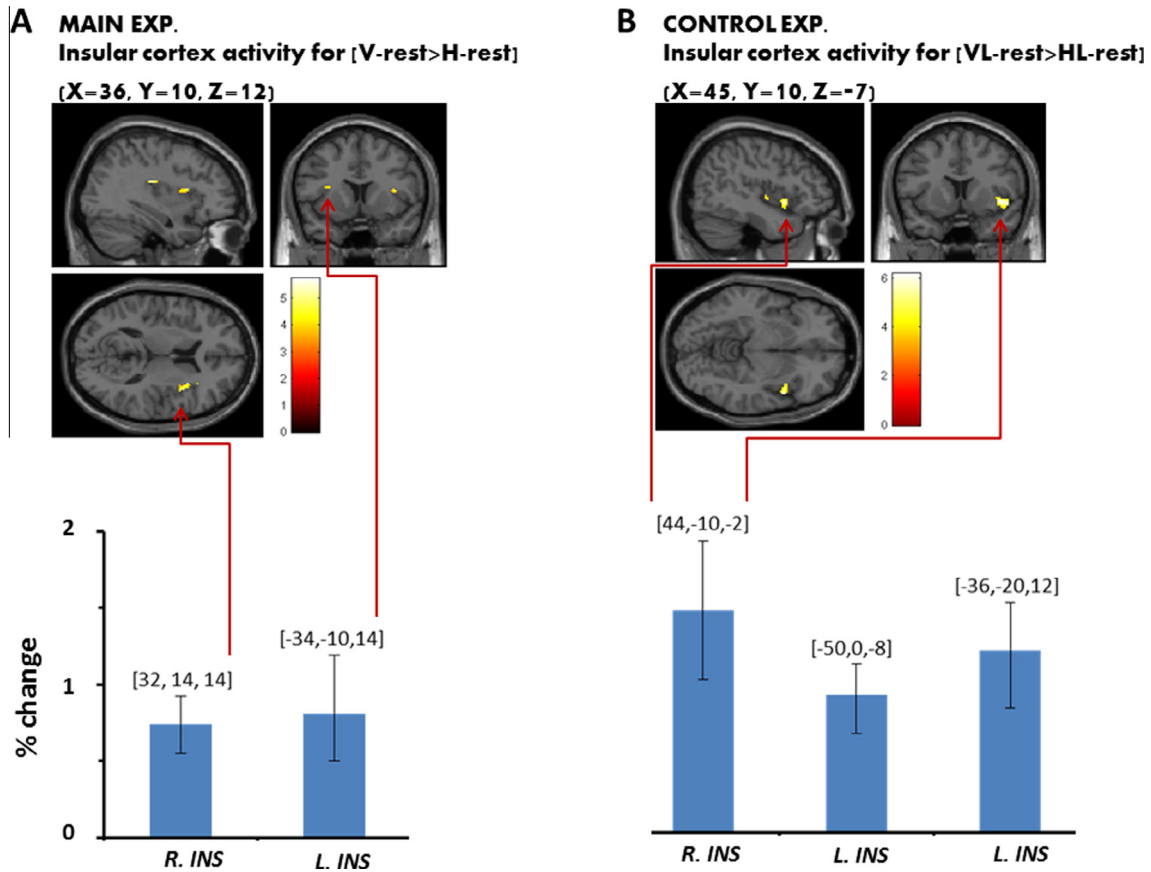


Fig. 3. We highlighted in yellow the clusters in the insula (single subject view T1 MNI) significantly activated for hand movements realized in the upward vertical versus horizontal direction for the main experiment (A) and control experiment (B). The percentage contrast estimates were reported below for the clusters found in the left (L. INS.) and the right (R. INS) insular cortex for the [V-rest > H-rest] (A) and [VL-rest > HL-rest] (B) contrasts of interest. Red arrows point to several clusters (single subject view T1 MNI).

Table 2. Significant activations to the contrast of interest [V-rest > H-rest] (p -uncorrected < 0.001). Brain lobe, regions from AAL atlas and coordinates (x, y, z) in the MNI-space are reported. The first region has the highest number of voxels in the cluster and the other regions [between brackets] belong to the cluster with lower number of voxels. The two last columns correspond respectively to the maximum T-value and the number of voxels in the cluster

