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## Understanding lateropulsion after stroke

Shenhao Dai

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## THÈSE

Pour obtenir le grade de

### DOCTEUR DE L'UNIVERSITE GRENOBLE ALPES

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Présentée par

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préparée au sein du **Laboratoire de Psychologie et Neuro Cognition - CNRS UMR 5105**

dans **l'École Doctorale Ingénierie pour la Santé la Cognition et l'Environnement**

## Comprendre la latéropulsion après AVC

## Understanding lateropulsion after stroke

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## Abstract

**This thesis on post-stroke lateropulsion is organized in three parts.** The first part sets the theoretical frame, assumes that post-stroke lateropulsion has been overlooked so far and is misunderstood, explained by our hypotheses at the light of the literature: 1) lateropulsion prevalence is high if one looks at beyond the pusher syndrome, the tree which hides the forest; 2) lateropulsion is a trinity with lateral body tilt (the cardinal sign), resistance and pushing; 3) lateropulsion is a deficit in body orientation with respect to gravity, and underlying mechanisms are in relation to a biased graviception and spatial neglect; 4) lateropulsion plays a key role in post-stroke balance and gait disorders; 5) one needs a new gold standard to assess lateropulsion.

### **The second part corresponds to personal contributions.**

The first paper reviews the history of different terminologies used to describe post-stroke lateropulsion (historical letter in preparation).

The second paper (submitted) is systematic review and meta-analysis of post-stroke lateropulsion prevalence, following standardized protocol (PROSPERO-CRD42020175037). Twelve studies of supratentorial stroke gave a pooled lateropulsion prevalence of 41% (95% Confidence Interval [CI] 33.5–48.5), decreasing from 52.8% in the acute phase to 22.8% in the late subacute phase. The ratio of right to left-hemisphere stroke with lateropulsion much increased as a function of time. This study appeals for a systematic detection to guide appropriate interventions as early as possible.

Next studies were performed from the dataset of the DOBRAS Cohort (ClinicalTrials.gov: NCT03203109), with 220 consecutive individuals enrolled after a first hemisphere stroke, and comprehensively assessed at D30, D60, D90 and discharge from the rehabilitation ward. The third and fourth papers were published as companion studies (Neurology, April 2021).

-In one, we investigated on D30 lateropulsion underlying mechanisms in relation to a biased graviception (Visual vertical, VV) and spatial neglect. We showed that lateropulsion assessed with the Scale for Contraversive Pushing (SCP) was a trinity constituted by body tilt, pushing and resistance, corresponding to an impaired orientation of the body against gravity in relation to an altered graviception. Referring to straight above, lateropulsion might correspond to a form of spatial neglect (referring to straight ahead), which would advocate for 3-D maps in the human brain involving the internal model of verticality.

-In the other we showed that lateropulsion was the primary factor altering balance and gait disorders, especially after right hemisphere stroke where lateropulsion explained  $\geq 90\%$  of the information contained in balance disorders and  $\geq 66\%$  in gait disorders. This result suggests that in the post-stroke subacute stage, balance and gait rehabilitation should be rethought and be focused on body orientation with respect to gravity.

The next papers correspond to longitudinal studies, still performed with the DOBRAS data set. We performed a longitudinal study investigating lateropulsion recovery, balance recovery, and the responsiveness of their assessment tools (in preparation). Meanwhile we conducted a narrative review aiming to synthesize clinimetrics of current tools used to assess lateropulsion, in compliance with the COSMIN guideline. We conclude there is a need for a novel lateropulsion scale having the quality to become the future gold standard (paper in about to be submitted). We also analyzed the effect of white matter hyperintensities (WMHs) on lateropulsion and balance recovery. We found that WMHs was a detrimental biomarker for balance recovery, whose effects were more significant on body stabilization than on body orientation (two papers published in Ann Phys Rehabil Med).

**Finally the third and the last part is a general discussion.**

**Key words:** lateropulsion, balance, gait, stroke recovery, verticality, spatial neglect

## Résumé

**Ce travail de thèse sur la latéropulsion post-AVC est organisé en trois parties.** La première partie pose le cadre théorique. La latéropulsion post-AVC a été négligée jusqu'à présent et est mal comprise, le travail scientifique que nous avons mené a pour but d'améliorer notre connaissance de ce déficit postural à la lumière de la littérature. Nous montrerons que : 1) la prévalence de la latéropulsion est élevée si l'on regarde au-delà du syndrome pusher, un arbre qui cache la forêt; 2) la latéropulsion est une trinité constituée par l'inclinaison latérale du corps (signe cardinal), la résistance et la poussée; 3) la latéropulsion est un déficit d'orientation corporelle par rapport à la gravité, et les mécanismes sous-jacents sont en relation avec une graviception biaisée et une négligence spatiale; 4) la latéropulsion joue un rôle clé dans l'équilibre post-AVC et les troubles de la marche; 5) une nouvelle échelle pour évaluer la latéropulsion est nécessaire.

**La deuxième partie présente les travaux personnels.** Le premier article passe en revue l'histoire des différentes terminologies utilisées pour décrire la latéropulsion post-AVC (lettre historique en préparation). Le deuxième article (soumis) est une revue systématique et méta-analyse de la prévalence de la latéropulsion post-AVC, suivant un protocole standardisé (PROSPERO-CRD42020175037). Douze études sur les AVC supratentoriels ont donné une prévalence de latéropulsion combinée de 41% (intervalle de confiance [IC] à [33,5–48,5]), passant de 59% en phase aiguë à 22,8% en phase subaiguë tardive. Par ailleurs, cette étude recommande une détection systématique pour guider les interventions appropriées le plus tôt possible.

Les études suivantes ont été réalisées à partir des données cliniques de la cohorte DOBRAS (ClinicalTrials.gov: NCT03203109) portant sur 220 personnes incluses consécutivement après un premier AVC hémisphérique. Ainsi dans un troisième article (Neurology 2021), nous avons

montré que la latéropulsion évaluée avec la Scale for Contraversive Pushing (SCP) était une trinité constituée par l'inclinaison du corps, la poussée et la résistance, correspondant à une orientation altérée du corps contre la gravité en lien avec une graviception altérée. En impliquant le référentiel du « droit-dessus » par analogie au « droit-devant » impliqué dans le syndrome de négligence spatiale, la latéropulsion pourrait correspondre à une forme de négligence spatiale. Une telle hypothèse suggère l'existence dans le cerveau humain de cartes 3D impliquant le modèle interne de la verticalité. Dans un quatrième article (Neurology 2021), publié en tant que « companion article », nous avons montré que la latéropulsion était le principal facteur altérant l'équilibre et les troubles de la marche, en particulier après un AVC de l'hémisphère droit où la latéropulsion expliquait  $\geq 90\%$  des troubles de l'équilibre et  $\geq 66\%$  des troubles de la marche.

Les articles suivants correspondent à des études longitudinales, toujours réalisées avec le jeu de données DOBRAS. Nous avons réalisé une étude longitudinale portant sur la récupération de la latéropulsion, la récupération de l'équilibre et le responsiveness de leurs outils d'évaluation (en préparation). Nous également proposons une revue narrative visant à synthétiser la clinimétrie des outils actuels utilisés pour évaluer la latéropulsion, conformément aux guidelines COSMIN (en cours de soumission). Nous avons aussi analysé l'effet des White Matter Hyperintensities (WMHs) sur la latéropulsion et la récupération de l'équilibre. Nous avons constaté que les WMHs étaient un biomarqueur délétère pour la récupération de l'équilibre, dont les effets étaient plus significatifs sur la stabilisation du corps que sur l'orientation du corps (deux papiers publiés dans Ann Phys Rehabil Med).

**Enfin troisième et dernière partie est une discussion générale.**

**Mots-clés : latéropulsion, équilibre, marche, récupération après AVC, verticalité, hémiparésie**

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## List of abbreviations

AST	Apraxia Screen of Tulia
BAG	Behavior against gravity
BLS	Burke Lateropulsion Scale
BMI	Body Mass Index
CBS	Catherine Bergego Scale
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
CST	CorticoSpinal Tract
DOBRAS	Determinants of Balance Recovery After Stroke
ES	Effect Size
FIM	Functional Independence Measure
FM-UE	Fugl-Meyer Assessment for upper extremity
LHS	Left Hemisphere Stroke
M-SCP	Modified Scale for Contraversive Pushing
MDC	Minimal Detectable Change
mFMA	modified Fugl-Meyer Assessment
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NPV	Negative Predictive Value
PASS	Postural Assessment Scale for Stroke
PPV	Positive Predictive Value
PS	Pusher Syndrome
PV	Postural Vertical
RHS	Right Hemisphere Stroke
ROC	Receiver operating characteristic
SCALA	SCAle for LAteropulsion
SCP	Scale for Contraversive Pushing
SRM	Standardized Response Mean
VV	Visual Vertical
WMHs	White Matter Hyperintensities
4PPS	4-Point Pusher Scale

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## ➤ **Brief introduction of the thesis**

This thesis is a comprehensive clinical investigation of the “post-stroke lateropulsion”. The first part of this thesis is a theoretic framework, where we demonstrate that lateropulsion would be the link of the spatial cognition and balance control. Following this part, the manuscript is constituted by a series of articles. The first two articles are two review papers, one dealing with the historical terminology of lateropulsion, the other dealing with the epidemiological data of reported lateropulsion prevalence by a meta-analysis. The third article introduces the mechanism of lateropulsion through a neuroscience prism. The fourth article presents the association between lateropulsion and balance and gait disorders after stroke and further introduces a new theoretic frame for post-stroke mobility. The fifth article investigates the lateropulsion and balance recoveries. The sixth and seventh articles explore the specific effect of white matter hyperintensities (WMHs) on body orientation and on body stabilization. The last article is narrative review on lateropulsion evaluation, where we discuss the insufficiencies of current tools according to COSMIN guideline and propose to develop a novel scale.

## ➤ Chapter 1: Theoretical framework

### 1. Spatial cognition

Spatial cognition refers to the ability of the central nervous system to integrate spatial information necessary for space perception and space navigation (Brandt *et al.*, 2017). From an evolutionary perspective, the ability to estimate one's own position and track and plan one's own path in physical space is key to survival. Spatial cognition cannot be isolated as simply a product of brains, because human behaviors emerge from the complex interaction between brains, bodies and environments. Spatial cognitive processes are multi-referenced, involving vestibular, somatosensory, visual and auditory information (Geva-Sagiv *et al.*, 2015; Cullen, 2019). In order to understand the computational basis of spatial cognition, we need to observe behaviors in an ecological circumstance and to investigate the underlying neural circuits.

Since Broca has found the predominance of language in left hemisphere in 1865 (Broca, 1865), we began to recognize the functional difference between two hemispheres. Right hemisphere has been considered as 'non-dominant hemisphere' (Karolis *et al.*, 2019), whose function is less known. But more and more evidences approve right hemisphere is predominant in space cognition (Bartolomeo and Seidel Malkinson, 2019) and postural control (Pérennou *et al.*, 1999; Pérennou, 2006).

In 1971, John O'Keefe discovered the first component of positioning system (O'Keefe and Dostrovsky, 1971). He concluded that certain 'place cells' determined the space navigation in rats. More studies suggested these special cells located in right hemisphere, particularly in right parietal cortex and hippocampus (Lopez and Blanke, 2011; Chen *et al.*, 2013). Similar results are also exhibited in birds and fishes (Brandt *et al.*, 2017). Studies of diverse avian species have revealed that the right hemisphere dominates attentional shifts and analysis of pictorial and spatial information.

However, there are differences in space coding between ground-based species and no ground-based species. Most swimming and flying species move and navigate isotropically in horizontal and vertical planes within the 3-D environment (Brandt *et al.*, 2017). They use path integration, continuously integrating direction and distance to their envisaged goals. Whereas, ground-based species, as humans and rats, also show anisotropy in spatial memory for horizontal and vertical dimensions during real navigation, but much better in horizontal plane (Zwergal *et al.*, 2016; Brandt *et al.*, 2017).

The different space coding may be resulted from different functions of ‘place cells’, some orienting in the horizontal plane, some in vertical plane (Chen *et al.*, 2013; Laurens *et al.*, 2016; Cullen, 2019). The 3-D coding function would be strongly associated with central vestibular system, one convinced evidence is those cells concentrated in vestibular cortex (dominant in right hemisphere) and vestibular related circuit within cerebellum (Lopez *et al.*, 2012; Brandt and Dieterich, 2019; Cullen, 2019). The vestibular system provides the brain with sensory signals about three-dimensional space coding, which is crucial for space perception and balance control (Dieterich and Brandt, 2019).

## **2. Representation of gravity**

How the brain computes accurate estimates of our orientation relative to gravity in order to ensure accurate perception and motor control is a fundamental neuroscientific question. Gravity is a defining force that anchors our perception of the environment. Animals as well as plants leaving under the constant acceleration of gravity have developed mechanisms to encode the direction of the gravitational pull and adapt their posture accordingly (Bastien *et al.*, 2013; Laurens *et al.*, 2016). Any human being on the earth is subject to the force of gravity, which is elementary signal to organize the spatial and postural behaviors between bodies and objects.

The human, the only biped mammal species, is remarkably efficient in controlling the orientation and stabilization of the body in vertical position in space. Such control requires the construction and updating by the brain of a 'sense of verticality' which can be defined as the ability of the human being to perceive explicitly the direction of the vertical, to develop a mental representation of verticality, and to use this representation to orient or guide a part of its spatial environment (Barra and Pérennou, 2013).



Figure 1: The verticality of plant on Earth (Bastien *et al.*, 2013).

The sense of verticality is a major spatial referential for perception and action in space. It allows determining our body position relatively to the gravity and it contributes to the organization of the postural control in humans (Barra *et al.*, 2010; Barra and Pérennou, 2013). Because our vertical posture has narrowed our base of support and raised our center of mass, it has also made us less stable than if we had a quadrupedal posture. That is why the perception of verticality is crucial to humans. We could imagine that we should lie down or return to quadrupedal posture without a sense of verticality, or as astronauts out of the earth. The perception of verticality is evolving with environments from a phylogenetic but also from an ontogenetic perspective. The newborns' position evolves from lying to climbing with four limbs, finally to walking with two



legs. This evolution of verticality is constructed and updated through multisensory integration processes within brain structures.

The sense of verticality is constructed and updated through vestibular, visual and somatosensory information about vertical orientation of the three-dimensional space relative to the earth-centered gravitational force (Barra and Pérennou, 2013). Those multisensory coordinates have to be matched by convergence to create the actual global percept of up and down, right and left, and fore and after (Brandt and Dieterich, 2019). This percept may apply to either the allocentric orientation of surrounding targets or to the egocentric orientation of body position within the environment. The sensory modalities involved cannot perceive different verticals at the same time independently- a visual and a vestibular one. This multisensory input establishes an internal model of space and verticality, which is updated via bottom-up and top-down processes (Barra *et al.*, 2012; Barra and Pérennou, 2013).

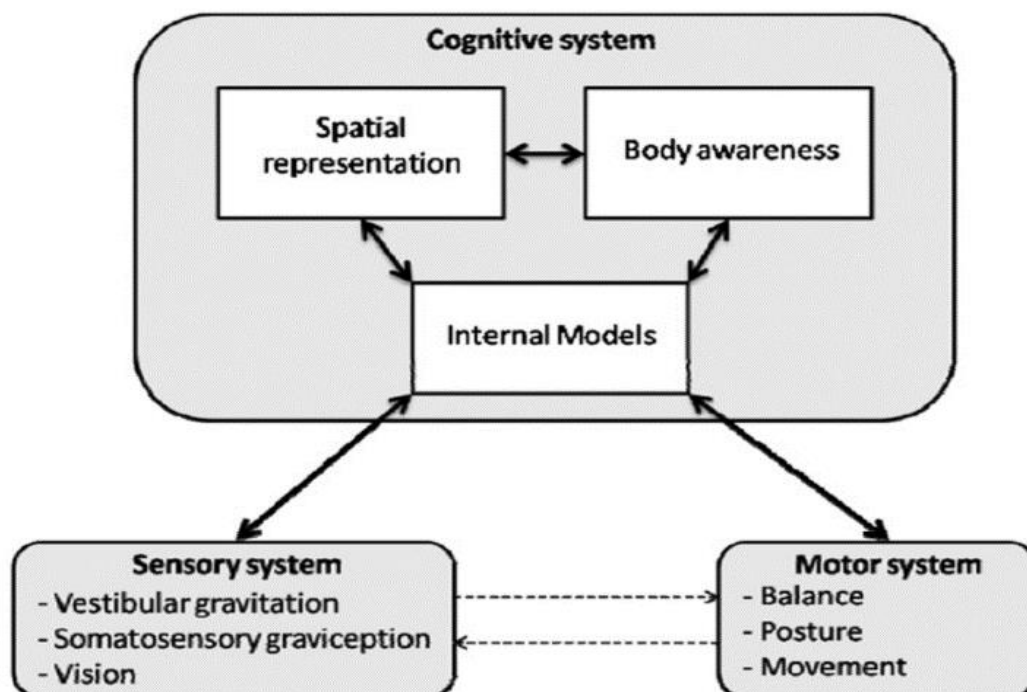


Figure 2: The internal model of verticality (Barra and Pérennou, 2013).

The internal model of verticality comprises at least two bottom-up processes (Barra and Pérennou, 2013), the integration and weighting of sensory information on the one hand, afferent and efferent signals involved in the control of posture and balance on the other hand. The interaction between the internal representation of verticality and the sensory and/or motor processes is represented in this model by a two-way link, expressing the referenced nature and reference source of the sense of verticality: motor and sensory processes participate in the construction of the sense of verticality which, in turn, is used implicitly or explicitly for spatially oriented postural behaviors and spatial perception. The innovative dimension of this model lies in the integration of top-down influences such as awareness of verticality.

### **3. Balance control**

Upright, bipedal locomotion is a hallmark of human mobility, allowing for independent walking on the earth. Successful locomotion depends on correct balance control to tough out different daily tasks. Without adequate balance control, locomotion becomes dyscoordinated, inefficient, unstable and potentially hazardous given the risk for falls during walking.

Balance control need vertical body orientation and stable body support. The control of body upright is termed ‘orientation’. The control of the body oscillations is termed ‘stabilization’ (Massion, 1992; Pérennou, 2006). These two components do not operate independently but interact, providing a stable physical basis for perception and action. Balance control is a complex system involving integration of sensory information of various origins. The sensory information available for controlling balance is fairly redundant and despite its great specificity, various kinds of sensory information can be used almost equally efficiently (Assaiante *et al.*, 1989; Barra *et al.*, 2010). The information in question may be vestibular, visual and somesthetic in origin – arising from sensory sources such as muscle, skin, and joints. When organizing a

given movement, the central nervous system has to coordinate all these information to the control of balance.

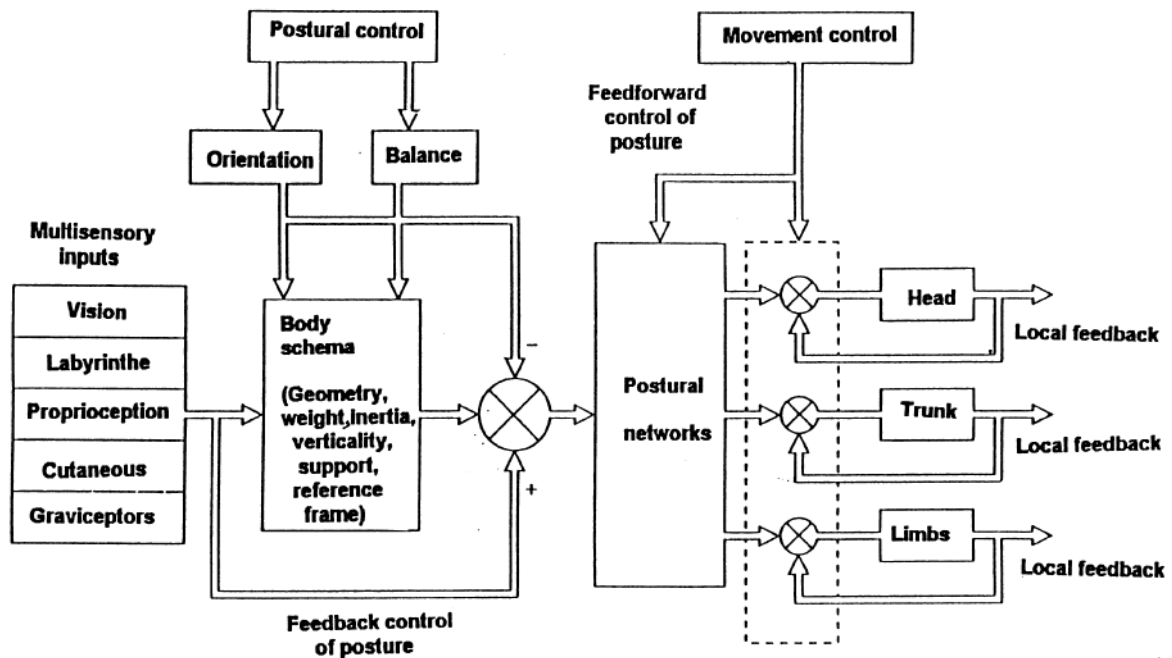


Figure 3: Theory of balance control (Massion, 1998).

Body orientation with respect to gravity can be estimated by the projection of the center of mass onto the ground only when the body is aligned along the gravitational force. Body stabilization with respect to control of the perturbation can be estimated by regain the center of mass in horizontal plan when the body is oscillated forward and backward or left and right (Massion, 1992; Massion *et al.*, 1998; Pérennou, 2006; Horak and Macpherson, 2011; Dai *et al.*, 2021).

In contemporary research of balance control, body stabilization appeals most attention, whereas body orientation seems to be overlooked. The deficits of body orientation could be presented in frontal and sagittal planes. The studies about body orientation was initiated by a series French neurologists in early 1900s. The most important person among them is Joseph Babinski, he repeatedly reported cases with deficit of body orientations resulting from different neurological pathologies. He termed the deficit of body orientation in frontal plane as ‘lateropulsion’

(Babinski and Nageotte, 1902) and the deficit of body orientation in sagittal plane as ‘retropulsion’ (Babinski, 1899).

Since the first observation of Babinski and Nageotte, we have known that the individual with lateropulsion has difficulty in keeping balance, inducing gait disorder and risk of falls (Babinski and Nageotte, 1902). Pérennou advocates the lateropulsion as the representative of deficit of body orientation due to the biased verticality (Pérennou *et al.*, 2008; Pérennou *et al.*, 2014). The multisensory internal model could be implicated in construction of body orientation with respect to gravity (Barra *et al.*, 2010).

In current literature, lateropulsion is linked to balance, gait and falling on one hand, and is linked to spatial neglect and biased verticality representation on the other hand (Pérennou, 2006). Maybe we could link the spatial cognition and balance control together owing to lateropulsion. In this thesis, we propose such integrative approach of lateropulsion linking locomotion and cognition.

#### **4. The recovery of lateropulsion and balance after stroke**

Stroke recovery is the next frontier in stroke medicine. Based on pre-clinical researches in animals and humans, the framework of biological post-stroke recovery has been recently developed (Bernhardt *et al.*, 2017), whose timeline has been defined as “acute”, “subacute” and “chronic” phases. From this framework, we can find that the first week until the first month post-stroke (acute and early sub-acute) is a critical time for stroke recovery, in particular for neural plasticity.

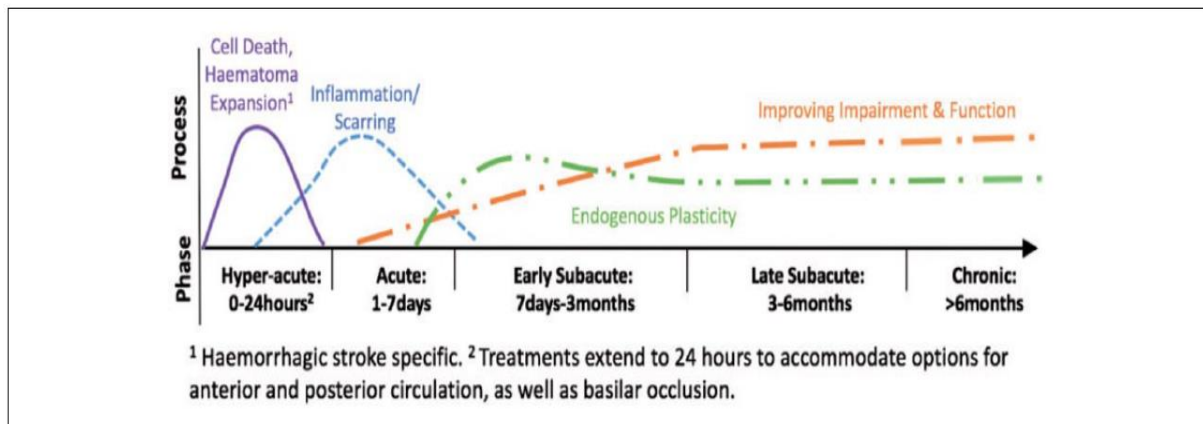


Figure 4: Framework of post-stroke recovery (Bernhardt, et al. 2017).

In discussing stroke recovery, acknowledging that any improvement in any domain of the International Classification of Functioning and Disability (ICF) can be viewed as a sign of ongoing recovery is important. Longitudinal studies have repeatedly demonstrated the time-dependency of neurological recovery after stroke, including motor (upper and lower limbs) and non-motor deficits (aphasia and spatial neglect) (Lazar *et al.*, 2008; Winters *et al.*, 2015; Ramsey *et al.*, 2017; Smith *et al.*, 2017; Winters *et al.*, 2017; Stinear *et al.*, 2020; van der Vliet *et al.*, 2020; Selles *et al.*, 2021).

Among the published models of recovery (Winters *et al.*, 2015; Stinear *et al.*, 2020; van der Vliet *et al.*, 2020; Selles *et al.*, 2021), the motor deficits of upper limbs has been the most studied so far. Spontaneous recovery is an important determinant of upper limbs' recovery and has been described by the 70% proportional recovery rule for the Fugl–Meyer motor upper extremity (FM-UE) scale (Prabhakaran *et al.*, 2008). The majority of the recovery occurred within the first three month after stroke, particularly the first month (van der Vliet *et al.*, 2020). Similar models of recovery are found in motor recovery of lower limbs (Smith *et al.*, 2017) as well as non-motor recovery, such as aphasia and spatial neglect (Lazar *et al.*, 2008; Ramsey *et al.*, 2017; Winters *et al.*, 2017).

All these recovery models share some common points, as follows: 1) rapid spontaneous recovery within the first month; 2) always with steadily continuous recovery from first to third months; 3) a potential plateau after the third month (some deficits after the sixth month). However, the exact timeline of recovery for different deficits is still questionable, we assume that the timeline of recovery of some deficits may differ from others. A typical example is the recovery of gait, some authors (Kollen *et al.*, 2005; Kwakkel *et al.*, 2006) showed that the specific recovery timeline of gait was somehow different from other deficits in same cohort. As we know, the gait is a complex mission for post-stroke individuals, engaging with both motor and non-motor functions.

As well as gait disorder, posture and balance disorders are complex and common deficits after stroke. This is rather surprising that posture and balance recovery has been little modelled so far, much less than other functions. Acquisition of specific knowledge about the post-stroke recovery of lateropulsion and balance is a prerequisite for future clinical trials focused on mobility.

Despite few knowledge of modeling posture and balance recovery after stroke, the theory of posture and balance recovery in other pathologies is soundly developed, especially in those vestibular pathologies. Both acute peripheral and central vestibular lesions cause lateropulsion and imbalance. These deficits of an acute unilateral peripheral vestibular loss gradually attenuate within weeks, even if there is no recovery of peripheral function. This so-called central vestibular compensation is considered the prototype of brain plasticity (Cnyrim *et al.*, 2007; Lacour and Bernard-Demanze, 2014; Grosch *et al.*, 2021), implicating not only in peripheral vestibular disorder, but also in central vestibular disorder. Given that lateropulsion and balance disorder after stroke are highly associated with multimodal vestibular network (Brandt and Dieterich, 2017), their recovery might be similar to that after peripheral vestibular disorder, therefore would have distinguished timeline owing to the vestibular compensation.

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## ➤ Chapter 2. Methodological framework

In this chapter we briefly introduce some of the key elements related to the methods that we used in this thesis.

### **DOBRAS cohort**

This was a monocentric observational study using the data of the DOBRAS (Determinants of Balance Recovery After Stroke; ClinicalTrials.gov: NCT03203109) cohort, with participants comprehensively assessed in routine care, initially during the first weeks after entry in the rehabilitation ward. The sample size was planned to conduct multivariate analyses in a large series of individuals ( $\geq 200$  observations). Sensory, motor, and cognitive deficits were assessed at a fixed date by trained and multidisciplinary examiners, with blinding to other data and the study hypotheses.

From January 2012 to October 2019, we included 248 consecutive individuals with a first-ever unilateral stroke limited to one hemisphere. Exclusion criteria were recurrent stroke; complication at the acute stage (malignant infarct, cerebral herniation, subarachnoid hemorrhage, and hydrocephalus); dementia; previous disability interfering with balance, gait or vestibular disorders; unstable medical condition or psychiatric problems; and not French speaking. These conditions were obtained from the hospital electronic file describing the history of every patient, by interviewing patients and relatives, and by a systematic clinical examination.

We conducted the initial assessments at about day 30 after stroke (D30) with a window of 3 days before and after to start and complete assessments. This date is a compromise between the desire to collect data as early as possible after the stroke and the need for sufficient medical

stability and attentional resources to afford a battery of comprehensive assessments performed during several days, at a time when almost all individuals have been admitted to the rehabilitation ward. These initial assessments collected information about handedness, all deficits, postural and gait disorders, and disability. All variables collected are listed below. The participants were comprehensively followed and assessed lateropulsion, balance and gait in routine care, on D60 ( $\pm 3$ ), on D90 ( $\pm 3$ ) and at discharge ( $\pm 3$ ).

Participants followed a personalized rehabilitation program, taking into account deficits and activity limitations, capacities to face intensive rehabilitation (fatigue or transitory medical problems), individual recovery, and the most appropriate guidelines. According to their abilities, participants had at least 2 physiotherapy and 1 occupational therapy sessions per day (each session lasting at least 30 min for a total daily time of sensori-motor rehabilitation over  $\geq 1.5$  hr per patient), plus sessions with a speech therapist, neuropsychologist, psychologist, or orthoptist if needed. The length of hospitalization of our participants was measured from stroke onset to discharge of the rehabilitation ward.

## Clinical assessments

Global disability was estimated by the modified Rankin Scale (mRS).

Handedness before stroke was assessed by interview (patient, relatives) by using a French translation of the Edinburgh inventory. Right-handedness was considered with a score  $> 0.4$ .

### Lateropulsion

Lateropulsion was assessed by the Scale for Contraversive Pushing (SCP), with increments of 0.25 and total score from 0 to 6 (Karnath *et al.*, 2000). The SCP has been designed to categorize individuals according to scores of the three signs defined by Davies (Davies, 1985): active

lateral body tilt, spontaneous action of abduction/extension of the ipsilesional upper or lower limb to push the body away from the upright (Pedersen *et al.*, 1996; Pérennou *et al.*, 2008), and resistance to passive correction making the body upright. As defined in the original method (Karnath *et al.*, 2000), individuals who met these three criteria with at least 1 point for each component were considered Pushers. They represent a small part of consecutive individuals, limited to severe lateropulsion (Pedersen *et al.*, 1996; Pérennou *et al.*, 2008; Abe *et al.*, 2012). Only considering Pushers would overlook individuals with moderate lateropulsion. As proposed previously (Pérennou *et al.*, 2008), we also used the SCP to differentiate individuals with an upright posture from those who were mildly tilted. To be conservative, we used the total SCP cut-off  $\leq 0.50$  to define the Upright group. Indeed, values of 0.25 or 0.5 were clearly marginal, not allowing to state that the individual was not upright most of the time. In this study, we called Tilters individuals of the intermediate group. They showed net lateral body tilt at least in one posture, sitting or standing, regardless of the two other lateropulsion signs, but did not show the criteria to be Pushers. In line with our hypothesis, this approach had the advantage of constituting a priori an intermediate group with individuals in whom mild degrees of body tilt, pushing, and resistance could be associated or not. To summarize, upright individuals had a total SCP score  $\leq 0.5$ ; Tilters had a total SCP score  $> 0.5$  and a score for at least one of the three components (body tilt, pushing or resistance)  $< 1$ , so were not Pushers; and Pushers had a total SCP score  $\geq 3$  and scores for all 3 components  $\geq 1$ .

Our study started at January 2012, when the SCP was the gold standard and dominated in Europe. We have used the Burke Lateropulsion Scale (BLS) (D'Aquila *et al.*, 2004) for some months in 2012. However, our physiotherapists found that there're some ambiguities in this

scale: ratings in supine, transfers and walking, and we had no French version of BLS. Therefore, our physiotherapists' team didn't continue to use this scale since the end of 2012.

### Balance and gait disorders

Balance disorders were assessed with the Postural Assessment Scale for Stroke (PASS), (Benaim *et al.*, 1999) the most appropriate balance scale at the subacute stage after stroke. The total score ranging from 0 to 36 (satisfactory balance) assesses balance abilities in daily life. The minimal detectable change (MDC<sub>95</sub>) of the PASS reported in subacute phase was 1.8 (1.7), (Hsueh *et al.*, 2013) thus we considered that there was an improvement of the PASS between 2 assessments if its change score >2. The last 2 items assess single limb stance on paretic and non-paretic sides, which are independent of other items because of their difficulty (Persson *et al.*, 2017). According to the scoring of these items, an individual who is able to maintain a single limb stance for >5 sec (whatever the side) has a total PASS score > 32/36, which we used as endpoint in this study. The 5-sec duration is the usual cutoff considered to indicate that this task is achieved. The side of the single limb stance is almost always the non-paretic side in individuals with stroke (Benaim *et al.*, 1999).

Gait disorders were assessed with the modified Fugl-Meyer Assessment of gait (mFMA-gait), designed to classify post-stroke gait in 7 levels of mobility (Lindmark and Hamrin, 1988). The mFMA-gait score ranges from 0 (no possibility to walk) to 6 (indicating a [quasi] normal gait). The 7 levels are as follows: 0, cannot walk at all; 1, can walk with the help of two persons; 2, can walk with the help of one person; 3, walk with the help of a walker, crutches or quadripod cane; 4, walk with the help of a simple cane or a crutch; 5; walk without any help but slowly or with lameness; 6, walk with normal speed for age. We used as the endpoint a score >4 indicating the ability to walk independently without a cane (or walker).

## Verticality perception

We used the visual vertical (VV) test and a procedure well described and validated (Pérennou *et al.*, 2008; Barra *et al.*, 2010; Piscicelli *et al.*, 2015a; Piscicelli *et al.*, 2015b; Piscicelli *et al.*, 2016) for testing individuals with postural disorders (Piscicelli *et al.*, 2015b; Piscicelli *et al.*, 2016; Piscicelli and Pérennou, 2017), with reliability (Piscicelli *et al.*, 2015a) and low measurement error (Piscicelli *et al.*, 2015a). VV tests were performed by trained examiners (CP and SD). To avoid any error due to the setting (Piscicelli *et al.*, 2015a), individuals were seated with their head and trunk maintained upright and straight by using lateral cushioning blocks in complete darkness (room without window, thick curtain over the door). Participants were asked to verbally adjust the line to the vertical, for 10 trials. We calculated two indices: VV orientation (VV-orient) and uncertainty (VV-uncert). VV-orient corresponded to the average of trials with negative values indicating a contralesional rotation, classified as follows (Pérennou *et al.*, 2008; Piscicelli and Pérennou, 2017): normal VV  $-2.5^\circ$  to  $2.5^\circ$ ; contralesional VV bias  $<-2.5^\circ$ ; and ipsilesional VV bias  $>2.5^\circ$ . VV-uncert corresponded to within-subject variability (standard deviation of the trials).

## Spatial neglect

Body and non-body neglect were assessed with a battery of six tests: ecological Catherine Bergego Scale (CBS) (Beis *et al.*, 2004; Azouvi *et al.*, 2006), thumb finding (Beis *et al.*, 2004; Azouvi *et al.*, 2006), Fluff (Rode *et al.*, 2017) (since 2014) and Bells tests (Beis *et al.*, 2004; Azouvi *et al.*, 2006), the bisection of two successive 200-mm lines (Beis *et al.*, 2004; Azouvi *et al.*, 2006), and the copy of Gainotti drawing (Beis *et al.*, 2004; Azouvi *et al.*, 2006). They were classified according to cut-offs proposed in seminal papers or revised later (Azouvi *et al.*, 2006). The Catherine Bergego Scale result was considered normal with score  $< 2$ , moderately



altered with score  $\geq 2$ , and markedly altered with score  $\geq 15$ . The thumb finding test result was considered abnormal with score  $>0$ . The Fluff test result was considered normal with  $\geq 13$  targets detached, moderately altered with  $\geq 9$  targets detached, and markedly altered with  $< 9$  targets detached. The Bells test result was considered normal with  $\leq 6$  omissions, moderately altered with  $\leq 15$  omissions, and markedly altered with  $> 15$  omissions. The line bisection (20 mm) result was considered normal at  $\leq 7$  mm, moderately altered at  $\leq 10$  mm, and markedly altered at  $> 10$  mm. The Gainotti copy result was considered abnormal if  $> 0$  omissions. Few individuals with severe comprehension (aphasia) or executive troubles were not able to complete the whole neglect battery but had to perform at least three tests to not be considered with missing data. Grouping for spatial neglect was as follows: No or light if all test results were normal or if only one test was marginally altered; Severe with results of at least two tests markedly altered (altered if binary categorized); or Moderate otherwise.

#### Other deficits

The presence of aphasia was evaluated by the gravity section of Boston Diagnostic Aphasia Examination; a score  $< 5$  was considered aphasia. Apraxia was assessed by the Apraxia Screen of Tulia (AST) (Vanbellinghen *et al.*, 2011) and participants with a score  $< 9$  had a diagnosis of upper-limb apraxia.

Motor weakness was assessed by a standardized examination of muscle strength adapted for participants with central neurological disorders (Pérennou *et al.*, 1998; Benaim *et al.*, 1999). Eight muscle groups of both the upper and lower limb were tested, and the final score was then adjusted to range from 0 to 80 (normal strength). Light weakness was considered a score  $> 64/80$  (every muscle had a motor command of  $4/5$ , on average), severe weakness a score  $\leq 32$  (every muscle had a motor command of  $\leq 2/5$ , on average), and moderate weakness otherwise.

