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Human against gravity: brain networks of graviception analyzed from a series of 170 post-stroke individuals

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**HUMAN AGAINST GRAVITY: BRAIN NETWORKS OF GRAVICEPTION ANALYZED FROM A SERIES OF
170 POST STROKE INDIVIDUALS**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE

DIPLÔME D'ÉTAT

Camille LEMAIRE

[Données à caractère personnel]

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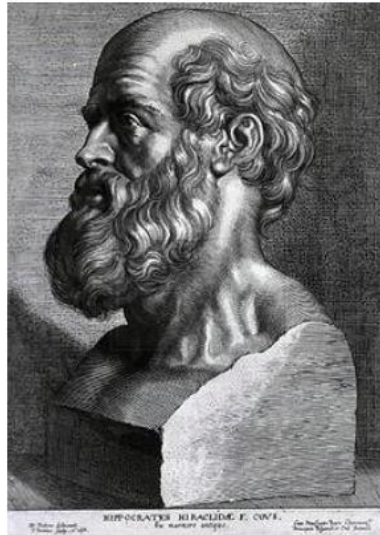
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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

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Résumé

La latéropulsion est un comportement postural fréquemment observé dans les suites d'un accident vasculaire cérébral (AVC), en particulier hémisphérique droit. Sa prévalence peut atteindre 10 à 60%. Ce comportement est maintenant considéré comme une trinité associant, à divers degrés, une inclinaison latérale du corps, une poussée active et une résistance aux corrections passives. Les patients alignent activement leur posture sur un référentiel interne de verticalité erroné. Mieux connaître les structures cérébrales impliquées dans la latéropulsion est un moyen d'explorer les bases neurales de la graviception, et au-delà celles de l'interface cérébrale perception-action en rapport à la gravité. Étonnamment, peu d'études à ce jour ont étudiés ces bases neurales, et aucune de manière exhaustive avec une analyse statistique minutieuse de la substance grise et de la substance blanche. C'est donc l'objectif de notre étude. Il s'agit d'une cohorte de 170 individus hospitalisés dans les suites d'un premier AVC (80 droits, 90 gauches) avec à la fois une IRM et une évaluation de la latéropulsion (avec l'échelle SCP). Pour analyser les relations entre la latéropulsion et les structures cérébrales lésées, une analyse voxel lesion symptom mapping (VLSM) a été faite que ce soit pour la substance grise (à partir des dessins lésionnels) et pour la substance blanche (à partir des cartes de dysconnection obtenues par le logiciel BCBtoolkit). Celle-ci révèle une forte association entre la latéropulsion et plusieurs structures clés de l'hémisphère droit. Pour la substance grise, on note l'implication du putamen, de l'insula postérieure et du noyau caudé. Pour la substance blanche, on retrouve une altération des projections thalamo-insulaires, du faisceau cortico-spinal et de la capsule interne. Aucune structure de l'hémisphère gauche n'était associée de manière significative à la latéropulsion. Il s'agit donc de la première étude qui étudie et identifie les bases neurales impliquées dans la latéropulsion, à partir d'une cohorte de 170 individus testés à la phase subaigue post AVC et avec une méthode d'analyse des corrélats neuro-anatomiques robuste. Cette analyse VLSM retrouve que, à droite, le putamen, l'insula postérieure, le noyau caudé, les projections thalamo-insulaires, le faisceau cortico-spinal et la capsule interne étaient significativement associés à la latéropulsion. Ces structures cérébrales contribuent à la construction et à la mise à jour du sens de verticalité et sous-tendent la commande motrice. Une meilleure compréhension neuroanatomique de la latéropulsion pourrait aider à développer des techniques modernes de rééducation.

Mots clés : contrôle postural, latéropulsion, Voxel Lesion Symptom Mapping, syndrome de dysconnection, bases neurales

Abstract

Lateropulsion is a postural behavior frequently observed after hemisphere stroke, especially after right hemisphere stroke where its prevalence reaches about 10 to 60 %. It is now considered as a trinity associating at various degrees a lateral body tilt, a spontaneous active pushing, and a resistance to passive corrections. Patients actively align their body posture onto a wrong internal reference of verticality, tilted the side oppose the stroke. Better knowing which structures of the cerebral hemispheres, when damaged, induce a contralesional lateropulsion is a way to explore the neural bases of the graviception, and beyond the brain interface between perception and action with respect to gravity. Surprisingly few studies have investigated these mechanisms, and none comprehensively with careful statistical analyses of grey and white matter on a large series of individuals. This is the objective of the present study. This is a large cohort of 170 individuals (80 rights, 90 lefts) with both MRI and an evaluation of lateropulsion (with SCP scale), in a subacute stage after a first hemisphere stroke. To analyze relationships between lateropulsion and damaged structures, same procedure was run for grey matter (from lesions' drawing) and white matter (from disconnectome maps computed on BCBtoolkit software). This procedure was based on mass univariate voxel-based lesion-symptom mapping. VLSM analysis reveals a strong association between lateropulsion and several key structures of the right hemisphere. For the grey matter were strongly involved, the putamen, the posterior insula and the caudate nucleus. For the white matter the study revealed a dramatic alteration of thalamo-insular projections, with alterations of cortico-spinal tract and internal capsule. No structure of the left hemisphere was significantly associated with lateropulsion. This is the first study that investigates and identifies neural bases and brain disconnection involved in lateropulsion, from a large cohort of 170 individuals tested at the subacute stage after a first hemisphere stroke and with a robust lesion analysis. We analyzed both grey and white matter. The putamen, the posterior insula, the caudate nucleus, thalamo-insular projections, cortico-spinal tract and internal capsule were significantly associated with lateropulsion. These brain structures contribute to the construction and updating of the sense of the upright and support the motor command. A better understanding of the neuroanatomical basis of lateropulsion could help shape novel interventions.