Lobes	AAL regions	X	Y	Z	T-Value	Voxels in cluster
V-rest > H-rest						
Temporal lobe	Right middle temporal gyrus	48	2	-26	6.58	85
Frontal lobe	Right superior motor area	10	-12	52	6.09	119
	[Right midcingulate area]					
Sub lobar	Right rolandic operculum	34	-24	22	5.74	84
	[Right insula]					
Sub lobar & frontal lobe	Right insula	32	14	14	5.74	102
Frontal lobe	Left superior motor area	-14	-8	60	5.55	71
Sub lobar & temporal lobe	Right hippocampus	38	-22	-14	5.51	75
Temporal lobe	Left middle temporal gyrus	-36	-54	10	5.44	35
Temporal et limbic lobe	Left hippocampus	-52	4	-10	4.73	125
Frontal lobe	Right superior motor area	12	0	60	4.69	35
Anterior lobe of cerebellum	Left cerebellum (lobule VI)	-8	-46	-26	4.59	82
Parietal lobe	Left postcentral gyrus	-50	-20	48	4.31	26
Sub lobar	Left insula	-30	10	16	4.13	15
Frontal lobe	Left superior frontal gyrus	-18	64	18	4.13	29
Temporal lobe	Left middle temporal gyrus	-46	-22	-4	4.1	15

direction were indeed similar as those found for hand movements performed without additional load. The contrasts [VL > rest] and [HL > rest] revealed brain

responses in the left primary motor and somatosensory cortices as well as in the left premotor cortex (Table 3; [VL > rest] [HL > rest], $p < 0.050$ corrected for multiple

Table 3. Significant activations to the contrasts [VL > rest] and [HL > rest] (p -corrected for multiple comparisons < 0.05). Brain lobe, regions from AAL atlas and coordinates (x, y, z) in the MNI-space are reported. The first region has the highest number of voxels in the cluster and the other regions [between brackets] belong to the cluster with lower number of voxels. The two last columns correspond respectively to the maximum T -value and the number of voxels in the cluster

Lobes	AAL regions	X	Y	Z	T-Value	Voxels in cluster
VL > rest						
Frontal and parietal lobe	Left precentral gyrus [Left postcentral gyrus]	−32	−26	66	16	533
Anterior and posterior lobe of cerebellum	Right cerebellum (lobules IV and V) [Right cerebellum (lobule VI)] [Vermis lobules IV & V] [Vermis lobule VI]	12	−52	−16	15.9	523
Sub-lobar and temporal lobe	Right insula	42	6	2	10.3	37
Parietal lobe	Left superior parietal lobule	−34	−46	66	10.2	12
Sub-lobar and frontal lobe	Left rolandic operculum [Left insula]	−46	−2	8	9.6	13
HL > rest						
Frontal and parietal lobe	Left precentral gyrus [Left postcentral gyrus]	−32	−24	68	14.4	573
Anterior and posterior lobe of cerebellum	Right cerebellum (lobules IV,V) [Right cerebellum (lobule VI)] [Vermis lobules IV & V]	16	−52	−16	12.4	198
Frontal lobe	Left superior motor area	−10	−8	68	11.2	14

comparisons). The right cerebellum also showed brain activity during loaded hand movements. Interestingly, the clusters found in the primary motor and somatosensory cortices were larger for Horizontal movements with additional load compared to Horizontal movements without additional load.

As expected, we only found insular cortex activation for hand movements performed along the vertical direction. By contrasting horizontal and vertical movements ([VL-rest > HL-rest]; p -uncorrected < 0.001, Fig. 3B), we also found several clusters in the insular cortex ($X = 42, Y = 10, Z = -4$; $X = -36, Y = -20, Z = 12$, $X = 44, Y = -10, Z = -2$; Table 4). Similarly to the

main experiment, there were also brain responses in bilateral premotor cortex (in particular in the left and right SMA), in the left superior temporal gyrus, in the left postcentral and right precentral gyri and also in the anterior cerebellum. The left inferior parietal gyrus and the left midcingulate area were also activated (see Table 4). When using an anatomical mask of the insular cortex, brain activity for the contrast [VL-rest > HL-rest, p -corrected < 0.050] was found in 2 clusters ($t = 6.17$; $X = 42, Y = 10, Z = -4$; $t = 5.49$; $X = -36, Y = -20, Z = 12$). In agreement with our prediction, loading the hand increased BOLD responses of networks obtained for each movement's direction (see [V > rest]

Table 4. Significant activations to the contrast of interest [VL-rest > HL-rest] (p -uncorrected < 0.001). Brain lobe, regions from AAL atlas and coordinates (x, y, z) in the MNI-space are reported. The first region has the highest number of voxels in the cluster and the other regions [between brackets] belong to the cluster with lower number of voxels. The two last columns correspond respectively to the maximum T -value and the number of voxels in the cluster