Spasticity was assessed with the Ashworth Scale (Pérennou *et al.*, 1998; Benaim *et al.*, 1999). Five muscle groups of both the upper and lower limb were tested, and the final score was adjusted to range from 0 to 40 (extremely severe and diffused spasticity). Participants were classified as follows in terms of spasticity: no or light (0-4), moderate or severe (> 4).

Hypoesthesia was manually tested on both contralesional upper and lower limbs by trained physicians who assessed tactile and pain sensibility (Pérennou *et al.*, 1998; Benaim *et al.*, 1999). Participants were classified as having no or light hypoesthesia if errors were seldom, moderate hypoesthesia if detection errors were frequent, and deep hypoesthesia if they did not perceive any stimuli. Hemianopia was manually tested by trained physicians.

Depression was assessed by the Aphasia Depression Rating Scale (Benaim *et al.*, 2004); participants with scores > 8 were considered depressed.

## **Brain imaging**

MRI was performed about 2 months post-stroke, with a reasonable interval that is recommended to avoid overestimating stroke volume (Nagaraja *et al.*, 2020). The machine was 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 mm<sup>3</sup>; TR/TE/TI/ $\alpha$ : 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 mm<sup>3</sup>; TR/TE/TI: 9000/74/2500 ms). Lesion volume, determined as the percentage of hemisphere encroached on by the lesion (number of voxels for the lesion/number of voxels for the hemisphere \*100) was measured by using MRICron after a manual lesion delineation from axial slices acquired with T2-FLAIR sequences. All drawings involved 2 trained operators, the

first from a panel of three (CL, SD, AC) and the second always the same and with blinding to behavioral data (CP). Any disagreements were resolved by consensus. Drawings were performed on axial slices of a T1-weighted MRI template from the Montreal Neurological Institute (<https://www.mcgill.ca/bic/neuroinformatics/brain-atlases-human>) normalized to Talairach's space. Cortico-spinal tract (CST) disruption was analyzed with the "Tractotron" tool of the BCBToolkit software (<http://toolkit.bcblab.com/>), which determines the disruption induced at the level of a given lesion. Each participant's lesion was compared with an atlas of white matter tracts for each voxel. As suggested, we analyzed both the proportion and probability of the ipsilesional CST disrupted by the stroke (Foulon *et al.*, 2018). The proportion corresponds to the number of damaged voxels in the CST divided by the total volume of this tract. The probability corresponds to the lesioned voxel with the highest percentage value. The CST was considered disrupted when an estimated proportion or probability was >50% (Foulon *et al.*, 2018).

The presence of white matter hyperintensities (WMHs) was sought on T2-FLAIR sequences from the first or second MRI (within the first 2 months after stroke) and graded with the Fazekas scale (Fazekas *et al.*, 1987). The scale simply grades WMHs in 4 levels: 0, no lesion; 1, focal lesions; 2, beginning lesions confluences; and 3, extended involvement with large confluent areas. Two trained independent examiners (SD, CP), carefully examined the absence, presence, and severity of WMHs in the hemisphere spared by the stroke. If any, their differences of grading were resolved by consensus (Wardlaw *et al.*, 2013).

### **Personal contribution during the thesis**

During the last 3 years, my personal contributions to the thesis were as follows: constitution of the DORBAS dataset based on multi-disciplinary assessments, and participation to the assessments of visual vertical and MRI drawings.

## **Statistical models for lateropulsion, balance and gait recovery**

In this thesis, we tried to investigate some recovery models of lateropulsion, balance and gait:

### Model 1

We used the discharge data as dependent variable and initial data of different features as independent variables in regression (linear or logistic) models or prediction models. In these models, our objectives were to explore the effect of initial data.

### Model 2

We investigated endpoints (single limb stance and independent gait) as censored cases by two survival tests (Kaplan-meier test and cox regression). These models investigated the effect of different deficits as a function of post-stroke time.

### Model 3

Proposed by experts in this domain (van der Vliet *et al.*, 2020; Selles *et al.*, 2021), we also analyzed recovery based on different time points (at least two times per patient) by linear mixed-effect model. For these models, time, deficits and all time\*covariates were analyzed by fixed effects, and the individual level and an interaction of subject and time were used as the random effects.

## **Overview of the following chapters**

The works carried out during the thesis will be presented in following chapters. Before the thesis, we had some hypothesis based on the literature. We assumed that post-stroke lateropulsion had been overlooked so far and was misunderstood, explained by our hypothesis

at the light of the literature: 1) lateropulsion prevalence was high if one looks at beyond the pusher syndrome, the tree which hid the forest; 2) lateropulsion was a trinity with lateral body tilt (the cardinal sign), resistance and pushing; 3) lateropulsion was a deficit in body orientation with respect to gravity, and underlying mechanisms are in relation to a biased graviception and spatial neglect; 4) lateropulsion played a key role in post-stroke balance and gait disorders; 5) one needed a new gold standard to assess lateropulsion.

Therefore, different chapters respond to different hypothesis. The chapter 4 aimed to investigate both lateropulsion prevalence and prevalence of its severe form – pushers. The chapter 5 aimed to investigate the unidimension of lateropulsion and its association with vertical perception and spatial neglect. The chapter 6 and 7 aimed to investigate the role of lateropulsion in balance and gait disorders after stroke. In the chapter 9, we discussed the current tools of assessment of lateropulsion, and proposed to develop a new proper scale.

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### ➤ **Chapter 3: Toward a renaissance of the terminology ‘lateropulsion’**

The first paper reviews the history of different terminologies used to describe post-stroke lateropulsion. Our objective is to clarify relevant terms about lateropulsion dated back to the beginning of 1900s. This paper is still under preparation, and we will submit it soon.

## Toward a renaissance of the terminology ‘lateropulsion’

**S Dai and D Pérennou, in preparation**

The terminology Lateropulsion refers to a lateral push at the origin of a lateral body tilt. This action performed by the upper or the lower limb (or both) may be obvious because even slight active lateral body tilts are easily detected or in contrast imperceptible for the examiner who just see the lateral body tilt, but not detect the active lateral push. We think that this gap, amplified by the fact that no tool has ever been validated to measure forces and moments involved in this lateral push, explains the vigorous debate about the meaning of the terminology lateropulsion, in the last 3 decades (Bohannon *et al.*, 1986; Dieterich and Brandt, 1992; Pedersen *et al.*, 1996; Karnath *et al.*, 2000; Pérennou *et al.*, 2008; Babyar *et al.*, 2019; Dai *et al.*, 2021b).

Here we revisit this recent but past debate at the light of successive terminologies and corresponding clinical pictures described from the seminal paper by Babinski and Nageotte in 1902 (Babinski and Nageotte, 1902). We suggest that a careful examination of this historical literature would have allowed to save time and energy, and avoid pointless and endless disputes.

The term Lateropulsion was introduced in the medical literature by two prominent neurologists - Joseph Babinski (1857-1932) and Jean Nageotte (1866-1948), in their seminal paper published in French language (1902) and entitled “Hemiasynergie, latéropulsion et myosis bulbaires avec hemianesthésie et hémiparésie croisées” (Babinski and Nageotte, 1902). They reported a medullary syndrome based on three somewhat similar cases of ischemic lesions involving the unilateral medulla oblongata (necropsy). They defined lateropulsion as a body tilt with a fall to this side (in the text, ‘corps incliné’, ‘tomber de ce côté’, ‘entraîner de ce côté’). In this clinical picture later termed Babinski-Nageotte syndrome the lateral push would be elicited by the

paretic side (contralateral to the lateropulsion). This major contribution made by Babinski (then several other papers) to the field has been too often overlooked. However, in this first paper Babinski and Nageotte misinterpreted lateropulsion mechanisms, viewed as a cerebellar disorder.

At the same period several other famous authors published papers describing lateral body tilts secondary to brain stem or hemisphere strokes, without using the terminology lateropulsion. Contrary to a widely spread opinion, Adolf Wallenberg (1862-1949) didn't mention the terminology lateropulsion, neither in his seminal paper (Wallenberg, 1895) which will remain as the description of the "Wallenberg syndrome" nor in his following papers (Wallenberg, 1901). His seminal paper was published in 1895 in German language with the title "Acute Bulbäraffection (Embolie der Art. cerebellar.post. inf. sinistr.?)" (Wallenberg, 1895). Instead Wallenberg used the terms "Schwindel, Neigung nach links zu fallen" and "Neigung nach links zu fallen beim Stehen und Gehen" translated as 'Dizziness, tendency to fall to the left' and 'Tendency to fall to the left when standing and walking'. But Wallenberg was the first to localize the lesion (necropsy) in the lateral medulla supplied by the posterior inferior cerebellar artery (PICA). Charles Edward Beevor (1854-1908) was the first to describe a lateral body tilt secondary to what was supposed to be a cortical stroke (Beevor, 1909). He wrote "When put into the sitting position in bed the patient fell over to the left side, and when he had fallen to that side he was unable to raise himself to the vertical position again". The terminology lateropulsion was not used, and the association between the lateral body tilt and weakness led Beevor to erroneously interpret the lateral trunk tilt as the consequence of the hemi trunk weakness caused by the stroke (Beevor, 1909).

The terminology lateropulsion was consecrated some years later, again mainly from the French literature. This is Jean-Alexandre Barré (1880-1967), a pupil of Babinski, who embedded the term lateropulsion in the semiology of the Wallenberg syndrome. In 1927 he published a paper

gathering four cases of ipsilesional lateropulsion associated either to a Babinski Nageotte syndrome or to a Wallenberg syndrome, lateropulsion being interpreted as a vestibular sign causing durable gait disability (Barré, 1927). Some years later in 1940, André Thomas (1867-1963) published a still famous book dedicated to Balance and Equilibrium (in French), in which he consecrated the terms lateropulsion and retropulsion (Thomas, 1940), to describe wrong body orientations with respect to gravity, in the frontal plane (lateropulsion) and in the sagittal plane (retropulsion). He observed these typical postural behaviors both in human and animals with brain and vestibular lesions, and pointed out their major impact on balance and gait abilities (Thomas, 1940). He described some patients showing active body tilt by pushing themselves away from the upright with sound upper or lower limbs and resisting any corrections. This description typically corresponds to what will be termed later on the pusher syndrome (Davies, 1985).

One must wait for the 60s to see appear the terminology lateropulsion in international databases (English spelling). First articles were mostly case studies of patients or even experimental studies inducing a lateral body tilt in healthy subjects. They referred either to the vestibular field (Torok and Kahn, 1960), to the neurovascular field (Bjerver and Silfverskiöld, 1968), or to the Parkinson field (Mamo *et al.*, 1965) in that latter case preceding what has been described later under the terminology Pisa syndrome. Dieterich and Brandt (1992) were the first to use the terminology lateropulsion in a series of patients showing a Wallenberg syndrome (n=36) and comprehensively explored (Dieterich and Brandt, 1992). They established a relationship between direction and magnitude of tilts bearing on the active body orientation with respect to gravity, the perception of the vertical, and ocular torsion, interpreted as the result of a vestibular dysfunction (Dieterich and Brandt, 1992). Roughly at the same period was also proposed the terminology eye lateropulsion, to depict lateral saccadic/ocular tilt to the same side as that of the body lateropulsion (Kommerell and Hoyt, 1973). In line with the seminal papers cited

above, and with the emergence of performant brain imaging investigations, the terminology lateropulsion was then continuously and non-ambiguously used to describe lateral whole body tilt induced by brain stem stroke, usually elicited because of a vestibulospinal asymmetry (Thomke *et al.*, 2005; Cnyrim *et al.*, 2007; Pérennou *et al.*, 2008). Inconstant associated signs described were mainly vestibulocular signs (Brandt and Dieterich, 2017).

In contrast things remained long unclear for the contralesional lateropulsion observed after hemisphere lesions associated signs initially described by Thomas were not vestibule-ocular signs but instead postural signs such as pushing away from the upright with sound limbs and resistance to passive corrections (Thomas, 1940). Depending on the prisms used by authors, some of these postural signs took over the body tilt, and various terminologies were used to describe clinical pictures stressing either the body tilt or its associated signs. In the stroke field most known terminologies were listing phenomenon (Bohannon *et al.*, 1986), pusher/pushing syndrome/behavior (Davies, 1985; Pedersen *et al.*, 1996; Karnath *et al.*, 2000; Danells *et al.*, 2004; Pérennou *et al.*, 2008; Brandt and Dieterich, 2017; Bergmann *et al.*, 2018), ease of falling (Fisher, 1982; Awerbuch and Labadie, 1989), and thalamic astasia (Masdeu and Gorelick, 1988; Brandt and Dieterich, 2017). In the field of the Parkinson disease, the terminology lateropulsion initially used (Mamo *et al.*, 1965) was progressively abandoned in favor of the terminology Pisa syndrome (Ekbohm *et al.*, 1972; Doherty *et al.*, 2011; Castrioto *et al.*, 2014; Piscicelli *et al.*, 2021).

Recent papers have demonstrated that lateral body tilt, resistance and pushing effectively constitute an entity, thus we suggest a unified view of the different terminologies, better termed as lateropulsion (Dai *et al.*, 2021b). Pusher syndrome is a just severe form of lateropulsion, so we recommend no longer focusing on it, the tree that “hides the forest”.

Finally we do think that in the future lateropulsion should be the convergent terminology, irrespective of its underpinning mechanisms, asymmetry in vestibulospinal pathways leading to an asymmetrical tone between hemibodies, or biased internal model of vertical leading the individuals to align their body posture to a tilted representation of the vertical (Pérennou *et al.*, 2008; Dai *et al.*, 2021b; Piscicelli *et al.*, 2021). Lateropulsion means an entity constituted by lateral body tilt, pushing and resistance, which corresponds to associated signs depends on the context and the diseases course. After hemisphere lesion, post-stroke lateropulsion occurs suddenly and is overall obvious at the subacute stage, whereas in Parkinson's disease, the lateral inclination most often occurs insidiously and worsens with the disease course. This low progression of the disease with a less lateralized brain damage explains why no spectacular pushing is observed in Parkinson's disease (Piscicelli *et al.*, 2021). After low brain stem lesion associated signs are rather vestibular and vestibulo-ocular.

Lateropulsion represents a milestone in balance, gait and falls (Dai *et al.*, 2021a; Piscicelli *et al.*, 2021), and a major challenge for future interventions based on rehabilitation techniques and programs (Bergmann *et al.*, 2018; Odin *et al.*, 2018; An *et al.*, 2021) or brain stimulation (Santos *et al.*, 2018; Piscicelli *et al.*, 2021).

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## ➤ Chapter 4: Post-stroke lateropulsion prevalence

This research is the first to investigate the prevalence of post-stroke lateropulsion by a systematic review and meta-analysis. We followed a standardized protocol (PROSPERO-CRD42020175037) as well as MOOSE and PRISMA guidelines, and Joanna Briggs Institute guidelines for quality assessment. Most individuals (55%) showed lateropulsion in the acute phase post-stroke. This finding, together with the well-known lateropulsion detrimental influence on balance and gait, appeals for its systematic detection to guide appropriate interventions as early as possible. This paper is under review in Neurology.

## Lateropulsion Prevalence after Stroke: a Systematic Review and Meta-analysis

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Table 2, figures 5

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**Key words:** Lateropulsion; pusher; stroke rehabilitation; right-hemisphere stroke

## Abstract

**Background and Objectives:** Lateropulsion is a deficit of active body orientation with respect to gravity in the frontal plane, mostly observed after a stroke. Its prevalence remains to be estimated, which is the main objective of this systematic review and meta-analysis.

**Methods:** We systematically searched MEDLINE, EMBASE, CINAHL, and Cochrane Clinical Trials up to 31 May 2021 for original research reporting a prevalence or incidence of post-stroke lateropulsion. We followed MOOSE and PRISMA guidelines. Eligibility for inclusion, data extraction, and study quality (Joanna Briggs Institute guidelines) were evaluated by two reviewers who used a standardized protocol: PROSPERO (CRD42020175037). A random-effects meta-analysis was used to obtain the pooled prevalence, whose heterogeneity was investigated by subgroup analysis (stroke locations and post-stroke phases) and meta-regression.

**Results:** We identified 22 studies (5125 individuals; mean age 68.5 years; 42.6% female; assessed 24 days, on average, after stroke), most published after 2000. The studies' quality was adequate, with only 8 (36.4%) showing risk of bias. The pooled lateropulsion prevalence was 55.1% (95% confidence interval [CI] [35.9–74.2]) and was consistent across assessment tools. After supratentorial stroke, lateropulsion prevalence was 41% (95% CI [33.5–48.5]); the prevalence was only 12.5% (95% CI [9.2–15.9]) in individuals with severe lateropulsion, called pushers. Meta-regression did not reveal any effect of age, sex, geographic region, publication year, or study quality. Lateropulsion prevalence progressively decreased from 52.8% (95% CI [40.7–65]) in the acute phase to 37% (95% CI [26.3–47.7]) in the early subacute phase and 22.8% (95% CI [0–46.3]) in the late subacute phase. The ratio of right- to left-hemisphere stroke with lateropulsion increased as a function of time: 1.7 in the acute phase to 7.7 in the late

subacute phase. After infratentorial stroke, lateropulsion prevalence was very high, reaching 83.2% (95% CI [63.9–100.3]).

**Conclusions:** Post-stroke lateropulsion prevalence is high, which appeals for its systematic detection to guide early interventions. Uprightness is a function of the right hemisphere.

## Introduction

Lateropulsion is a deficit of the active body orientation with respect to gravity in the frontal plane, mostly observed after a stroke. It limits and delays the ability and recovery to sit, stand, and walk (Verheyden *et al.*, 2007; Abe *et al.*, 2012; Babyar *et al.*, 2015; Bergmann *et al.*, 2018; An *et al.*, 2021) and creates safety challenges and greater burden on caregivers and family (Gomes-Osman and Kloos, 2021).

The underpinning mechanisms differ according to the stroke location. After low-brainstem strokes, lateropulsion is usually ipsilesional and mainly secondary to vestibulospinal disorders, inducing an asymmetric tone with co-occurrence of vestibulo-ocular signs (Cnyrim *et al.*, 2007; Pérennou *et al.*, 2008; Brandt and Dieterich, 2017). After hemisphere strokes, lateropulsion is contralesional, owing to an internal model of verticality tilted to the contralesional side (Pérennou *et al.*, 2008; Dai *et al.*, 2021b). Individuals align their body onto this erroneous reference of verticality, (Pérennou *et al.*, 2008; Dai *et al.*, 2021b) possibly in relation to a damaged multimodal vestibular network (Brandt and Dieterich, 2017).

The increasing interest in lateropulsion mechanisms and consequences is starting to be translated into efforts to design specific interventional studies (Bergmann *et al.*, 2018). These efforts require some basic knowledge of epidemiology, which is insufficient today because many studies have focused on a few severe forms in individuals called pushers (Davies, 1985; Pedersen *et al.*, 1996; Abe *et al.*, 2012). Today, lateropulsion is considered more of a postural behavior with a continuum between light and severe forms, often associating three signs: lateral body tilt, active pushing from sound limbs to initiate or amplify the body tilt, and resistance to correction (D'Aquila *et al.*, 2004; Babyar *et al.*, 2016; Babyar *et al.*, 2019; An *et al.*, 2021; Dai *et al.*, 2021a; Dai *et al.*, 2021b; Nolan *et al.*, 2021).

A systematic review and meta-analysis are urgently required for clinical practice and research. We assumed that the actual prevalence of lateropulsion (whatever the side, mechanisms, and severity, including mild forms) has been underestimated and that it might encompass at least half of individuals with stroke (Amarenco *et al.*, 1990; D'Aquila *et al.*, 2004; Danells *et al.*, 2004; Baccini *et al.*, 2008). The primary aim of our study was to estimate the lateropulsion prevalence (regardless of severity) in supra- and infratentorial stroke. The secondary aim was to analyze the evolution of lateropulsion prevalence as a function of time after stroke.

## Methods

### **Standard Protocol Approvals, Registrations, and Patient Consent**

The systematic review and meta-analysis were performed according to a predefined protocol registered in PROSPERO (CRD42020175037), with the reporting following the appropriate guidelines: the Meta-analysis of Observational Studies in Epidemiology (MOOSE) as well as the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.

### **Search strategy**

We systematically searched the literature for English articles published up to 31 May 2021 in the databases MEDLINE, EMBASE, CINAHL, and Cochrane Clinical Trials. Searches involved using medical subject heading (MeSH) terms and text words (or synonyms) for “lateropulsion” and “stroke”, detailed in e-Methods. The reference lists of studies retrieved were reviewed to identify additional studies. We did not include grey literature (i.e., conference abstracts, unpublished studies, or reports).

## Study selection

The inclusion criteria were original research (observational or interventional) including at least 30 individuals, reporting prevalence (point or period) or incidence of post-stroke lateropulsion in adults (including its most severe form with individuals called pushers), or information allowing for its estimation.

According to recent recommendations by several teams in different continents, (D'Aquila *et al.*, 2004; Pérennou *et al.*, 2008; Babyar *et al.*, 2016; Babyar *et al.*, 2019; An *et al.*, 2021; Dai *et al.*, 2021a; Dai *et al.*, 2021b; Nolan *et al.*, 2021) we retained the diagnosis of lateropulsion when at least one of the three usual signs (lateral body tilt, spontaneous pushing, resistance to passive corrections) was clearly documented according to a scale or by qualitative assessment. When a scale was used, we respected the cut-off values proposed in the papers: for the Scale of Contraversive Pushing (SCP), (Karnath *et al.*, 2000) scores  $> 0$  (Danells *et al.*, 2004; Baccini *et al.*, 2008) or  $> 0.5$  (Pérennou *et al.*, 2008; Dai *et al.*, 2021a; Dai *et al.*, 2021b); for the Burke Lateropulsion Scale (BLS), scores  $> 1$  (D'Aquila *et al.*, 2004); for the Four-Point Pusher Scale (4PPS) (Lafosse *et al.*, 2005; Chow *et al.*, 2019) and the Grading of Lateropulsion (Dieterich and Brandt, 1992; Ye *et al.*, 2010), scores  $> 0$  (Dieterich and Brandt, 1992; Ye *et al.*, 2010).

The diagnosis of a pusher associated the three signs (lateral body tilt, spontaneous pushing, resistance to passive corrections) (Davies, 1985; Pedersen *et al.*, 1996; Karnath *et al.*, 2000; Premoselli *et al.*, 2001; Pérennou *et al.*, 2008; Baier *et al.*, 2011; Bergmann *et al.*, 2018; Dai *et al.*, 2021b) constituting a severe lateropulsion form (Dai *et al.*, 2021b). Among the scales mentioned above, only the SCP could clearly be used to identify pushers according to these criteria. Corresponding authors were contacted if eligibility for our study or data categorization seemed unclear. We carefully analyzed potential series overlaps between studies, based on geographical setting and recruitment period. In case of overlap, we included only the largest sample to avoid multiple publication bias.



Two investigators (SD and CL) independently screened titles and abstracts of articles retrieved from the search. The full texts of potentially relevant studies were independently reviewed by the two independent investigators. Disagreements were resolved by consensus or involvement of a third author (CP).

### **Quality assessment**

The same two independent investigators (SD and CL) assessed the risk of bias of all included studies. Risk of bias was assessed according to the Joanna Briggs Institute guidelines for prevalence/incidence systematic reviews (9 items) (Munn *et al.*, 2015). Any discrepancies were discussed until final agreement. As recently pointed out, quality control of studies is better when the threshold is determined according to raters' judgement (Migliavaca *et al.*, 2020). We chose to suspect risk of bias when at least 5/9 items were not achieved and if so, to run a sensitivity analysis to decide whether or not studies at supposed risk of bias were kept in the analyses.

### **Data extraction**

Data extraction was completed in duplicate by the same independent investigators (SD and CL) by use of a predefined and standardized data collection form. Data extracted included 1) characteristics of the publication (authors, year of publication, journal, study type, country and setting); 2) characteristics of the sample (total sample size, age, sex, stroke type, and handedness); 3) stroke location (right/left hemisphere if supratentorial; brainstem/cerebellum if infratentorial; encroaching both supra- and infratentorial regions), based on brain imaging; 4) time of assessment since stroke, predefined (Bernhardt *et al.*, 2017; Powers *et al.*, 2019) as acute phase (0-14 days), early subacute phase (15-90 days), and late subacute phase (91-180 days); 5) the tool used to diagnose lateropulsion; 6) presence of pusher syndrome, considered the most severe form of lateropulsion; and 7) lateropulsion side, ipsi- or contralesional.

## **Statistical analysis**

The primary outcome was the estimation of the pooled prevalence of lateropulsion after stroke. We used random-effects meta-analysis to generate pooled prevalence (with 95% confidence intervals [CIs]). Stroke location (supra-, infratentorial, or mixed) was analyzed by subgroups. The extent of heterogeneity across studies was assessed with the  $I^2$  statistic:  $I^2$  0% to 50% was considered low, 50% to 75% moderate, and >75% high heterogeneity (Higgins *et al.*, 2003). To help understand the sources of heterogeneity, meta-regression analysis was performed using study characteristics as moderator variables, including age, sex, geographic region, published year and study quality. Sensitivity analysis was used to assess the risk of bias and consistency of results across different diagnostic tools and cut-offs. We then analyzed lateropulsion prevalence as a function of stroke side (right- vs left-hemisphere stroke). Finally, we analyzed the evolution of this prevalence as a function of time since stroke, by subgroups. We also estimated the evolution of the ratio of right- to left-hemisphere stroke with lateropulsion as a function of time.

Publication bias was assessed with the Egger test. P values were two-sided, and  $P < 0.05$  was considered statistically significant. All statistical analyses were performed with STATA 15.1.

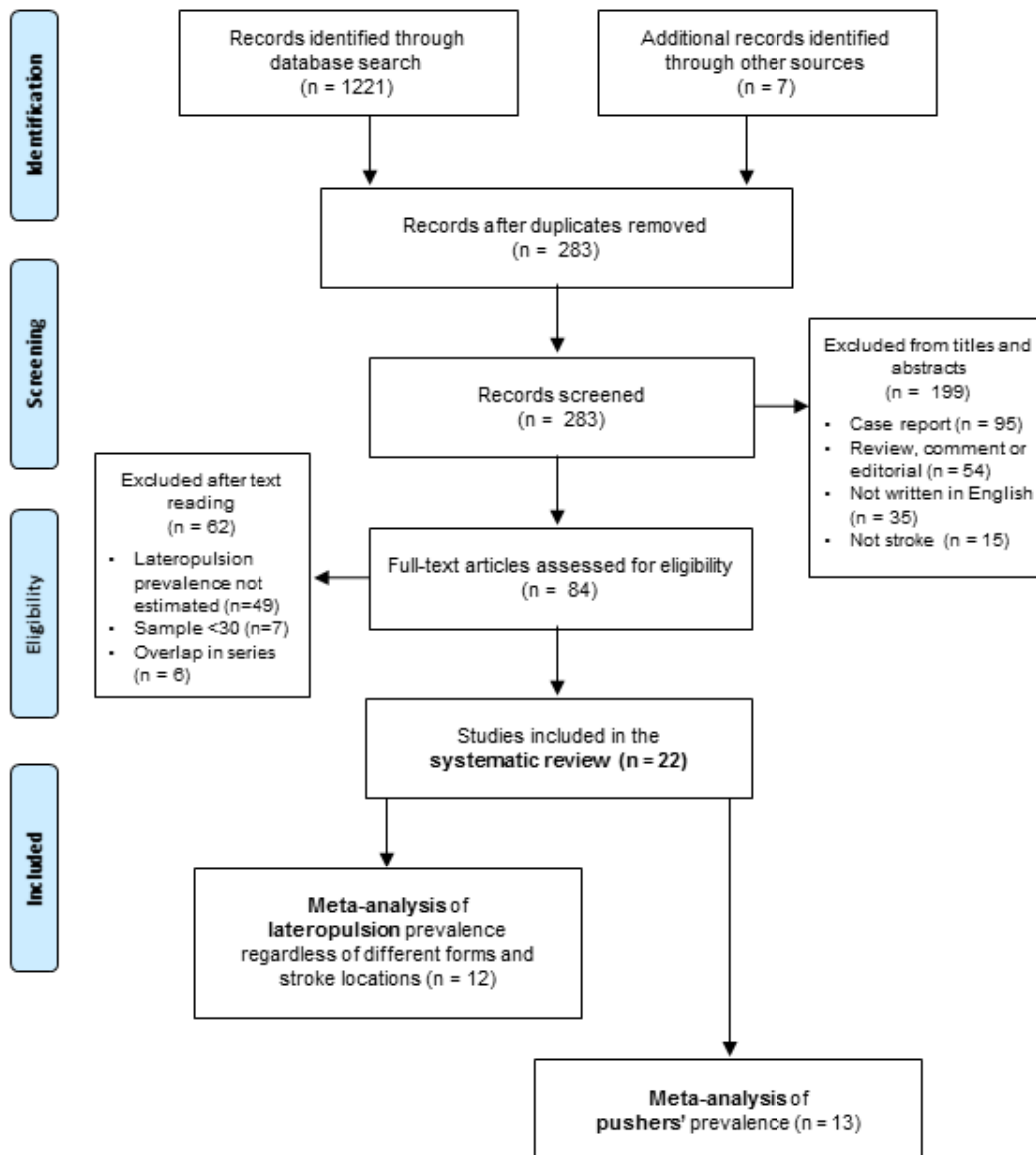
## **Data availability**

The analysis is based on published individual studies. All extracted data used for performing this meta-analysis can be made available upon reasonable request to the corresponding author.

## Results

### Literature review

Figure 1 (PRISMA flow diagram) illustrates the study selection process. The literature search yielded 283 articles that were screened for eligibility; 22 articles were included in the systematic review,(Bohannon *et al.*, 1986; Dieterich and Brandt, 1992; Kim and Heo, 1996; Pedersen *et al.*, 1996; Premoselli *et al.*, 2001; D'Aquila *et al.*, 2004; Danells *et al.*, 2004; Lafosse *et al.*, 2005; Lagerqvist and Skargren, 2006; Baccini *et al.*, 2008; Pérennou *et al.*, 2008; van Nes *et al.*, 2009; Ye *et al.*, 2010; Baier *et al.*, 2011; Kwon *et al.*, 2011; Abe *et al.*, 2012; Clark *et al.*, 2012; Krewer *et al.*, 2013; Lee *et al.*, 2013; Chow *et al.*, 2019; Dai *et al.*, 2021a; Nolan *et al.*, 2021) 16/22 of supratentorial stroke,(Bohannon *et al.*, 1986; Pedersen *et al.*, 1996; Premoselli *et al.*, 2001; D'Aquila *et al.*, 2004; Danells *et al.*, 2004; Lafosse *et al.*, 2005; Lagerqvist and Skargren, 2006; Baccini *et al.*, 2008; van Nes *et al.*, 2009; Baier *et al.*, 2011; Kwon *et al.*, 2011; Abe *et al.*, 2012; Krewer *et al.*, 2013; Lee *et al.*, 2013; Dai *et al.*, 2021a; Nolan *et al.*, 2021) 3/22 of mixed series with both supra- and infratentorial stroke (Pérennou *et al.*, 2008; Clark *et al.*, 2012; Chow *et al.*, 2019) and 3/22 of infratentorial stroke (Dieterich and Brandt, 1992; Kim and Heo, 1996; Ye *et al.*, 2010).



**Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.**

Three studies reported both the prevalence of lateropulsion and pushers. Pusher, having a severe form of lateropulsion.

## **Study characteristics**

This is recent literature: all 22 studies were published between 1986 and 2021, and 18/22 (81.8%) in the last 2 decades. Half had been conducted in Europe, 8 (36.4%) in Australasia, 3 (13.6%) in North America, all from high-income countries: Australia, Belgium, Canada, Denmark, France, Germany, Italy, Japan, The Netherlands, South Korea, Sweden, and United States. The median sample size was 110 (Q1–Q3 66–220).

Table 1 presents characteristics of the 22 studies included in the systematic review (Bohannon *et al.*, 1986; Dieterich and Brandt, 1992; Kim and Heo, 1996; Pedersen *et al.*, 1996; Premoselli *et al.*, 2001; D'Aquila *et al.*, 2004; Danells *et al.*, 2004; Lafosse *et al.*, 2005; Lagerqvist and Skargren, 2006; Baccini *et al.*, 2008; Pérennou *et al.*, 2008; van Nes *et al.*, 2009; Ye *et al.*, 2010; Baier *et al.*, 2011; Kwon *et al.*, 2011; Abe *et al.*, 2012; Clark *et al.*, 2012; Krewer *et al.*, 2013; Lee *et al.*, 2013; Chow *et al.*, 2019; Dai *et al.*, 2021a; Nolan *et al.*, 2021). Twelve (54.5%) assessed lateropulsion in the acute phase and 10 (45.5%) in the subacute phase. Only four studies (Danells *et al.*, 2004; Lafosse *et al.*, 2005; Dai *et al.*, 2021a; Nolan *et al.*, 2021) assessed lateropulsion a few weeks apart, all in a rehabilitation context. Lateropulsion was diagnosed on the basis of a specific scales in 18 (81.8%) studies, predominantly with the SCP (66.7%, 12/18), and on the basis of expert judgment without any scale in 4 studies.

## **Quality assessment**

Table 1 contains the final scores of quality assessment. Details of the 9 item scores are given in Table e-1. For the 22 studies, the quality was adequate, with median score 6 for a theoretical maximum 9 (Q1–Q3 4–8). Eight (36.4%) studies had an insufficient score (<5), and two items dealing with the sample process and size strongly affected the quality assessment score.

**Table 1. Summary of identified studies reporting the prevalence of lateropulsion after stroke.**

Authors	Year	Region	Sample size	Lateropulsion, n (%)	Pushers, n (%)	Phase	Age, y, mean (SD) or median (Q1-Q3)	Female, %	Scale	Quality assessment score (0-9)
<b>Supratentorial stroke</b>										
Bohannon	1986	North America	172	-	14 (8)	late subacute	-	-	-	2
Pedersen, et al.	1996	Europe	327	-	34 (10)	acute	76.3 (9)	59	-	6
Premoselli, et al.	2001	Europe	202	-	21 (10)	early subacute	-	-	-	2
D'Aquila, et al.	2004	North America	68	31 (46)	-	early subacute	-	59	BLS	5
Danells, et al.	2004	North America	62	39 (63)	-	acute	68.2	47	SCP	8
Lafosse, et al.	2005	Europe	114	52 (46)	-	early subacute	67.7 (12.1)	50	4PPSa	7
Lagerqvist & Skargren	2006	Europe	444	-	19 (4)	acute	82	-	M-SCP	3
Baccini, et al.	2008	Europe	105	65 (62)	17 (16)	early subacute	70.6 (11.2)	49	SCP	8
van Nes, et al.	2009	Europe	78	-	3 (4)	acute	71.2 (11.6)	42	SCP	8
Kwon, et al.	2011	Asia	50	-	19 (38)	early subacute	70 (10.9)	46	SCP	4
Baier, et al.	2012	Europe	66	-	23 (35)	acute	64 (12)	-	SCP	3
Abe, et al.	2012	Asia	1155	-	154 (13)	acute	69.9 (13.1)	-	SCP	6
Lee, et al.	2013	Asia	114	-	12 (11)	acute	65.9 (3.9)	-	SCP	4
Krewer, et al.	2013	Europe	398	-	69 (17)	early subacute	72 (10)	-	SCP	7
Dai, et al.	2021	Europe	220	62 (28)	30 (14)	early subacute	63.6 (12.2)	33	SCP	9
Nolan, et al.	2021	Australia	1087	483 (44)	-	acute	79 (7.5)	48	4PPSb	9
<b>Mixed series (supra + infratentorial stroke)</b>										
Pérennou, et al.	2008	Europe	86	41 (48)	6 (8)	early subacute	55.4 (13.1)	34	SCP	8
Clark, et al.	2012	Australia	160	43 (27)	-	early subacute	-	-	BLS	4
Chow, et al.	2019	Australia	85	45 (53)	-	acute	57 (48-63)	35	4PPSb	8
<b>Infratentorial stroke</b>										
Dieterich & Brandt	1992	Europe	36	36 (100)	-	acute	54	33	GLa	5
Kim & Heo	1996	Asia	30	19 (63)	-	acute	59.1	43	-	4
Ye, et al.	2010	Asia	66	54 (82)	-	acute	62	24	GLb	6

Table 1 is synthesized according to chronological order of supra- and infratentorial strokes.

Pushers = severe forms of lateropulsion. “-” = not indicated. Acute phase = 0-14 days. Early subacute phase = 15-90 days. Late subacute phase = 91-180 days. BLS = Burke Lateropulsion Scale. SCP = Scale for Contraversive Pushing. 4PPSa = Four-Point Pusher Scale (Belgian). M-SCP = Modified Scale for Contraversive Pushing. 4PPSb = Four-Point Pusher Score (Australian). GLa = Grading of Lateropulsion (German). GLb = Grading of Lateropulsion (Korean).

## **Population characteristics**

The 22 studies included a total of 5125 individuals with mean age 68.5 years (95% CI [64.5–72.5],  $I^2=99.3\%$ ) and 42.6% females (95% CI [37.5–47.6],  $I^2=82.4\%$ ). Overall, 81.7% of these individuals (95% CI [76.9–86.6],  $I^2=82.6\%$ ) had an infarct. Lateropulsion was sought at a mean of 23.7 days after stroke (95% CI [17.3–30.1],  $I^2=99\%$ ). Publication biases for demographic variables were related to age ( $t = -2.49$ ,  $p=0.032$ ) and sex ( $t = -2.54$ ,  $p=0.026$ ).

Most participants were right-handed: 91.5% (95%CI [87.8–95.2],  $I^2=36.3\%$ ), and this proportion was even higher in individuals showing lateropulsion. When this information was collected, the frequency of right-handers was 124/131 (95%) in individuals with lateropulsion and 35/36 (97%) in pushers (Pérennou *et al.*, 2008; Chow *et al.*, 2019; Dai *et al.*, 2021a).