Key words: Lateropulsion, Voxel Lesion Symptom Mapping, neural correlate, disconnection syndrom, postural disorder

Introduction

Lateropulsion is a postural behavior frequently observed after hemisphere stroke, especially after right hemisphere stroke where its prevalence reaches about 10 to 60 % depending on stroke severity studied (Pedersen et al., 1996; Danells et al., 2004; Babyar et al., 2008; Perennou et al., 2008). It is now considered as a trinity associating at various degrees a lateral body tilt, a spontaneous active pushing, and a resistance to passive corrections (Dai et al., 2021). All these three components express a unique dimension referring to an impaired active body orientation with respect to gravity (Dai et al., 2021), caused by a biased internal model of verticality (Perennou et al., 2008; Dai et al., 2021). Patients actively align their body posture onto a wrong internal reference of verticality, tilted the side opposite the stroke. In sum the contralesional lateropulsion is elicited by a contralesional tilt of the biological vertical (Perennou et al., 2008; Pérennou et al., 2014; Dai et al., 2021).

Better knowing which structures of the cerebral hemispheres, when damaged, induce a contralesional lateropulsion is a way to explore the neural bases of graviception, and beyond brain interface between perception and action with respect to gravity. Surprisingly few studies have investigated these mechanisms, and none comprehensively with careful statistical analyses of grey and white matter on a large series of individuals. The first studies in the early 2000s were limited to the extreme form of lateropulsion (Karnath et al., 2000; Karnath et al., 2005; Johannsen et al., 2006; Ticini et al., 2009). They relied on qualitative analyses of brain imaging comparing small sampling of individuals pre-classified (in average 27 individuals per group in these series). They pointed out the involvement of postero-lateral thalamus, posterior insula, superior temporal gyrus, inferior parietal lobule and post central gyrus (Karnath et al., 2000; Karnath, 2005; Johannsen et al., 2006; Ticini et al., 2009), the role of which remained to be demonstrated. A fourth categorization study has been recently published (Baier et al., 2020), still comparing two groups of individuals with a right hemisphere stroke, one constituted of 25 individuals showing an extreme form of lateropulsion (pusher syndrome) compared to another group (n=57) mixing individuals with lateropulsion of moderate severity and individuals without lateropulsion. According to us this sampling bias explained why only a tiny part of the insula was statistically found involved in the pusher group. To the best of our knowledge only two studies have investigated the neural bases of the lateropulsion using lateropulsion scores in continuously, both examining individuals at the acute stage several days post-stroke (Baier et al., 2012; Babyar et al., 2019;). Using the SCP which assesses the three lateropulsion components, body tilt, spontaneous pushing, and resistance, in a series of 66 consecutive

individuals with a right or a left hemisphere stroke, Baier et al failed to find any statistically significant neural correlate of the lateropulsion. Using the BLS which assesses the resistance to passive correction of the lateral body orientation in erect and lying postures, in a series of 50 consecutive individuals with a right or a left hemisphere stroke, Babyar et al found the involvement of the inferior parietal lobule when all maps were flipped to the right hemispheres regardless irrespective of their original side.

One may assume that these disappointing results not congruent with clear findings revealed by studies exploring the neural bases of verticality perception (Kheradmand & Winnick, 2017; Lemaire et al., 2020), are due to methodological aspects. No study has ever been performed on a large series of individuals. No study has ever tested individuals later, when they are clinically more stable and may be tested in standing. This might lead to more robust clinical data. No study has ever analyzed brain imaging performed at distance of the stroke, about two months, the optimal time to better link behaviors to imaging (Nagaraja et al., 2020). Overall no study has ever analyzed what might cause the white matter alterations on lateropulsion with adapted method.

Here we overcome these gaps and investigate the neural correlate of lateropulsion assessed only with respect to gravity around 30 days post-stroke with the SCP used as a continue score (Perennou et al., 2008; Dai et al., 2020; Dai et al., 2021), on a large series of individuals with a first right or left hemisphere stroke, who had a second MRI at about 2 months. The relationship between symptoms and brain mapping was analyzed both on grey and white matters, using robust statistical tools.

We hypothesized that structures involved in the internal model of verticality (Kheradmand & Winnick, 2017; Lemaire et al., 2020) are those underpinning lateropulsion, i.e posterior insula, parietal operculum, postero-lateral thalamus, with a dramatic disconnection between posterior parts of thalamus and insula (Lemaire et al., 2020).

Method

Study design

This was a monocentric study using data of the DOBRAS cohort (Determinants of Balance Recovery After Stroke; NCT03203109) with participants comprehensively assessed in routine care after a first hemispheric stroke. For the present study focused on the neural bases of lateropulsion, we analyzed the initial assessments of lateropulsion mostly performed 30 ± 3

days post-stroke (D30) and brain imaging from the MRI performed two months after stroke. Establishing anatomo-clinical correlations with VLSM method does not require a theoretical number of participants (Karnath et al., 2019), so the sample size had not to be a priori calculated. However the cohort DOBRAS was planned to follow a large series of patients and support several studies of important sample sizes, in order to conclude with a very low p value, including for brain imaging studies (Dai et al., 2021).