Lobes	AAL regions	X	Y	Z	T-Value	Voxels in cluster
VL-rest > HL-rest						
Temporal lobe	Left superior temporal gyrus	−50	0	8	6.37	19
Sub-lobar and temporal lobe	Right insula	42	10	−4	6.17	124
Sub-lobar and temporal lobe	Left superior temporal gyrus [Left insula]	−36	−20	12	5.49	129
Frontal lobe	Right precentral gyrus	56	−8	50	4.77	7
Sub-lobar and temporal lobe	Right insula	44	−10	−2	4.71	12
Limbic lobe	Left midcingulate area [Right superior motor area]	−4	−6	44	4.68	44
Frontal lobe	Left superior motor area	−4	−10	64	4.66	27
Anterior lobe of cerebellum	Vermis lobules I & II	4	−40	−20	4.64	22
Parietal lobe	Left postcentral gyrus [Left inferior parietal gyrus]	−46	−28	48	4.37	15
Frontal and parietal lobe	Left postcentral gyrus [Left precentral gyrus]	−36	−20	52	4.29	33
Parietal lobe	Left postcentral gyrus	−52	−18	54	4.26	15
Frontal lobe	Right superior motor area	4	−4	74	4.11	10

[H > rest]; [Table 1](#) and [VL > rest] [HL > rest]; [Table 3](#)). Finally, the contrast [HL-rest > VL-rest] did not highlight any significant activation (p -uncorrected < 0.001).

DISCUSSION

When we accelerate a massive object or limb, our CNS calculates the required muscular commands to compensate for the inertial loads. In addition, the constant gravitational acceleration also induces a constant weight that adds to the former inertial force. It is therefore reasonable to assume that over evolution, the CNS developed specific predictive mechanisms to control for gravito-inertial constraints. Many earlier studies focused on the role of visual information in gravity processing. Here, we assess whether brain areas are dedicated to non-visual inputs sensitive to how gravity is taken into account.

Many investigations found a neural network (the so-called vestibular network) that was activated specifically when processing motion of an object in the gravitational field ([Lacquaniti and Maioli, 1989](#); [Lacquaniti et al., 1993](#)). Catching and visualizing falling ball experiments revealed that anticipation for tuning motor behavior takes into account Newton's laws of dynamics due to gravitational attraction ([Lacquaniti and Maioli, 1987](#); [Mcintyre et al., 2001](#); [Zago et al., 2004](#)). It confirms that the brain uses an internal model of gravity to supplement sensory information. Other approaches used fMRI coupled with visual stimuli showed that when subjects visualized an object "falling" at natural gravity ([Indovina et al., 2005](#)) or underwent vertical visual motions compatible with self-motion in the gravity field ([Indovina et al., 2013](#)), brain responses were found in a vestibular network composed of neural correlates also activated by direct vestibular stimuli ([Bottini et al., 1994](#); [Bense et al., 2001](#)). Thus, previous experiments demonstrated that the internal representation of gravity is a key to achieving movements successfully.

However, all the aforementioned tasks relied dominantly on vision. The question therefore remains open as to whether specific brain areas of the vestibular system are also direction-dependent when the CNS takes into account gravity effects coded in non-visual signals. We asked participants to perform hand movements along vertical and horizontal directions in a block design paradigm. The procedure ruled out brain activations caused by differences in muscle activation patterns between the two orientations. Position of the hand palm was chosen in order to involve the same flexor-extensor muscles ([Mendell and Florence, 1990](#); [Hislop and Montgomery, 2002](#)). We also limited head movement artifacts by asking participants to move the hand instead of the arm.

The motor network activated for [V > rest] did not encompass strictly as much regions with similar intensity as those highlighted for [H > rest]. We firstly found brain responses in areas of the contralateral hemisphere and dedicated to the processing of muscular commands in the primary motor and somatosensory cortices in both directions. Indeed,

relevant motor control areas, involved in motor planning, also showed greater activations, such as the left premotor cortex, the supplementary motor area, and the cerebellum ([Cheney, 1985](#); [Roland, 1993](#); [Tseng et al., 2007](#); [Shadmehr et al., 2010](#)).

Both vertical and horizontal movements necessitate the integration of gravity. Joint torques vary differently over time when one performs vertical or horizontal movements. Therefore, we expected to find a greater sensitivity to gravity for vertical movements compared to horizontal movements. Interestingly, our findings revealed specific brain responses in the insular cortex only for vertical hand movements. This suggests that the insular cortex is associated to the neural site of the internal model engaged in this task. Furthermore, the contrast [V-rest > H-rest] showed activation in a network that included the premotor cortex (bilateral SMA), bilateral insular cortex, and also the left primary somatosensory cortex, bilateral hippocampus, the dorso-posterior cingulate cortex, the left prefrontal cortex, bilateral middle temporal gyrus, and the anterior cerebellum ([Table 2](#)). Most of these neural substrates belong to the vestibular network that is activated by visual motion coherent with natural gravity and by vestibular stimulation ([Bottini et al., 1994](#); [Bense et al., 2001](#); [Indovina et al., 2005](#)). In sum, the vestibular network we highlighted is direction-dependent and processes high-order computations on non-visual sensory inputs to optimize gravity effects thanks to sensory cues and prior information. Our control experiment involved the same movements but required larger motor commands to move the off-center mass. Its results showed similar brain networks for vertical and horizontal movements, with specific activation in the insular cortex only for vertical movements, but with larger clusters. Consequently, these data confirmed and magnified the results of the main experiment.