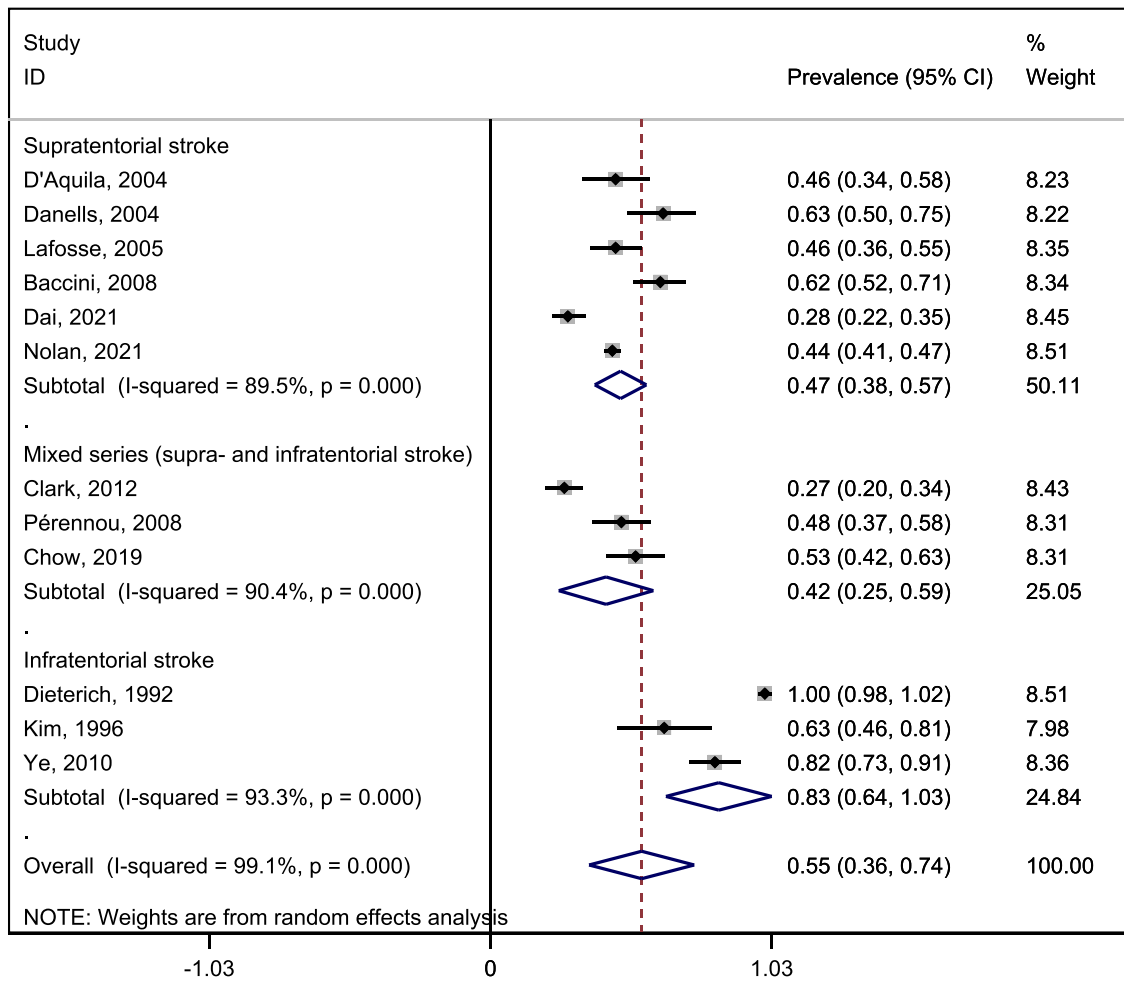
## **Prevalence of individuals with lateropulsion**

After supratentorial stroke, lateropulsion was always contralesional. After infratentorial stroke, lateropulsion could be ipsilesional or contralesional depending on the lesion location (Table e-2). One paper (Ye *et al.*, 2010) even mentioned that lateropulsion could be both ipsi- and contralesional in the same individual.

Twelve studies (Dieterich and Brandt, 1992; Kim and Heo, 1996; D'Aquila *et al.*, 2004; Danells *et al.*, 2004; Lafosse *et al.*, 2005; Baccini *et al.*, 2008; Pérennou *et al.*, 2008; Ye *et al.*, 2010; Clark *et al.*, 2012; Chow *et al.*, 2019; Dai *et al.*, 2021a; Nolan *et al.*, 2021) (2119 individuals) analyzed lateropulsion regardless of its severity and side. This gave a pooled lateropulsion prevalence of 55.1% (95% CI [35.9–74.2],  $I^2=99.1\%$ ; Figure 2). Considering that 2 of the 12 studies had potential risk of bias (quality assessment score <5), we also conducted a sensitivity analysis discarding these 2 studies (Kim and Heo, 1996; Clark *et al.*, 2012). This gave a pooled prevalence of 57.1% (95% CI [36.3–78],  $I^2=99.2\%$ ). The lack of substantial difference between



both analyses indicated the robustness of the result obtained with the 12 initial studies. Meta-regression did not reveal any effect of age, sex, geographic region, publication year, or study quality on lateropulsion prevalence. On subgroup analysis, supratentorial stroke and mixed series (majority of supratentorial with infratentorial strokes) had comparable lateropulsion prevalence: 47.4% (95% CI [38–63.9],  $I^2=89.5$ ) and 42.1% (95%CI [24.9–59.4],  $I^2=90.4$ ). Lateropulsion prevalence was much higher with pure infratentorial stroke: 83.2% (95%CI [63.9–100.3],  $I^2=93.3$ ).



**Figure 2. Pooled prevalence of lateropulsion after supratentorial stroke.**

Forest plot shows lateropulsion prevalence regardless of its severity and side by stroke location.

We found publication bias ( $t = -3.42$ ,  $p=0.007$ ), which disappeared ( $t = -0.13$ ,  $p=0.902$ ) when the analysis of lateropulsion prevalence was limited to the nine studies of supratentorial stroke,(D'Aquila *et al.*, 2004; Danells *et al.*, 2004; Lafosse *et al.*, 2005; Baccini *et al.*, 2008; Pérennou *et al.*, 2008; Clark *et al.*, 2012; Chow *et al.*, 2019; Dai *et al.*, 2021a; Nolan *et al.*, 2021) including three with mixed locations although predominating in supratentorial regions (Pérennou *et al.*, 2008; Clark *et al.*, 2012; Chow *et al.*, 2019). We then analyzed the effect of diagnostic tools and their cut-off values in these nine studies. Sensitivity analyses detailed in Table 2 found a consistency in lateropulsion prevalence whatever the diagnostic tool, especially when the diagnostic process was conservative (i.e., based on a cut-off discarding slight lateropulsion). A robust lateropulsion prevalence could be estimated from the seven studies that met this condition (1820 individuals)(D'Aquila *et al.*, 2004; Lafosse *et al.*, 2005; Pérennou *et al.*, 2008; Clark *et al.*, 2012; Chow *et al.*, 2019; Dai *et al.*, 2021a; Nolan *et al.*, 2021): 41% (95%CI [33.5–48.5],  $I^2=86.8$ ) regardless of lateropulsion severity, stroke side, and time since stroke.

**Table 2. Summary of sensitivity analyses of lateropulsion prevalence\* based on the four diagnostic tools and their different cut-offs.**

Sensitivity analyses	Studies (k)	Sample (n)	Lateropulsion prevalence % (95% CI)	I <sup>2</sup>
Omitting BLS >1	7	1759	48.3 (40-56.7)	88.1
Omitting SCP >0.5	7	1681	48 (39.5-56.5)	87.6
Omitting 4PPSa >0	8	1873	45.6 (37.1-54.2)	90.3
Omitting 4PPSb >0	7	815	45.1 (33.8-56.3)	90.7
Omitting SCP >0	7	1820	41 (33.5-48.5)	86.8

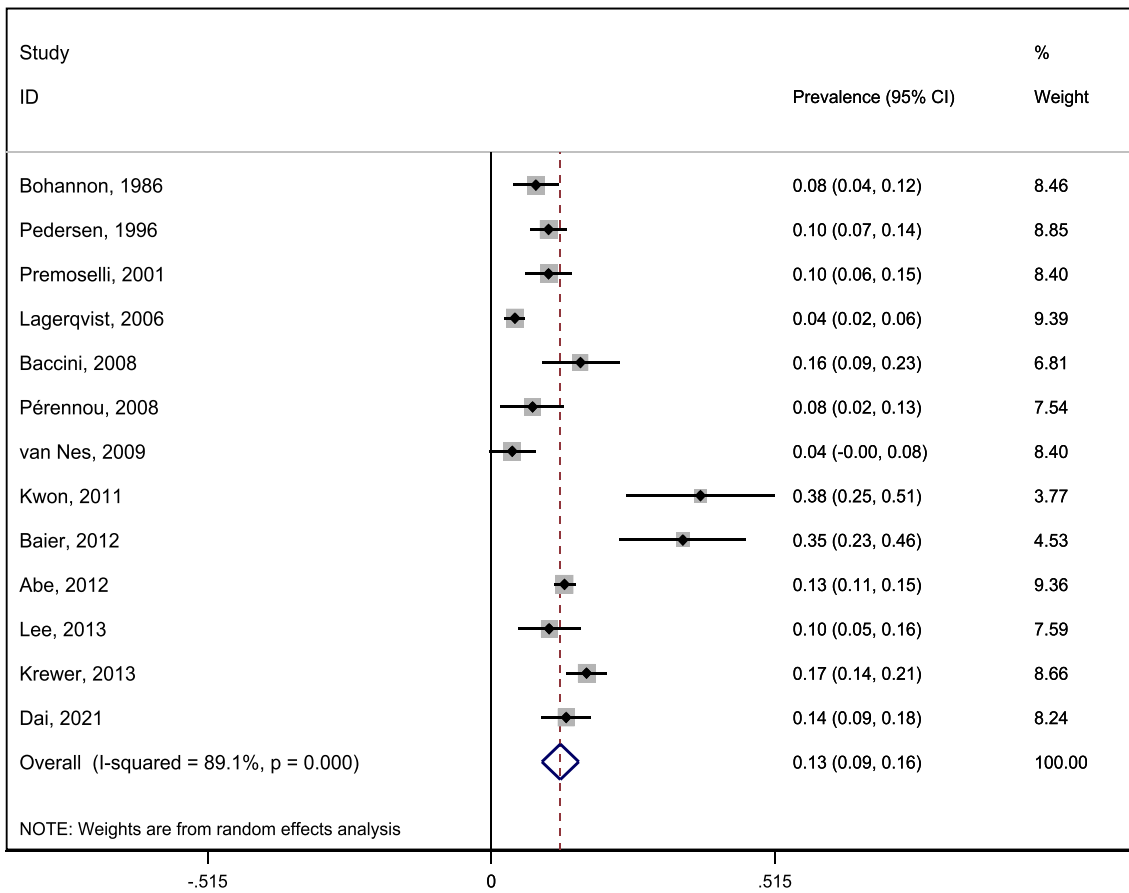
\*Nine pooled studies with supratentorial stroke including 3 studies with mixed locations predominating in supratentorial regions.

CI = confidence interval. BLS = Burke Lateropulsion Scale. SCP = Scale for Contraversive Pushing. 4PPSa = Four-Point Pusher Scale (Belgian). 4PPSb = Four-Point Pusher Score (Australian).

## Detailed analysis of lateropulsion prevalence in supratentorial stroke

### *Pushers*

Until recently, severe lateropulsion forms called pusher syndrome have attracted the most research, which explains why their prevalence has been well analyzed, in 13 studies (3411 individuals). (Bohannon *et al.*, 1986; Pedersen *et al.*, 1996; Premoselli *et al.*, 2001; Lagerqvist and Skargren, 2006; Baccini *et al.*, 2008; Pérennou *et al.*, 2008; van Nes *et al.*, 2009; Baier *et al.*, 2011; Kwon *et al.*, 2011; Abe *et al.*, 2012; Krewer *et al.*, 2013; Lee *et al.*, 2013; Dai *et al.*, 2021a) Their pooled prevalence was 12.5% (95%CI [9.2–15.9],  $I^2=89.1\%$ ; Figure 3), with no publication bias ( $t = -0.55$ ;  $p=0.593$ ). Considering that six of the studies had a quality assessment score  $<5$ , we also conducted an analysis discarding these six studies, (Bohannon *et al.*, 1986; Premoselli *et al.*, 2001; Lagerqvist and Skargren, 2006; Baier *et al.*, 2011; Kwon *et al.*, 2011; Lee *et al.*, 2013) which gave a pooled prevalence of 11.7% (95%CI [8.5–14.9],  $I^2=79.4\%$ ). The lack of substantial difference between both analyses indicated the robustness of the result obtained with the 13 initial studies. Meta-regression did not reveal any effect of age, sex, geographic region, publication year, or study quality on the prevalence of pusher syndrome.



**Figure 3. Pooled pushers' prevalence after supratentorial stroke.**

Pusher, having a severe form of lateropulsion.

### *Stroke side*

Regardless of lateropulsion severity, this analysis was possible for seven studies (D'Aquila *et al.*, 2004; Danells *et al.*, 2004; Lafosse *et al.*, 2005; Pérennou *et al.*, 2008; Chow *et al.*, 2019; Dai *et al.*, 2021a; Nolan *et al.*, 2021) (1694 individuals). Lateropulsion prevalence was 56.3% after right-hemisphere stroke (95%CI [48.8–63.9],  $I^2=67.4$ ) and 34.3% after left-hemisphere stroke (95%CI [22.5–46.1],  $I^2=90.3\%$ ).

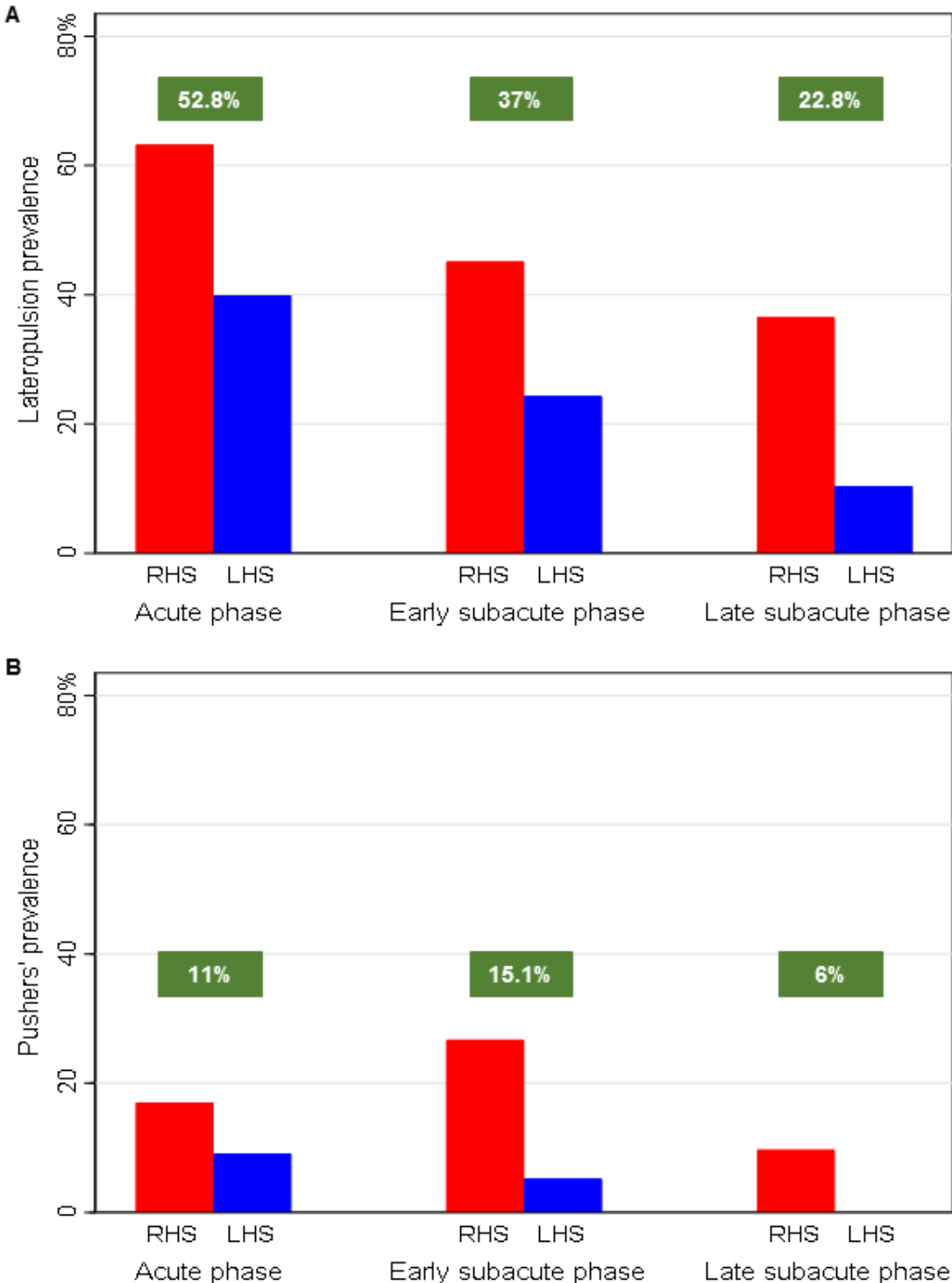
The same analysis for pushers was possible for eight studies (Pedersen *et al.*, 1996; Pérennou *et al.*, 2008; van Nes *et al.*, 2009; Baier *et al.*, 2011; Kwon *et al.*, 2011; Abe *et al.*, 2012; Krewer *et al.*, 2013; Dai *et al.*, 2021a) (2081 individuals). Pusher prevalence was 20% after right-hemisphere stroke (95%CI [13.7–26.3],  $I^2=80.3\%$ ) and 8.7% after left-hemisphere stroke (95%CI [5–12.4],  $I^2=69.8\%$ ).

### *Time post-stroke*

Regardless of lateropulsion severity, its prevalence as a function of time since stroke could be analyzed in eight studies (D'Aquila *et al.*, 2004; Danells *et al.*, 2004; Lafosse *et al.*, 2005; Baccini *et al.*, 2008; Pérennou *et al.*, 2008; Chow *et al.*, 2019; Dai *et al.*, 2021a; Nolan *et al.*, 2021) including 12 samples. Figure 4A shows that the prevalence progressively decreased from 52.8% in the acute phase (95%CI [40.7–65],  $I^2=79.7$ ) to 37% in the early subacute phase (95%CI [26.3–47.7],  $I^2=93.7\%$ ) and 22.8% in the late subacute phase (95%CI [0–46.3],  $I^2=95.7\%$ ).

Prevalence of pusher syndrome as a function of time since stroke could be analyzed in 13 studies (Bohannon *et al.*, 1986; Pedersen *et al.*, 1996; Premoselli *et al.*, 2001; Lagerqvist and Skargren, 2006; Baccini *et al.*, 2008; Pérennou *et al.*, 2008; van Nes *et al.*, 2009; Baier *et al.*, 2011; Kwon *et al.*, 2011; Abe *et al.*, 2012; Krewer *et al.*, 2013; Lee *et al.*, 2013; Dai *et al.*, 2021a) including 14 samples. Figure 4B shows that it evolved from 11% in the acute phase

(95%CI [6–16],  $P=92.6$ ) to 15.1% in the early subacute phase (95%CI [10.3–19.9],  $P=78.6\%$ ) and 6% in the late subacute phase (95%CI [1–10],  $P=69\%$ ).



**Figure 4. Pooled prevalence of lateropulsion as a function of time after supratentorial stroke.**

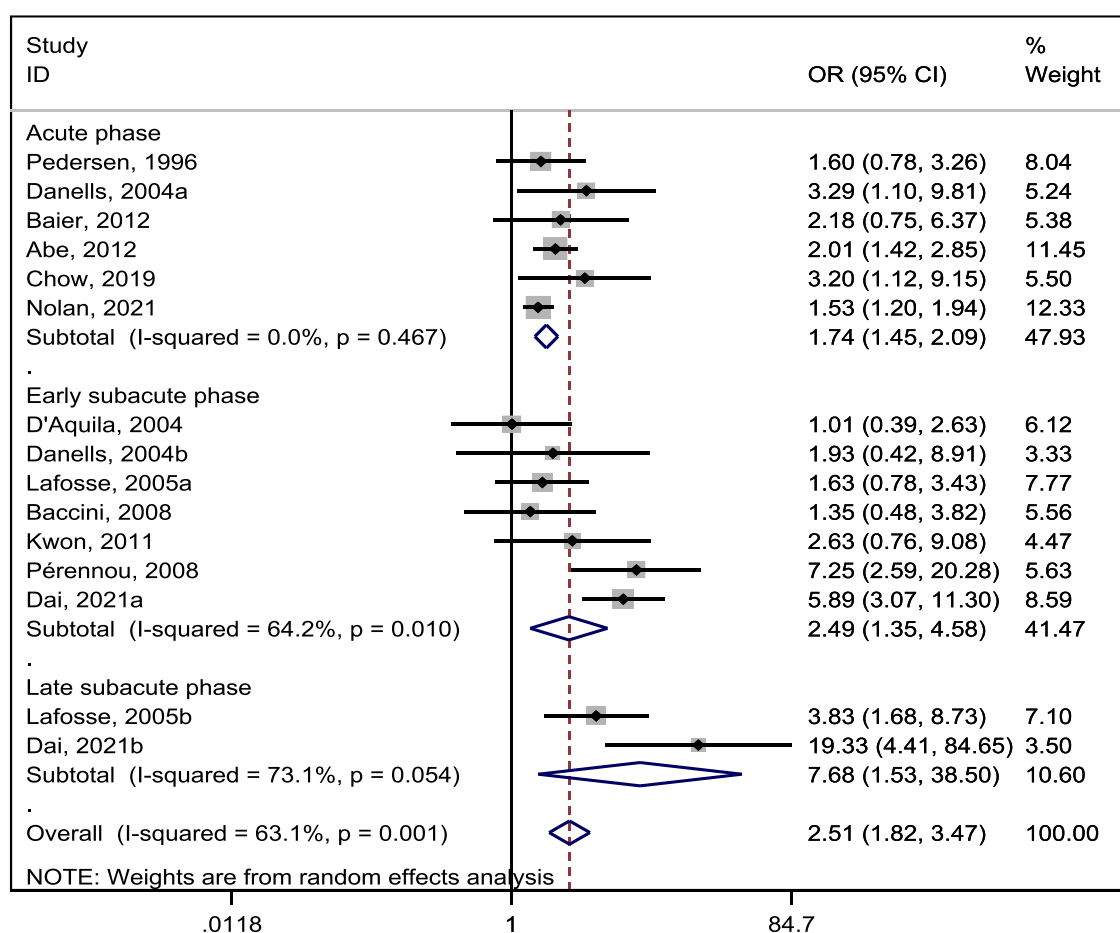


A) Lateropulsion prevalence regardless of severity as a function of time. The number of studies enrolled was three in the acute phase, seven in the early subacute phase, and two in the late subacute phase.

B) Prevalence of severe forms of lateropulsion (pushers) prevalence as a function of time. The number of studies enrolled was six in the acute phase, six in the early subacute phase, and two in the late subacute phase. RHS, right hemisphere stroke; LHS, left hemisphere stroke.

*Evolution of the right-hemisphere predominance with lateropulsion over time*

Finally, we analyzed the evolution of the ratio of right- to left-hemisphere stroke with lateropulsion as a function of time (Figure 5). Overall, 48.1% of participants had a right-hemisphere stroke (95% CI [45.1–51.1],  $I^2=32.4\%$ ). Right-hemisphere predominance with lateropulsion increased with time since stroke: acute phase odds ratio (OR) =1.7 (95%CI [1.5–2.1],  $I^2=0\%$ ); early subacute phase OR=2.5 ([1.4–4.6],  $I^2=64.2\%$ ); late subacute phase OR=7.7 ([1.5–38.5],  $I^2=73.1\%$ ).



**Figure 5. Evolution of the ratio of right- to left-hemisphere stroke with lateropulsion as a function of time.**

a, first assessment; b, second assessment.

## Discussion

This systematic review of lateropulsion prevalence after stroke, regardless of its severity and side, identified 22 studies (5125 individuals) and generated a pooled prevalence of lateropulsion of 55.1%. The results confirmed our hypothesis of a high lateropulsion prevalence whatever the stroke location. After supratentorial stroke, lateropulsion was always contralesional, with a prevalence estimated at 47.4%, decreasing from 52.8% in the acute phase to 22.8% in the late subacute phase. After infratentorial stroke, lateropulsion was always contralesional, with a prevalence estimated at 41% consistently across the four diagnostic tools, especially when slight forms of lateropulsion were discarded (marginal values). This prevalence decreased from 52.8% in the acute phase to 22.8% in the late subacute phase and was greater after right- than left-hemisphere stroke, with the ratio of right- to left-hemisphere stroke increasing as a function of time since stroke: 1.7 in the acute phase to 7.7 in the late subacute phase. Severe forms of contralesional lateropulsion (pushers) had a low pooled prevalence estimated at 12.5%. After infratentorial stroke, the effect of lesion location was less clear. Lateropulsion was ipsilesional for lateral lesions of the lower part of the brainstem and ipsilesional or contralesional elsewhere. The estimated lateropulsion prevalence was high, reaching 83.2% in the acute phase.

### **Lateropulsion prevalence after supratentorial stroke**

Despite recent literature attesting to the increasing interest in the question of lateropulsion, the attractiveness of the field has long been clouded by “fuzzy” terminology, with several terms used to describe different phenomena: body tilt, lateropulsion, listing phenomenon, ease of falling, pusher/pushing syndrome/behavior, thalamic astasia, and biased behavioral vertical (see details elsewhere (Dai *et al.*, 2021a)). Lateropulsion is now well accepted as a deficit of the active body orientation with respect to gravity in the frontal plane, in relation to a biased internal model of verticality,(Pérennou *et al.*, 2008; Dai *et al.*, 2021b) encompassing all these

terms. The lateral body tilt was recently demonstrated as the cardinal sign, possibly associated with two other postural signs: an active pushing from the sound limbs initiating or magnifying the body tilt and a resistance to passive corrections reducing this body tilt (Dai *et al.*, 2021b). This situation corresponds to the current terminology, which should be now adopted (Pérennou *et al.*, 2008; Babyar *et al.*, 2019; An *et al.*, 2021; Dai *et al.*, 2021b; Nolan *et al.*, 2021). However, to ensure an exhaustive review of the literature we included these older terminologies in the search terms.

### *Pusher, a tree that hides the forest*

Until recently, lateropulsion prevalence had mostly been assessed with the most severe form, in affected individuals called pushers (n=415). However, this is the “tree that hides the forest”. Our meta-analysis confirms its relatively low prevalence, about 12.5%, with reduced dispersion. Indeed, the 95% CIs ranged from 9.2 to 15.9, despite a great variability in the assessment of the three signs, (Pedersen *et al.*, 1996; Baccini *et al.*, 2008; Pérennou *et al.*, 2008; Abe *et al.*, 2012) always clinically obvious. This finally leads to very homogenous diagnostic criteria that may be qualitatively assessed without tools (Davies, 1985; Bohannon *et al.*, 1986; Pedersen *et al.*, 1996; Premoselli *et al.*, 2001). Our study failed to show a clear decrease in pusher prevalence before the late subacute stage. There are two complementary interpretations. First, this prevalence is under-estimated in the acute phase owing to the difficulty in properly assessing the three signs in sitting and standing in patients presenting unstable medical conditions and severe deficits. Second, because of a very severe clinical picture, lateropulsion recovery is delayed.

### *Lateropulsion prevalence as a function of stroke side*

Functional lateralization is a fundamental principle of the human brain. Our study confirms that lateropulsion is more frequent after right-hemisphere stroke, estimated by our meta-analysis at

56.3%, versus 34.3% after left-hemisphere stroke. This definitively advocates for the strong right-hemisphere predominance for the control of the body upright, as suggested in some studies (Pérennou *et al.*, 2008; Abe *et al.*, 2012; Brandt and Dieterich, 2017; Dai *et al.*, 2021a; Dai *et al.*, 2021b; Kennedy *et al.*, 2021). We found that the ratio of right- to left-hemisphere stroke was multiplied by 4 between the acute and late subacute phase. This finding might be partly related to a possible diaschisis (Carrera and Tononi, 2014) altering the functioning of both hemispheres during the days following the stroke, whatever the side. A connectivity study (Lemaire *et al.*, 2020) found a bilateral and relatively symmetric network able to serve the construction and updating of the internal model of verticality. This observation 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, the right hemisphere, to become more efficient, as for other spatial functions. The release of the diaschisis should increase the predominance of the right hemisphere for processing spatial information, including control of the upright. This suggestion remains to be demonstrated by further studies. The existence of a potential network for verticality perception within the left hemisphere also explains that lateropulsion prevalence is not negligible after left-hemisphere stroke.

#### *Lateropulsion prevalence decreases as a function of time since stroke*

Time after stroke is another critical factor affecting lateropulsion prevalence. The overall lateropulsion prevalence after supratentorial stroke progressively decreases: about 53% in the acute phase, about 37% in the early subacute phase, and about 23% in the late subacute phase. In other words, more than half of individuals with lateropulsion recover an upright posture within the first 6 months. As expected, the pattern is that reported for spatial neglect, (Esposito *et al.*, 2020) another strong similarity between both deficits in spatial cognition (Dai *et al.*, 2021b).

Four studies (Danells *et al.*, 2004; Lafosse *et al.*, 2005; Dai *et al.*, 2021a; Nolan *et al.*, 2021) assessed lateropulsion twice, a few weeks apart within the subacute phase, all in a rehabilitation context. Lateropulsion prevalence considerably decreased before the end of the subacute phase. However, data were insufficient to analyze the specific role played by the rehabilitation on lateropulsion recovery.

We did not find any data regarding lateropulsion prevalence in the chronic phase. However, our study may help infer this result. The firm decrease we found from the acute phase (53%) to the end of late subacute phase (23%) suggests that lateropulsion prevalence should be < 10% at the chronic phase. This would mean that brain plasticity occurs relatively early in terms of active body orientation with respect to gravity, possibly in relation to vestibular mechanisms, (Cnyrim *et al.*, 2007) and suggests that the first 6 months constitute the appropriate windows for lateropulsion rehabilitation.

### **Lateropulsion prevalence after infratentorial stroke**

The term “lateropulsion” was initially introduced in medicine to illustrate the postural effects of infratentorial stroke (proved by necropsy). (Babinski and Nageotte, 1902) Despite hundreds of articles published in the past century about lateropulsion caused by infratentorial strokes, few were designed to investigate its actual prevalence. Our study found three consecutive series of limited sample size (Dieterich and Brandt, 1992; Kim and Heo, 1996; Ye *et al.*, 2010). Viewed as a general sign among many others (ataxia, ocular motor disorders, dysarthria, dysphagia, Horner syndrome etc.), lateropulsion is frequent, with a prevalence estimated at more than 80% in the acute phase. Several other small series not analyzed in our study because of sample size < 30 found comparable results (Amarenco *et al.*, 1990; Ogawa *et al.*, 2013). The effect of stroke side has not been analyzed in any study.

## **Convergences between supratentorial and infratentorial stroke**

A striking common point is that the lateropulsion prevalence is high both for supratentorial and infratentorial stroke in the acute phase. Lateropulsion prevalence is also high after acute peripheral vestibular diseases (Tomanovic and Bergenius, 2010). These convergences advocate for an interpretation related to a “rope ladder” vestibular network, (Brandt and Dieterich, 2017) which travels from the vestibular organ to the vestibular cortex via the vestibular nuclei, the brainstem, the vestibular cerebellum, and the thalamus. Lateropulsion is ipsilateral to the lesion (ipsilesional) when it damages the vestibular nerve, vestibular nuclei in the lateral medulla oblongata, or culmen lobule and inferior cerebellar peduncle (Amarenco *et al.*, 1990; Dieterich and Brandt, 1992; Ye *et al.*, 2010; Brandt and Dieterich, 2017). It is contralateral to the lesion (contralesional) when it damages the medial medulla oblongata, pontine tegmentum, rostral paramedian midbrain nodulus, nucleus prepositus hypoglossi, thalamus or multimodal vestibular cortex (Amarenco *et al.*, 1990; Pérennou *et al.*, 2008; Ye *et al.*, 2010; Brandt and Dieterich, 2017; Babyar *et al.*, 2019; Lemaire *et al.*, 2020; Dai *et al.*, 2021b). One study reported a few cases showing bilateral lateropulsion after cerebellar stroke (Ye *et al.*, 2010). How a same lesion in a same individual might induce ipsilesional or contralesional lateropulsion is difficult to explain. It might rather be the expression of a cerebellar ataxia, which by nature induces body tilts in several directions.

In the subacute phase after a supratentorial stroke, lateropulsion is often under-recognized by physicians, whereas physical therapists are more familiar with this postural behavior, (Brandt and Dieterich, 2017) often ignoring types of lateropulsion, ipsi- or contralesional, which result from different mechanisms (Dieterich and Brandt, 1992; Cnyrim *et al.*, 2007; Pérennou *et al.*, 2008; Brandt and Dieterich, 2017). We hope that our study will urge the community involved in stroke to pay more attention to lateropulsion.

## Study limitations

The methodological quality of one third of studies reviewed showed risk of bias, and those retained had relatively low sample size (median, n=110). However, our approach based on sensitivity analyses allowed to check that these features did not bias our study. Selecting articles entirely written in English did not create an additional bias. In contrast, in the field of post-stroke balance disorders, not limiting the writing language to English clearly alter the quality of papers selected for analyses (Hugues *et al.*, 2020).

Three publication biases were detected in the meta-analysis. One concerned the pooled lateropulsion prevalence, increased by the number of infratentorial strokes. We know that lateropulsion mechanisms are different for supra- and infratentorial stroke (see introduction). Their prevalence not being comparable advocates for separate analyses in subgroups. This approach suppressed this bias. Two other publication biases were found, both dealing with demographic data. We assume that the one related to age was due to different approaches by countries in referring patients to rehabilitation centers after a stroke (Nolan *et al.*, 2021). We also assume that the one related to sex was due to a high female proportion (Pedersen *et al.*, 1996) in stroke populations of some specific regions (Appelros *et al.*, 2009).

The heterogeneity among lateropulsion prevalence was high, so we used random-effects models to pool prevalence estimates, by subgroups, as well as meta-regression analysis. This heterogeneity could not be explained by age, sex, geographic region, published year or study quality. It was explained by different stroke locations and time since stroke.

The use of several tools (and cut-offs) to diagnose lateropulsion (D'Aquila *et al.*, 2004; Danells *et al.*, 2004; Lafosse *et al.*, 2005; Baccini *et al.*, 2008; Pérennou *et al.*, 2008; Clark *et al.*, 2012; Chow *et al.*, 2019; Dai *et al.*, 2021a; Nolan *et al.*, 2021) questions the robustness of our results. An interesting finding of our study was the consistency of lateropulsion prevalence across



different tools used, especially when slight forms related to some supratentorial strokes were discarded (marginal values). This finding supports the validity of our study.

In addition to these factors, the generalizability of our study was affected by a lack of geographical diversity. Indeed, all enrolled studies came from high-income countries, which agrees with specialized acute stroke units offering intensive and specialized care (e.g., thrombolysis and thrombectomy). This suited care might limit the severity of strokes and hence attenuate the lateropulsion prevalence.

## **Conclusions**

Lateropulsion prevalence is high within the first 3 months after a stroke, regardless of its location. This prevalence firmly decreases before the chronic phase, which indicates that brain plasticity occurs relatively early in terms of the active body orientation with respect to gravity and suggests that most rehabilitation efforts to facilitate lateropulsion recovery should be at the acute and subacute phases. This observation appeals for an early systematic detection of lateropulsion after stroke by using existing tools, to guide appropriate interventions. This study also reveals that lateropulsion is more frequent after right- versus left-hemisphere stroke, with the ratio of right to left-hemisphere stroke increasing with time. This observation confirms that uprightiness is a highly lateralized brain function, mainly located in the right hemisphere.

## Appendix 1. Authors

Name	Location	Contribution
Shenhao Dai, MD, PhD	Grenoble Alpes University Hospital, France	Design of the study protocol, screening of the literature, data collection, statistical analyses, and drafting and critical revision of the manuscript
Camille Lemaire, MD	Grenoble Alpes University Hospital, France	Screening of the literature, data collection, and drafting and critical revision of the manuscript
Céline Piscicelli, PhD	Grenoble Alpes University Hospital, France	Screening of the literature, data collection, and drafting and critical revision of the manuscript
Dominic Pérennou, MD, PhD	Grenoble Alpes University Hospital, France	Design of the study protocol, study supervision, statistical analyses, drafting and critical revision of the manuscript and obtaining funding

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## **SUPPLEMENTAL MATERIAL**

### **Search strategy for databases**

Search population: post-stroke adults

Search terms: ((stroke OR (“Stroke”[MeSH Terms]) OR (“Cerebrovascular Disorders”[MeSH Terms]) OR (“Brain Infarction”[MeSH Terms]) OR (“Hemorrhagic Stroke”[MeSH Terms]) OR (“Ischemic Stroke”[MeSH Terms]) OR Cerebrovascular\*)) AND (Lateropulsion OR (Lateral AND Pulsion) OR Pusher OR Pushing OR (Pusher AND (Behavi\* OR Syndrome)) OR (Pushing AND (Behavi\* OR Syndrome)) OR (Contraversive Pushing) OR Listing Phenomenon OR Astasia OR Thalamic Astasia OR Ease of Falling OR Body Tilt OR Trunk Tilt OR Body Alignment OR Postural Asymmetry)



**Supplemental Table I. Quality assessment using the Joanna Briggs Institute guidelines for prevalence/incidence systematic reviews.**

	Year	1. Was the sample frame appropriate to address the target population?	2. Were study participants sampled in an appropriate way?	3. Was the sample size adequate?	4. Were the study subjects and the setting described in detail?	5. Was the data analysis conducted with sufficient coverage of the identified sample?	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way for all participants?	8. Was there appropriate statistical analysis?	9. Was the response rate adequate, and if not, was the low response rate managed appropriately?
<b>Supratentorial stroke</b>										
Bohannon	1986	No	Unclear	Yes	Yes	Unclear	No	Unclear	No	Unclear
Pedersen, et al.	1996	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	Unclear
Premoselli, et al.	2001	Unclear	Unclear	Yes	Unclear	Unclear	No	Unclear	No	Yes
D'Aquila, et al.	2004	Unclear	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Yes
Danells, et al.	2004	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Lafosse, et al.	2005	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Lagerqvist & Skargren	2006	No	Unclear	Yes	Unclear	No	Yes	Unclear	Yes	Unclear
Baccini, et al.	2008	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
van Nes, et al.	2009	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Kwon, et al.	2010	Yes	Unclear	No	Unclear	Yes	Yes	Unclear	Yes	Unclear
Baier, et al.	2012	Unclear	Unclear	No	Unclear	Unclear	Yes	Yes	Yes	Unclear
Abe, et al.	2012	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No
Lee, et al	2013	Unclear	Unclear	No	Unclear	Unclear	Yes	Yes	Yes	Yes
Krewer, et al.	2013	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Chow, et al.	2019	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Dai, et al.	2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Nolan, et al.	2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<b>Mixed series (supra + infratentorial stroke)</b>										
Pérennou, et al.	2008	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Clark, et al.	2012	Unclear	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Unclear
Chow, et al.	2019	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
<b>Infratentorial stroke</b>										
Dieterich & Brandt	1992	Yes	Unclear	No	Yes	Unclear	No	Yes	Yes	Yes
Kim & Heo	1996	Yes	Unclear	No	Yes	Yes	No	Unclear	No	Yes
Ye, et al.	2010	Yes	Yes	No	Yes	Yes	No	Unclear	Yes	Yes

The agreement between 2 independent investigators (SD and CL) was high, with only 7/198 (3.5%) points which differed, mainly for the item-2. This result confirms the appropriateness of the Joanna Briggs Institute guidelines. All disagreements were resolved by consensus.