Ethical considerations and reporting

The DOBRAS cohort was approved by our institutional review board (CHU Grenoble Alpes) who validated the ClinicalTrials.gov registration (NCT03203109). The study was also registered at the National Committee for Informatics and Freedom (Commission Nationale Informatique et Liberté; CNIL-No.2014874-v1) and was performed in accordance with the Helsinki Declaration. According to French law, observational studies do not require approval by an ethics committee, provided that participants have been informed of the specific research and are not opposed to use of their data. All eligible individuals were informed of the DOBRAS study (orally and in writing) and those who did not want to participate signed an opposition form.

Participants

For the DOBRAS cohort inclusion criteria were age between 18 years and 80 years, first unilateral hemispheric stroke (right or left), and exclusion criteria were: recurrent stroke, previous disability interfering with balance or vestibular function, complication at the acute stage (malignant infarct, cerebral herniation, severe subarachnoid hemorrhage and hydrocephalus), dementia, severe cognitive or psychiatric disorders, unstable medical conditions, language barriers (not French speaking).

For the present study were applied additional specific criteria which were for inclusion a right handedness (Edinburgh inventory (Oldfield, 1971) > 0.6) and a morphometric brain MRI performed at subacute stage and for exclusion a bilateral or multiple brain damages detected after careful analysis.

Participants' features

Stroke clinical features comprised the initial stroke severity estimated by the US National Institutes of Health Stroke Scale (NIHSS) at 24 hour post-stroke (range 0-42, higher scores indicating greater stroke severity), stroke type (ischemic or hemorrhagic), stroke side (right or left hemisphere) and stroke size (in voxels).

Most deficits presented in this paper aimed at describing participants: motor weakness, spasticity, hypoesthesia, hemianopsia, spatial neglect, aphasia, apraxia. Same for *their disability* assessed with the modified Fugl-Meyer Assessment (mFMA) for gait, and the Modified Rankin Scale (mRS). Details on these assessments and the way to categorize these data are explained in the first paper of the DOBRAS cohort (Dai et al., 2020) .

Lateropulsion

The contralesional lateropulsion was assessed by trained physiotherapists who were not aware of study hypothesis, with the Scale for Contraversive Pushing (SCP), proposed to quantify the lateral body tilt, the active pushing and the resistance to passive corrections (Karnath et al., 2000b). These three characteristics are now considered as the three components of a deficit in the active body orientation with respect to gravity, called lateropulsion (Babyar et al., 2019; Dai et al., 2020; Dai et al., 2021). The SCP has become the gold standard for assessing lateropulsion. For statistical analyses we used the SCP as a continuum score ranging from 0 (upright) to 6 (very severe lateropulsion), with 24 increments of 0.25 points (Karnath et al., 2000). This procedure has been shown valid (Perennou et al., 2008; Dai et al., 2020; Dai et al., 2021) .

Brain imaging

Acquisition

Controlled MRI was performed routinely at about 2 months post-stroke by using a 1.5T MR Magnetom Aera (Siemens, Erlangen, Germany). Whole-brain anatomical studies were acquired in an axial plane parallel to the anterior commissure-posterior commissure consisting of 3-D gradient recalled echo (GRE) T1-weighted images (160 contiguous slices; voxel size=0.9x0.9x0.9 mm³;TR/TE/TI/ α : 1900/3.67/1100 ms/15°; acquisition time=4.5 min); axial T2 Fluid Attenuated Inversion Recovery (FLAIR) images (30 slices; voxel size=0.7x0.7x4

mm3; TR/TE/TI:9000/74/2500 ms). Lesion mapping plots were carefully examined for vascular lesions apart from the stroke area or brain oedema which might distort the lesion mapping. Acquisition of imaging data about two months post-stroke is well suited for lesion-behaviour mapping analyses, allowing to better delineate the areas of infarcted and irretrievably lost neural tissue, so to better link behaviours to imaging (Nagaraja et al., 2020).

Lesion drawing

Lesions were reconstructed by using MRICron (Rorden & Brett, 2000) from MRI axial slices (axial AC-PC, T2 flair, 4-mm thickness). They were manually drawn by a first skilled operator on a standard anatomical MRI template of the Montreal Neurological Institute, furnished with the MRICron software (ch2, <http://www.mccauslandcenter.sc.edu/mricro/mricron/>) on axial slices of a T1-weighted MRI template from the Montreal Neurological Institute (www.bic.mni.mcgill.ca/cgi/icbm_view) normalized to Talairach's space. Lesions drawing were controlled by a second trained operator. Both operators were blinded to lateropulsion data. Disagreements were resolved by consensus. We did not use automatic segmentation and normalization algorithms on these MRI performed in clinical setting. Indeed, after stroke with many elderly a manual reconstruction is a reliable option for lesion analysis (Kimberg et al., 2007), given the frequent modification of the cerebral architecture (mostly ventricular dilatation or cerebral atrophy) inducing lag between the damage area and the template image used for automated segmentation and normalization techniques (Rorden & Karnath, 2004).

Disconnectome map for white matter lesions

Disconnectome maps were computed with the 'disconnectome map' tool of the BCBToolkit software (Foulon et al., 2018). The first step of the procedure was the tracking of white matter fibers passing through each patient's lesion, by means of the registration of lesions on the diffusion weighted imaging dataset of 10 healthy controls (Thiebaut de Schotten et al., 2017). This produced a percentage overlap map that takes into account the inter-individual variability of tractography in healthy controls' dataset (Croxson et al., 2018). Therefore, in the resulting disconnectome maps computed for each lesion, voxels showed the probability of disconnection from 0% to 100% (Thiebaut de Schotten et al., 2015). These disconnection probabilities of each patient were then used for statistical analyses.