Although we found only contralateral activation of the insula, [Indovina et al. \(2005\)](#) highlighted bilateral activity in the insular cortex when acceleration of a visual target is coherent with represented natural gravity. The authors suggested it reflected the neural basis of gravitational visual processing. In the present experiment, participants performed a motor task with the right hand, which highly activated primary and somatosensory cortices of the left hemisphere. Consequently, brain responses of the left insula may be due to the proximity of the left motor cortex activity. Thus, lateralization of the insular activity strongly supports that it is associated to the processing of gravitational effects integrated to the movement execution.

Besides, brain response in the left insula was localized in the anterior part and slightly differed from those observed by the same authors, for which peak activation was obtained in the posterior part ([Indovina et al., 2005](#)). This difference is not surprising since it is related to neural activity of brain regions engaged in visual task implying visual signal processing for which the posterior parietal cortex is known to play a fundamental role in visuomotor transformations ([Buneo and Andersen, 2006](#)). Activation in the thalamus at which the posterior insula is reciprocally connected to the vestibular nuclei was also

observed in visual motion and not highlighted for moving limb in our present experiment.

While many caloric and galvanic stimulation experiments as well as fMRI studies (Fasold et al., 2002; Lopez et al., 2012) evidenced that the posterior insula belongs to the vestibular cortex, less investigations were done concerning the anterior insula because its exact functions in movement processing are still unknown. Nevertheless, Fasold et al. (2002) highlighted activation following galvanic and caloric stimulation in anterior insula but did not reliably ascribe its activation to vestibular mechanisms. An interesting fMRI study about the sense of agency revealed that this part of insula is linked to the integration of all the concordant multimodal sensory signals associated with voluntary movements. Being aware of causing an action depends, in part, on the sensory signals that result from actions and necessitate their integration in higher order brain processing. Concerning limb movements, PET activation has been reported at the floor of the left insular cortex during voluntary arm and hand movements in normal subjects (Colebatch et al., 1991) and in intermediate or anterior parts of the insula bilaterally (not in the posterior insula) during voluntary limb movements of the recovered hand after a first hemiplegic stroke (Chollet et al., 1991). Accordingly, the anterior parts of the insula could be a secondary motor area, which is activated in paced, stereotyped tasks (Anderson et al., 1994), like the one performed in our experiment, and in which gravity must be integrated.

At this stage of the discussion, some limitations of the study may be mentioned. First, we adopted a block design protocol and could therefore not precisely identify when the effects of gravity are processed by the brain structures: During motor planning? After primary sensory feedback? For each movement? Furthermore, we were also not able to highlight any learning process which may have occurred very quickly for these simple and natural movements: At the beginning? At the end of the first block? Second, a lack of kinematic data (as well as EMG data) to demonstrate that subjects did not produce slightly different movements in one particular direction (vertical or horizontal) is also detrimental. However, because we adopted a block design paradigm rather than an event-related one, participants executed several movements during one block which was modeled as one event in the GLM. Consequently, we did not identify activity for one movement but several movements produced during one block. This averaging process increases chances to find the same kinematics (or muscular activity) between blocks but impedes the possibility to find subtle effects of, e.g. slight differences in movement directions on insular activity. It is worth reporting that Papaxanthis and colleagues showed that relative time to peak velocity (TPV) was not significantly different between upward vertical (0°) and upward oblique (45°) movements. However, TPV in downward movements remained significantly different from TPV in upward oblique and upward vertical movements (Papaxanthis et al., 1998b). Altogether, that study shows that small differences between movement directions do

not impact how the effects of gravity are treated. Instead, whether movement is assisted or resisted by gravity modulates TPV.

Altogether, we showed that the neural substrates engaged during vertical hand movements largely – but not completely – overlap brain areas of the well-known vestibular network, sensitive to self-motion in natural gravitational force field and the visual processing of gravity. The major, albeit subtle difference with previous work, concerns the localization of the activation within the insular cortex. Indeed, the anterior insula is direction-dependent and plays a central role in processing gravity signals not only routed by the visual pathway.

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