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**S. Table 2. Details of identified studies reporting the prevalence of lateropulsion after infratentorial stroke.**

<b>Authors</b>	<b>Year</b>	<b>Latero- pulsion side</b>	<b>Area of the lesion</b>	<b>Structure damage</b>
Dieterich & Brandt	1992	100% ipsi	Brainstem	Lateral medulla
Kim & Heo	1996	79% ipsi, 21% contra	Brainstem and cerebellum	Pons, medulla oblongata and cerebellum
Ye, et al.	2010	45% ipsi, 15% contra	Cerebellum	Caudal vermis (folium-tuber, uvula, tonsil, and nodulus) and posterior paravermis

## MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on
Reporting of background should include		
1	Problem definition	Introduction
2	Hypothesis statement	Introduction
3	Description of study outcome(s)	Methods: Study selection
4	Type of exposure or intervention used	Methods: Study selection
5	Type of study designs used	Methods: Study selection
6	Study population	Methods: Study selection
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	Methods; Title page
8	Search strategy, including time period included in the synthesis and key words	Methods
9	Effort to include all available studies, including contact with authors	Methods: Study selection
10	Databases and registries searched	Methods: Search strategy
11	Search software used, name and version, including special features used (eg, explosion)	Methods: Search strategy
12	Use of hand searching (eg, reference lists of obtained articles)	Methods: Search strategy; Figure 1
13	List of citations located and those excluded, including justification	Figure 1; Tables 1
14	Method of addressing articles published in languages other than English	Methods: Search strategy
15	Method of handling abstracts and unpublished studies	Methods: Search strategy; Figure 1
16	Description of any contact with authors	Methods: Study selection
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Methods: Study selection
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Methods: Study selection; Data extraction
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	Methods
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Methods: Data extraction
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	Methods: Quality assessment
22	Assessment of heterogeneity	Methods: Statistical analysis
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Methods: Statistical analysis
24	Provision of appropriate tables and graphics	Tables 1; Figure 1

Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figures 2-5
26	Table giving descriptive information for each study included	Tables
27	Results of sensitivity testing (eg, subgroup analysis)	Results; Table2; Figure 2,5
28	Indication of statistical uncertainty of findings	Results; Figures 2-5
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	Study limitations
30	Justification for exclusion (eg, exclusion of non-English language citations)	Study limitations
31	Assessment of quality of included studies	Study limitations
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	Discussion
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Discussion; Study limitations
34	Guidelines for future research	Conclusions
35	Disclosure of funding source	Funding

*From:* Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.



**PRISMA 2020 Checklist**

Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	Title page
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
<b>METHODS</b>			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods: Study selection
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods: Search strategy
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods: Search strategy
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods: Study selection; Figure 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods: Data extraction
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods: Data extraction
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods: Data extraction
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods: Quality assessment
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Methods: Data extraction; Statistical analysis
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods: Study selection
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods: Data extraction
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods: Data extraction
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods: Statistical analysis
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods: Statistical analysis



**PRISMA 2020 Checklist**

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods: Statistical analysis
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods: Quality assessment
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods: Statistical analysis
<b>RESULTS</b>			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results: Literature review; Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results: Literature review; Quality assessment; Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Results: Study characteristics
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results: Quality assessment
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1; Figure 2-5; Supplemental material
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1; Supplemental material
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results; Figure 2-5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results; Figure 2-5
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Results; Table 2
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results: Quality assessment
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results; Figure 2-5
<b>DISCUSSION</b>			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion: para 1
	23b	Discuss any limitations of the evidence included in the review.	Discussion: Study limitations
	23c	Discuss any limitations of the review processes used.	Discussion: Study limitations
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion; Conclusions



## PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
<b>OTHER INFORMATION</b>			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods: Standard protocol registration
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods: Standard protocol registration
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	PROSPERO declaration (CRD42020175037)
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding
Competing interests	26	Declare any competing interests of review authors.	Competing interests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Methods: Data availability

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71  
For more information, visit: <http://www.prisma-statement.org/>

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## ➤ Chapter 5: Graviceptive Neglect

In this paper, we investigate the mechanisms of lateropulsion after hemispheric stroke. Our findings draw a parallel between behavior against gravity, spatial neglect, and vertical perception after hemisphere stroke. Our paper conceptualizes lateropulsion as a form of graviceptive neglect. This would suggest that the human brain uses 3-D maps involving the internal model of verticality rather than a mosaic of 2-D maps. We think that this finding has a high impact on understanding the mechanisms of spatial cognition, beyond lateropulsion and spatial neglect. This paper is published in *Neurology* (Volume 96, Number 17, April 27, 2021, DOI: 10.1212/WNL.00000000000011826).



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## Lateropulsion after Hemispheric Stroke, a Form of Spatial Neglect Involving Graviception

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## Abstract

**Objective** To test the hypothesis that lateropulsion is an entity expressing an impaired body orientation with respect to gravity, in relation to a biased graviception and spatial neglect.

**Methods** Data from the DOBRAS cohort (ClinicalTrials.gov:NCT03203109), were collected 30 days after a first hemisphere stroke. Lateral body tilt, pushing and resistance were assessed with the Scale for Contraversive Pushing.

**Results** Among 220 individuals, 72% were Upright and 28% showed lateropulsion (Tilters=14% less severe than Pushers=14%). The three signs had very high factor loadings (>0.90) on a same dimension, demonstrating that lateropulsion was effectively an entity comprising body tilt (cardinal sign), pushing and resistance. The factorial analyses also showed that lateropulsion was inseparable from the visual vertical (VV), a criterion referring to vertical orientation (graviception). Contralesional VV biases were frequent (44%), with a magnitude related to lateropulsion severity: Upright  $-0.6^{\circ}(-2.9;2.4)$ , Tilters  $-2.9^{\circ}(-7;0.8)$ , Pushers  $-12.3^{\circ}(-15.4;-8.5)$ . Ipsilesional VV biases were less frequent and milder ( $p<0.001$ ). They did not deal with graviception, 84% being found in upright individuals. Multivariate, factorial, contingency, and prediction analyses congruently showed strong similarities between lateropulsion and spatial neglect, the latter encompassing the former.

**Conclusions** Lateropulsion (pusher syndrome) is a trinity constituted by body tilt, pushing and resistance. It is a way to adjust the body orientation in the roll plane to a wrong reference of verticality. Referring to straight above, lateropulsion might correspond to a form of spatial neglect (referring to straight ahead), which would advocate for 3-D maps in the human brain involving the internal model of verticality.

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## Introduction

Thomas (Thomas, 1940) first reported cases of brain-damaged individuals (also animals) who showed active lateral body tilt, pushed themselves away from the upright with sound limbs, and resisted any corrections. Davies (Davies, 1985) carefully detailed these striking signs she observed after stroke, empirically combined in the so-called pusher syndrome, confirmed later by the Copenhagen Stroke Study (Pedersen *et al.*, 1996). The term syndrome lacks accuracy, and its usage is decreasing (Chen *et al.*, 2019). Simply using “lateropulsion” has been proposed (D'Aquila *et al.*, 2004; Babyar *et al.*, 2009).

To what extent lateropulsion signs are associated remained to be investigated. Indeed, mechanisms underlying pushing and resistance are controversial, viewed as a way to adjust the body orientation to a wrong reference of verticality (Pérennou *et al.*, 2008) or as a postural reflex reacting to a sensory conflict (Karnath *et al.*, 2000). Actions to push or resist might even result from inappropriate muscular over-activity (Thomas, 1940).

For hemisphere stroke, we hypothesized that signs of contralesional lateropulsion would represent a same dimension corresponding to an impaired orientation of the body against gravity, in relation to an altered graviception. We tested this unidimensionality by analyzing data collected in a large series of consecutive individuals covering the whole range of lateropulsion severity.

Spatial neglect is frequently associated with lateropulsion, sometimes systematically (Karnath *et al.*, 2000; Pérennou *et al.*, 2002; Vaes *et al.*, 2015). Is it a co-occurrence (Pérennou, 2006) or rather the result of a process underpinning an impaired spatial referential linking straight above (verticality) and straight ahead (left/right gradient)? Lateropulsion might be considered a form of spatial neglect bearing on graviception (Pérennou *et al.*, 2002; Pérennou, 2006). We addressed this question.

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## Methods

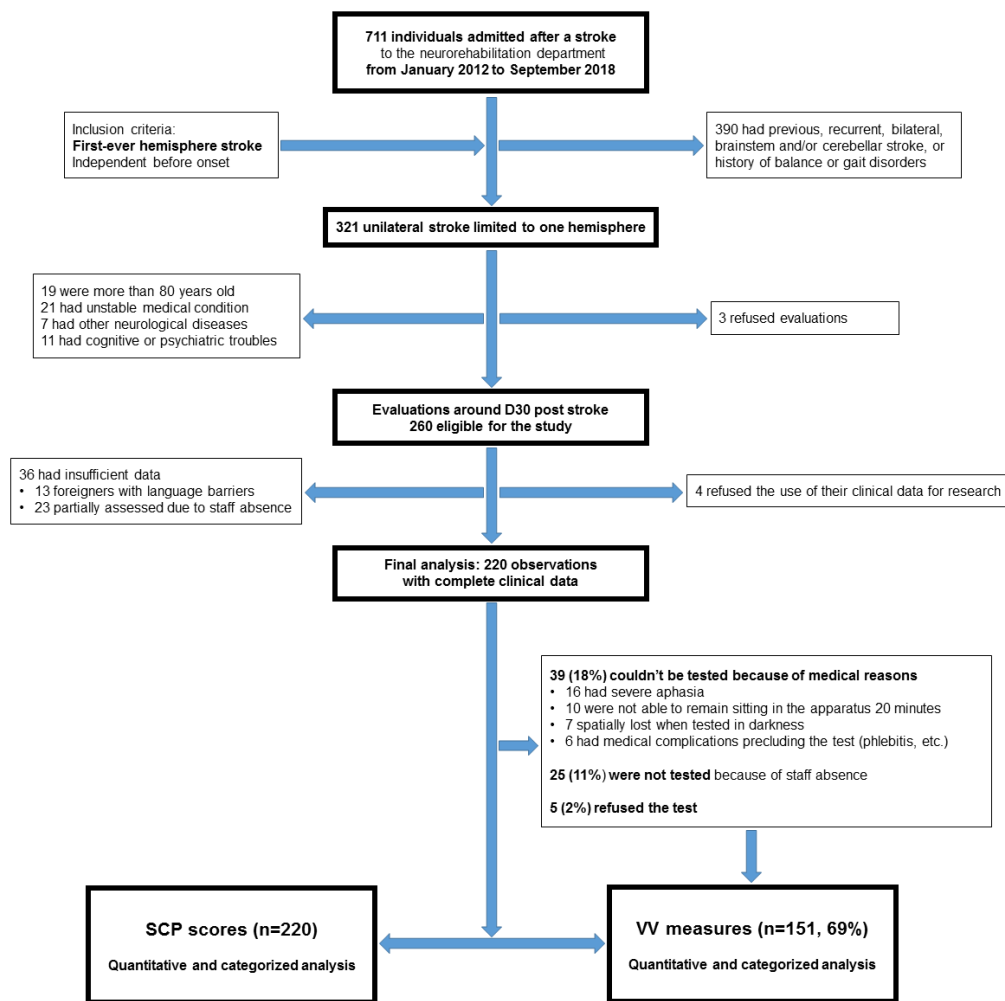
### Study design

This was a monocentric observational study using the data of the DOBRAS (Determinants of Balance Recovery After Stroke) cohort, with participants comprehensively assessed in routine care, initially during the first weeks after entry in the rehabilitation ward. The sample size was planned to conduct multivariate analyses in a large series of individuals ( $\geq 200$  observations). Sensory, motor, and cognitive deficits were assessed at a fixed date by trained and multidisciplinary examiners, with blinding to other data and the study hypotheses. The reporting follows the STROBE statement.

### Participants and assessment timing

From January 2012 to September 2018, we included 220 consecutive individuals (Figure 1) with a first-ever unilateral stroke limited to one hemisphere. Details on inclusion and exclusion criteria are given in the companion paper (Dai *et al.*, 2021).

Initial assessments were performed if possible on about day 30 after stroke (D30) with a 3-day window before and after. The rationale for this timing is explained in the companion paper (Dai *et al.*, 2021). Among the 220 participants, 207 (94%) were admitted during the first month post-stroke and so were assessed on D30. For the 13 others admitted after D30 (6%), the initial assessment was performed on day 60 (D60, window of 3 days before and after).



**Figure 1. Flow of participants in the study**

Flow diagram of the study, explaining the processing of inclusion and assessments. We enrolled 220 participants for analyses of the postural behavior (n=220) and VV measures (n= 151). D30=day 30. SCP= Scale for Contraversive Pushing. VV= visual vertical.

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### **Behavior against gravity (BAG)**

BAG was assessed by the Scale for Contraversive Pushing (SCP), with increments of 0.25 and total score from 0 to 6 (Karnath *et al.*, 2000). The SCP has been designed to categorize individuals according to scores of the three signs defined by Davies (Davies, 1985): active lateral body tilt, spontaneous action of abduction/extension of the ipsilesional upper or lower limb to push the body away from the upright (Pedersen *et al.*, 1996; Pérennou *et al.*, 2008), and resistance to passive correction making the body upright. As defined in the original method (Karnath *et al.*, 2000), individuals who met these three criteria with at least 1 point for each component were considered Pushers. They represent a small part of consecutive individuals, limited to severe lateropulsion (Pedersen *et al.*, 1996; Pérennou *et al.*, 2008; Abe *et al.*, 2012). Only considering Pushers would overlook individuals with moderate lateropulsion. As proposed previously (Pérennou *et al.*, 2008), we also used the SCP to differentiate individuals with an upright posture from those who were mildly tilted. To be conservative, we used the total SCP cut-off  $\leq 0.50$  to define the Upright group. Indeed, values of 0.25 or 0.5 were clearly marginal, not allowing to state that the individual was not upright most of the time. In this study, we called Tilters individuals of the intermediate group. They showed net lateral body tilt at least in one posture, sitting or standing, regardless of the two other lateropulsion signs, but did not show the criteria to be Pushers. In line with our hypothesis, this approach had the advantage of constituting *a priori* an intermediate group with individuals in whom mild degrees of body tilt, pushing, and resistance could be associated or not. To summarize, upright individuals had a total SCP score  $\leq 0.5$ ; Tilters had a total SCP score  $> 0.5$  and a score for at least one of the three

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components (body tilt, pushing or resistance)  $<1$ , so were not Pushers; and Pushers had a total SCP score  $\geq 3$  and scores for all 3 components  $\geq 1$ .

### **Verticality perception**

We used the visual vertical (VV) test and a procedure well described and validated (Pérennou *et al.*, 2008; Barra *et al.*, 2010; Piscicelli *et al.*, 2015a; Piscicelli *et al.*, 2015b; Piscicelli *et al.*, 2016) for testing individuals with postural disorders (Piscicelli *et al.*, 2015b; Piscicelli *et al.*, 2016; Piscicelli and Pérennou, 2017), with reliability (Piscicelli *et al.*, 2015a) and low measurement error (Piscicelli *et al.*, 2015a). VV tests were performed by trained examiners (CP and SD). To avoid any error due to the setting (Piscicelli *et al.*, 2015a), individuals were seated with their head and trunk maintained upright and straight by using lateral cushioning blocks in complete darkness (room without window, thick curtain over the door). Participants were asked to verbally adjust the line to the vertical, for 10 trials. We calculated two indices: VV orientation (VV-orient) and uncertainty (VV-uncert). VV-orient corresponded to the average of trials with negative values indicating a contralesional rotation, classified as follows (Pérennou *et al.*, 2008; Piscicelli and Pérennou, 2017): normal VV  $-2.5^\circ$  to  $2.5^\circ$ ; contralesional VV bias  $<-2.5^\circ$ ; and ipsilesional VV bias  $>2.5^\circ$ . VV-uncert corresponded to within-subject variability (standard deviation of the trials).

### **Spatial neglect**

Body and non-body neglect were assessed with a battery of six tests: ecological Catherine Bergego Scale (CBS) (Beis *et al.*, 2004; Azouvi *et al.*, 2006), thumb finding (Beis *et al.*, 2004; Azouvi *et al.*, 2006), Fluff (Rode *et al.*, 2017) (since 2014) and Bells tests (Beis *et al.*, 2004; Azouvi *et al.*, 2006), the bisection of two successive 200-mm lines (Beis *et al.*, 2004; Azouvi



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*et al.*, 2006), and the copy of Gainotti drawing (Beis *et al.*, 2004; Azouvi *et al.*, 2006). They were classified according to cut-offs proposed in seminal papers or revised later (Azouvi *et al.*, 2006), and detailed in the companion paper (Dai *et al.*, 2021). A few individuals with severe comprehension (aphasia) or executive troubles were not able to complete the whole neglect battery but had to perform at least three tests to not be considered with missing data. Grouping for spatial neglect was as follows: No or light if all test results were normal or if only one test was marginally altered; Severe with results of at least two tests markedly altered (altered if binary categorized); or Moderate otherwise.

### **Other assessments**

We also assessed handedness, aphasia, apraxia, motor weakness, spasticity, hypoesthesia, hemianopia and depression. Details are given in the companion paper (Dai *et al.*, 2021). Disability was assessed by the Functional Independence Measure (FIM).

### **Statistical analysis**

Continuous data are presented as median with interquartile range (Q1;Q3) and dichotomized and categorical data as number (%). When useful, 95% confidence intervals (CIs) are given. Demographics of BAG groups were compared by using omnibus tests (Kruskal-Wallis or chi-square), then when significant, Mann-Whitney U or chi-square test. Here corrected P values were set at 0.013 (0.05/4).

To test the first part of our hypothesis that body tilt, pushing and resistance represent the same dimension of a trouble corresponding to an impaired orientation of the body against gravity, we performed a factorial analysis to determine the number of dimensions they represented. We also analyzed their gradient of severity as a function of BAG, and sought their dissociations. To test

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the second part of our hypothesis that this impaired body orientation was related to an altered graviception, we added VV-orient in the factorial analysis and also analyzed VV abnormalities as a function of BAG. BAG groups were compared by using omnibus tests (Kruskal-Wallis or chi-square), then when significant, Mann-Whitney U or chi-square test. Because of multiple comparisons for VV indices supposed to be dependent on each other, corrected P values were set at 0.0025 (0.05/5 variables\*4 comparisons). Because VV could not be tested in all individuals (reasons explained in Figure 1), VV was analyzed after multiple imputations.

The question of the link between lateropulsion and spatial neglect was comprehensively investigated and addressed by means of multivariate, factorial, contingency, and prediction analyses. We first analyzed the clinical profiles of the three BAG groups by comparing their deficits using omnibus tests (Kruskal-Wallis or chi-square), then when significant, Mann-Whitney U or chi-square test. Because of multiple comparisons, corrected P values (deficits independent of each other) were set at 0.013 (0.05/4 tests for each deficit). Variables found significant were included in a multivariate ordinal regression to further explore their association with BAG; odds ratios (ORs) were calculated. Then, similarities between clinical profiles of BAG groups and spatial neglect severity were sought by a principal component analysis with varimax rotation and Kaiser Normalization. Contingency analyses with Venn diagrams further explored how lateropulsion and spatial neglect nested. Finally, receiver operating characteristic (ROC) curves were plotted, and the area under the ROC curve (AUC) was calculated to predict one deficit from the other.

Unless otherwise indicated (corrections), two-tailed  $P < 0.05$  was considered statistically significant. Effect sizes were calculated by using the H values of the Kruskal-Wallis test ( $\eta^2 = H - k + 1/n - k$ ), the Z values of the Mann-Whitney test ( $r = Z/\sqrt{n}$ ) and the  $X^2$  values of the chi-square test ( $v = \sqrt{(X^2/n * \text{degree of freedom})}$ ) (Tomczak and Tomczak, 2014). Statistical analysis involved using SPSS 21.0.

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### **Standard protocol approvals, registrations, and patient consents**

The DOBRAS cohort was approved by our institutional review board (CHU Grenoble Alpes) who opened and validated the ClinicalTrials.gov declaration (NCT03203109). The study was also registered at the National Committee for Informatics and Freedom (CNIL-No.2014874-v1) and performed in accordance with the Helsinki Declaration. According to French law, eligible individuals were informed of the DOBRAS study (orally and in writing) and those who did not want to participate signed an opposition form. Authorization was obtained from patients (or families) for disclosure of any recognizable persons in videos.

### **Data availability**

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

## **Results**

The demographic characteristics and stroke type of the 220 individuals (median age 66.9 [58;73] years, 147 [67%] males) are in Table 1. Most were right-handed (90%) and with infarcts (83%). Most stood upright (158/220, 72%; Video 1), 32 (14%) were Tilters (Video 2) and 30 (14%) were Pushers (Video 3). Disability was greater (lower FIM scores) in Pushers than Tilters (45 [37;56] vs 62 [50;76];  $r=0.37$ ,  $p=0.004$ ), and greater in Tilters than upright individuals (62 [50;76] vs 107 [85;118];  $r=0.45$ ,  $p<0.001$ ).

**Table 1: Demographic data and stroke features as a function of behaviors against gravity**

	All (n=220)	Upright (n=158)	Tilters (n=32)	Pushers (n=30)	Omnibus test	Group comparisons <sup>a</sup>		
						Upright vs Tilters	Upright vs Pushers	Tilters vs Pushers
<b>Age (years)</b>	66.9 (58;73)	66.2 (54;72)	66 (60;71)	70.4 (64;76)	$\eta^2=0.03$ p=0.013	r= -0.03 p=0.707	r= -0.21 p=0.004	r= -0.28 p=0.027
<b>Sex, male</b>	147 (67%)	109 (69%)	21 (66%)	17 (57%)	v=0.06 p=0.417			
<b>BMI (kg/m<sup>2</sup>)</b>	25 (22;28)	26 (23;28)	24 (22;27)	25 (21;29)	$\eta^2=0.01$ p=0.196			
<b>Right-handers</b>	198 (90%)	138 (87%)	30 (94%)	30 (100%)	v=0.11 p=0.072			
<b>Stroke type, infarct</b>	183 (83%)	133 (84%)	26 (81%)	24 (80%)	v=0.03 p=0.813			
<b>Stroke side, RH</b>	94 (43%)	49 (31%)	20 (63%)	25 (83%)	v=0.28 p<0.001	v=0.24 p<0.001	v=0.39 p<0.001	v=0.23 p=0.066

Data are n (%) or median (Q1; Q3), unless stated otherwise. BMI=body mass index. RH= right hemisphere.  $\eta^2$ = effect size of the Kruskal-Wallis test. r= effect size of the Mann-Whitney test. v=effect size of the Chi-square test. The values 0.01, 0.06 and 0.14 represent a small, medium and large effect for the Kruskal-Wallis test. The values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both the Mann-Whitney test U and 2\*2 chi-square test. For the 2\*3 chi-square test, effect sizes of 0.07, 0.21, and 0.35 represent small, medium, and large effect, respectively.

<sup>a</sup> The significant P values for group comparisons were adjusted to 0.013 (0.05/4) owing to multiple comparisons.

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## **Video Legends**

### **Video 1. Upright individual**

Individual in rehabilitation after right hemisphere stroke (posterior limb of the internal capsule) causing left hemiparesia. He is considered Upright, with postural disorders due to impaired body stabilization attested by lateral oscillations (see companion paper).

### **Video 2. Tilter**

Individual in rehabilitation after right hemisphere stroke (small thalamic lesion) causing slight left hemiparesia. He shows moderate contralesional lateropulsion compatible with a quiet standing posture. He is considered a Tilter with a predominant lateral body tilt without obvious active spontaneous pushing or resistance to passive correction. The lateropulsion is amplified with feet together, eliciting a fall. Postural disorders are mainly due to impaired body orientation with respect to gravity (see companion paper).

### **Video 3. Pusher**

Individual in rehabilitation after right hemisphere stroke (extended parieto-temporo-insular lesion) causing left hemiplegia. She shows severe contralesional lateropulsion incompatible with standing. She is considered a Pusher because in addition to the lateral body tilt, she shows pronounced spontaneous active pushing aiming at initiating and amplifying the body tilt from the sound lower and upper limbs as well as resistance to passive corrections by the physiotherapist.

## **Missing data**

The total number of missing data represented only 4.5% of the dataset. No missing data concerned the SCP, and few missing data concerned clinical deficits: spatial neglect (n=2, with

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left hemisphere stroke and severe aphasia), apraxia (n=5), hemianopia (n=1) and depression (n=9). Most missing data concerned VV, mainly because of the procedure requiring precise instructions in darkness, which precluded testing every patient (see details in Figure 1). This explained why VV data decreased with deficit severity: 114/158 (72%) for upright individuals, 22/32 (69%) for Tilters and 15/30 (50%) for Pushers. However, we could assess VV in 151/220 individuals (69%), mostly on D30 (123/151, 81%) and otherwise on D60 (28/151, 19%). Owing to very few missing data for other variables (0.4% of the whole dataset) and no missing data on the primary outcome (SCP), we performed multiple imputations (bearing exclusively on VV values) and compared the two datasets: one with estimated values and the original one with VV measurements. The comparison revealed no difference in VV values ( $-1.1^{\circ}$  [-4.8; 1.9] vs  $-1.6^{\circ}$  [-5.4; 1.7]) or bias frequency (contralesional: 36% vs 44%, ipsilesional: 21% vs 22%). Sensitivity indices were high: 0.82 (95%CI [0.73;0.89]) and 0.96 (95%CI [0.86;0.99]) for frequencies of contralesional and ipsilesional biases, respectively. Therefore, all analyses involving VV were performed with a complete dataset obtained by multiple imputations.

### **Behavior against gravity (BAG)**

Table 2 shows that body tilt, pushing and resistance were not only more severe in Pushers than in Tilters and upright individuals but were also more severe in Tilters than upright individuals. Therefore, the construction of our intermediate group was relevant.

Among the 158/220 (72%) individuals considered upright, most sat and stood perfectly upright (146/158, 95%). Only 12 (5%) showed some degree of isolated body tilt in sitting and/or standing without fall tendency. One (perfectly upright) exhibited mild pushing only when changing positions in standing. None showed any sign of resistance. When isolated, body tilts were always slight and in the upright group. All Tilters exhibited a lateral body tilt in sitting

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and/or standing, always accompanied by resistance (13/32, 41%), pushing (4/32, 12%), or both (15/32, 47% with signs insufficiently pronounced to be a Pusher). These data confirm the appropriateness to call this intermediate group Tilters.

Among the 220 individuals of the series, 145 (66%) presented no lateropulsion sign, 45 (20%) presented the three signs, 17 (8%) two signs (always body tilt, mostly associated with resistance), and 13 (6%) only one sign, almost constantly a lateral body tilt. Among individuals who showed at least one sign, lateropulsion was almost always present (74/75, 99%), whereas resistance (58/75, 77%) and pushing (50/75, 67%) were less frequent.

Finally, the factorial analysis of the three signs revealed that they represented a same dimension. The lateral body tilt had the highest factor loading: 0.98 vs 0.96 for pushing and 0.95 for resistance.

### **Verticality perception**

Table 2 shows that BAG was greatly influenced by biases of VV-orient, both in magnitude and frequency. VV-orient was mostly distributed within the normality range in upright individuals, mostly tilted to the contralesional side, with a moderate magnitude in Tilters and strongly tilted to the contralesional side in Pushers. The effect size was medium between the first two groups and large between the last two groups. The prevalence of contralesional VV biases reached 97% in Pushers. About half of upright individuals showed a normal VV and half a mild bias, either contralesional or ipsilesional.

Several results indicated that contralesional and ipsilesional VV tilts corresponded to different mechanisms. Most Tilters and Pushers (77%) had contralesional VV biases (quasi-systematic in Pushers), and half of the 44% of individuals with a contralesional VV bias were Tilters and Pushers. In contrast, ipsilesional VV biases were poorly related to BAG, individuals showing

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ipsilesional VV biases being mostly upright (84%, except for seven Tilters and one Pusher). Ipsilesional VV biases were less frequent and with lesser magnitudes than contralesional biases (22%; 3.7° [2.6;5.6] vs 6° [3.9;9.1];  $r=-0.81$ ,  $p<0.001$ ).

Adding VV-orient in the previous factorial analysis demonstrated that lateropulsion and VV-orient were two criteria of a same dimension (i.e., the vertical orientation). The 0.78 factor loading of VV-orient was less high than others (which became 0.96 for body tilt, 0.95 for pushing, and 0.94 for resistance) because of some ipsilesional biases.



**Table 2: Lateropulsion signs and verticality perception as a function of behaviors against gravity**

	All (n=220)	Upright (n=158)	Tilters (n=32)	Pushers (n=30)	Omnibus test	Group comparisons <sup>a</sup>		
						Upright vs Tilters	Upright vs Pushers	Tilters vs Pushers
<b>Behavior against gravity</b>								
<b>Lateral body tilt (0-2)</b>	0 (0;0.3)	0 (0;0)	0.5 (0.3;0.8)	1.3 (1;2)	$\eta^2=0.83$ $p<0.001$	$r=-0.82$ $p<0.001$	$r=-0.87$ $p<0.001$	$r=-0.8$ $p<0.001$
<b>Pushing (0-2)</b>	0 (0;0)	0 (0;0)	0.5 (0;0.5)	1.5 (1;2)	$\eta^2=0.83$ $p<0.001$	$r=-0.71$ $p<0.001$	$r=-0.98$ $p<0.001$	$r=-0.87$ $p<0.001$
<b>Resistance (0-2)</b>	0 (0;1)	0 (0;0)	1 (1;1)	2 (2;2)	$\eta^2=0.92$ $p<0.001$	$r=-0.92$ $p<0.001$	$r=-0.99$ $p<0.001$	$r=-0.68$ $p<0.001$
<b>Total SCP score (0-6)</b>	0 (0;1.3)	0 (0;0)	1.8 (1.3;2.4)	4.8 (4;6)	$\eta^2=0.87$ $p<0.001$	$r=-0.87$ $p<0.001$	$r=-0.86$ $p<0.001$	$r=-0.86$ $p<0.001$
<b>Visual vertical (VV) - Estimated values after multiple imputations for untested VV<sup>b</sup></b>								
<b>VV-orient (°)</b>	-1.6 (-5.4;1.7)	-0.6 (-2.9;2.4)	-2.9 (-7;0.8)	-12.3 (-15.4;-8.5)	$\eta^2=0.32$ $p<0.001$	$r=-0.24$ $p=0.001$	$r=-0.58$ $p<0.001$	$r=-0.66$ $p<0.001$
<b>VV-uncert (°)</b>	1.5 (1;2.8)	1.3 (1;2)	1.9 (1.4;2.7)	4.5 (3.4;5.7)	$\eta^2=0.28$ $p<0.001$	$r=-0.22$ $p=0.003$	$r=-0.55$ $p<0.001$	$r=-0.63$ $p<0.001$
<b>VV Biases</b>								
<b>Contralesional</b>	96 (44%)	48 (30%)	19 (59%)	29 (97%)	$v=0.33$ $p<0.001$	$v=0.23$ $p=0.002$	$v=0.49$ $p<0.001$	$v=0.45$ $p<0.001$
<b>No bias</b>	75 (34%)	69 (44%)	6 (19%)	0 (0%)	$v=0.24$ $p<0.001$	$v=0.19$ $p=0.009$	$v=0.33$ $p<0.001$	$v=0.32$ $p=0.024$
<b>Ipsilesional</b>	49 (22%)	41 (26%)	7 (22%)	1 (3%)	$v=0.13$ $p=0.024$	$v=0.03$ $p=0.629$	$v=0.2$ $p=0.006$	$v=0.28$ $p=0.054$

Data are n (%) or median (Q1; Q3), unless stated otherwise. SCP= Scale for Contraversive Pushing. VV= visual vertical. Orient= orientation. Uncert= uncertainty.  $\eta^2$ = effect size of the Kruskal-Wallis test.  $r$ = effect size of the Mann-Whitney test.  $v$ =effect size of the Chi-square test. The values 0.01, 0.06 and 0.14 represent a small, medium and large effect for the Kruskal-Wallis test. The values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both the Mann-Whitney test U and 2\*2 chi-square test. For the 2\*3 chi-square test, effect sizes of 0.07, 0.21, and 0.35 represent small, medium, and large effect, respectively.

<sup>a</sup> The significant P values for group comparisons were adjusted to 0.003 (0.05/4\*4) for BAG and 0.0025 (0.05/5\*4) for VV owing to multiple comparisons.

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<sup>b</sup> Among 220 observations, 151/220 (69%) individuals have tested the VV. Owing to very few missing data of other variables (0.4% of the whole dataset), we applied multiple imputations to those untested VV values.

### **Clinical profile as a function of BAG**

Tables 3 shows that Pushers differed from Tilters only by more severe spatial neglect, and that most clinical deficits were more severe in Tilters than in upright individuals (except aphasia and apraxia).

Ordinal regression of clinical deficits on the three categories of BAG revealed that only spatial neglect and weakness were independently associated with lateropulsion. The model was sound (likelihood: $X^2=160.1$ ,  $p < 0.001$ ), without interaction between the two variables (parallel test: $X^2=2.9$ ,  $p=0.561$ ), and explained much information on the orientation of the body against gravity (Nagelkerke:  $R^2=0.66$ ). Spatial neglect was the strongest determinant of lateropulsion (severe spatial neglect: OR=15.4, 95%CI [4.5;52.3],  $p < 0.001$ ; moderate spatial neglect: OR=5.1, 95%CI [1.8;14.6],  $p=0.002$ ). Severe weakness was a secondary determinant of lateropulsion (OR=5.6, 95%CI [2;15.6],  $p=0.001$ ).

**Table 3: Clinical deficits as a function of behaviors against gravity**

	All (n=220)	Upright (n=158)	Tilter (n=32)	Pusher (n=30)	Omnibus test	Group comparisons <sup>a</sup>		
						Upright vs Tilters	Upright vs Pushers	Tilters vs Pushers
<b>Spatial neglect</b>								
No or light	120 (55%)	120 (77%)	0	0				
Moderate	54 (25%)	35 (22%)	16 (50%)	3 (10%)	v=0.45 p<0.001	v=0.5 p<0.001	v=0.59 p<0.001	v=0.3 p<0.001
Severe	44 (20%)	1 (1%)	16 (50%)	27 (90%)				
<b>Aphasia, yes</b>	89 (41%)	70 (44%)	13 (41%)	6 (20%)	v=0.16 p=0.003	v=0.09 p=0.702	v=0.18 p=0.009	v=0.22 p=0.078
<b>Apraxia, yes</b>	46 (21%)	28 (18%)	6 (19%)	12 (40%)	v=0.13 p=0.028	v=0.01 p=0.952	v=0.19 p=0.009	v=0.24 p=0.066
<b>Weakness</b>								
Light	109 (50%)	106 (67%)	3 (9%)	0				
Moderate	61 (28%)	44 (28%)	10 (31%)	7 (23%)	v=0.36 p<0.001	v=0.39 p<0.001	v=0.47 p<0.001	v=0.17 p=0.18
Severe	50 (23%)	8 (5%)	19 (59%)	23 (77%)				
<b>Spasticity, yes</b>	64 (29%)	25 (16%)	18 (56%)	21 (70%)	v=0.33 p<0.001	v=0.36 p<0.001	v=0.47 p<0.001	v=0.14 p=0.263
<b>Hypoesthesia</b>								
No or light	57 (26%)	55 (35%)	2 (6%)	0				
Moderate	103 (47%)	85 (54%)	12 (38%)	6 (20%)	v=0.3 p<0.001	v=0.31 p<0.001	v=0.43 p<0.001	v=0.19 p=0.088
Severe	60 (27%)	18 (11%)	18 (56%)	24 (80%)				
<b>Hemianopia, yes</b>	73 (33%)	34 (22%)	19 (59%)	20 (67%)	v=0.29 p<0.001	v=0.31 p<0.001	v=0.36 p<0.001	v=0.08 p=0.553
<b>Depression, yes</b>	124 (59%)	77 (51%)	25 (81%)	22 (73%)	v=0.17 p=0.002	v=0.22 p=0.003	v=0.16 p=0.027	v=0.09 p=0.497

Data are n (%).r= effect size of the Mann-Whitney test. v=effect size of the Chi-square test. The values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both the Mann-Whitney test U and 2\*2 chi-square test. For the 2\*3 chi-square test, effect sizes of 0.07, 0.21, and 0.35 represent small, medium, and large effect, respectively. For the 3\*3 chi-square test, effect sizes of 0.05, 0.15, and 0.25 represent small, medium, and large effect, respectively.