Statistical analyses

To analyze relationships between lateropulsion and damaged structures, same procedure was run for grey matter (from lesions' drawing) and white matter (from disconnectome maps). This procedure was based on mass univariate voxel-based lesion-symptom mapping (VLSM; (Bates

et al., 2003) using NiiStatV9 (<https://www.nitrc.org/projects/niistat/>) a software running on Matlab R2019b (<https://in.mathworks.com/products/matlab.html>) and SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>). Behavioral data (SCP score) was processed continuously and a general linear model (pooled-variance t-test, linear regression) was conducted. Analyses were performed with 5000 permutations (statistical threshold $p < 0.05$) to correct for multiple comparisons ($p < 0.05$ controlled for familywise error). VLSM analyses were conducted on voxels in which at least 10% of participants shared a lesion. Lesion volume was used as regressor.

Statistics

Regarding behavioral data, statistical analyses were realized using SPSS software (version 20, IBM Corporation, Armonk, NY, USA). Descriptive statistics were generated for each variable. The correlation between SCP score and lesion size was analyzed using spearman test. Lesion sizes between RHS and LHS were compared using Mann-Whitney test. Unless specified otherwise, the significance level was fixed at $p=0.05$. Unless otherwise indicated, continuous data are presented in the form mean (SD) and categorical data as number with percentage. For statistic regarding data of brain imaging, refer to specific paragraph above.

Results

Participants' features

Figure 1 shows the flow diagram. They were 65 (11) years old, with 109 males (64%). Mean weight and height were 7200g (1300) and 169 cm (9), respectively. Strokes were as well distributed in right (47%) and left hemispheres (53%), were mostly infarct (78%), of moderate severity with a mean NIHSS = 12 (6) at day one and a mean lesion volume, of 36394 (51233) voxels i.e 4.7 (7) % of the entire hemisphere.

Participants had a moderate weakness (mean score 47/80 (28)), a moderate spasticity (mean score 3/40 (5)); 73% had a moderate or severe hypoesthesia, 52% a moderate or severe spatial neglect, 43 % an aphasia, 42% an apraxia, 33% an hemianopsia. Their median gait level was 3 [0;6], corresponding to the possibility to walk several meters with a roller, a tripod or a crutch. Participants had a moderate handicap (mean mRS score 3/5 (1)).

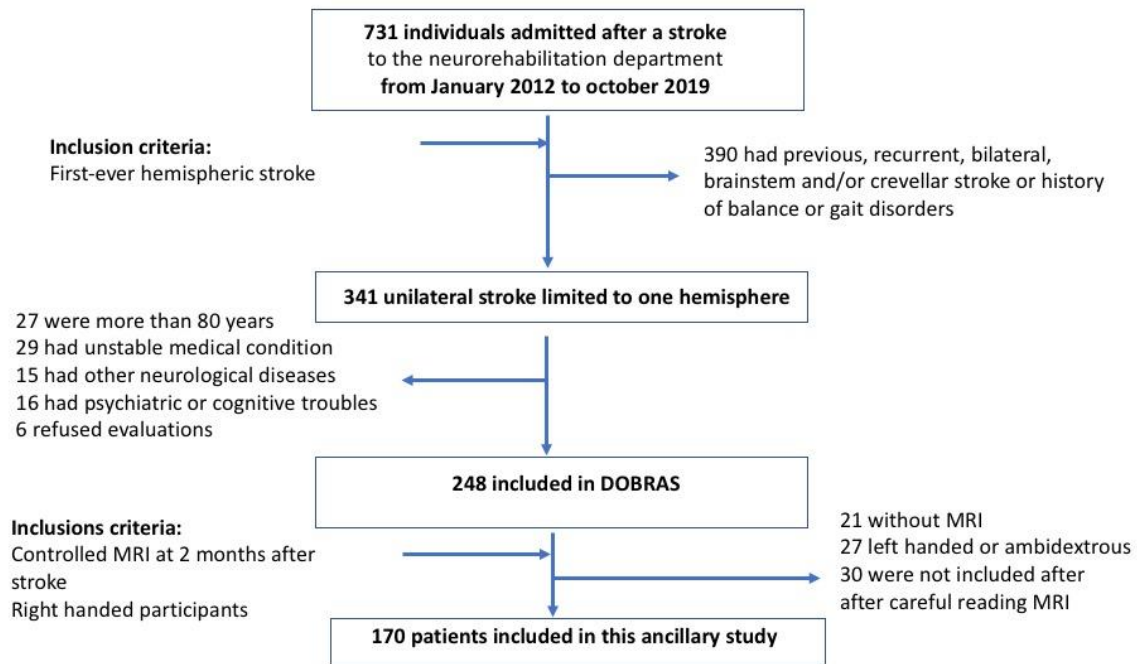


Figure 1: Flow of participants in the study

Lateropulsion

Figure 2 shows the distribution of SCP scores. The entire spectrum was covered, with a little more than half of individuals being perfectly upright with a SCP score of 0 (97, 57%), and a little less than half of individuals showing lateropulsion (ranging from slight to severe forms) with a SCP score > 0 (73,43 %). The mean SCP score was 1.2 (1.9).