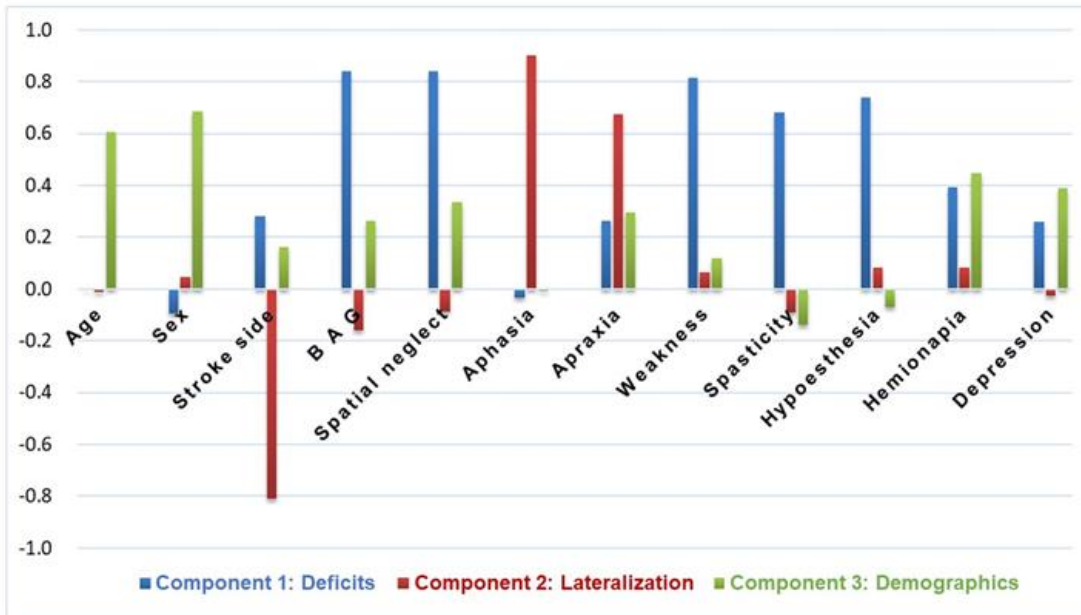
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<sup>a</sup>The significant P values for group comparisons were adjusted to 0.013 (0.05/4) owing to multiple comparisons.

Missing data: spatial neglect (n=2), apraxia (n=5), hemianopia (n=1), depression (n=9).

### **Relationship between lateropulsion and spatial neglect**

We first ran a principal component analysis with main demographics, stroke side, and all deficits including BAG. This dataset was organized in three components corresponding to: demographics, brain lateralization supporting functions, and deficits per se. Figure 2 shows their contribution to each variable, pointing out a similarity in the construction of lateropulsion and spatial neglect, both sharing similar levels of components.



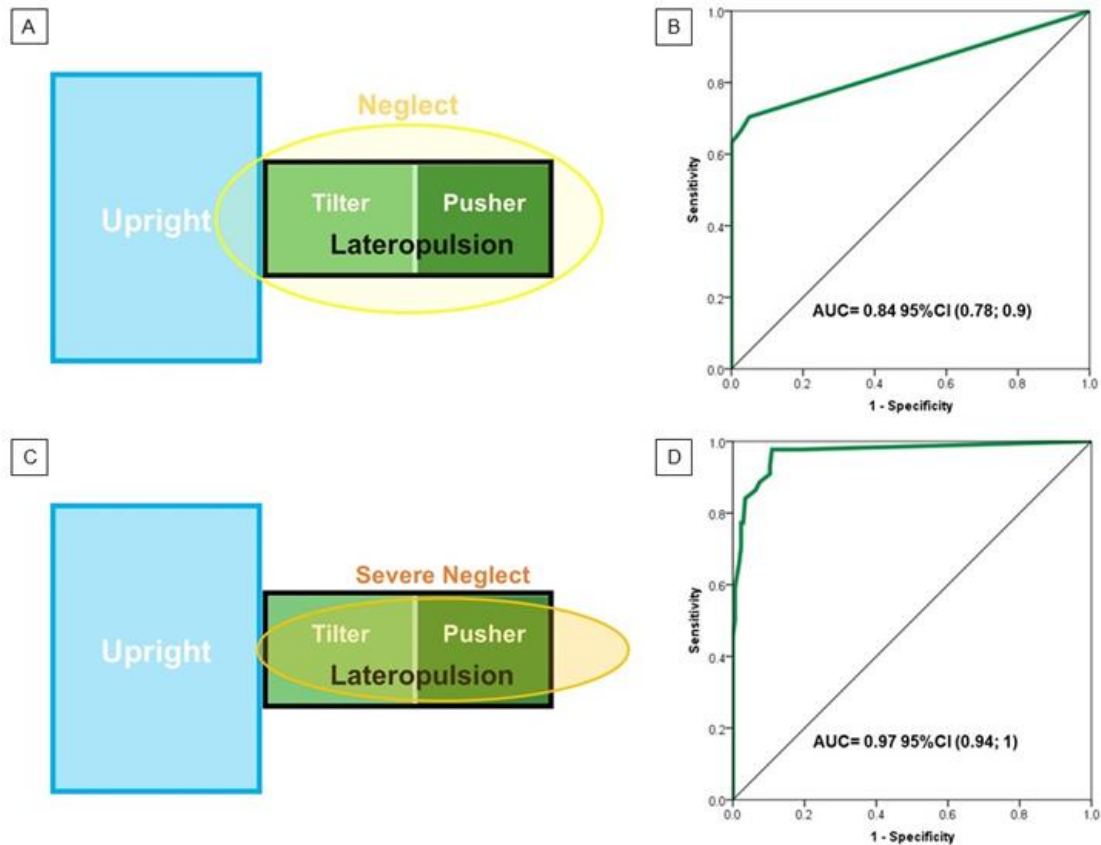
**Figure 2. Factorial analysis of clinical and demographic features**

The 12 features that comprehensively described the 220 individuals of the study were analyzed by factorial analysis. This figure displays how every feature analyzed is determined by the three components resulting from the factorial analysis: demographics in green, deficits in blue, and brain lateralization in red. Behavior against gravity (BAG) and spatial neglect have similar clinical profiles in terms of demographics, deficits, and brain lateralization.

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Contingency analyses displayed in Table 3 show that spatial neglect was found in 23% of upright individuals but in 100% of Tilters and Pushers. Severe spatial neglect was found in 90% of Pushers but only 1% of upright individuals. Conversely, lateropulsion prevalence increased with spatial neglect: 0% if no neglect, 35% with moderate neglect, and 98% with severe neglect. Figure 3A and 3C schematize how lateropulsion was nested in spatial neglect.

Finally, we plotted ROC curve analyses (Figures 3B and 3D). SCP scores predicted spatial neglect (moderate or severe, with high AUC (0.84; 95%CI [0.78;0.9],  $p < 0.001$ ), for a cut-off of 0.25 (sensitivity 0.7, specificity 0.95, positive 0.94 and negative 0.75 predictive values). Hence, individuals with a net lateral body tilt in standing or sitting, even without risk of falling (Karnath *et al.*, 2000), had a 94% probability (95%CI [88;97]) of showing spatial neglect. SCP scores also predicted severe spatial neglect with high AUC (0.97; 95%CI [0.94;1],  $p < 0.001$ ), for a cut-off of 0.75 (sensitivity 0.98, specificity 0.89, positive 0.68 and negative 0.99 predictive values).



**Figure 3. Association of behavior against gravity (BAG) and spatial neglect**

A) Venn diagram of the relationship between BAG and spatial neglect (moderate or severe). All Tilters and Pushers had spatial neglect, and a few upright individuals had spatial neglect. B) Receiver operating characteristic (ROC) curve predicting spatial neglect (moderate or severe) from the Scale for Contraversive Pushing (SCP). C) Venn diagram of the relationship between BAG and severe spatial neglect. Almost all Pushers (90%) had a severe spatial neglect. D) ROC curve predicting severe spatial neglect from the Scale for Contraversive Pushing (SCP).

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## Discussion

Our study is the first to analyze the three signs of the contralesional lateropulsion in a large series of individuals examined after a hemisphere stroke, in parallel with careful assessments of verticality perception and spatial neglect. We hypothesized that the three signs of contralesional lateropulsion represent a same dimension corresponding to an impaired orientation of the body against gravity in relation to an altered graviception. We also addressed the issue that lateropulsion might be considered a form of spatial neglect bearing on graviception.

Resistance and pushing were almost constantly associated with lateral body tilt, which was present in 99% of individuals showing at least one sign and also could be found in isolation. Factorial analysis showed that the three signs represented a same dimension, lateral body tilt having the highest factor loading (0.98). All together, these results demonstrate that lateropulsion is an entity consisting of three postural components, lateral body tilt being the cardinal sign of an impaired body orientation against gravity.

Group comparisons and factorial analysis demonstrated that contralesional VV biases and contralesional lateropulsion were two inseparable criteria referring to the vertical orientation, one dealing with graviception (VV) and the other being a postural behavior aiming to orientate the body against gravity. Hence, lateropulsion is a way to adjust the body orientation in the roll plane to a wrong reference of verticality. Ipsilesional VV biases were not negligible, found overall in upright individuals and in some Tilters.

Multivariate, factorial, contingency, and prediction analyses clearly showed similarities between lateropulsion and spatial neglect, the latter encompassing the former.



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### **Need to clarify terminology**

Lateropulsion was first described by Babinski and Nageotte in the early 1900s (Babinski and Nageotte, 1902), as a lateral body tilt caused by ipsilateral low-brainstem lesions (details in companion paper (Dai *et al.*, 2021)). Lateropulsion was then described after contralateral hemisphere lesions, with several additional signs not clearly delineated, until the pusher syndrome definition by Davies (Davies, 1985). The term “syndrome” introduced the idea of a singular behavior. Progressively pushing and resistance became predominant in the literature, leading to a search for their origin in motor and tone disorders. In fact, in our study, we found that only severe motor weakness played a role, in agreement with previous studies (Danells *et al.*, 2004). Weakness does not trigger the body tilt but intervenes in magnifying it. Spasticity and apraxia did not play any role in our study, so lateropulsion is not plausibly elicited by a peculiar movement disorder.

In contrast, we show that Pushers and Tilters responded to a gradient of severity found not only for the three postural signs (lateral body tilt, pushing, resistance) but also for VV and spatial neglect. We demonstrate that Tilters and Pushers belong to the same entity, which may be called lateropulsion, with lateral body tilt as a cardinal sign of an impaired body orientation against gravity. This finding confirms the assumption made two decades ago that the term lateropulsion could encompass all three signs (D'Aquila *et al.*, 2004; Babyar *et al.*, 2007; Babyar *et al.*, 2009; Babyar *et al.*, 2015; Koter *et al.*, 2017; Babyar *et al.*, 2019). By showing that a contralesional body tilt or even pushing may be isolated and that the three signs are not always associated, our study provides a unified view of the different terminologies. We suggest that together or in isolation, these signs constitute lateropulsion. Another argument for using the term lateropulsion is the analogy with the term retropulsion, also related to a bias in verticality perception, this time backward in the pitch plane (Manckoundia *et al.*, 2007). In our study, Pushers were diagnosed according to the original criteria (Karnath *et al.*, 2000), focused on

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most severe forms of lateropulsion, as attested by a median SCP score of 4.8 (maximum 6) and severe disability (median FIM score 45/126). They represented 14% of the series, which corresponds to the literature (Pedersen *et al.*, 1996; Abe *et al.*, 2012) and hence allows for generalizing our findings. These individuals are known to not recover well (Pedersen *et al.*, 1996; Danells *et al.*, 2004; Abe *et al.*, 2012; Babyar *et al.*, 2015) and are those who do not benefit most from intensive rehabilitation. We recommend no longer focusing on pusher syndrome, the tree that “hides the forest”.

### **Lateropulsion is caused by an impaired graviception**

Our study shows that contralesional VV biases and contralesional lateropulsion are two inseparable criteria referring to a same dimension, the vertical orientation. VV is a physiological measure testing graviception (Gresty *et al.*, 1992; Piscicelli and Pérennou, 2017) and lateropulsion is a postural behavior leading to orientate the body against gravity. The frequency and magnitude of contralesional VV biases increased as a function of lateropulsion severity, which cannot be just a question of co-occurrence. The procedure to test VV excludes that VV biases result from an abnormal BAG. The only possibility is that abnormal lateropulsion is secondary to an impaired graviception, quantified by contralesional VV biases. The three lateropulsion signs constitute a way to adjust the body orientation in the roll plane to a wrong reference of verticality. Stroke often affects core structures involved in construction of the internal modal of verticality (Dieterich and Brandt, 1993; Brandt *et al.*, 1994; Barra *et al.*, 2010; Baier *et al.*, 2016; Brandt and Dieterich, 2019; Dieterich and Brandt, 2019; Lemaire *et al.*, (in-press 2021)) leading to lateropulsion (Babyar *et al.*, 2019). This novel finding supported by a factorial analysis, goes beyond studies having shown that lateropulsion is the rule in individuals with an abnormal contralesional VV tilt (Johannsen *et al.*, 2006; Pérennou *et al.*, 2008; Baier *et al.*, 2011). However, the VV factor loading was less high than for lateropulsion signs. We

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assume that this is likely due to some ipsilesional VV biases, dealing with something else than verticality (see below).

Our current study and the previous one (Pérennou *et al.*, 2008) (same testing) included 97 patients showing lateropulsion. The magnitude of their contralesional VV biases, which increased with lateropulsion severity, was twice greater than that found in two series of Pushers tested early (Johannsen *et al.*, 2006; Baier *et al.*, 2011). Conversely, they occasionally showed normal (10/97, 10%) and ipsilesional (9/97, 9%) VV. This clear pattern obtained in almost 100 patients contradict studies claiming that normal VV is the rule in Pushers (Karnath *et al.*, 2000; Bergmann *et al.*, 2018; Fukata *et al.*, 2020). Such discrepancies might have been marred by technical differences in VV tests (Piscicelli and Pérennou, 2017), concerning settings, procedures, number of trials, parameters, and eventually level of training of examiners. The reliability of VV tests in stroke individuals strongly depends on the quality of procedures (Piscicelli *et al.*, 2015a; Piscicelli *et al.*, 2015b; Piscicelli *et al.*, 2016; Piscicelli and Pérennou, 2017). As recommended by experts when VV tests entered the clinic (Gresty *et al.*, 1992; Brandt *et al.*, 1994; Anastasopoulos *et al.*, 1997), we test VV in a black room in complete darkness, without any visual clues. This is not the case for all studies. We install individuals in a device maintaining the head and trunk upright during the test. Together with the number of trials considered sufficient (Piscicelli *et al.*, 2015b), this procedure led to robust data, as attested by a satisfactory within-subject variability (Barra *et al.*, 2010; Barra *et al.*, 2012). Results are less reliable otherwise in Pushers (Piscicelli *et al.*, 2016). However, these constraints do not allow for testing all patients. In addition to participants who had medical complications, 33 (15%) had not been able to complete the VV test because of the procedure: inability to remain sitting in the apparatus 20 min, lost in darkness (8%) or severe aphasia (7%). Conditions were met to perform multiple imputations and we conducted analysis with complete VV data.

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Ipsilesional VV biases may be somewhat frequent after some hemisphere strokes (9-21%) (Dieterich and Brandt, 1993; Brandt *et al.*, 1994; Pérennou *et al.*, 2008; Baier *et al.*, 2016; Piscicelli *et al.*, 2016; Fukata *et al.*, 2020), especially after inferior and median thalamic lesions (Baier *et al.*, 2016). Of note, five individuals in our series had an ipsilesional VV bias despite a contralesional body tilt. All had relatively limited lesions encroaching the basal ganglia: two the thalamus, totally (7.9°) or small posterior part (2.6°), and three the putamen, with internal and medial temporal lobe (9.8°), with adjacent insula (5.1°), or caudate nuclei (4.6°). The pathophysiology of these puzzling ipsilesional VV biases remains to be elucidated. They are not associated with a vestibulo-ocular sign (Baier *et al.*, 2016), which argues against an ipsiversive cyclo-ocular torsion and furthermore are not so frequent after hemisphere stroke (Brandt *et al.*, 1994). Anatomical and functional imaging studies of the vestibular network in normal individuals and patients have revealed complex ipsilateral and contralateral vestibular pathways running from both vestibular nuclei to both parieto-insular junctions, one bypassing the thalamus (Baier *et al.*, 2016; Dieterich and Brandt, 2019). Depending on the precise lesion location, VV tilts might be contralesional or ipsilesional (Dieterich and Brandt, 1993; Baier *et al.*, 2016; Dieterich and Brandt, 2019), which would explain the frequency of both modalities. However, this interpretation does not take into account the lack of ipsilesional bias when the lesion damages somaesthetic graviception (Pérennou *et al.*, 2008) nor the different functional impact of ipsi-contralesional VV tilts discovered in our study. Indeed, individuals with ipsilesional VV biases (many of low magnitude) were mostly upright, sometimes Tilters, rarely Pushers. None had an ipsilesional lateropulsion.

When discarding ipsilesional VV biases, we found a strong parallel severity gradient between VV biases and BAG, with a huge VV increment between groups: upright individuals, median -0.6°; Tilters, -2.9°; Pushers, -12.3°. This association was much greater than that previously reported without discarding ipsilesional VV biases (Pérennou *et al.*, 2008). With this

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precaution, the VV test would become relevant to guide and monitor a specific rehabilitation of the sense of upright after stroke, by detecting and quantifying contralesional biases in the internal model of verticality. Since we showed that contralesional VV tilts represent a biased verticality representation, it was not necessary to analyze other modalities of verticality perception. Data obtained with a visuo-haptic test must be interpreted with caution, Pushers being inclined to push the rod away, which may induce some ipsilesional tilts (Saj *et al.*, 2005). The literature reports opposite results for the postural vertical (PV) (Karnath *et al.*, 2000; Pérennou *et al.*, 2008), and in our experience VV is much easier to test than PV.

### **Graviceptive neglect?**

In addition to pusher syndrome, the clinical picture described by Davies (Davies, 1985) comprised signs of spatial neglect (not explicitly termed). Since then, spatial neglect has been repeatedly found in series investigating lateropulsion, reaching even 100% prevalence in several studies by several groups (Karnath *et al.*, 2000; Pérennou *et al.*, 2002; Vaes *et al.*, 2015).

With a battery of six well-validated tests assessing body and non-body neglect (with an ad-hoc grouping in three categories) and by means of complementary analyses (multivariate, factorial, contingency, prediction), we clearly showed similarities between lateropulsion and spatial neglect, the latter encompassing the former.

Both are deficits of spatial cognition. Lateropulsion is a deficit of active body orientation with respect to gravity, expressed in the roll plane by a tilt with respect to the vertical axis. Spatial neglect is a deficit of spatial representation/attention mainly expressed in the horizontal plane by a right/left deviation. How can one link these two forms of impaired spatial cognition, one referring to straight above in a frontal plane (lateropulsion) and the other straight ahead in the horizontal plane (spatial neglect)? The strong similarity we congruently found between

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lateropulsion and spatial neglect suggests that some areas, when damaged, simultaneously induce both behaviors (Pérennou, 2006). They might be centered on the multimodal thalamo-cortical network coding space in three dimensions and often viewed as the vestibular cortex (Kerkhoff, 1999; Brandt and Dieterich, 2019). Because we demonstrated that the postural behavior leading to an impaired body orientation against gravity (lateropulsion) was inseparable from a physiological measure testing graviception (VV), lateropulsion might correspond to a kind of graviceptive neglect, bearing on vestibular and somesthetic graviception (Karnath and Dieterich, 2006; Pérennou, 2006). Rather than using a mosaic of 2-D representations (Chen *et al.*, 2013; Finkelstein *et al.*, 2016), the human brain might use 3-D maps (Chen *et al.*, 2013; Finkelstein *et al.*, 2016) involving the internal model of verticality.

We found that spatial neglect encompassed lateropulsion. This may be explained by the fact that spatial neglect is not solely the consequence of a distorted spatial referential but also relies on other components such as attentional bias, impaired disengagement of attention, or defective arousal (Bartolomeo *et al.*, 2012), which contribute to altering clinical test results (Rode *et al.*, 2017).

The association of lateropulsion and spatial neglect raises the question of the right hemisphere predominance for both deficits. In our companion paper (Dai *et al.*, 2021), we show that the ratio of the lateropulsion prevalence between right and left hemisphere stroke increases with time since stroke. A similar pattern is well known for spatial neglect (Stone *et al.*, 1991), which is another similarity between both deficits.

### **Study limitations**

Karnath and Broetz (Karnath *et al.*, 2000) invented the SCP to diagnose PS, and lateropulsion assessment with this scale may be considered as a limitation. Our study shows that the original

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criteria are not relevant to constitute two groups: Pushers versus non-Pushers (Karnath *et al.*, 2000). This would categorize as non-Pushers many individuals associating lateral body tilt, resistance and pushing to various degrees. To not overlook individuals with moderate lateropulsion, we used the SCP beyond its initial objective and constituted three BAG groups, as previously advocated (Pérennou *et al.*, 2008; Dai *et al.*, 2021). The appropriateness of this approach is again confirmed by our study. The novelty is the demonstration that the SCP is uni-dimensional, referring to body orientation with respect to gravity. This property allows for using the SCP to quantify lateropulsion.

A second limitation concerns VV data. We did not examine ocular torsion and therefore cannot exclude that some VV tests might have under- or over-estimated the part played by verticality representation. If any, this error should be weak given the substantial magnitude of contralesional tilts we found and the low prevalence of ocular torsions after hemisphere stroke (Brandt *et al.*, 1994). In 15% of individuals, the VV test could not be completed because of the procedure. Multiple imputation giving a complete data set comprising some estimated values confirmed the results obtained with measured data. However, this diminishes the generalizability of the study, which will need an external validity.

In most European countries, as in our practice, only one third of individuals admitted in stroke units are then referred to rehabilitation (Schnitzler *et al.*, 2013). Lateropulsion is a major rehabilitation challenge, so it is important that our findings be generalized to the rehabilitation context.

## **Conclusion**

Our study shows that lateral body tilt, resistance and pushing effectively constitute an entity, better termed lateropulsion than pusher syndrome. Body tilt is its cardinal sign. Contralesional VV biases and contralesional lateropulsion are two inseparable criteria referring to the vertical

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orientation, one dealing with graviception (VV) and the other being a postural behavior aiming to orientate the body against gravity. Ipsilesional VV biases were not negligible, found overall in upright individuals and in some Tilters. Weakness played a minor role in magnifying the lateropulsion, without triggering it. Several analyses congruently found similarities between lateropulsion and spatial neglect. Spatial neglect encompasses lateropulsion, which might be considered a form of spatial neglect, bearing on graviceptive information (graviceptive neglect). Overall, these findings suggest that the human brain uses 3-D maps involving the internal model of verticality and not just a mosaic of 2-D representations.

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### **Appendix Authors**

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Shenhao Dai, MD	Grenoble Alpes University Hospital, France	Author	Analyzed and interpreted the data; drafted the manuscript for intellectual content
Céline Piscicelli, PhD	Grenoble Alpes University Hospital, France	Author	Acquisition of data; revised the manuscript for intellectual content



Emmanuelle Clarac, PT	Grenoble Alpes University Hospital, France	Author	Acquisition of data; material support
Monica Baciuc, MD, PhD	Grenoble Alpes university, France	Author	Revised the manuscript for intellectual content
Marc Hommel, MD, PhD	Grenoble Alpes university, France	Author	Interpreted the data; revised the manuscript for intellectual content
Dominic Pérennou, MD, PhD	Grenoble Alpes University Hospital, France	Author	Design and conceptualized study; study supervision; interpreted the data; drafted the manuscript for intellectual content; obtaining funding

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➤ **Chapter 6: Balance, lateropulsion and gait disorders in subacute stroke**

The current theoretical model of balance control involves two domains, devoted to body orientation with respect to gravity and to body stabilization with respect to the base of support. Balance disorders that are among the most devastating sequelae after stroke might be conceptualized this way. The novelty of our paper is to investigate the part played by body orientation with respect to gravity (lateropulsion) in post-stroke balance and gait disorders. This paper is published in *Neurology* (Volume 96, Number 17, April 27, 2021, DOI: 10.1212/WNL.00000000000011152).

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## Balance, lateropulsion, and gait disorders in subacute stroke

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## Abstract

**Objective** To test the hypothesis that the impaired body orientation with respect to gravity (lateropulsion) would play a key role in post-stroke balance and gait disorders.

**Methods** Cohort study of 220 individuals consecutively admitted to a neurorehabilitation ward after a first hemisphere stroke (Cohort DOBRAS 2012-2018, ClinicalTrials.gov: NCT03203109), with clinical data systematically collected at 1 month, then at discharge. Primary outcomes were balance and gait disorders, quantified by the Postural Assessment Scale for Stroke (PASS) and the modified Fugl-Meyer Gait Assessment (mFMA), to be explained by all deficits on day 30, including lateropulsion assessed with the Scale for Contraversive Pushing (SCP). Statistics comprised linear regression analysis, uni- and multivariate analyses, and receiver operating characteristic curves.

**Results** Lateropulsion was frequent, especially after right hemisphere stroke (RHS, D30, 48%; discharge 24%), almost always in right-handers. Among all deficits, impaired body orientation (lateropulsion) had the most detrimental effect on balance and gait. After RHS, balance disorders were proportional to lateropulsion severity, which alone explained almost all balance disorders at initial assessment (90%; 95% confidence interval [CI] [86–94],  $p < 0.001$ ) and at discharge (92%, 95%CI [89–95],  $p < 0.001$ ) and also the greatest part of gait disorders at initial assessment (66%, 95%CI [56–77],  $p < 0.001$ ) and at discharge (68%, 95%CI [57–78],  $p < 0.001$ ).

**Conclusions** Lateropulsion is the primary factor altering post-stroke balance and gait at the subacute stage and therefore should be systematically assessed. Post-stroke balance and gait rehabilitation should incorporate techniques devoted to misorientation with respect to gravity.

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## Introduction

The current theoretical model of balance control involves two domains, devoted to body orientation with respect to gravity and to body stabilization with respect to the base of support (Massion, 1992; Horak and Macpherson, 2011). This model might help in better understanding balance disorders in the clinic, in order to guide their rehabilitation. It could be especially useful after stroke (Pérennou, 2006; Pérennou *et al.*, 2008) owing to the devastating sequelae (Winstein *et al.*, 2016) induced by balance disorders, which may be explained in terms of impaired body orientation or stabilization.

As early as 1900, cases of brain stem (Babinski and Nageotte, 1902) or hemisphere (Beevor, 1909) stroke showing a lateral body tilt with fall tendency were described and initially termed lateropulsion (Babinski and Nageotte, 1902), then variously according to authors' consideration for additional postural signs and lesion location. Most known terms are listing phenomenon (Bohannon *et al.*, 1986), thalamic astasia (Masdeu and Gorelick, 1988; Brandt and Dieterich, 2017), ease of falling (Fisher, 1982; Awerbuch and Labadie, 1989), pusher/pushing syndrome/behavior (Davies, 1985; Pedersen *et al.*, 1996; Karnath *et al.*, 2000; Danells *et al.*, 2004; Pérennou *et al.*, 2008; Brandt and Dieterich, 2017; Bergmann *et al.*, 2018), and biased behavioral vertical (Pérennou *et al.*, 1998). Here we adopt "lateropulsion", the most frequently used (Babinski and Nageotte, 1902; D'Aquila *et al.*, 2004; Thomke *et al.*, 2005; Pérennou *et al.*, 2008; Babyar *et al.*, 2009; Babyar *et al.*, 2015; Koter *et al.*, 2017; Yun *et al.*, 2018; Babyar *et al.*, 2019).

Lateropulsion interpretation has long erred across mechanisms involving cerebellar and motor pathways. Today, lateropulsion is considered to have a vestibular origin with different mechanisms depending on lesion location (Pérennou *et al.*, 2008; Brandt and Dieterich, 2017; Brandt and Dieterich, 2019). After low-brainstem lesions, lateropulsion is ipsilesional and

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mainly secondary to vestibulospinal disorders, inducing an asymmetric tone with a co-occurrence of vestibulo-ocular signs (Bronstein *et al.*, 2003; Thomke *et al.*, 2005; Pérennou *et al.*, 2008). After hemispheric lesion, lateropulsion is contralesional, owing to an internal model of verticality tilted to the contralesional side (opposite the stroke) (Brandt *et al.*, 1994; Pérennou *et al.*, 2008). Individuals align their body onto this erroneous reference of verticality (Brandt *et al.*, 1994; Pérennou *et al.*, 1998; Pérennou *et al.*, 2008), possibly in relation to a damaged multimodal network (Brandt and Dieterich, 2019). At the beginning, individuals are unaware of the latéropulsion (Fisher, 1982; Awerbuch and Labadie, 1989), which strengthens the interpretation of a biased internal model of verticality (Pérennou *et al.*, 2008; Barra *et al.*, 2010).

Severe cases of lateropulsion jeopardize the ability to walk, stand, or even sit (Davies, 1985; Masdeu and Gorelick, 1988; Thomke *et al.*, 2005; Bergmann *et al.*, 2018; Bergmann *et al.*, 2019), with poor recovery (Pedersen *et al.*, 1996; Danells *et al.*, 2004; Abe *et al.*, 2012; Babyar *et al.*, 2015). Beyond these extreme forms, which represent only 10% (Pedersen *et al.*, 1996; Abe *et al.*, 2012), the effect of lateropulsion on balance abilities has been little investigated. A few cross-sectional studies of limited sample size have ancillary reported a moderate correlation between lateropulsion indices and balance abilities (Benaim *et al.*, 1999; Bergmann *et al.*, 2019). To our knowledge, the effect of lateropulsion on balance capacity after stroke has never been investigated longitudinally in a large series. Our main hypothesis was that even mild forms of lateropulsion represent a key determinant of post-stroke balance disorders. Indeed, any lateral body tilt generates a destabilizing effect of gravity, with a projection of the center of mass on the ground moving toward the limit of the base of support, which alters balance capacities.

For post-stroke gait disorders, a common view is that they are mostly caused by sensorimotor deficits such as weakness (Nonnekes *et al.*, 2018), muscular overactivity and neuro-orthopedic complication of spasticity (Gracies *et al.*, 2017; Nonnekes *et al.*, 2018), with an additional

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detrimental role of balance disorders (Huang *et al.*, 2016; Fulk *et al.*, 2017). We hypothesized that mild forms of lateropulsion also greatly affect gait abilities.

## Methods

### Study design

This was a monocentric observational study of the DOBRAS cohort (Determinants of Balance Recovery After Stroke; NCT03203109). Participants were comprehensively assessed twice in routine care, initially in the first weeks after entry in the rehabilitation ward, then at discharge.

We assessed balance and gait abilities as well as sensory, motor, and cognitive deficits. Assessments were performed by trained and multidisciplinary examiners, with blinding to the study hypothesis. The sample size was planned to conduct multivariate analyses in a large series of individuals ( $\geq 200$  observations).

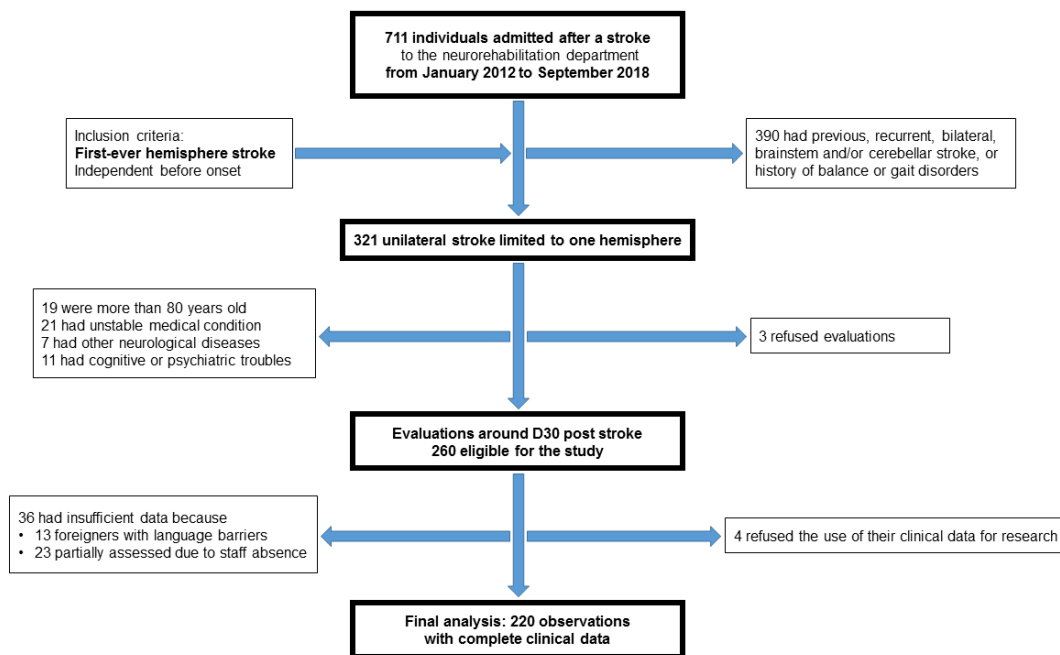
### Standard protocol approvals, registrations, and patient consents

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.

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## **Participants**

From January 2012 to September 2018, we included 220 consecutive individuals (Figure 1). Inclusion criteria were age  $\geq$  18 to 80 years and a first-ever unilateral stroke limited to one hemisphere (right hemisphere stroke [RHS]; left hemisphere stroke [LHS]). Exclusion criteria were recurrent stroke; complication at the acute stage (malignant infarct, cerebral herniation, subarachnoid hemorrhage, and hydrocephalus); dementia; previous disability interfering with balance, gait or vestibular disorders; unstable medical condition or psychiatric problems; and not French speaking. These conditions were obtained from the hospital electronic file describing the history of every patient, by interviewing patients and relatives, and by a systematic clinical examination. They followed a personalized rehabilitation program, taking into account deficits and activity limitations. According to their abilities, individuals had 2 physiotherapy and 1 occupational therapy sessions per day (total 1h30), plus, if needed, sessions with speech therapist, neuropsychologist, psychologist, or orthoptist.



**Figure 1. Flow of participants in the study**

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## Assessments

We conducted the initial assessments at about day 30 after stroke (D30) with a window of 3 days before and after to start and complete assessments. This date is a compromise between the desire to collect data as early as possible after the stroke and the need for sufficient medical stability and attentional resources to afford a battery of comprehensive assessments performed during several days, at a time when almost all individuals have been admitted to the rehabilitation ward. Among the 220 participants, 207 (94%) were admitted during the first month post-stroke and so were assessed on D30. For the 13 others admitted after D30 (6%), the initial assessment was also performed in due time, on day 60 (D60, window of 3 days before and after). These initial assessments collected information about handedness, all deficits, postural and gait disorders, and disability. All variables collected are listed below. The second assessment was performed at discharge and only focused on postural and gait disorders.

Global disability was estimated by the modified Rankin Scale (mRS).

Handedness before stroke was assessed by interview (patient, relatives) by using a French translation of the Edinburgh inventory. Right-handedness was considered with a score  $>0.4$ .

To assess body orientation with respect to gravity in the frontal plane, we used the Scale for Contraversive Pushing (SCP) (Karnath *et al.*, 2000). The SCP assesses the three components of the pusher syndrome defined by Davies (Davies, 1985), that is, contralesional lateral body tilt (while sitting and standing), active pushing of the unaffected arm or leg to the contralesional side (while sitting and standing), and resistance to passive correction of posture (while sitting and standing). The total score ranges from 0 to 6. As defined in the original paper (Karnath *et al.*, 2000), individuals who met these three criteria with at least 1 point for each were considered pushers. As proposed previously (Pérennou *et al.*, 2008), we also used the SCP to differentiate individuals with an upright posture from those who were mildly tilted. To be conservative, we used the same SCP cut-off  $> 0.5$  as in a previous paper (Pérennou *et al.*, 2008), which classifies



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as Lw/oP, according to the SCP scoring, only individuals who showed net lateral body tilt at least in one posture, sitting or standing, but without pushing or resistance. So constituted, the three groups corresponded to individuals differently oriented with respect to gravity: individuals upright were correctly oriented, individuals showing Lw/oP presented a moderate deficit in orientation with respect to gravity, and pushers presented a severe deficit in orientation with respect to gravity. We also used SCP scores to test relationships with balance and gait scores. Details on the validity of these approaches are given in the section “study limitations”.

Balance disorders were assessed with the Postural Assessment Scale for Stroke (PASS) (Benaim *et al.*, 1999), the most appropriate balance scale at the subacute stage after stroke (Mao *et al.*, 2002; Persson *et al.*, 2013). The total score ranges from 0 to 36 (satisfactory balance), and a score  $\geq 28$  indicates the ability to stand independently without any help (Benaim *et al.*, 1999).

Gait disorders were assessed with the modified chart of the Fugl-Meyer Assessment (mFMA), designed to classify post-stroke gait with 7 levels of mobility (Lindmark and Hamrin, 1988). The mFMA ranges from 0 (no mobility) to 6 (normal gait), and a score  $\geq 5$  indicates the ability to walk independently without a cane (or rollator).

Deficits were assessed by means of a comprehensive battery of tests investigating: Spatial neglect (body and non-body domains) was assessed with a battery of 6 tests: ecological Catherine Bergego Scale (Beis *et al.*, 2004), thumb finding (Beis *et al.*, 2004), Fluff (since 2014) (Cocchini *et al.*, 2001) and Bells tests (Beis *et al.*, 2004), line bisection (Beis *et al.*, 2004), and drawing copy (Beis *et al.*, 2004). The Catherine Bergego Scale result was considered normal with score  $< 2$ , moderately altered with score  $\geq 2$ , and markedly altered with score  $\geq 15$ . The thumb finding test result was considered abnormal with score  $> 0$ . The Fluff test result was considered normal with  $\geq 13$  targets detached, moderately altered with  $\geq 9$  targets detached,

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and markedly altered with  $< 9$  targets detached. The Bells test result was considered normal with  $\leq 6$  omissions, moderately altered with  $\leq 15$  omissions, and markedly altered with  $> 15$  omissions. The line bisection (20 mm) result was considered normal at  $\leq 7$  mm, moderately altered at  $\leq 10$  mm, and markedly altered at  $> 10$  mm. The Gainotti copy result was considered abnormal if  $> 0$  omissions. A few individuals with severe comprehension (aphasia) or executive troubles were not able to complete the whole neglect battery but had to perform at least three tests to not be considered with missing data. Spatial neglect was considered absent if all test results were normal or slight if only one test result was marginally altered, severe with results of least two tests markedly altered (altered if binary categorized), or moderate otherwise.

The presence of aphasia was evaluated by the gravity section of Boston Diagnostic Aphasia Examination; a score  $< 5$  was considered aphasia. Apraxia was assessed by the Apraxia Screen of Tulia (AST) (Vanbellinghen *et al.*, 2011) and participants with a score  $< 9$  had a diagnosis of upper-limb apraxia.