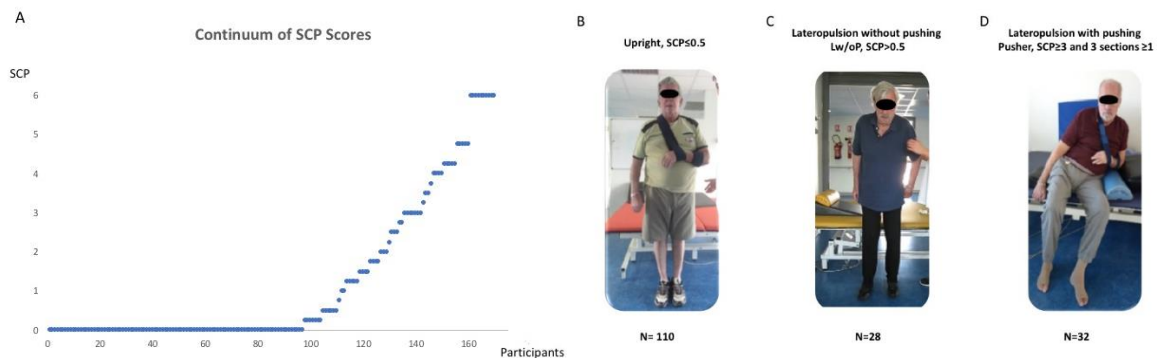


Figure 2: A. Distribution of SCP scores increasingly ranked for the 170 participants. Each point corresponds to an individual data. B., C. and D. Participants were classified into three groups by SCP score: 110 (65%) were upright (B.) and 60 (35%) showed contralesional lateropulsion: 28 (16%) showed lateropulsion without pushing (C., Lw/oP) and 32 (19%) were pushers (D.).

Brain imaging

Fig. 2 shows conventional lesion density plots for all participants with a right (2A) and a left (2B) stroke. Lesions were located in all arterial territories, mostly found in the territories of the middle cerebral artery or the posterior cerebral artery (deep structures). The mean lesion volume represented 36394 voxels i.e 4.7 % of the hemisphere size, without difference between right hemisphere stroke (RHS) (36788 voxels i.e 4.8 % of the hemisphere size) and left hemisphere stroke (LHS) (32639 voxels i.e 4.2% of the hemisphere size) (U test=3106, $p=0.123$). Lesion volume influenced lateropulsion in the whole series ($Rho= 0.367$, $p<0.01$), more strongly for RHS ($Rho=0.413$, $p<0.01$) than for LHS ($Rho=0.241$, $p<0.05$).

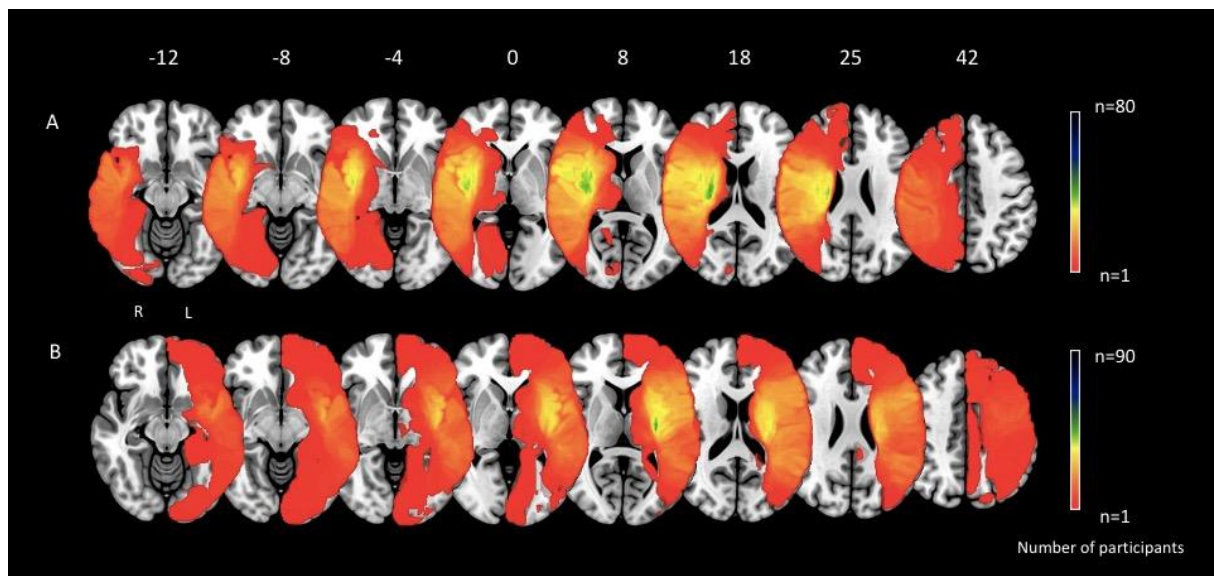


Figure 2: Overlay lesion plot

A. Overlay lesion plot of all participants with a right lesion ($n=80$). The number of overlapping lesions is illustrated by different colours representing increasing frequency from red ($n = 1$) to dark ($n = 80$). B. Overlay lesion plot of all participant with a left lesion ($n = 90$). Number of overlapping lesions is illustrated by different colours representing increasing frequency from red ($n = 1$) to dark ($n = 90$).

We then conducted VLSM analyses. The neural bases of lateropulsion are represented in Figure 3, both for grey (Fig 3A) and white (fig 3B) matters. No structure of the left hemisphere was significantly associated with lateropulsion, whereas several key structures of the right hemisphere, when damaged, caused lateropulsion. VLSM analyses on lesion sites (Fig 3A), found three grey matter areas strongly involved: posterior insula ($x=33, y=-15, z=4$; $p<10^{-4}$), putamen ($x=28, y=-10, z=10$; $p=10^{-5}$), and caudate nucleus ($x=17, y=-3, z=21$; $p<10^{-3}$), as well

as a very large white matter area ($x=25, y=-10, z=18$; $p<10^{-6}$). The white matter was further analyzed on disconnectome maps (Figure 3.B) and revealed dramatic alterations of thalamo-insular projections ($x=20, y=-23, z=4$; $p=10^{-7}$) with alterations of cortico-spinal tract ($x=26, y=-34, z=26$; $p<10^{-6}$) and internal capsule ($x=24, y=-38, z=30$; $p<10^{-6}$).

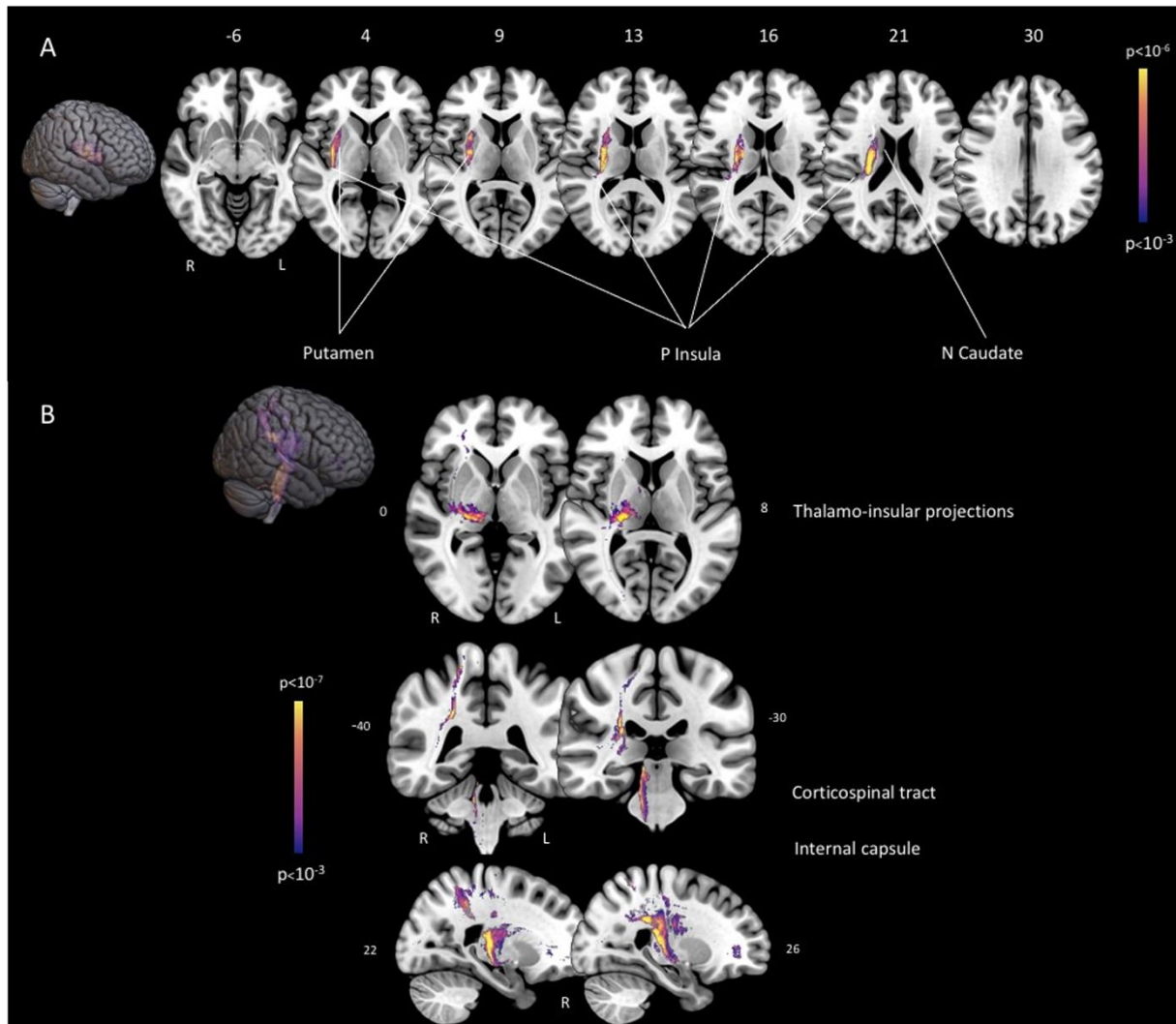


Figure 3: Neural correlates of lateropulsion.

A. corresponds to the result of VLSM computed on the lesion sites and indicates grey matter structures involved in lateropulsion. B. corresponds to the result of VLSM computed on white matter maps of disconnection and indicates tracts involved in lateropulsion.

Results are presented in the form of color code according to the significance of p .

Abbreviations: P insula= posterior insula ; N caudate= caudate nucleus

Discussion

The present study is the first that investigates neural bases involved in lateropulsion, searching any types of brain damage in the whole brain: from cortical to subcortical areas including main white matter connections between grey matter structures. This is the first that investigates neural bases involved in lateropulsion in a large cohort > 100 consecutive individuals. Other original approaches were: the analyses of MRI performed about 2 months, the optimal time to better link behaviors to imaging; lateropulsion assessed with a scale specifically dedicated to the assessment of the impaired body orientation with respect to gravity (Dai et al., 2020; Dai et al., 2021) at a time when almost all are able to stand (eventually with human help). We used well validated and robust statistical tools applied to brain imaging (Rorden & Karnath, 2004; Foulon et al., 2018), and controlled for lesion size. All key structures causing lateropulsion when damaged were localized in the right hemisphere. This clearly demonstrates the right lateralization of networks underpinning the body orientation with respect to gravity. Overall this study reveals a dramatic alteration of posterior thalamo-insular projections, with alteration of other basal ganglia, putamen and caudate nucleus. Cortico-spinal tract and internal capsule were also involved. The sample size and the clinical characteristics of participants comparable to those usually found in the literature of studies performed in rehabilitation after a first stroke of various sizes (small and large), advocate for the generalizability of our findings.