Motor weakness was assessed by a standardized examination of muscle strength adapted for participants with central neurological disorders (Pérennou *et al.*, 1998; Benaim *et al.*, 1999). Eight muscle groups of both the upper and lower limb were tested, and the final score was then adjusted to range from 0 to 80 (normal strength). Light weakness was considered a score  $> 64/80$  (every muscle had a motor command of  $4/5$ , on average), severe weakness a score  $\leq 32$  (every muscle had a motor command of  $\leq 2/5$ , on average), and moderate weakness otherwise. Spasticity was assessed with the Ashworth Scale (Pérennou *et al.*, 1998; Benaim *et al.*, 1999). Five muscle groups of both the upper and lower limb were tested, and the final score was adjusted to range from 0 to 40 (extremely severe and diffused spasticity). Participants were classified as follows in terms of spasticity: no or light (0-4), moderate or severe ( $> 4$ ).

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Hypoesthesia was manually tested on both contralesional upper and lower limbs by trained physicians who assessed tactile and pain sensibility (Pérennou *et al.*, 1998; Benaim *et al.*, 1999). Participants were classified as having no or light hypoesthesia if errors were seldom, moderate hypoesthesia if detection errors were frequent, and deep hypoesthesia if they did not perceive any stimuli. Hemianopia was manually tested by trained physicians.

Depression was assessed by the Aphasia Depression Rating Scale (Benaim *et al.*, 2004); participants with scores > 8 were considered depressed.

### **Statistical analysis**

Continuous data are presented as median with interquartile range (Q1–Q3) and dichotomized and categorical data as number (%). When useful, 95% confidence intervals (CIs) are given.

Data for upright, Lw/oP, and pusher groups were compared by the Mann-Whitney U-test or chi-square test (Fisher exact test). Effect sizes were calculated by using the Z values of the Mann-Whitney test,  $r = Z/\sqrt{n}$ , and the  $X^2$  of the chi-square test,  $v = \sqrt{(X^2/n * \text{degree of freedom})}$ . With  $p < 0.05$ , effect sizes are given; values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both the Mann-Whitney test and chi-square test.

The relationship of balance and gait was analyzed by linear regression. Our primary hypothesis was that lateropulsion would be the most detrimental determinant on balance and gait disorders. All the clinical features related to balance and gait disorders were first analyzed by non-parametric univariate analysis (Kruskal-Wallis or Mann-Whitney U test). The significant P values for univariate analyses were adjusted to 0.004 (0.05/12) owing to multiple comparisons. Variables with  $p < 0.004$  on univariate analysis were selected for the multivariate regression model. Because PASS and mFMA scores followed a Poisson distribution, we used a Generalized Linear Model (GzLM, Poisson regression).

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Then we analyzed the consequences of a misorientation with respect to gravity on balance and gait abilities by using linear regression on initial and discharge data. Owing to the well-known RHS predominance for postural control (Pérennou *et al.*, 1998; Benaim *et al.*, 1999; Danells *et al.*, 2004; Pérennou, 2006; Pérennou *et al.*, 2008; Abe *et al.*, 2012), we separately analyzed RHS and LHS.

We further investigated these relationships and tested the value of initial SCP scores to predict the ability to stand ( $PASS \geq 28$ ) or walk independently ( $mFMA \geq 5$ ) at discharge. We plotted receiver operating characteristic (ROC) curves and calculated areas under the ROC curve (AUC). Optimal cut-off values were determined by the Youden Index. From the SCP cut-off values, we calculated sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV).

Missing data were few, so imputation was not performed. As recommended, (Harrington *et al.*, 2019) P values were limited to the main hypothesis, with two-sided  $P < 0.05$  considered statistically significant. Only confidence intervals and effect sizes were given for analyses of secondary endpoints. Statistical analysis involved using SPSS 21.0.

### **Data availability**

Anonymized data that support the findings of this study are available from the corresponding author, upon reasonable request.

### **Results**

Clinical data for the 220 individuals investigated are presented in Table 1. Their median age was 66.9 years (Q1–Q3 58-73), 147 were males (67%), and most were right-handed (90%) and with infarcts (83%). The median mRS score was 3 (2-4); 150 (68%) individuals had moderate

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or severe disability (mRS score >2). The median hospital stay in the rehabilitation ward was 81 days (51–138).

Missing initial data concerned spatial neglect (n = 2), apraxia (n = 5), hemianopia (n = 1), and depression (n = 9). Discharge data could not be collected for 3 (1%) individuals (2 deaths, 1 urgent transfer).

In this series, 158 individuals (72%) were considered upright, with 2 scenarios: 146 (66%) sat and stood perfectly upright (including 1 who exhibited pushing when changing positions in standing), and 12 (6%) showed some degree of isolated body tilt in sitting and/or standing, without fall tendency. The 62 others (28%) were considered misoriented with respect to gravity in erect posture; among them, 32 (15%) showed Lw/oP and 30 (14%) were pushers. Individuals with lateropulsion were almost all right-handed (97%), and pushers were all right-handed, which indicates that the orientation of the self with respect to gravity relies on a lateralized brain function. Lateropulsion (with or without pushing) prevalence was much greater after RHS than LHS (45/94 [48%] vs 17/126 [13%];  $v = 0.38$ ), which indicates a strong right-hemisphere predominance for the upright orientation (lateropulsion 3.7 times more frequent after RHS than LHS).

**Table 1: Clinical data for participants as a function of lateropulsion in three categories**

	<b>All</b>	<b>Upright</b>	<b>Lw/oP</b>	<b>Pushers</b>	Upright vs Lw/oP	Upright vs Pushers	Lw/oP vs Pushers
	<b>(n=220)</b>	<b>(n=158)</b>	<b>(n=32)</b>	<b>(n=30)</b>			
<i>Socio-demographic</i>							
<b>Sex</b>							
Female	73 (33%)	49 (31%)	11 (34%)	13 (43%)	v = 0.03	v = 0.1	v = 0.09
<b>Age (years)</b>							
	66.9 (58–73)	66.2 (54–72)	66 (60–71)	70.4 (64–76)	r = -0.03	r = -0.21	r = -0.28
<b>Right-handers</b>							
	198 (90%)	138 (87%)	30 (94%)	30 (100%)	v = 0.07	v = 0.15	v = 0.18
<i>Stroke features</i>							
<b>Test date</b>							
D30	207 (94%)	151 (96%)	29 (91%)	27 (90%)	v = 0.08	v = 0.09	v = 0.01
<b>Stroke types</b>							
Infarcts	183 (83%)	133 (84%)	26 (81%)	24 (80%)	v = 0.03	v = 0.04	v = 0.02
<b>Stroke side</b>							
Right hemisphere	94 (43%)	49 (31%)	20 (63%)	25 (83%)	v = 0.24	v = 0.39	v = 0.23

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<b><i>Modified Rankin scale</i></b>							
mRS (0-6)	3 (2-4)	3 (2-3)	4 (4-4)	5 (4-5)	r = -0.58	r = -0.65	r = -0.56

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<b><i>Length of hospital stay</i></b>							
(days)	81 (51-138)	64 (45-91)	151 (113-180)	169 (143-202)	r = -0.47	r = -0.55	r = -0.19
Onset to discharge							

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Data are n (%) or median (Q1-Q3), unless stated otherwise.

Lw/oP = lateropulsion without pushing. Pusher = lateropulsion with pusher syndrome. D30= Day 30 (others were tested at day 60). FET= Fisher's exact test. r = effect size of the Mann-Whitney test. v = effect size of chi-square test.

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## **Relationship between gait and balance disorders**

Balance and gait scores were highly correlated, both initially ( $r = 0.89$ ,  $p < 0.001$ ) and at discharge ( $r = 0.86$ ,  $p < 0.001$ ), which indicates that balance capacities highly explained the information contained in gait capacities: 79% (95% CI [75–84]) initially (about 1 month) and 74% (95% CI [68–80]) at discharge.

## **Determinants of balance and gait abilities**

We sought determinants of balance and gait disorders from initial data. On univariate analyses, only two variables did not affect balance or gait (stroke type and aphasia), and two did not affect gait (age and stroke side) (Table 2). All other variables were kept in the multivariate analyses (Table 2).

For balance disorders, the GzLM revealed only three deficits with an independent detrimental role: lateropulsion, weakness, and hypoesthesia when severe. The model was sound with strong likelihood ( $X^2 = 806.2$ ,  $p < 0.001$ ). Lateropulsion was the strongest determinant of balance disorders, with PASS scores multiplied by a B coefficient of 0.4 (95% CI [0.3-0.5],  $p < 0.001$ ) for pushers or 0.9 (95% CI [0.8-1],  $p = 0.037$ ) with Lw/oP, everything being equal as compared with upright individuals. Weakness also had a negative effect on balance ability, with PASS scores multiplied by a B coefficient of 0.7 (95% CI [0.6-0.7],  $p < 0.001$ ) with severe weakness and 0.9 (95% CI [0.8-1],  $p = 0.001$ ) with moderate weakness. Severe hypoesthesia was an independent factor affecting balance, with PASS scores multiplied by 0.9 (95% CI [0.8-1],  $p = 0.002$ ).

For gait disorders, the GzLM revealed only two deficits with an independent detrimental role: lateropulsion and weakness. The model was sound with strong



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likelihood ( $X^2 = 390.4$ ,  $p < 0.001$ ). Gait scores were multiplied by a B coefficient of 0.1 (95% CI [0-0.2],  $p < 0.001$ ) for pushers, so no participant was able to walk independently, and 0.6 (95% CI [0.3-0.9],  $p = 0.014$ ) for individuals with Lw/oP. Beyond the pusher feature, gait ability was affected by mild forms of lateropulsion, whereas 92% of upright individuals could walk without human aid. Weakness had also a strong independent effect on gait ability, with a B coefficient of 0.2 (95% CI [0.1-0.3],  $p < 0.001$ ) with severe weakness and 0.6 (95% CI [0.5-0.8],  $p < 0.001$ ) with moderate weakness.

**Table 2: Univariate and multivariate analysis of effect of clinical features on balance disorders and gait disorders**

		Balance				Gait			
		PASS	P-value*	Exp	(B) P-value	mFMA	P-value*	Exp	(B) P-value
		Median (Q1-Q3)	(Univariate)	(95% CI)	(Multivariate)	Median (Q1-Q3)	(Univariate)	(95% CI)	(Multivariate)
<b>Age, years</b>	≤60 (n=67)	33 (28-36)	p=0.003	1	p=0.161	5 (3-6)	p=0.012		
	>60 (n=153)	32 (19-34)		1 (0.9-1)		3 (0-6)			
<b>Stroke type</b>	Infarct (n=183)	32 (22-35)	p=0.374			4 (1-6)	p=0.97		
	Hemorrhage (n=37)	30 (24-34)		3 (2-5)					
<b>Stroke side</b>	Left (n=126)	33 (29-36)	p<0.001	1	p=0.831	4.5 (3-6)	p=0.012		
	Right (n=94)	29 (16-34)		1 (1-1.1)		3 (0-6)			
<b>Lateropulsion</b>	Upright (n=158)	34 (31-36)	p<0.001	1	p=0.037	5 (3-6)	p<0.001	1	p=0.014
	Lw/oP (n=32)	20.5 (18-25)		0.9 (0.8-1)		0.5 (0-2)		0.6 (0.3-0.9)	
	Pushers (n=30)	8 (3-15)		0.4 (0.3-0.5)		0 (0-0)		0.1 (0-0.2)	
<b>Spatial neglect</b>	No or light (n=120)	34.5 (32-36)	p<0.001	1	p=0.912	5 (4-6)	p<0.001	1	p=0.942
	Moderate (n=54)	30 (21-33)		1 (0.9-1.1)		3 (1-5)		1 (0.8-1.2)	
	Severe (n=44)	14 (6-19)		1 (0.9-1.2)		0 (0-0)		0.9 (0.5-1.7)	
<b>Aphasia</b>	No (n=131)	32 (21-35)	p=0.801			4 (1-6)	p=0.951		
	Yes (n=89)	32 (24-35)		4 (2-6)					
<b>Apraxia</b>	No (n=169)	33 (26-36)	p<0.001	1	p=0.419	5 (2-6)	p=0.003	1	p=0.484
	Yes (n=46)	26.5 (13-32)		1 (0.9-1.1)		3 (0-5)		0.9 (0.7-1.2)	
<b>Weakness</b>	Light (n=109)	35 (33-36)		1		6 (5-6)		1	

	Moderate (n=61)	29 (24-33)	p<0.001	0.9 (0.8-1)	p=0.001	3 (2-3)	p<0.001	0.6 (0.5-0.8)	p<0.001
	Severe (n=50)	13 (7-20)		0.7 (0.6-0.7)	p<0.001	0 (0-0)		0.2 (0.1-0.3)	p<0.001
<b>Spasticity</b>	No or light (n=156)	33.5 (30-36)		1		5 (3-6)		1	
	Moderate or severe (n=64)	21 (12-30)	p<0.001	1 (0.9-1.1)	p=0.694	1 (0-3)	p<0.001	1 (0.8-1.2)	p=0.793
<b>Hypoesthesia</b>	No or light (n=57)	35 (34-36)		1		6 (5-6)		1	
	Moderate (n=103)	32 (29-35)	p<0.001	1 (0.9-1)	p=0.404	4 (3-6)	p<0.001	0.9 (0.8-1.1)	p=0.234
	Severe (n=60)	17 (8-26)		0.9 (0.8-1)	p=0.002	0 (0-3)		0.8 (0.6-1)	p=0.086
<b>Hemianopia</b>	No (n=146)	33 (29-36)		1		5 (3-6)		1	
	Yes (n=73)	26 (15-33)	p<0.001	1 (0.9-1)	p=0.257	2 (0-5)	p<0.001	1 (0.8-1.2)	p=0.983
<b>Depression</b>	No (n=87)	34 (30-36)		1		5 (3-6)		1	
	Yes (n=124)	30 (19-34)	p<0.001	1 (0.9-1)	p=0.54	3 (0-5)	p<0.001	1 (0.8-1.1)	p=0.524

Data are median (Q1-Q3). PASS = Postural Assessment Scale for Stroke. mFMA gait scale = modified Fugl-Meyer Assessment gait scale. Lw/oP = lateropulsion without pushing. CI = confidence interval.

\*The significant P value for univariate analyses were adjusted as 0.004 (0.05/12) owing to multiple comparisons.

Missing data: spatial neglect (n=2), apraxia (n=5), hemianopia (n=1), and depression (n=9).

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### **Postural, balance and gait recovery**

Table 3 shows that individuals who were initially tilted with respect to gravity were better oriented at discharge, with a large effect size both with Lw/oP ( $r = -0.62$ ) and for pushers ( $r = -0.61$ ). The predominance of lateropulsion after RHS was even greater than initially: RHS (22/92 [24%]) vs LHS (2/125 [2%],  $v=0.35$ ). At discharge, lateropulsion was 12 times more frequent after RHS than LHS, in which the prevalence became negligible.

At discharge, balance ( $r = -0.49$ ) and gait ( $r = -0.46$ ) abilities were both much better in the whole series and in each group (with moderate to large effect sizes).

### **Mobility limitation as a function of body orientation with respect to gravity**

Balance and gait capacities greatly depended on body orientation against gravity (Table 3). Upright individuals had much better balance and gait capacities than others. Individuals with Lw/oP had much better balance and gait capacities than pushers. All differences had  $p$  values  $\leq 0.003$  with moderate to large effect sizes, both initially and at discharge. As a corollary, the length of hospital stay (stroke onset-discharge of the rehabilitation ward) for individuals with lateropulsion was much longer than that of upright individuals (164 days [126-192] vs 64 days [45-91];  $r = -0.62$ ).

**Table 3: Initial and discharge data of balance and gait for participants as a function of lateropulsion in three categories**

	<b>All</b> (n=220)	<b>Upright</b> (n=158)	<b>Lw/oP</b> (n=32)	<b>Pushers</b> (n=30)	Upright vs Lw/oP	Upright vs Pushers	Lw/oP vs Pushers
<b>D30</b>							
<b>Body orientation</b>							
<b>against gravity</b> SCP (0-6)	0 (0-1.3)	0 (0-0)	1.8 (1.3-2.4)	4.8 (4-6)	r = -0.87 p<0.001	r = -0.86 p<0.001	r = -0.86 p<0.001
<b>Balance</b> PASS (0-36)	32 (22-35)	34 (31-36)	20.5 (17-24)	8 (3-15)	r = -0.57 p<0.001	r = -0.63 p<0.001	r = -0.74 p<0.001
<b>Gait</b> mFMA (0-6)	4 (1-6)	5 (3-6)	0.5 (0-2)	0 (0-0)	r = -0.58 p<0.001	r = -0.64 p<0.001	r = -0.49 p<0.001
<b>Discharge</b>							

<b>Body orientation</b>							
<b>against gravity</b>	0 (0-0)	0 (0-0)	0 (0-0)	1.6 (0.4-3.1)	r = -0.22	r = -0.79	r = -0.66
SCP (0-6)					p=0.003	p<0.001	p<0.001
<b>Balance</b>							
PASS (0-36)	34 (32-36)	35 (34-36)	32 (29-33.5)	24.5 (16.5-31)	r = -0.42	r = -0.57	r = -0.53
					p<0.001	p<0.001	p<0.001
<b>Gait</b>							
mFMA (0-6)	5 (4-6)	6 (5-6)	4 (3-5)	2 (0.5-4)	r = -0.43	r = -0.53	r = -0.39
					p<0.001	p<0.001	p=0.003

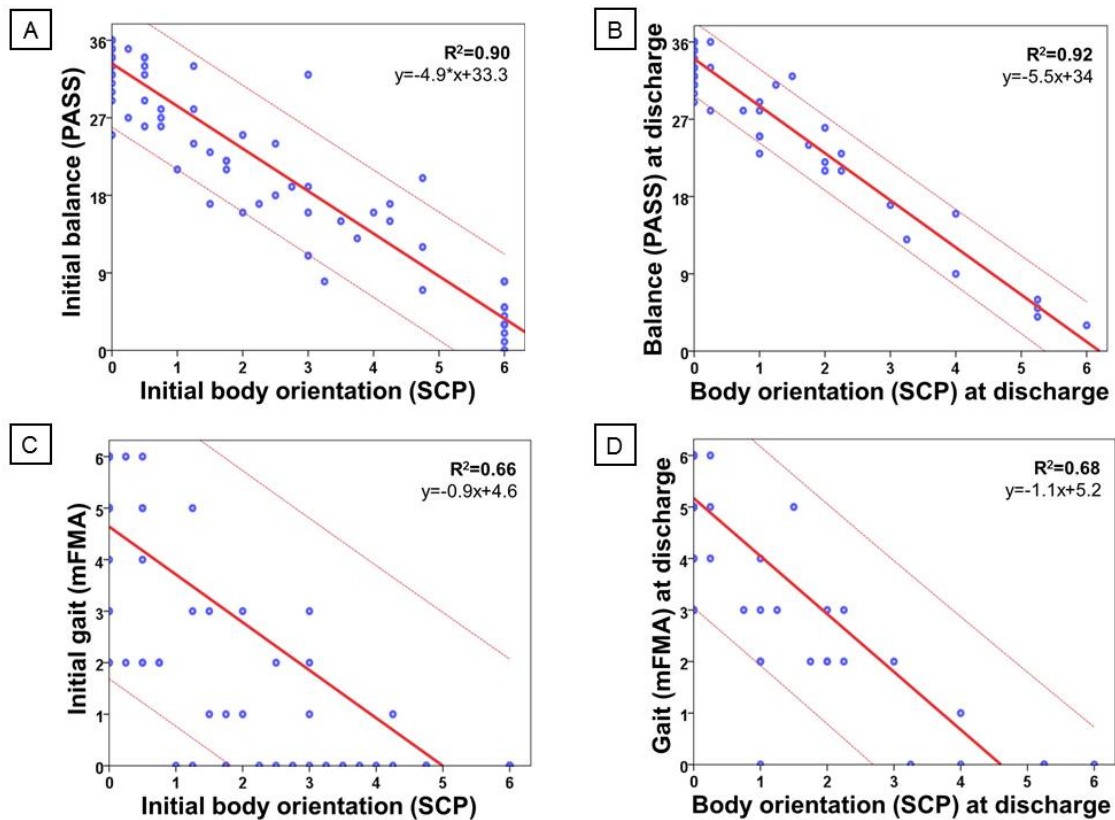
Data are median (Q1–Q3). Lw/oP=lateropulsion without pushing. Pusher = lateropulsion with pusher syndrome. SCP = Scale for Contraversive Pushing. PASS = Postural Assessment Scale for Stroke. mFMA gait scale = modified Fugl-Meyer Assessment gait scale. r = effect size of the Mann-Whitney test.

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### **Body orientation with respect to gravity explains mobility limitation**

After RHS, lateropulsion explained almost all the information contained in balance disorders: 90% (95% CI [86–94],  $p < 0.001$ ) initially (about 1 month after onset) (Figure 2A) and 92% (95% CI [89–95],  $p < 0.001$ ) at discharge (Figure 2B) and also the greatest part of gait disorders: 66% (95% CI [56–77],  $p < 0.001$ ) initially (Figure 2C) and 68% (95% CI [57–78],  $p < 0.001$ ) at discharge (Figure 2D).

After LHS, lateropulsion also explained a substantial part of mobility limitation initially: 59% (95% CI [48–69],  $p < 0.001$ ) of balance disorders and 43% (95% CI [30–56],  $p < 0.001$ ) of gait disorders. No analysis was performed at discharge for LHS because only 2/125 (2%) individuals still presented lateropulsion.



**Figure 2. Relationship between body orientation with respect to gravity and balance/gait capacities after right hemisphere stroke**

Figure 2A and Figure 2C correspond to initial data (about 1 month after onset), and Figure 2B and Figure 2D correspond to data collected at discharge.

All the linear regressions were valid because of high  $R^2$  and fit Durbin-Watson statistics ranging from 1.8 to 2.2 (Durbin-Watson 2A = 2; 2B = 1.9; 2C = 2; 2D = 2.2).

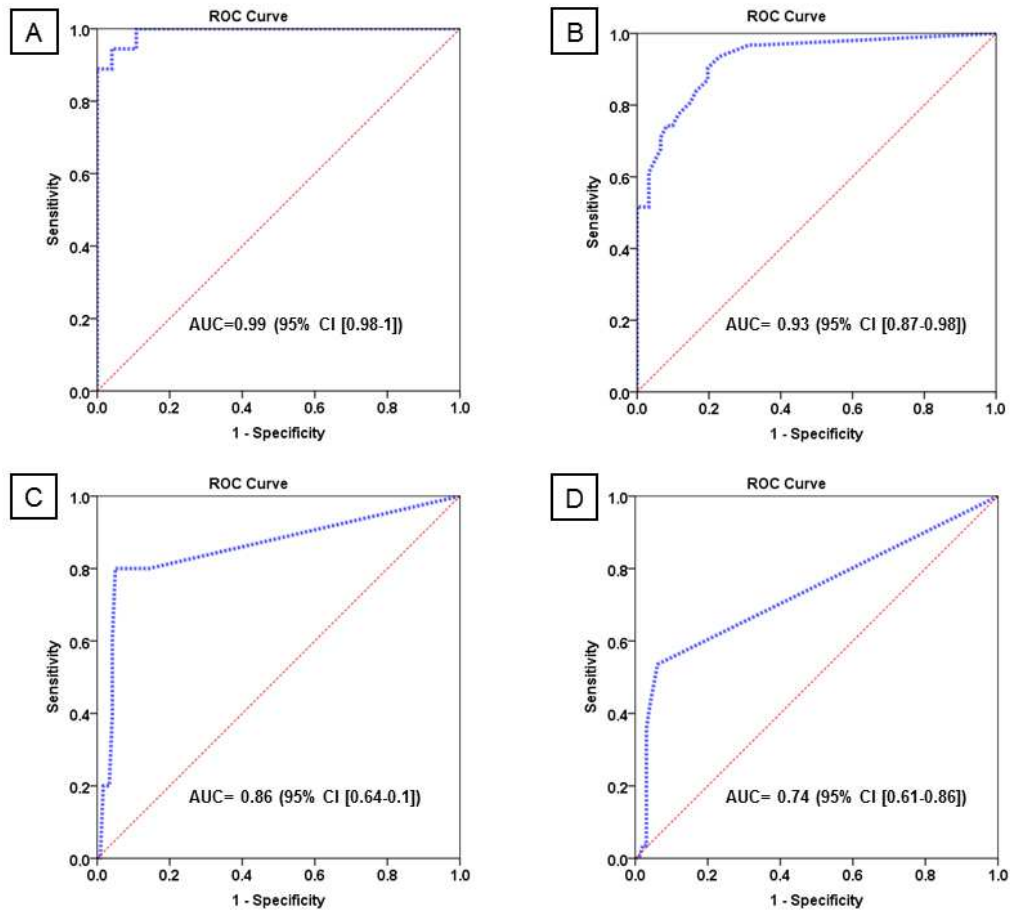


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### **Initial body orientation predicts balance and gait at discharge**

ROC curves were plotted from initial SCP scores and dichotomized balance (erect stance) and gait (independent walking) abilities at discharge (Figure 3) for RHS and LHS.

For RHS, the AUC was 0.99 (95% CI [0.98-1]) for balance (Figure 3A) and 0.93 (95% CI [0.87-0.98]) for gait (Figure 3B). The SCP cut-off values calculated from the Youden Index were 3.5 for balance (sensitivity 0.94, specificity 0.96, PPV 0.86, NPV 0.99) and 1 for gait (sensitivity 0.9, specificity 0.8, PPV 0.67, NPV 0.95). Low values of these indices were satisfactory predictors of good recovery. Specifically, individuals with an initial SCP score < 3.5 would be able to stand independently at discharge (probability 99%, 95% CI [92–100]), and individuals with an initial SCP score < 1 (upright or light lateropulsion) would be able to walk without any help at discharge (probability 95%, 95% CI [87–98]). For LHS, the AUC was 0.86 (95% CI [0.64-0.1]) for balance and only 0.74 (95% CI [0.61-0.86]) for gait. For balance, the SCP cut-off value calculated from the Youden Index was 2 (sensitivity 0.8, specificity 0.95, PPV 0.45, NPV 0.99), so that individuals with an initial SCP score < 2 would be able to stand independently at discharge (probability 99%, 95% CI [95–100]). No other robust prediction was possible with LHS (see Figure 3C and 3D).



**Figure 3. Initial body orientation predicts balance and gait at discharge**

Scale for Contraversive Pushing (SCP) score predicts balance and gait abilities in individuals after a right hemisphere stroke (RHS, A[balance]+B[gait]) (n=92 at discharge) and a left hemisphere stroke (LHS, C[balance]+D[gait]) (n=125 at discharge).

Receiver operating characteristic (ROC) curves predicting, from the initial SCP score, the inability to stand without assistance (Postural Assessment Scale for Stroke [PASS] score < 28) at discharge after a RHS (A) and a LHS (C). ROC curves predicting, from the initial SCP score, the inability to walk independently without a cane or rollator (modified Fugl-Meyer Assessment [mFMA] score <5) after a RHS (B) and a LHS (D). AUC= area under the ROC curve.

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## Discussion

To reduce the destabilizing effect of gravity, the body must be oriented vertical, which corresponds to one of the two domains of postural control (Massion, 1992; Horak and Macpherson, 2011). Here we analyzed the contribution of an impaired body orientation in the frontal plane (known as lateropulsion) on daily life balance and gait disorders after stroke. Our findings reveal that lateropulsion is the primary cause of balance and gait disorders at the subacute stage after stroke. This finding contradicts a general feeling that the key problem deals with the stabilization component of balance control. It is of major importance for post-stroke balance and gait rehabilitation, which should be rethought.

In a series of 220 non-selected individuals with a first hemisphere stroke, we found that at initial assessment (D30), most individuals with an LHS remained upright (87%), whereas half with RHS showed lateropulsion (48%), almost always in right-handers (97%). Therefore, the control of uprightness is a highly lateralized brain function, mainly located in the right hemisphere, which justifies our approach to separately analyze RHS and LHS. This analysis requires four subgroups of individuals, therefore a large series. Only two studies have addressed this question in a large series (>200) of consecutive individuals (Pedersen *et al.*, 1996) (Abe *et al.*, 2012). When individuals were assessed early in the acute stroke unit, no significant RHS predominance was found (Pedersen *et al.*, 1996). When individuals were assessed later at entry in the rehabilitation unit, RHS predominance was found (Abe *et al.*, 2012). Together with these two studies, ours clearly demonstrates that the gradient RHS/LHS for lateropulsion increases as a function of time after stroke: lateropulsion 1.3 times more frequent after RHS than LHS a few days post-stroke (Pedersen *et al.*, 1996), 1.8 times

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more frequent at admission to rehabilitation (Abe *et al.*, 2012), 3.7 times more frequent on D30 (our study), and 12 times more frequent at rehabilitation discharge (our study). We assume that this finding might be related to a possible diaschisis (Carrera and Tononi, 2014), altering the functioning of both hemispheres during the days following the stroke, whatever the side, because lateropulsion may result from similar lesions of both hemispheres (Babyar *et al.*, 2019). The release of the diaschisis should increase the predominance of the right hemisphere for processing spatial information, including control of the upright. This suggestion remains to be demonstrated by further studies. Beyond the underlying mechanisms, our findings explain why the recovery of balance and gait disorders is worse after RHS than LHS, a well-known finding (Pérennou, 2006).

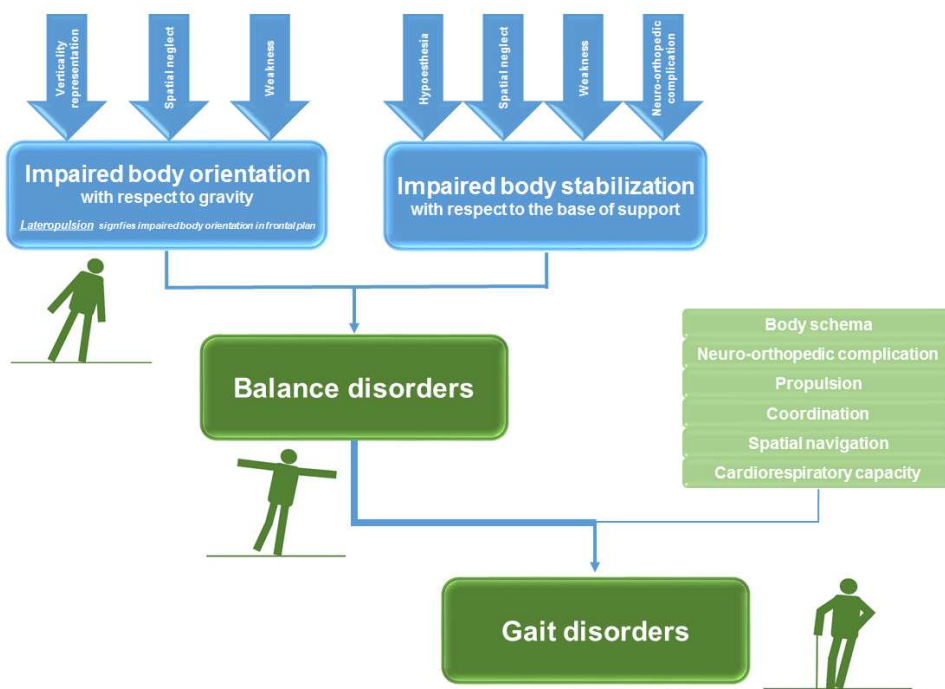
Lateropulsion plays a primary role in balance and gait disorders during the subacute phase after hemisphere stroke. In RHS, balance disorders were quasi-proportional to lateropulsion severity, which explained them almost entirely in initial and discharge assessments. This novel finding has a major scope because of the high lateropulsion prevalence and the great impact of balance disorders on autonomy.

These results bring new insights into how to conceive post-stroke balance and gait disorders (Figure 4), so far considered to result from motor and tone deficits (Pérennou, 2006; Nonnekes *et al.*, 2018) and from spatial neglect (Benaim *et al.*, 1999; Kollen *et al.*, 2005; Pérennou, 2006; van Nes *et al.*, 2009), thus leading to impaired postural stabilization and walking propulsion (Kollen *et al.*, 2005; van Nes *et al.*, 2009; Fulk *et al.*, 2017). An interesting result of our study is that at the subacute stage, gait disorders are mainly due to balance disorders. Overall, from a comprehensive battery of deficits and appropriate multivariate analyses, our study shows that sensory-motor deficits and

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spatial neglect are less determinant than are deficits in body orientation to generate postural and gait disorders. Thus, lateropulsion is a key determinant of balance and gait disorders at the subacute phase after stroke. Our results advocate for better considering lateropulsion as a rehabilitation target and the need to design and validate novel techniques and programs, partly supported by modulations of the internal model of verticality (Pérennou *et al.*, 2008; Barra *et al.*, 2010).

Predicting recovery is of great importance for patients and their relatives. It has been repeatedly showed that balance capacity the first weeks after the stroke is a good indicator of final gait ability and falls occurrence (Huang *et al.*, 2016; Laren *et al.*, 2018). Our study goes further by showing that a satisfactory orientation with respect to gravity (no lateropulsion) predicts a good balance and gait recovery, with very high accuracy. After an RHS, individuals with an initial SCP score  $< 3.5$  would be able to stand independently at discharge (probability 99%). In other words, the lateropulsion severity at D30 determines the long-term walking prognosis.



**Figure 4. Theoretic model of balance and gait disorders after stroke**

We considered the clinical application of the theoretical model of balance control (Massion, 1992; Horak and Macpherson, 2011). At the subacute stage after stroke, body misorientation (lateropulsion) is the primary cause of balance disorders, which mostly explains gait disorders.

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## Limitations

Data were collected by a multidisciplinary team that was well trained and motivated, with few missing data given the large sample size and the study duration. Evaluators were therapists, and blinding was not possible or beneficial in this observational study. To ensure non-biased assessments, therapists and patients were not informed of the study hypothesis.

How we assessed the orientation with respect to gravity might be viewed as a limitation. Lateropulsion is currently assessed with the Burke Lateropulsion Scale (BLS) (D'Aquila *et al.*, 2004; Babyar *et al.*, 2009; Koter *et al.*, 2017) or the SCP (Babyar *et al.*, 2009; Koter *et al.*, 2017). The BLS assesses lateropulsion in erect and also recumbent postures. Because we wanted to focus on behaviors against gravity, we used the SCP, which is also reliable (Baccini *et al.*, 2008; Koter *et al.*, 2017), despite the lack of cross-cultural validation and several reformulations of items by authors. If we categorized pushers using the seminal cut-off (Karnath *et al.*, 2000), we also used the SCP beyond its initial objective, to objectively distinguish individuals upright from those showing lateropulsion without being pushers. The appropriateness of this approach, already adopted in some studies (Danells *et al.*, 2004; Pérennou *et al.*, 2008), was confirmed by the fact that the three groups (upright, Lw/oP, pushers) differed in their behavior with respect to gravity (all three domains differed, body tilt, pushing, and resistance) and in the severity of other deficits. With a SCP score increment of 0.25 from 0 to 6, the construction of the SCP (Karnath *et al.*, 2000) allows for quantifying the magnitude of the body tilt and the intensity of additional signs (pushing and resistance), thus, lateropulsion severity, which is strongly correlated with magnitudes of biases in the postural perception of the vertical (Pérennou *et al.*, 2008). Therefore, it

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is appropriate to test relationships between SCP, balance, and gait scores, with good statistical fit. In our care pathways, only one third of individuals admitted in the acute stroke units are then referred to rehabilitation units (Schnitzler *et al.*, 2013), the others having too slight or too severe disabilities. These criteria, which correspond to those adopted in most European countries (Schnitzler *et al.*, 2013), condition the generalizability of our results. However, our findings may be generalized to the rehabilitation context, which is overall important because lateropulsion is a major rehabilitation challenge. One cannot even exclude that the scope of the study might have been reduced by the inclusion criteria (first-ever hemisphere stroke without the cerebral complications listed in methods) and the time of the initial assessment (D30). Indeed, lateropulsion prevalence and severity are greater earlier after stroke (D'Aquila *et al.*, 2004; Danells *et al.*, 2004; Baccini *et al.*, 2008) and likely in cases of preexisting altered brain functions, recurrent strokes, or neurological complications.

## **Conclusion**

Body misorientation with respect to gravity is the primary factor altering balance and gait during the post-stroke subacute stage. So lateropulsion should be systematically assessed. We suggest that post-stroke balance and gait rehabilitation incorporate techniques specifically devoted to lateropulsion.



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## Appendix Authors

Name	Location	Role	Contribution
Shenhao Dai, MD	Grenoble Alpes University Hospital, France	Author	Analyzed and interpreted the data; drafted the manuscript for intellectual content
Céline Piscicelli, PhD	Grenoble Alpes University Hospital, France	Author	Acquisition of data; revised the manuscript for intellectual content
Emmanuelle Clarac, PT	Grenoble Alpes University Hospital, France	Author	Acquisition of data; material support
Monica Baciuc, MD, PhD	Grenoble Alpes university, France	Author	Revised the manuscript for intellectual content
Marc Hommel, MD, PhD	Grenoble Alpes university, France	Author	Interpreted the data; revised the manuscript for intellectual content

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Dominic Pérennou, MD, PhD	Grenoble Alpes University Hospital, France	Author	Design and conceptualized study; study supervision; interpreted the data; drafted the manuscript for intellectual content; obtaining funding
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## ➤ Chapter 7: Lateropulsion and balance recoveries

Following article 4, this current article further analyzes the recoveries between lateropulsion and balance disorders after stroke. We hypothesize that lateropulsion alleviation is one of the determinants to balance recovery. Thus our principle aim is to investigate the interplay between lateropulsion and balance recoveries at the subacute stage, in a longitudinal cohort of more than 100 people examined on D30, D60 and D90 after a first hemisphere stroke. Meanwhile, based on this longitudinal cohort, we analyze the responsiveness of the current gold standard of assessment of lateropulsion, which is another novelty of this paper. This paper is under preparation.



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**After stroke, recovering a better orientation with respect to gravity magnifies balance recovery: Study from the DOBRAS cohort**

**S Dai, Piscicelli C, C Lemaire, Clarac E, O Detante, A Chrispin, P Davoine, D Pérennou, in préparation**

**Abstract**

**Background** Mobility is one of the top priorities after stroke. Recent literature showed that mobility disability is mainly due to balance disorders, which is predominated at the subacute stage by an impaired body orientation with respect to gravity in the frontal plan (lateropulsion).

**Aims** Here we test the hypothesis that a satisfactory lateropulsion recovery magnifies balance recovery and investigate the responsiveness of the assessment measuring the lateropulsion, the Scale for Contraversive Pushing (SCP).