The right-hemisphere controls body orientation with respect to gravity

No structure of the left hemisphere was significantly associated with lateropulsion. This negative result was due to the low number of individuals presenting a lateropulsion after LHS (15 of the 90 LHS) leading to an insufficient statistical power to statistically identify the structures of the LH causing a right lateropulsion when damaged. This confirms that the right hemisphere is strongly predominant for graviception, a concept widely demonstrated (Perennou et al., 2008; Dai et al., 2021). These results are congruent with the predominance of the right vestibular cortex (Dieterich et al., 2003), conferring to the right hemisphere the status of the postural brain (Pérennou et al., 1999). Our results do not indicate that the LH plays no role in graviception, indeed Babyar et al showed the involvement of the left inferior parietal lobule (Babyar et al., 2019). Moreover a recent connectivity study has shown that there is a bilateral and relatively symmetric network able to serve the construction of the internal model of verticality (Lemaire et al., 2020). This may be viewed as a potential network distributed in both

hemispheres and partly shared with other functions. With human evolution, this network developed in one hemisphere to become more efficient, the right hemisphere, as for other spatial functions (Karolis et al., 2019). How this potential bi-hemispheric network for graviception might support brain plasticity after stroke (Siegel et al., 2018) remains to be investigated in further studies.

Thalamo-insular projections: a key role for the sense of the upright

Several studies have shown that structural lesions of the postero-lateral thalamus induce lateropulsion (Karnath et al., 2005; Ticini et al., 2009) and altered verticality perception (Perennou et al., 2008; Barra et al., 2010; Maffei et al., 2016; Santos et al., 2019; Piscicelli et al., in preparation). However, Johannsen et al. (Johannsen et al., 2006) described pushing syndrome in patients with cortical damage sparing the thalamus, lesions being centered on the insular cortex (Brandt et al., 1994). While, grey matter analyses of the present study did not show the involvement of the thalamus, white matter analyses showed that orienting body against gravity, at least in the frontal plane, requires the integrity of thalamo-insular projections. These results are in agreement with connectivity within the network of verticality: the more disrupted the thalamo-insular projections, the more biased the verticality perception (Lemaire et al., 2020). The results of the present study showed that disconnection mechanisms occurred beyond the lesion site. The thalamo-insular projections connect the posterior part of the insula and the thalamus. The regions connected by these white matter fibers are involved in multisensorial integration. Postero-lateral thalamus plays a functional role in the processing of both vestibular (Dieterich et al., 2005) and somaesthetic (Perennou et al., 2008) graviception. Through the postero-lateral thalamus, ipsilateral or contralateral pathways reach the posterior part of the insular cortex (Dieterich et al., 2017; Kheradmand & Winnick, 2017). Posterior insular cortex treats higher-order neural mechanisms to solve the problem of different sensory reference frames in the process of integrating various sensory information: vestibular (Mazzola et al., 2014) and somaesthetic (Baier et al., 2013; Mazzola et al., 2014; Maffei et al., 2016;). Posterior part of the insula is well known in lateropulsion (Johannsen et al., 2006; Ticini et al., 2009; Kheradmand & Winnick, 2017; Baier et al., 2020) and verticality perception biases (Barra et al., 2010; Baier et al., 2012; Kheradmand & Winnick, 2017).

Disorder of body orientation with respect to gravity: a disconnectome syndrome

Previous lesion mapping studies on lateropulsion have focused on the role of cortical lesions in areas such as the inferior parietal cortex (Babiar et al., 2019) and the insular cortex (Baier et al., 2020), arguing that these areas play a central role in the integration of somatosensory, visual, and vestibular inputs. Our study which combines cortical and disconnection mechanisms analyses suggest that orienting body against gravity depend on the coordinated activity of different regions rather than single areas in the insular or parietal cortex. Even the exact contribution of cortical and disconnection mechanisms remains to be defined with more precision, the lateropulsion should be seen more as a disconnection syndrome involving disruptions in tracts and structures belonging two systems. The first one involved the sense of verticality pathway through disconnection of thalamo-insular projections (Lemaire et al., 2020) and the second the motor control through the cortico-spinal tract and the internal capsule. The alteration of cortico-spinal tract would be a determinant of slower recovery from lateropulsion (Abe, 2017) and damage of internal capsule have been considered as the anatomical location explaining the more severe paresis observed in thalamic patients with contraversive pushing compared to those without (Karnath et al., 2005). This theoretical conceptualization of the lateropulsion, requiring a functional network of multisensory integration areas for verticality representation coupled with a normal motor control, is consistent with clinical features of lateropulsion. Patients with a lateropulsion actively align their body posture onto a wrong internal reference of verticality, tilted the side opposite the stroke (Perennou et al., 2008; Pérennou et al., 2014; Dai et al., 2021) with an other detrimental determinant, the weakness (Dai et al., 2020).

The involvement of deep brain structures such as the putamen and the caudate nucleus is in keeping with this comprehensive approach of the lateropulsion conceived as a dysfunction of an extended network of cortical and subcortical areas connected by several tracts. In verticality perception, the involvement of these structures has already been shown (Baier et al., 2012; Piscicelli et al., in preparation). These subcortical areas are also part of the cortico-striato-thalamo-cortical loops involved in movement disorders such as in parkinson disease. Parkinson disease patients may have lateral trunk tilt, mainly in the direction opposite to the affected side of the body, named Pisa Syndrome (Duvoisin & Marsden et al., 1975). The patients with Pisa syndrome show significantly larger VV errors toward the trunk tilt in comparison to those without trunk tilt (Scocco et al., 2014; Gandor et al., 2016). A recent study (Piscicelli et al., in

revision) showed the implication of the basal ganglia circuitry in the somaesthetic and vestibular graviception. The modulation of this subcortical network by the deep brain stimulation of the subthalamic nuclei might recalibrate the sense of verticality and this could lead to long-term changes in trunk orientation.

Lesion size

The present study clearly showed that lesion extent influences lateropulsion severity. Only one study (Babyar et al., 2019) had already been interested in the relationship between lesion size and severity of lateropulsion. Babyar et al. found a correlation when right and left sided brain lesions were pooled, on the other hand this correlation no longer found for isolated right lesions. The present study showed that correlation was stronger after a right-sided brain lesion than a left-sided brain lesion. These findings are consistent with those of Pérennou's study (Perennou et al., 2008) which showed that subjective postural vertical perception was related to lesion size only for patients with right-sided brain lesions. If lesion size influences lateropulsion severity, lesion size could also influence cerebral reorganization, plasticity which occurs in the aftermath of a brain acquired injury. Lesion size could therefore influence lateropulsion recovery, this has never been investigated. Plasticity might be ipsilesional, near the lesion, far from the lesion or even contralesional with reorganization or recruitment of areas in the non-damaged hemisphere. This hypothesis might explain the recent findings of our study on functional connectivity of the sense of verticality (Lemaire et al., 2020) showing a connection in the contralesional side recruited after a stroke. Clinically, one may assume that a large lesion could be responsible for many deficits. It is well known that when lateropulsion is associated with other deficits, its recovery prognosis is less good (Babyar et al., 2015). Advocating for more time in rehabilitation may be indicated for patients with large lesion size, more severe lateropulsion (Babyar et al., 2015).

Perspectives

Knowing precisely the neural bases of lateropulsion allows, with a systematic MRI after stroke or in future with a systematic DTI, to quickly detect patients who will develop lateropulsion and therefore to predict hospital's length in rehabilitation and overall adapt rehabilitation program.

Alteration of thalamo-insular projections seems to be associated with the development of lateropulsion. These projections appear to be essential in the graviception pathway. From a clinical perspective, improving the connectivity of these projections and the communication between postero-lateral thalamus and posterior part of insula might improve recovery of lateropulsion. Selectively influencing thalamo-insular projections and more precisely thalamus via somatosensory stimulation at the neck level with Transcutaneous Electric Nerve Stimulation may be indicated (Pérennou et al., 2001).

Based on the current findings implicating deep brain structures, it is difficult to speculate that modulating the activity of these deep structures is possible via transcranial magnetic stimulation. Transcranial direct current stimulation seems to be more adapted to deep structures and provide a rational therapeutic strategy to test as a potential intervention for lateropulsion.

Limitations

The main limitations of the study are related to manual lesion delineation and registration methods (Rorden & Karnath, 2004; de Haan & Karnath, 2018;) and the sensitivity level of neuroimaging techniques that do not depict the full extent of damage produced by stroke lesions (Hillis et al., 2000). However, these limitations mainly apply to small sample studies, while here the large number of patients investigated reduces these risks. Furthermore, even if SCP score is the reference to quantify lateropulsion both in practice and in clinical research (Babyar et al., 2009), this scale has several limitations including poor sensitivity to change (Bergmann et al., 2014) and poor reproducibility (Clark et al., 2012).

Conclusion

This study was the first that investigated structures playing a key role in lateropulsion, when damaged or when disconnected, from a large cohort of 170 individuals tested at the subacute stage after a first hemisphere stroke and with a robust lesion analysis. It clearly demonstrated the right lateralization of networks underpinning the body orientation with respect to gravity. Our findings revealed, beyond the identification of the locus and extent of cortical and subcortical brain lesions responsible of lateropulsion, that the disruption extended to connections projecting to areas distant from the lesion, in particular with a key role of the thalamo-insular projections.

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THÈSE SOUTENUE PAR: **Camille LEMAIRE**

TITRE: **HUMAN AGAINST GRAVITY: BRAIN NETWORKS OF GRAVICEPTION
ANALYZED FROM A SERIES OF 170 POST-STROKE INDIVIDUALS**

CONCLUSION

This is the first study that investigates and identifies neural bases and brain disconnection involved in lateropulsion, from a large cohort of 170 individuals tested at the subacute stage after a first hemisphere stroke and with a robust lesion analysis. We analyzed both grey and white matter.

No structure of the left hemisphere was significantly associated with lateropulsion. Several key structures of the right hemisphere when damaged caused lateropulsion. For the grey matter were strongly involved, the putamen, the posterior insula and the caudate nucleus. For the white matter the study revealed a dramatic alteration of thalamo-insular projections, with alterations of cortico-spinal tract and internal capsule. These brain structures contribute to the construction and updating of the sense of the upright and support the motor command. A better understanding of the neuroanatomical basis of lateropulsion could help shape novel interventions.

VU ET PERMIS D'IMPRIMER
Grenoble, le : 01/02/2021

LE DOYEN



Pr. Patrice MORAND

Pour le Président
et par délégation
—
Le Doyen de Médecine
Pr. Patrice MORAND

LE PRÉSIDENT DE LA THÈSE



Pr. Dominic PÉRENNOU