**Methods** Data from DOBRAS cohort study of 106 individuals consecutively admitted to a neurorehabilitation ward after a first hemisphere stroke (ClinicalTrials.gov: NCT03203109), were systematically collected on day30, day60 and day90 after stroke. Primary outcomes were lateropulsion and balance disorders, quantified by the SCP and the Postural Assessment Scale for Stroke (PASS). Effect size (ES) and standardized response mean (SRM) were used to estimate the scale's responsiveness.

**Results** The correlation between changes in SCP and PASS scores was moderate from D30 to D60 ( $r= 0.63$ , 95%CI [0.47-0.76],  $p<0.001$ ) meaning that between D30 and D60 lateropulsion recovery explains 40% (95%CI [22-58]) of balance recovery. This relationship was smaller however substantial from D60 to D90 ( $r= 0.44$ , 95%CI [0.15-0.63],  $p<0.001$ ). Within the 46 individuals with a satisfactory lateropulsion recovery between D30 and D60 ( $SCP \geq 0.75$ ), 43/46 (93%) had a satisfactory balance improvement (PASS minimal detectable change [ $MDC_{95}$ ]  $>2$ )

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and only 3/46 (7%,  $v=0.44$ ,  $p<0.001$ ) had a poor balance improvement. Conversely within the 60 individuals with a poor lateropulsion recovery, only half (32, 53%) had a satisfactory balance improvement, with a mean change lower than that observed with a good lateropulsion recovery (5.4 [3.1] vs 8.1 [3.8];  $d=0.77$ ,  $p<0.001$ ). The responsiveness of the SCP was small to moderate (D30-60, ES=0.38, 95%CI [0.29-0.47], SRM=0.81, 95%CI [0.63-1.01]; D60-90, ES=0.21, 95%CI [0.15-0.28], SRM=0.64, 95%CI [0.44-0.82]), with a considerable floor effect since D30 ( $\geq 34\%$ ).

**Conclusions** Balance improvement is amplified when lateropulsion recovers. After stroke, rehabilitation programs should better consider body orientation with respect to gravity. The current gold standard tool (SCP) is inadequate to implicate in monitoring lateropulsion recovery, which calls for a novel scale to bridge the gap.

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## Introduction

Regaining mobility is one of the top priorities after stroke,(Pollock *et al.*, 2012) which seems more than ever achievable since recent theoretical models disentangling mechanisms leading to this disability.(Nonnekes *et al.*, 2018; Dai *et al.*, 2021a; Dai *et al.*, 2021c) The primary target should be balance disorders, and specially the lateral misorientation with respect to gravity,(Dai *et al.*, 2021a) known as lateropulsion,(Babayar *et al.*, 2019; Dai *et al.*, 2021a) and caused by a wrong internal model of verticality tilted the side opposite hemisphere strokes.(Pérennou *et al.*, 2008; Dai *et al.*, 2021b) Even mild forms of lateropulsion have a detrimental effect on balance and gait,(Dai *et al.*, 2021a) as well as on their recovery.(Dai *et al.*, 2021a) The next step is to investigate the closeness of the link between lateropulsion recovery and balance recovery. Is lateropulsion alleviation a prerequisite to any balance recovery? In contract, is balance recovery independent from lateropulsion recovery? We made a more plausible and intermediate hypothesis that lateropulsion alleviation is one of the determinants to balance recovery, which should rely both on progresses obtained for body orientation with respect to gravity and body stabilization with respect to the base of support?(Massion, 1992; Pérennou, 2006; Horak and Macpherson, 2011; Dai *et al.*, 2021a) Addressing these questions for the first time was the main objective of this study.

To design relevant clinical trials with the aim to enhance lateropulsion and balance recovery, one needs robust outcomes criteria based on well validated specific tools, in particular adequate responsiveness to monitor the changes. As for balance assessment after stroke, the gold standard is the Postural Assessment Scale for Stroke (PASS),(Mao *et al.*, 2002) the responsiveness of which has been well analyzed and congruently found adequate (Mao *et al.*, 2002; Clark *et al.*, 2012; Hsueh *et al.*, 2013). As for lateropulsion assessment the gold standard is the Scale for Contraversive Pushing (SCP),(Karnath *et al.*, 2000; Babayar *et al.*, 2009; Koter *et al.*, 2017) the

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responsiveness of which has never been analyzed. Given the huge recent interest for post-stroke lateropulsion assessment and rehabilitation, it was urgent to investigate the SCP responsiveness, in relation with its possible floor and ceiling effects. On the basis of professional impressions (Pérennou *et al.*, 2008; Babyar *et al.*, 2009; Koter *et al.*, 2017; Dai *et al.*, 2021a; Dai *et al.*, 2021b) that we share, we hypothesized that the SCP has a strong floor effect with inadequate responsiveness.

## Aims

Our first aim was to investigate the interplay between lateropulsion and balance recoveries at the subacute stage, in a longitudinal cohort of more than 100 people examined on D30, D60 and D90 after a first hemisphere stroke. Our second aim was to analyze the responsiveness of the SCP, in parallel to that of the PASS.

## Methods

### Study design

This was a monocentric observational study of the DOBRAS cohort (Determinants of Balance Recovery After Stroke; NCT03203109). All participants were comprehensively followed and assessed three times in routine care, initially on day 30 after stroke (window of 3 days before and after), then on D60 ( $\pm 3$ ) and D90 ( $\pm 3$ ). Assessments were performed by trained and multidisciplinary examiners, with blinding to the study hypothesis.

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## **Standard protocol approvals and registrations**

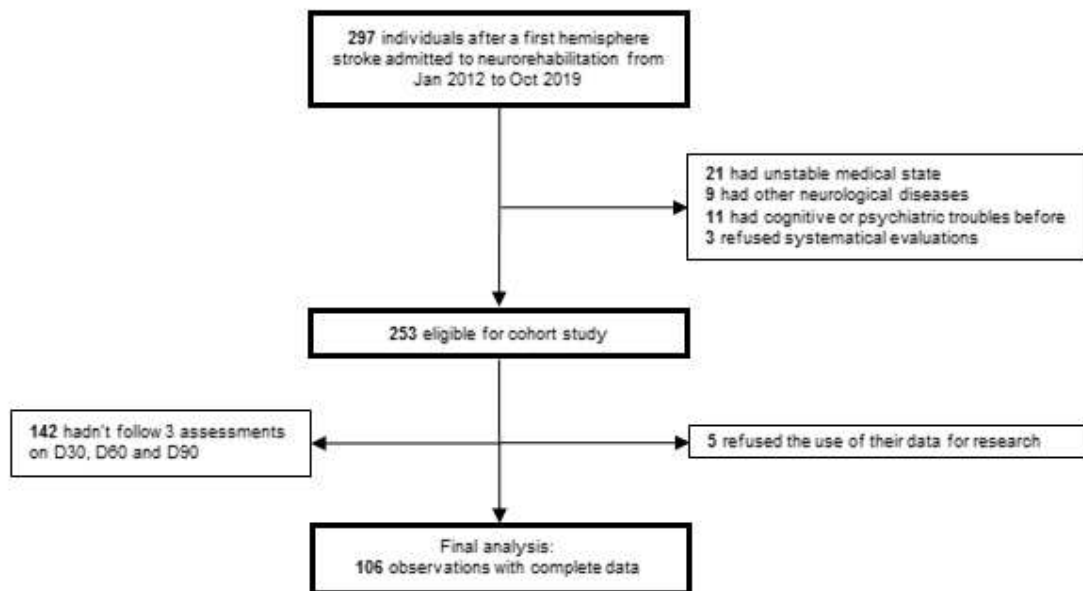
The DOBRAS cohort was approved by our institutional review board (CHU Grenoble Alpes) who validated the ClinicalTrials.gov registration (NCT03203109). The study was also registered at the National Committee for Informatics and Freedom (Commission nationale informatique et liberté; CNIL-No.2014874-v1) 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**

From January 2012 to October 2019, we included 106 consecutive individuals (age 18 to 80 years), with a first-ever unilateral hemisphere stroke confirmed by MRI or CT. Exclusion criteria were recurrent stroke, complications at the acute stage (malignant infarct, cerebral herniation, severe subarachnoid hemorrhage and hydrocephalus), dementia, previous disability interfering with balance or vestibular disorders, and unstable medical condition or psychiatric problems jeopardizing data reliability (Figure 1). These conditions were obtained from the hospital electronic file describing the history of every patient, by interviewing patients and relatives, and by a systematic clinical examination. Participants followed a personalized rehabilitation program, taking into account deficits and activity limitations, capacities to face intensive rehabilitation (fatigue or transitory medical problems), individual recovery, and the most appropriate guidelines. According to their abilities, participants had at least 2 physiotherapy and 1 occupational therapy sessions per day (each session lasting at least 30 min

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for a total daily time of sensori-motor rehabilitation over  $\geq 1.5$  hr per patient), plus sessions with a speech therapist, neuropsychologist, psychologist, or orthoptist if needed.



**Figure 1. Flow of participants in the study.**

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## Assessments

Global disability was estimated with the modified Rankin Scale (mRS), whose total score ranges from 0 to 6.

Balance disorders were assessed with the Postural Assessment Scale for Stroke (PASS),(Benaim *et al.*, 1999) the most appropriate balance scale at the subacute stage after stroke. The total score ranging from 0 to 36 (satisfactory balance) assesses balance abilities in daily life. The minimal detectable change (MDC<sub>95</sub>) of the PASS reported in subacute phase was 1.8 (1.7),(Hsueh *et al.*, 2013) thus we considered that there was an improvement of the PASS between 2 assessments if its change score >2.

Lateropulsion was assessed with the Scale for Contraversive Pushing (SCP),(Karnath *et al.*, 2000) in both sitting and standing position. The total score ranges from 0 to 6 (extreme form of lateropulsion).

## Data analyses and statistics

Continuous data are presented as mean with standard deviation (SD) and dichotomized data as number (%). When useful, 95% confidence intervals (CIs) are given. Statistical analysis involved using STATA 15.1. Two-tailed P<0.05 was considered statistically significant, unless other indicated for corrected comparisons.

Balance and lateropulsion recovery were analyzed by comparing data of D30, D60, and D90 by paired t test, independently for the PASS and the SCP. A threshold P value of 0.017 was set for significance after Bonferroni correction for multiple comparisons. Effect sizes of the recovery were calculated by using the t values of the paired t test,  $d = 2t / \sqrt{(\text{degree of freedom})}$ . The values 0.2, 0.5 and 0.8 represent a small, medium and large effect for the t test.

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The relationship between balance and lateropulsion recovery was first analyzed with continuous data. Pearson correlation was tested between changes on both scores, PASS and SCP:  $r$  values of 0.30, 0.50 and 0.70 being considered related, moderate and good correlations, respectively. We then analyzed categorical data (and mean values per category). For balance we classified individuals as having poor or satisfactory recovery over one month according to the average minimal detectable change (MDC<sub>95</sub>) value of 2 arbitrary units (a.u.) reported for the PASS in the literature.(Hsueh *et al.*, 2013) No MDC having ever been reported for the SCP, we classified individuals as having poor or satisfactory lateropulsion recovery over one month according to the cut-off 0.75 a.u. . This value corresponds to the minimum score required to diagnose the existence of a mild lateropulsion,(Pérennou *et al.*, 2008; Dai *et al.*, 2021a; Dai *et al.*, 2021b) in relation to a biased verticality representation.(Pérennou *et al.*, 2008; Dai *et al.*, 2021b)

PASS and SCP floor and ceiling effects were analyzed from their distributions at D30, D60 and D90, and quantified by the proportion of individuals scoring the possible minimum (floor) or maximum (ceiling). Ceiling and floor effects  $\geq 15\%$  were considered significant.(Terwee, *et al.*, 2007) We further investigated SCP responsiveness, as compared to that of the PASS, over the two periods of time of the study: from D30 to D60 on one hand, and from D60 to D90 on the other hand. The responsiveness was analyzed with two complementary indices,(Husted *et al.*, 2000) the standardized effect size (ES) and the standardized response mean (SRM). The ES is a measure of change obtained by dividing the mean change in scores between the former and the latter assessments by the SD of the former assessment. The SRM is the mean change in scores between two assessments divided by the SD of those changes in scores. ES and SRM values of 0.2, 0.5, and 0.8 were considered to show small, moderate, and large responsiveness, respectively.(Husted *et al.*, 2000) Moderate and large ESs and SRMs indicated adequate responsiveness.



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## Results

In total, 106 individuals were investigated. Their mean age was 66.5 (9.7) years; 69 were males (65%), and 98/106 (92%) were right-handed. Most had an infarct (86/106, 81%), and a RHS (56/106, 53%). The mean mRS score on D30 was 4 (0.8), indicating moderate to severe disability.

### **Relationship between balance and lateropulsion recovery**

#### Balance recovery

Figure 2A summarizes balance recovery. PASS scores increased steadily from D30 to D90. Differences were highly significant with a medium effect size from D30 to D60 ( $d=0.59$ ,  $p<0.001$ ) and with a small effect size from D60 and D90 ( $d=0.31$ ,  $p<0.001$ ). Over a two-month period of time (from D30 to D90), the effect size became much larger ( $d=0.89$ ,  $p<0.001$ ).

#### Lateropulsion recovery

Figure 2B summarizes lateropulsion recovery. SCP scores decreased smoothly from D30 to D90. Differences were highly significant with small effect sizes from D30 to D60 ( $d=0.4$ ,  $p<0.001$ ) and from D60 and D90 ( $d=0.25$ ,  $p<0.001$ ). The effect size remained moderate over a two-month period of time from D30 to D90 ( $d=0.67$ ,  $p<0.001$ ).

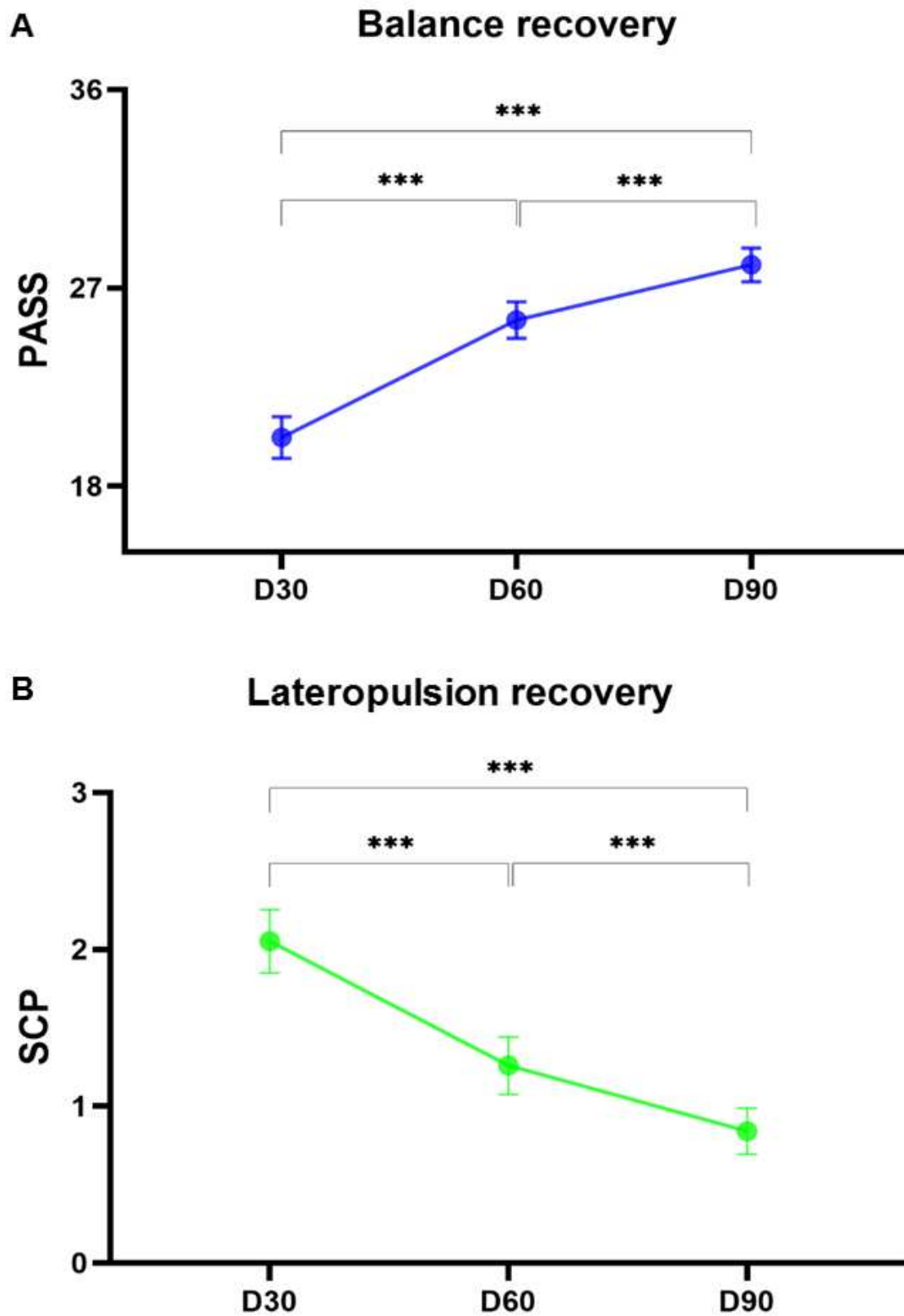


Figure 2. Recovery of balance and lateropulsion at the subacute stage after stroke.

\*\*\*p<0.001.

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## Relationship between balance and lateropulsion recovery

The first analyses were conducted on continue data. From D30 to D60 the correlation was moderate between changes in SCP and PASS scores ( $r= 0.63$ , 95%CI [0.47-0.76],  $p<0.001$ ). During this period of time lateropulsion recovery explained 40% (95%CI [22-58]) of balance recovery. The correlation was smaller from D60 to D90 ( $r= 0.44$ , 95%CI [0.15-0.63],  $p<0.001$ ), where lateropulsion recovery explained only 19% (95%CI [2-40]) of balance recovery. The correlation between lateropulsion and balance recovery was significantly smaller in the third month as compared to the second one ( $z=1.93$ ,  $p=0.027$ ).

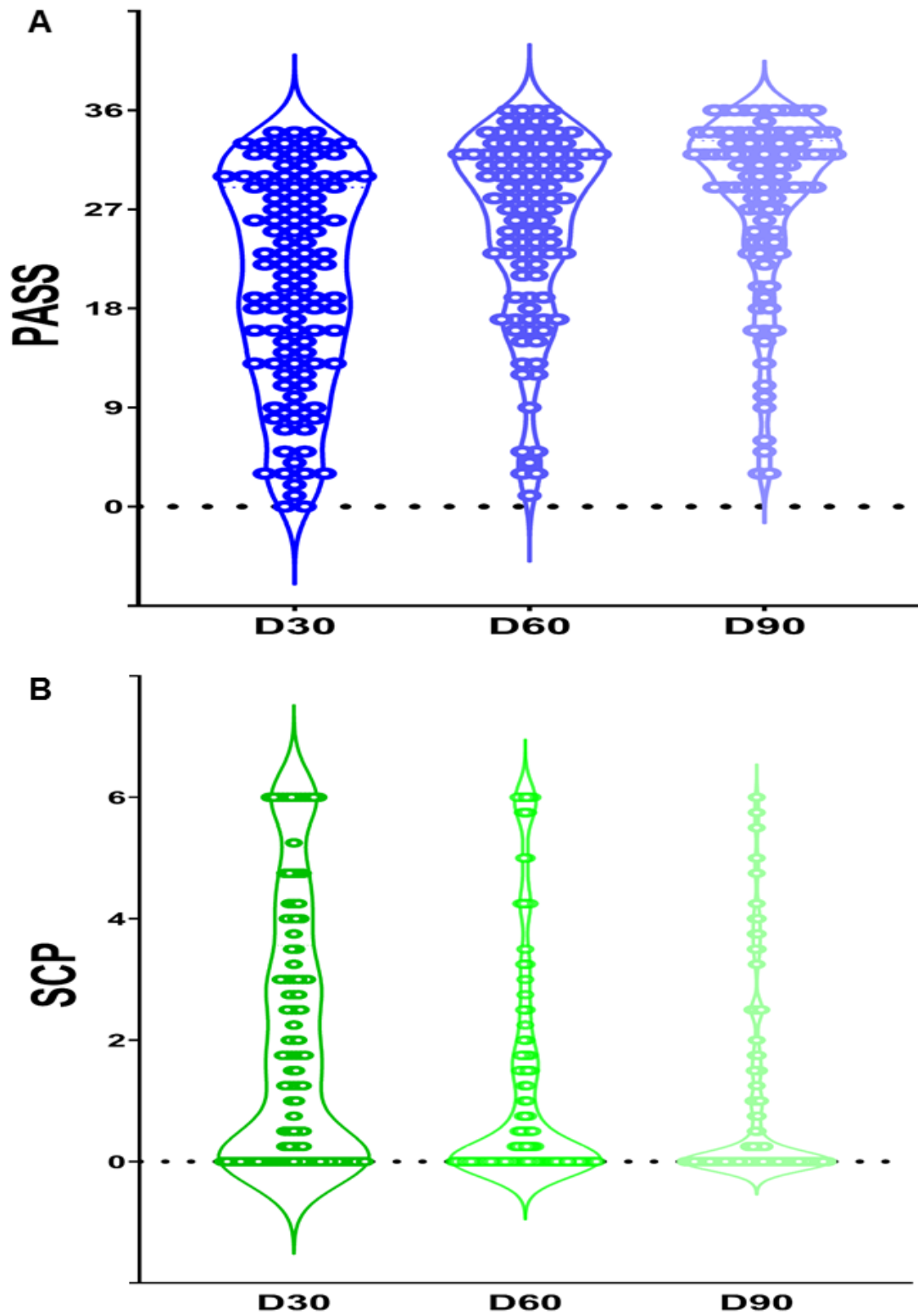
The covariation between PASS and SCP changes were then analyzed on categorical data, only during the period of time D30-60 with the strongest recovery. Among the 106 individuals of the series, most (75, 71%) had a satisfactory balance recovery (increased PASS score  $> 2$  a.u.), and 31 (29%) a poor balance recovery (increased PASS score  $\leq 2$  a.u.); only 46 (43%) had a satisfactory lateropulsion alleviation (decreased SCP score  $\geq 0.75$  a.u.) whereas 60 (57 %) had a poor lateropulsion alleviation (decreased SCP score  $<0.75$  a.u.). Within those with a satisfactory lateropulsion alleviation 43/46 (93%) had a satisfactory balance recovery whereas only 3/46 (7%) had a poor balance recovery ( $v=0.44$ ,  $p<0.001$ ). Conversely within the 60 individuals with a poor lateropulsion recovery, about half (32, 53%) had a satisfactory balance recovery. In individuals in whom lateropulsion recovery was satisfactory between D30 and D60, the mean increased in PASS score during the same period of time was 50% higher than that of individuals who showed a poor lateropulsion recovery (8.1 [3.8] vs 5.4 [3.1];  $d=0.77$ ,  $p<0.001$ ). These findings indicate that balance improvement was possible without substantial lateropulsion alleviation, but when it occurred this better orientation with respect to gravity amplified balance recovery.

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### **PASS and SCP floor and ceiling effects**

Figure 3A shows the distribution of balance scores through the follow-up period. The number and proportion of individuals with a PASS score of 0 (minimum) was 2 on D30 (2%), and none on D60 and D90. These results indicated the absence of any floor effect for the PASS. The number and proportion of individuals with a PASS score of 36 (maximum) was none on D30, 4 on and D60 (4%), and 11 on D90 (10%), which didn't reach the threshold value (15%) to state the existence of a ceiling effect of the PASS within the first 3-month post-stroke.

Figure 3B shows the distribution of lateropulsion scores through the follow-up period. The number of individuals with a SCP score of 0 (minimum) was 36 on D30, 51 on D60, and 67 on D90, giving very important floor effects of 34% on D30, 48.1% on D60, and 63.2% on D90. The number and proportion of individuals with a SCP score of 6 (maximum) was 12 on D30 (11%), 6 on and D60 (6%), and 1 on D90 (1%), which didn't reach the threshold value (15%) to state the existence of a ceiling effect of the SCP within the first 3-month post-stroke.



**Figure 3. PASS and SCP floor and ceiling effects.**

Figure 3A and 3B show the distribution of balance scores and lateropulsion scores through the follow-up period.

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## **SCP and PASS responsiveness**

The information allowing to calculate the SCP responsiveness is presented in the first part of the Table 1. The SCP responsiveness assessed with the ES was small from D30 to D60, very small from D60 to D90, but large from D30 to D90. The SCP responsiveness was lightly better when assessed with the SRM: marginally adequate from D30 to D60, moderate from D60 to D90, and large from D30 to D90. Taken together these findings indicated that the SCP responsiveness was inadequate to monitor lateropulsion recovery after the second month post stroke, and questionable before, unless over a period of time of 2 months.

The information allowing to calculate the PASS responsiveness is presented in second part of the Table 1. The PASS responsiveness assessed with the ES was moderate from D30 to D60, small from D60 to D90, but large from D30 to D90. The PASS responsiveness was better when assessed with the SRM: large from D30 to D60 and from D60 to D90, and excellent from D30 to D90. Taken together these findings indicated that the PASS responsiveness was adequate to monitor balance recovery in the subacute phase after the stroke.

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**Table 1. Responsiveness of the SCP and the PASS at the subacute stage after stroke.**

<b>Responsiveness</b>	<b>ES</b>	<b>95% CI</b>	<b>SRM</b>	<b>95% CI</b>
<b>SCP</b>				
D30-D60	0.38	0.29-0.47	0.81	0.63-1.01
D60-D90	0.21	0.15-0.28	0.64	0.44-0.82
D30-D90	0.58	0.47-0.69	1	0.82-1.2
<b>PASS</b>				
D30-D60	0.55	0.47-0.63	1.29	1.12-1.49
D60-D90	0.29	0.24-0.35	0.93	0.74-1.11
D30-D90	0.81	0.7-0.92	1.42	1.24-1.62

SCP, Scale for Contraversive Pushing; PASS, Postural Assessment Scale for Stroke; ES, effect size; SRM, standardized response mean; CI, confidence interval.

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## Discussion

Our longitudinal study, investigated post-stroke balance recovery and lateropulsion recovery, with their interplay. We consecutively enrolled 106 individuals and soundly followed and assessed them 3 times in the subacute phase. Our study sample with careful follow-up is distinguished in current literature about post-stroke posture and balance, which is the major novelty of this study. Our findings demonstrate that balance improvement is possible without substantial change in body orientation with respect to gravity, but better orientation with respect to gravity amplified balance improvement during the same period. In particular, from D30 to D60, the improvement of lateropulsion could explain 40% of balance recovery. Another novelty of our study is that we provide novel information on the responsiveness of the SCP. Our findings show only small to moderate ES and SRM of the SCP, indicating an inadequate responsiveness of the SCP. Another clinimetric shortage of the SCP is the considerable floor effect since the first month after stroke. These 2 insufficient clinimetric properties don't suggest that the SCP is an adequate tool to monitor the lateropulsion recovery. In contrast, given good responsiveness and no floor and ceiling effect, we consider that the PASS should be a reliable tool to implicate in post-stroke balance recovery for both clinical and research use.

This study highlights again the effect of body orientation with respect to gravity affects the post-stroke balance control. Our previous study(Dai *et al.*, 2021a) shows that lateropulsion is the primary cause of balance disorders on D30. The current study reinforces the effect of lateropulsion persisting in balance recovery, at least in the first three months after stroke. Postural balance is ensured when the projection of the center of mass on the ground is inside the base of support. To reduce the destabilizing effect of gravity, the body must be oriented vertical (body orientation) and the oscillations around this orientation controlled (body stabilization).(Massion, 1992; Horak and Macpherson, 2011; Dai *et al.*, 2021a) Our results indicate that restoring the body upright is the primary objective in post-stroke balance recovery,



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contradicting a general knowledge that key objective is to regain are the stabilization component. In particular, from D30 to D60 balance improvement is amplified when lateropulsion recovers. From D60 to D90, the effect of lateropulsion seems to less affect the balance recovery. Given that some stabilization component determines long term balance recovery, such as single limb stance,(Dai *et al.*, 2021c) we assume that balance improvement is possible without substantial change in body orientation with respect to gravity, and due to an amelioration of body stabilization; the effect of body orientation on balance recovery would be attenuated by the post-stroke time, while the effect of body stabilization would be predominant in late subacute and chronic phases after stroke.

Responsiveness is a critical clinimetric property for posture and balance measures designed to evaluate change. We investigate the responsiveness of two scales as the second objective based on this large sample, which is sufficient to investigate this clinimetric property. However, our results reveal that the responsiveness of the SCP is inadequate, especially after D60. The binary “resistance” section scoring of the SCP potentially reduces its responsiveness. In addition, the considerable floor effect of the SCP is another clinimetric deficit, which can also affect the responsiveness. Our findings lead to no longer consider the SCP as a gold standard. The responsiveness of another lateropulsion scale, the Burke Lateropulsion Scale (BLS) has been studied once in a small simple (n=43), which was good (SRM=1.48 and 2.24) at 4 and 8 weeks, respectively.(Clark *et al.*, 2012) Although the floor effect of the BLS hasn’t been reported, we could find potential floor effect in some studies that used this scale.(Bergmann *et al.*, 2019; Chow *et al.*, 2019) Thus, we should question about the tool to monitor the lateropulsion recovery and seek a new one to bridge the gap. We find adequate responsiveness of the PASS to monitor the changes in the subacute phase after stroke, and don’t find any floor or ceiling effect. These findings are congruent to abundant literature about the good clinimetric properties

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of the PASS,(Mao *et al.*, 2002; Clark *et al.*, 2012; Hsueh *et al.*, 2013) indicating the PASS is one of the best validated tool to monitor balance disorders after stroke.(Mao *et al.*, 2002)

One major limitation of our study concerns the generalizability of our results. Our study aimed to examine the recovery in individuals followed inpatient rehabilitation at least till D90 after stroke, which precluded many individuals with light deficits who already returned to community or outpatient rehabilitation on D90. Our baseline mRS indicates our enrolled individuals have moderate to severe disabilities. Therefore, our findings may be generalized to the context of rehabilitation of post-stroke individuals with critical disabilities, which is overall important because lateropulsion is a major rehabilitation challenge. Another limitation of our study is that the SCP is lack of cross-cultural validation from the original language of German into English and has several reformulations of items by authors.

To conclude, in this longitudinal cohort, our findings indicate that balance improvement is amplified when lateropulsion recovers. After stroke, rehabilitation programs should better consider body orientation with respect to gravity. The current gold standard tool (SCP) is inadequate to implicate in monitoring lateropulsion recovery, which calls for a novel scale to bridge the gap.

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## ➤ Chapter 8

This research is the first to investigate the role of white matter hypertensities (WMHs) on post-stroke balance and lateropulsion recovery. This chapter has 2 related parts. The first one investigating the balance and gait recovery is already published online in Ann Phys Rehabil Med (DOI: 10.1016/j.rehab.2021.101488). The second one investigating the lateropulsion recovery has been accepted by Ann Phys Rehabil Med.

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**Part I: Recovery of balance and gait after stroke is deteriorated by confluent white matter hyperintensities: Cohort study**

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## Abstract

**Background.** White matter hyperintensities (WMHs) are well known to affect post-stroke disability, mainly by cognitive impairment. Their impact on post-stroke balance and gait disorders is unclear.

**Objectives.** We aimed to test the hypothesis that WMHs would independently deteriorate post-stroke balance and gait recovery.

**Methods.** This study was performed in 210 individuals of the cohort Determinants of Balance Recovery After Stroke (DOBRAS), consecutively enrolled after a first-ever hemisphere stroke. Clinical data were systematically collected on day  $30\pm 3$  (D30) post-stroke and at discharge from the rehabilitation ward. WMHs were searched on MRI, graded with the Fazekas scale, and dichotomized as no/mild (absence/sparse) or moderate/severe (confluent). The primary endpoint was the recovery of the single limb stance, assessed with the Postural Assessment Scale for Stroke (PASS). The secondary endpoint was the recovery of independent gait, assessed with the modified Fugl-Meyer Gait Assessment (mFMA). The adjusted hazard ratios (aHRs) of achievements of these endpoints by level of WMHs were estimated by using Cox models, accounting for other relevant clinical and imaging factors.

**Results.** Individuals with moderate/severe WMHs ( $n=86$ , 41%) had greater balance and gait disorders and were more often fallers than others ( $n=124$ , 59%). Overall, they had worse and slower recovery of single limb stance and independent gait ( $p<0.001$ ). Moderate/severe WMHs was the most detrimental factor for recovery of balance (aHR 0.46, 95% confidence interval [CI] 0.32–0.68,  $p<0.001$ ) and gait (0.51, 0.35–0.74,  $p<0.001$ ), along with age, stroke severity, lesion volume and disrupted corticospinal tract. With cerebral infarct, endovascular treatments had an independent positive effect, both on the recovery of balance (aHR 1.65, 95% CI 1.13–2.4,  $p=0.009$ ) and gait (1.78, 1.24–2.55,  $p=0.002$ ).



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**Conclusions.** WMHs magnify balance and gait disorders after stroke and worsen their recovery. They should be better accounted for in post-stroke rehabilitation, especially to help establish a prognosis of mobility.

**ClinicalTrials.gov registration:** NCT03203109.

**Key words.** white matter hyperintensities, balance, gait, stroke recovery, single limb stance

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## Introduction

After a stroke, predicting the functional prognosis is of major importance. With mobility limitation as one of the most frequent complains (Langhorne *et al.*, 2011) and one of the most severe causes of disability (Langhorne *et al.*, 2011), patients and relatives ask about the prognosis of mobility and express their hope of a good recovery. Although recovering balance control is a prerequisite for an independent gait and a satisfactory mobility (Dai *et al.*, (in-press)), the recovery of balance and gait disorders after stroke has been little modelled so far (de Haart *et al.*, 2005; Kollen *et al.*, 2005; Nardone *et al.*, 2009; Buvarp *et al.*, 2020; Dai *et al.*, (in-press)). There is a pressing need to acquire specific and in-depth knowledge in this domain, both for establishing individual prognosis and improving clinical trials focused on mobility (de Haart *et al.*, 2005; Yelnik *et al.*, 2008; Moucheboeuf *et al.*, 2020; Dai *et al.*, (in-press)).

Several factors may affect balance and gait recovery after stroke: stroke volume (Gentson *et al.*, 2008) and severity (Buvarp *et al.*, 2020), the disruption of the corticospinal tract (CST) (Marsden *et al.*, 2005), as well as the nature of clinical deficits (Nadeau *et al.*, 1999; Nardone *et al.*, 2009; Nonnekes *et al.*, 2018). Although highly suspected (Wardlaw *et al.*, 2019; Sagnier *et al.*, 2020), the detrimental role of preexisting brain alterations related to small vessel disease remains to be established for balance and gait recovery, as it has been for the recovery of generally disability (Georgakis *et al.*, 2019; Wardlaw *et al.*, 2019) and cognitive functions (Prins and Scheltens, 2015; Hachinski *et al.*, 2019; Zamboni *et al.*, 2019). Small vessel disease alters the whole brain, thus especially deteriorating functions such as balance control, which involve numerous areas distributed in both hemispheres, the cerebellum and the brain stem, interconnected in networks (Pérennou, 2006; Jahn and Zwergal, 2010; Lemaire *et al.*, (in-press 2021)). Overall, after a stroke, the reorganization of these networks supporting brain plasticity should be greatly altered by diffused brain alterations caused by small vessel disease. For

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example, the reorganization might alter the retuning of interhemispheric balance, involved in the sensorimotor recovery (Xu *et al.*, 2019).

White matter hyperintensities (WMHs) constitute the most striking marker of small vessel disease (Wardlaw *et al.*, 2013; Wardlaw *et al.*, 2019), associated with worse balance and gait capacities in older people (Masdeu *et al.*, 1989; Baezner *et al.*, 2008; Pinter *et al.*, 2017). If any, WMHs may be sparse or confluent (Fazekas *et al.*, 1987; Wardlaw *et al.*, 2019), which represents an indicator of severity, with greater and more diffuse whole brain alteration (Fazekas *et al.*, 1987; Wardlaw *et al.*, 2019).

This study analyzed the effect of WMHs (dichotomized as no/mild or moderate/severe) on balance and gait recovery in a large cohort of individuals followed at the subacute phase after a first hemisphere stroke. The primary endpoint was the recovery of the single limb stance, a challenging task requiring an efficient postural control of the trunk and the four limbs that involves precise spatial representation and a coordinated sensori-motor control of body segments, thus the whole brain (Marquer *et al.*, 2014). The second endpoint was independent gait, which involves a single limb stance. We used multivariate analyses dedicated to the follow-up to detect the possible effects of several other relevant clinical or imaging factors. We hypothesized that individuals with a stroke and preexisting confluent WMHs not only have greater balance disorders than others but also exhibit overall worse recovery of their balance abilities, especially the capacity to regain the single limb stance and to re-walk without a cane. The reporting of the study follows the STROBE statement (checklist in Appendix A.1).

## Methods

### Study design

This was a monocentric observational study involving data from the cohort Determinants of Balance Recovery After Stroke [DOBRAS]; ClinicalTrials.gov: NCT03203109) with

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participants comprehensively assessed in routine care in the rehabilitation ward (Dai *et al.*, (in-press)). For this study we used balance and gait data collected at 30 ( $\pm 3$ ) days after stroke (D30), then at discharge (within the last 3 days) in the neurorehabilitation ward. Assessments were performed by trained and multidisciplinary examiners, with blinding to other data and the study hypothesis. We also used demographic data and main clinical and imaging features. The sample size of the DOBRAS cohort was planned to conduct multivariate analyses focused on balance and gait recovery in a large series of individuals ( $\geq 200$  observations), including multivariate ( $\geq 3$  variables) Cox models performed in this study.

### **Ethical considerations and reporting**

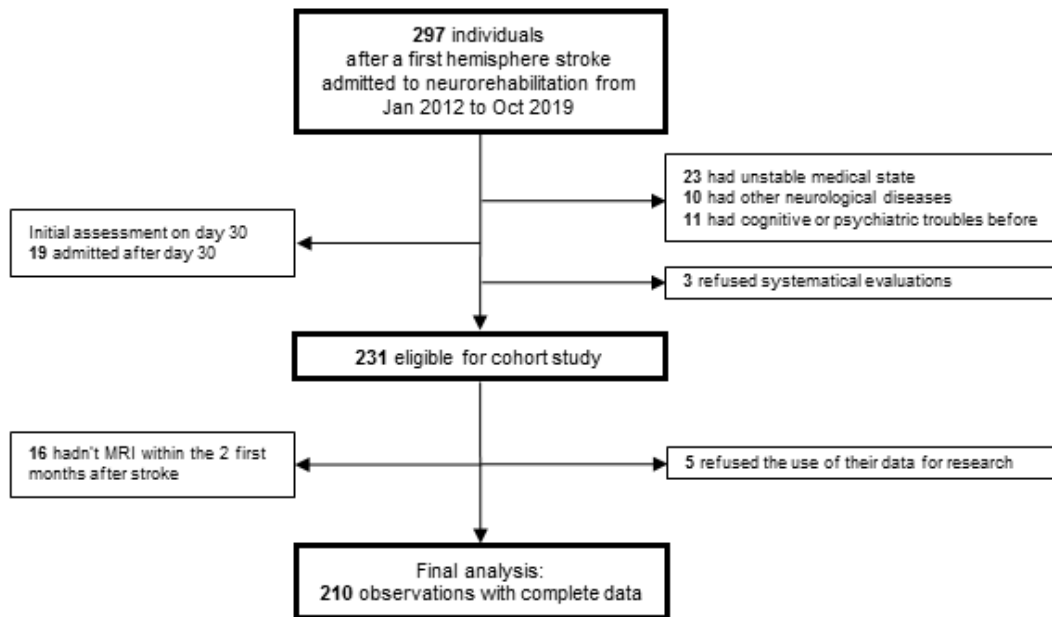
The DOBRAS cohort was approved by our institutional review board (CHU Grenoble Alpes) who validated the ClinicalTrials.gov registration (NCT03203109). The study was also registered at the National Committee for Informatics and Freedom (*Commission nationale informatique et liberté*; CNIL-No.2014874-v1) and was performed in accordance with the Helsinki Declaration. According to French law, observational studies do not require approval by a national 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**

From January 2012 to October 2019, we included 210 consecutive individuals (age 18 to 80 years), with a first-ever unilateral hemisphere stroke analyzed by MRI. Exclusion criteria were recurrent stroke, complications at the acute stage (malignant infarct, cerebral herniation, severe subarachnoid hemorrhage and hydrocephalus), dementia, previous disability interfering with

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balance or vestibular disorders, and unstable medical condition or psychiatric problems jeopardizing data reliability (Fig. 1). These conditions were obtained from the hospital electronic file describing the history of every patient, by interviewing patients and relatives, and by a systematic clinical examination. Participants followed a personalized rehabilitation program, taking into account deficits and activity limitations, capacities to face intensive rehabilitation (fatigue or transitory medical problems), individual recovery, and the most appropriate guidelines. According to their abilities, participants had at least 2 physiotherapy and 1 occupational therapy sessions per day (each session lasting at least 30 min for a total daily time of sensori-motor rehabilitation over  $\geq 1.5$  hr per patient), plus sessions with a speech therapist, neuropsychologist, psychologist, or orthoptist if needed. The length of hospitalization of our participants was measured from stroke onset to discharge of the rehabilitation ward.



**Figure 1.** Flow of participants in the study.

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### **Risk factors related to WMHs**

The categorical diagnosis of hypertension, diabetes, and dyslipidemia and information on consumption of tobacco and of alcohol were retrieved from hospital records for each participant. Thresholds were all those internationally recommended (details in Appendix A.1) (Williamson *et al.*, 2018).

### **Clinical assessments**

Balance disorders were assessed with the Postural Assessment Scale for Stroke (PASS), the most appropriate balance scale at the subacute stage after stroke [30,34]. The total score ranging from 0 to 36 (satisfactory balance) assesses balance abilities in daily life. The PASS score > 27/36 indicates a upright standing. The last 2 items assess single limb stance on paretic and non-paretic sides, which are independent of other items because of their difficulty (Persson *et al.*, 2017). According to the scoring of these items, an individual who is able to maintain a single limb stance for >5 sec (whatever the side) has a total PASS score > 32/36 [30], which we used as endpoint in this study. The 5-sec duration is the usual cutoff considered to indicate that this task is achieved [30,31]. The side of the single limb stance is almost always the non-paretic side in individuals with stroke (Benaim *et al.*, 1999).

Gait disorders were assessed with the modified Fugl-Meyer Assessment of gait (mFMA-gait), designed to classify post-stroke gait in 7 levels of mobility (Lindmark and Hamrin, 1988). The mFMA-gait score ranges from 0 (no possibility to walk) to 6 (indicating a [quasi] normal gait) [35]. The 7 levels are as follows: 0, cannot walk at all; 1, can walk with the help of two persons; 2, can walk with the help of one person; 3, walk with the help of a walker, crutches or quadripod cane; 4, walk with the help of a simple cane or a crutch; 5; walk without any help but slowly or with lameness; 6, walk with normal speed for age. We used as the endpoint a score >4 indicating the ability to walk independently without a cane (or walker).

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A fall was defined as an event that results in a person coming to rest inadvertently on the ground (Zecevic *et al.*, 2006). Falls during the rehabilitation ward (wherever the room and the time of occurrence) were monitored by the multidisciplinary team all during the rehabilitation stay. Any fall was declared on a specific hospital register and recorded in the patient's electronic file. The presence and number of falls were counted at the end of the stay. A faller was defined as a person who fell at least once.

Global disability was estimated with the modified Rankin Scale (mRS).

Clinical features of stroke comprised the initial stroke severity estimated by the US National Institutes of Health Stroke Scale (NIHSS) at 24 hr post-stroke (range 0-42, higher scores indicating greater stroke severity), stroke type (ischemic or hemorrhagic) and side (right or left hemisphere) as well as cortical or subcortical stroke location. Intravenous thrombolysis and/or thrombectomy were also considered for ischemic strokes.

### **Brain imaging**

The presence of WMHs was sought on T2-FLAIR sequences from the first or second MRI (within the first 2 months after stroke) and graded with the Fazekas scale (Fazekas *et al.*, 1987). The scale simply grades WMHs in 4 levels: 0, no lesion; 1, focal lesions; 2, beginning lesions confluences; and 3, extended involvement with large confluent areas [32]. Two trained independent examiners (SD, CP), carefully examined the absence, presence, and severity of WMHs in the hemisphere spared by the stroke. If any, their differences of grading were resolved by consensus (Wardlaw *et al.*, 2013).

According to recommendations (Wardlaw *et al.*, 2014; Georgakis *et al.*, 2019), we a priori planned to regroup grades 0 and 1 and grades 2 and 3. This approach takes into account the low frequency of grade 3 in individuals with a first hemisphere stroke and the fact that the difference between grades 0 and 1 may be tenuous. Its appropriateness was confirmed by our data.



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Complementary analyses were performed to control for possible confounders, such as stroke volume and CST disruption, known to affect balance and gait disorders (Pérennou *et al.*, 2000; Marsden *et al.*, 2005; Genthon *et al.*, 2008; Soulard *et al.*, 2020). These imaging confounders were analyzed in the second MRI, with a reasonable interval that is recommended to avoid overestimating stroke volume (Nagaraja *et al.*, 2020). Details about the machine and acquisition parameters are given in Appendix A.1. Lesion volume, determined as the percentage of hemisphere encroached on by the lesion (number of voxels for the lesion/number of voxels for the hemisphere \*100) was measured by using MRICron after a manual lesion delineation from axial slices acquired with T2-FLAIR sequences. All drawings involved 2 trained operators, the first from a panel of three (CL, SD, AC) and the second always the same and with blinding to behavioral data (CP). Any disagreements were resolved by consensus. Drawings were performed on axial slices of a T1-weighted MRI template from the Montreal Neurological Institute (<https://www.mcgill.ca/bic/neuroinformatics/brain-atlases-human>) normalized to Talairach's space. CST disruption was analyzed with the "Tractotron" tool of the BCBToolkit software (<http://toolkit.bcblab.com/>), which determines the disruption induced at the level of a given lesion. Each participant's lesion was compared with an atlas of white matter tracts for each voxel. As suggested, we analyzed both the proportion and probability of the ipsilesional CST disrupted by the stroke (Foulon *et al.*, 2018). The proportion corresponds to the number of damaged voxels in the CST divided by the total volume of this tract. The probability corresponds to the lesioned voxel with the highest percentage value. The CST was considered disrupted when an estimated proportion or probability was >50% (Foulon *et al.*, 2018).

For clarity reasons and length constraint, the effect of stroke location on balance and gait recovery was not analyzed in this study focused on the effects of WMHs as a marker of small vessel disease.

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## Statistical analysis

The two groups of WMH severity were compared with Mann-Whitney and chi-square tests. Effect sizes were calculated for significant factors by using the Z values of the Mann-Whitney test,  $r=Z/\sqrt{n}$ , and the  $X^2$  of the chi-square test,  $v=\sqrt{(X^2/n*\text{degree of freedom})}$ . Values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both tests (Tomczak and Tomczak, 2014). Factors found significant on univariate analysis were entered into a binary logistic regression to determine independent factors associated with moderate/severe WMHs. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated.

Cox proportional-hazard regression was used to determine factors independently associated with the achievement of the single limb stance and the achievement of the independent gait. We adopted this type of model because it determines independent factors involved in the recovery of these endpoints, taking into account individual timelines for this recovery (from D30 to discharge). Cases were censored as follows: recovery of single limb stance regardless of supporting lower limb with PASS score  $>32/36$ , recovery of independent gait with mFMA-gait score  $>4/6$ . We used backward Cox models to estimate the adjusted hazard ratios (aHRs) of these endpoints (with 95% CIs). Two Cox models were run, for the recovery of balance (primary criteria) and gait, a primary model with relevant clinical factors (age, stroke severity and type, sex, BMI and endovascular treatments limited to infarcts), and a complementary model with imaging factors being potential confounders (stroke volume, CST disruption).

In addition, Kaplan-Meier survival tests were performed to compare the timeline of the achievement of single limb stance (and independent gait) between individuals with no/mild WMHs and those with moderate/severe WMHs. Differences between participants with no/mild and moderate/severe WMHs were compared by the log-rank test.

The relationships between balance and gait disorders (at D30 and discharge) were tested by linear regression. Continuous data are presented as median (Q1–Q3) and categorical data as

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number (percentage, %). Two-sided  $p < 0.05$  was considered statistically significant. Statistical analyses involved using SPSS 24.0 and Stata 15.1. The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Results

The median age of the 210 participants was 67.3 years (57.4–72.7); 68 (32%) were females. In total, 172/210 (82%) had a brain infarct; 65 (38%) received thrombolysis and/or thrombectomy. The initial stroke severity was moderate to severe (median NIHSS on D1 12 [7–16]).

No data were missing for the primary analyses. Complementary analyses with stroke volume and CST disruption were conducted on the 182/210 observations of participants who had a second MRI (87%). To ensure the validity of the complementary cox model for imaging data, we analyzed the data sensitivity within the frame of the whole series. Sensitivity was high: 0.88 and 0.87 for the endpoints of single limb stance and independent gait, respectively. These results indicated that missing data for brain imaging were randomly distributed, inducing no bias.

### Features of individuals with WMHs

A total of 44 (21%) participants did not show WMHs (grade 0); 166 (79%) presented WMHs graded as follows: grade 1, 80 (38%); 2, 71 (34%); and 3, 15 (7%). We constituted 2 groups: no/mild WMHs ( $n=124$ , 59%) and moderate/severe WMHs with confluent lesions ( $n=86$ , 41%). Characteristics are compared in Table 1. The latter group was older, more often female, more often hypertensive, and with more hematomas than the former group. When these 4 variables were analysed by binary logistic regression, sex did not remain significant, in contrast to hematoma (aOR 2.5, 95% CI 1.12–5.73,  $p=0.025$ ), hypertension (2.17, 1.1–4.28,  $p=0.025$ ), and age (1.08, 1.04–1.12,  $p < 0.001$ ). The 2 groups did not differ in brain imaging, including stroke

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volume or proportion/probability of CST disruption. Disability was greater with moderate/severe than no/mild WMHs, both at D30 and discharge. The length of hospitalization since stroke (acute/subacute neurological units, then neurorehabilitation ward) was longer in the moderate/severe than no/mild WMHs group.

**Table 1. Demographic and clinical features of individuals with no/mild or moderate/severe white matter hyperintensities (WMHs).**

	No/mild WMHs (n=124)	Moderate/severe WMHs (n=86)	P-value	Effect size
<b>Demographics</b>				
Age (years)	63.6 (53–69)	70.9 (66–74)	<0.001	r = -0.37
Sex, female (%)	32 (26)	36 (42)	0.014	v = 0.16
BMI (kg/m <sup>2</sup> )	24.5 (22–28)	26.2 (23–28)	0.134	
<b>WMH risk factors</b>				
Hypertension (%)	62 (50)	66 (77)	<0.001	v = 0.28
Diabetes (%)	21 (17)	22 (26)	0.127	
Dyslipidemia (%)	56 (45)	42 (49)	0.6	
Tobacco smoking (%)	77 (62)	44 (51)	0.115	
Alcohol drinking (%)	32 (26)	17 (20)	0.309	
<b>Stroke features</b>				
Stroke type: infarct (%)	108 (87)	64 (74)	0.019	v = 0.16
Thrombolysis and/or thrombectomy (%)	42 (39)	23 (36)	0.7	
Stroke side: right hemisphere (%)	56 (45)	39 (45)	0.979	
Stroke location (%):			0.284	
-Subcortical	34 (27)	30 (35)		
-Cortical	47 (38)	24 (28)		
-Subcortical+cortical	43 (35)	32 (37)		
Initial NIHSS score (0-42)	12 (7–16)	11 (7–16)	0.948	
<b>*Imaging features</b>				
*Delay of MRI (in rehabilitation) after stroke onset (days)	62 (59–74)	63 (58–76)	0.673	
*Lesion volume			0.497	
-in voxels	17,353 (3,781–40,600)	9,720 (2,061–38,202)		
-in %	2.3 (0–5)	1.3 (0–5)		
*Disrupted CST			0.654	
-Proportion > 50% (%)	62 (59)	48 (62)		
-Probability > 50% (%)	104 (99)	77 (100)	1	
<b>Disability</b>				
mRS on D30 (0-6)	3 (2–3)	3 (3–4)	<0.001	r = -0.31
mRS at Discharge (0-6)	2 (1–2)	2 (2–3)	0.001	r = -0.3
<b>#Length of hospitalization since stroke (days)</b>	69 (48–111)	107 (61–166)	0.001	r = -0.23

Data are n (%) or median (Q1–Q3).

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BMI, body mass index. NIHSS, US National Institutes of Health Stroke Scale. CST, corticospinal tract. D30, day 30. mRS, modified Ranking Scale. Effect sizes are given as “r” for the Mann-Whitney test and “v” for chi-square test. With  $p < 0.05$ , effect sizes are given; values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both the Mann-Whitney and chi-square tests.

\*Imaging features were analyzed in 182 individuals with control MRI around day 60.

# Duration from stroke onset to discharge from the rehabilitation ward.

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### **Balance and gait disorders**

Balance and gait scores were highly correlated, both at D30 ( $r=0.89$ ,  $p<0.001$ ) and at discharge ( $r=0.86$ ,  $p<0.001$ ), so balance capacity highly explained the information contained in gait capacity: 79% (95% CI 75–84,  $p<0.001$ ) at D30 and 73% (67–79,  $p<0.001$ ) at discharge.

Balance and gait disorders were worse with moderate/severe than no/mild WMHs, both at D30 and discharge (Table 2).

Fallers more frequently had moderate/severe than no/mild WMHs (Table 2). The mean (SD) incidence of falls during rehabilitation was 0.6 (0.1) per person for 100 days with moderate/severe WMHs and 0.2 (0.1) per person for 100 days in others.

**Table 2. Balance and gait between groups with no/mild versus moderate/severe white matter hyperintensities (WMHs).**

	No/mild WMHs (n=124)	Moderate/severe WMHs (n=86)	P-value	Effect size
<b>D30</b>				
Balance (PASS, 0-36)	33 (27–36)	29 (16–33)	<0.001	r = -0.28
Gait (mFMA-gait, 0-6)	5 (3–6)	3 (0–5)	<0.001	r = -0.26
<b>Discharge</b>				
Balance (PASS, 0-36)	35 (33–36)	33 (31–34)	<0.001	r = -0.36
Gait (mFMA-gait, 0-6)	5 (5–6)	5 (3–6)	0.013	r = -0.25
<b>Fallers (%)</b>	20 (16)	32 (36)	0.001	v = 0.23

Data are n (%) or median (Q1–Q3).

D30, day 30. PASS, Postural Assessment Scale for Stroke. mFMA-gait, modified Fugl-Meyer Assessment of gait.



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## Balance recovery

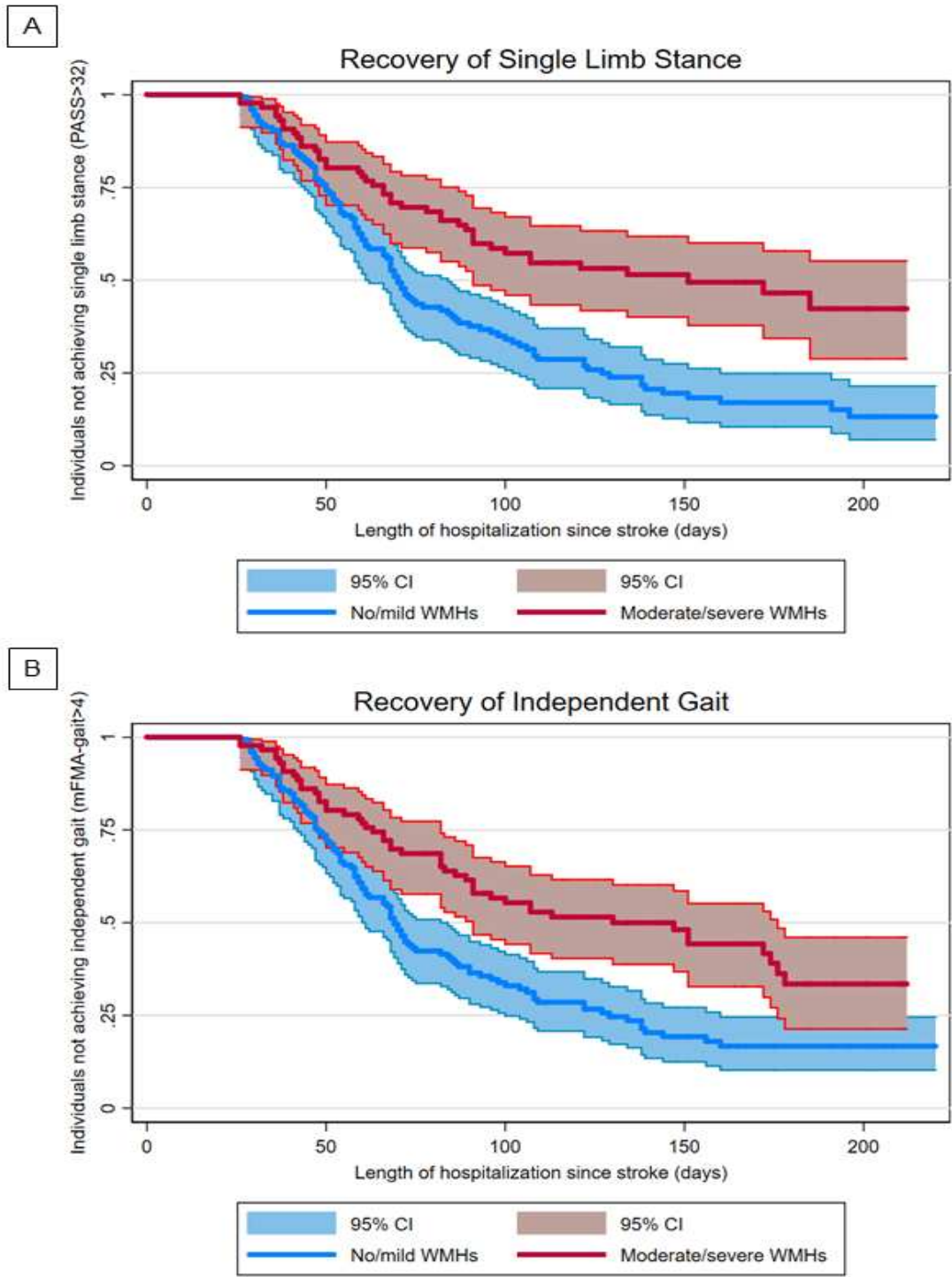
In the first Cox model with clinical features (Table 3, upper part), moderate/severe WMHs had an independent detrimental role in balance recovery (aHR 0.46, 95% CI 0.32–0.68,  $p < 0.001$ ), along with age and initial NIHSS score. The aHR value of 0.46 meant that the chance to achieve the single limb stance (>5 sec) at discharge for individuals with moderate/severe WMHs was 0.46-fold that of individuals of the same age and stroke severity but with no/mild WMHs. Stroke type, sex, and BMI were not independently associated with poor balance recovery. This model limited to infarcts to include endovascular treatments (Appendix A.1) showed thrombolysis and/or thrombectomy with an independent beneficial effect on balance recovery (aHR 1.65, 95% CI 1.13–2.4,  $p = 0.009$ ). In the second model with imaging factors (Table 3, lower part), WMHs also played a primary detrimental role in balance recovery (aHR 0.46, 95% CI 0.31–0.67,  $p < 0.001$ ), along with disrupted ipsilesional CST and stroke volume. The aHR value of 0.46 meant that the chance to achieve the single limb stance (>5 sec) at discharge of individuals with moderate/severe WMHs was 0.46-fold that of individuals of the same lesion volume and CST disruption but with no/mild WMHs. The Kaplan-Meier survival test showed that the achievement of single limb stance was less frequent and delayed with moderate/severe than no/mild WMHs (Fig. 2A;  $X^2 = 19.2$ ,  $p < 0.001$ ). The single limb stance was achieved with a median delay of 151 (66–196) days with moderate/severe WMHs and 70 (50–127) days for others. At discharge, 49% of participants with moderate/severe WMHs could not maintain the single limb stance for 5 sec versus 19% of those with no/mild WMHs ( $X^2 = 20.5$ ,  $v = 0.31$ ,  $p < 0.001$ ).

**Table 3. Multivariate Cox regression models\* of factors associated with achieving single limb stance after stroke.**

<i>Variables</i>	<b>aHR</b>	<b>95% CI</b>	<b>P-value</b>
<b>Model 1 with clinical features (n = 210)</b>			
<b>WMHs</b> (moderate/severe vs no/mild)	0.46	0.32–0.68	<0.001
<b>Age</b> (per year)	0.98	0.97–0.99	0.005
<b>Initial NIHSS score</b> (per point)	0.84	0.81–0.87	<0.001
<b>Model 2 with imaging features (n =182)</b>			
<b>WMHs</b> (moderate/severe vs no/mild)	0.46	0.31–0.67	<0.001
<b>Lesion volume</b> (per 1% of hemisphere)	0.94	0.91–0.98	0.003
<b>Disrupted CST</b> (proportion > 50% vs ≤ 50%)	0.59	0.4–0.89	0.01

WMHs, white matter hypertensities. NIHSS, US National Institutes of Health Stroke Scale. CST, corticospinal tract. aHR, adjusted hazard ratio. CI, confidence interval.

\*Two models were tested. Model 1 involved clinical features of the 210 individuals with follow-up from day 30 post-stroke to discharge from the rehabilitation ward. Model 2 involved imaging features analyzed on MRI performed about 2 months after the stroke (182 individuals).



**Figure 2.** Recovery of balance and gait. Time to achieve A) single limb stance (Postural Assessment Scale for Stroke score >32) and B) independent gait (modified Fugl-Meyer Assessment of Gait score >4) for 2 groups of white matter hyperintensities (WMHs).

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## Gait recovery

In the first Cox model with clinical features (Table 4, upper part), moderate/severe WMHs had an independent detrimental role in gait recovery (aHR 0.51, 95% CI 0.35–0.74,  $p < 0.001$ ), along with age and initial NIHSS score. Stroke type, sex, and BMI were not independently associated with poor gait recovery. This model limited to infarcts to include endovascular treatments (Appendix A.1) showed that thrombolysis and/or thrombectomy had an independent beneficial effect on gait recovery (aHR 1.78, 95% CI 1.24–2.55,  $p = 0.002$ ). In the second model with imaging factors (Table 4, lower part), WMHs played a detrimental role in gait recovery (aHR 0.52, 95% CI 0.36–0.75,  $p = 0.001$ ), along with disrupted ipsilesional CST and stroke volume. The Kaplan-Meier survival test showed that the achievement of independent gait was less frequent and delayed with moderate/severe than no/mild WMHs ( $X^2 = 15.1$ ,  $p < 0.001$ ) (Fig. 2B). Independent gait was achieved at a median delay of 130 (63–176) days with moderate/severe WMHs versus 69 (47–129) days with no/mild WMHs. At discharge, 43% of participants with moderate/severe WMHs could not regain independent gait versus 19% of those with no/mild WMHs ( $X^2 = 13.8$ ,  $v = 0.26$ ,  $p < 0.001$ ).

**Table 4. Multivariate Cox regression models\* of factors associated with achieving independent gait after stroke.**

<i>Variables</i>	<b>aHR</b>	<b>95% CI</b>	<b>P-value</b>
<b>Model 1 with clinical features (n =210)</b>			
<b>WMHs</b> (moderate/severe vs no/mild)	0.51	0.35–0.74	<0.001
<b>Age</b> (per year)	0.98	0.97–1	0.006
<b>Initial NIHSS score</b> (per point)	0.83	0.8–0.86	<0.001
<b>Model 2 with imaging features (n =182)</b>			
<b>WMHs</b> (moderate/severe vs no/mild)	0.52	0.36–0.75	0.001
<b>Lesion volume</b> (per 1% of hemisphere)	0.94	0.91–0.98	0.002
<b>Disrupted CST</b> (proportion > 50% vs ≤ 50%)	0.61	0.42–0.9	0.013

WMHs, white matter hypertensities. NIHSS, US National Institutes of Health Stroke Scale. CST, corticospinal tract. aHR, adjusted hazard ratio. CI, confidence interval.

\*Two models were tested. Model 1 included clinical features of the 210 individuals with a follow-up from day 30 post-stroke to discharge from the rehabilitation ward. Model 2 included imaging features analyzed by MRI performed about 2 months after the stroke (182 individuals).

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## Discussion

Our study confirms that gait disorders after stroke are more severe with confluent WMHs (Nadeau *et al.*, 2016; Sagnier *et al.*, 2020), reveals that this is due to balance disorders, and extends this finding to the risk of being a faller. Using multivariate Cox regression models and Kaplan-Meier survival tests to master possible confounding variables and rank independent effects, we confirm our hypothesis that WMHs independently alter the recovery of balance and gait, regardless of other clinical and imaging factors. The study goes even beyond our hypothesis, discovering that the presence of confluent WMHs plays a primary detrimental role on the recovery of endpoints such as the ability to maintain the single limb stance for 5 sec or the ability to walk without a cane, achieved roughly twice less frequently than for other patients of same age, stroke severity and volume, and disruption of CST. The single limb stance appears to be a key milestone, which should deserve more attention in balance and gait rehabilitation after stroke. These findings were obtained in a large series of consecutive individuals admitted to rehabilitation after a first hemisphere stroke (n=210), with stroke severity (NIHSS, lesion volume, disability) comparable to that reported in the literature.

### WMHs

Described 3 decades ago, under the terms leukoaraiosis and WMHs (Fazekas *et al.*, 1987), altered brain white matter has become a major topic in gerontology and in vascular and neurological sciences. The literature is abundant and congruent about the detrimental effects of WMHs on cognitive functions (Prins and Scheltens, 2015; Hachinski *et al.*, 2019; Zamboni *et al.*, 2019). However, the literature is more limited but still consensual about the detrimental effect of WMHs on mobility (Masdeu *et al.*, 1989; Baezner *et al.*, 2008; Pinter *et al.*, 2017), most cohorts involving older people or people with neurodegenerative diseases (Zheng *et al.*, 2011; Hachinski *et al.*, 2019).

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WMHs and stroke share common risk factors (Wardlaw *et al.*, 2014; Lane *et al.*, 2019), and WMHs increase the risk of stroke (Georgakis *et al.*, 2019). We found WMHs associated with usual demographic, cardiovascular and clinical factors (i.e., age, hypertension, and hemorrhagic stroke).

### **Balance disorders and their recovery after stroke**

Balance ability refers to a dual control: for body orientation with respect to gravity and body stabilization with respect to the base of support (Horak and Macpherson, 2011). Balance disorders combine both types of impairments (Dai *et al.*, (in-press)), especially after stroke, and are globally assessed in daily life by the PASS, used in our study. We showed that individuals with moderate/severe WMHs have worse balance disorders than others at the subacute phase after stroke but did not analyse the specific effect of WMHs or body orientation with respect to gravity or body stabilization with respect to the base of support. This remains to be investigated. Single limb stance is considered one of most challenging balance tests in the general population (Vellas *et al.*, 1997; Horak and Macpherson, 2011), a predictor of age-related decline (Vellas *et al.*, 1997) and also a milestone of satisfactory balance after stroke (Benaim *et al.*, 1999; Persson *et al.*, 2017). For these reasons, the single limb stance would represent a particularly relevant aspect to investigate the impact of diffused brain alterations related to small vessel disease on balance recovery after stroke.

Using comprehensive multivariate analyses (Cox models), we showed that moderate/severe WMHs was one of the most detrimental factors affecting recovery of the single limb stance, whose achievement in individuals with confluent WMHs (grades 2 and 3) was twice less frequent than in individuals without or with sparse WMHs (grades 0 and 1), regardless of other clinical and imaging factors. We do not exclude that the preexistence of the WMHs might have affected the capacity of some individuals to balance on one leg before the stroke, particularly

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in the oldest participants. Although preexisting balance disorders was an exclusion criterion for this study, balance abilities had not been quantified before the stroke, which leads us to remain cautious with this assumption. However, several studies have indicated that abnormal single limb stance would be a marker of pathological cognitive and motor decline, a predictor of severe falls (with lesion) in older adults (Vellas *et al.*, 1997). Given its simplicity, the single limb stance deserves wider utilization in medicine, to detect the consequence of general vascular risk factors on the brain.

Our study also underlines the detrimental effects of age, stroke severity, lesion volume, and disruption of CST, mainly taken into account in our models as possible confounders. There is a rich literature on the detrimental effect of CST disruption on the functional ability of upper and lower limbs after stroke (Stinear *et al.*, 2020), but the literature is more sparse on the effect of disrupted CST on post-stroke balance disorders (Marsden *et al.*, 2005). Our study revealed that achieving the ability to maintain the single limb stance for 5 sec is greatly affected by an important disruption of CST.

Age (de Haart *et al.*, 2005), stroke severity and lesion volume (Pérennou *et al.*, 2000; Genthon *et al.*, 2008; Moon *et al.*, 2017) are well-known factors affecting post-stroke balance abilities. Our study is one of the first to reveal the independent detrimental effect of these factors on the recovery of balance after stroke, especially on the achievement of the single limb stance.

In our study, the probability to recover the ability to stand on one leg (for >5 sec) was 65% greater for individuals who underwent recanalization than others with a cerebral infarct but no endovascular treatment, regardless of other factors. This finding supports the view that individuals with confluent WMHs may be considered for endovascular treatments (Charidimou *et al.*, 2016; Boulouis *et al.*, 2019).



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## **Gait disorders and their recovery after stroke**

In our series of individuals examined at the subacute stage after stroke, gait ability was mainly linked to balance ability, so gait and balance were similarly affected by WMHs. WMHs predicted the recovery of an independent gait (walking without any assistance), considered an endpoint for recovery of satisfactory gait in the context of post-stroke rehabilitation. The single stance is the critical event of a gait without technical aid, requiring the ability to bear the body's weight on a single lower limb (alternatively non-paretic and paretic) and to master the control of a dynamic balance on this narrow base of support. This challenging task involves both hemispheres, which explains the detrimental role of moderate/severe WMHs on regaining independence of gait. This result was obtained with multivariate analyses, which again revealed the negative effect of age, stroke severity, lesion volume, and also marked disruption of the ipsilesional CST. These findings confirm previous results of studies of gait recovery after stroke, reporting the negative effect of age (Kollen *et al.*, 2005; Buvarp *et al.*, 2020), stroke severity (Buvarp *et al.*, 2020) and lesion volume (Moon *et al.*, 2017). The effect of disrupted CST on gait ability (Soulard *et al.*, 2020) has been more recently demonstrated. Of note, our study also showed a beneficial effect of endovascular therapy on gait recovery.

## **Falls**

WMHs are a well-known determinant of falls in older people (Masdeu *et al.*, 1989) and also a factor increasing the risk of falls after stroke (Sibolt *et al.*, 2014). We confirmed these findings, fallers being twice more frequent with moderate/severe than no/mild WMHs, which call for better fall prevention in stroke individuals showing moderate/severe WMHs. The analysis of brain imaging should be more systematic for assessing the individual risk of fall after stroke.

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### **Impact of these results to the field**

Predicting functional prognosis is of major importance after a stroke, and our study revealed that individuals with confluent WMHs had 2-fold less chance than others to recover an independent gait (without a cane), other things being equal, likely because of difficulty mastering the single limb stance (Guillebastre *et al.*, 2012). Preexistence of severe comorbidity (Buvarp *et al.*, 2020), stroke severity including severe weakness (Nadeau *et al.*, 1999) and spatial neglect (Pérennou, 2006), together with the presence of a net lateropulsion (Dai *et al.*, (in-press)) are the principle indicators of poor functional prognosis, jeopardizing the recovery of an efficient or even independent gait several months after the stroke. Our study reveals that whole brain alteration by small vessel disease is another major indicator raising fears of poor gait recovery, found the primary one in our study. The patient and the relatives must be informed, and solutions found to ensure, if possible by other ways, an independent mobility (wheelchair), with a house adapted as early as possible to prepare for discharge (to not inappropriately extend the length of stay). More positively, a reasonable short length of stay may be expected for individuals with no or sparse WMHs. An intact brain parenchyma outside the stroke should facilitate brain plasticity and recovery. We do not know whether a rigorous mastering of small-vessel disease risk factors might have a positive effect on long-term balance and gait recovery. With this hope at least for individuals with moderate forms, a systematic detection of WMHs after stroke is useful to treat the accessible risk factors. With a therapeutic education leading to appropriate lifestyle modification (Lane *et al.*, 2019), this should be a major challenge during the stay in the rehabilitation ward.

For research, our study suggests that stratifying trials of post-stroke balance and gait rehabilitation by level of WMH severity could be relevant. This stratification has been performed rarely, which might contribute to the high rate of negative trials in the field. MRI should be more systematically considered in this context. CST disruption is an important factor

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increasingly being taken into account to explain a poor recovery (Rondina *et al.*, 2017; Stinear *et al.*, 2020). Our study suggests adding WMHs as another possible brain imaging biomarker of post-stroke recovery, at least for balance and gait.

### **Limitations**

We used the Fazekas scale to quantify WMHs alterations, so we partly assessed MRI signs of small vessel disease and did not quantify WMHs in specific areas (periventricular or deep white matter) but rather hemisphere globally (side opposite the stroke). The Fazekas scale classifies individuals into 4 grades. Because of the limited number of individuals in grades 0 and 3, we merged grades 0 and 1 (no/mild WMHs) and grades 2 and 3 (moderate/severe WMHs). With this procedure that is frequently adopted (Wardlaw *et al.*, 2014; Georgakis *et al.*, 2019), sample sizes were satisfactory in both groups (124 vs 86), ensuring clear and robust conclusions. However, the specific impact of grades 0 and 3 on balance and gait recovery remained unanswered. We do not frequently admit individuals >80 years old in our ward for rehabilitation after stroke, which explains why individuals of our series are among the youngest in the literature, with a relatively low prevalence of Fazekas grade 3. The ceiling effects of PASS and mFMA scores might be considered another limitation of the study. This is why we did not use scores but rather endpoints, analyzed with Cox regression models and Kaplan-Meier survival tests. The generalizability of our findings is limited to post-stroke rehabilitation (Langhorne *et al.*, 2011; van der Vliet *et al.*, 2020). In this context, the results seem generalizable because participants had the usual demographic, cardiovascular and clinical factors associated with WMHs.

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## Conclusions

After stroke, WMHs alter balance and gait recovery and increase the number of fallers. These findings appeal for a systematic detection of WMHs in post-stroke rehabilitation, both in routine practice and research. In routine practice, knowing the existence and severity of WMHs should help establish the prognosis in terms of mobility recovery. For research, our study highlights the interest of a stratification by WMH grades for trials of balance and gait rehabilitation.

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**Conflict of interest.** None declared.

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## Appendix A.1

### Supplemental Methods

#### **Risk factors related to white matter hyperintensities (WMHs)**

Main WMHs risks were defined as follows: “hypertension” with systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg; “diabetes” with glycated hemoglobin A1c level  $\geq 6.5\%$ ; “dyslipidemia” with low-density lipoprotein cholesterol level  $\geq 100$  mg/dL ( $\geq 2.6$  mmol/L); “tobacco consumption” with smoking at least 1 cigarette per day for at least 6 months, both former and current smokers concerned; “alcohol consumption” with drinking at least 8 drinks (usually about 10 g of alcohol/drink in Europe) per week, both former and current drinkers concerned.

#### **Brain imaging**

For the second MRI performed about 2 months post-stroke, the machine was 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 mm<sup>3</sup>; TR/TE/TI/ $\alpha$ : 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 mm<sup>3</sup>; TR/TE/TI: 9000/74/2500 ms).

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**Supplemental Table 1.** Multivariate Cox regression model of factors (including endovascular treatments, n=172) associated with achieving single limb stance after stroke.

Variables	aHR	95% CI	P-value
WMHs (moderate/severe vs no/mild)	0.47	0.31–0.75	0.001
Age (per year)	0.98	0.97–1	0.007
Initial NIHSS score (per point)	0.83	0.79–0.87	<0.001
Endovascular treatments (yes vs no)	1.65	1.13–2.4	0.009

WMHs, white matter hyperintensities; NIHSS, US National Institutes of Health Stroke Scale; aHR, adjusted hazard ratio; CI, confidence interval; Endovascular treatments, intravenous thrombolysis and/or thrombectomy.

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**Supplemental Table 2.** Multivariate Cox regression model of factors (including endovascular treatments, n=172) associated with achieving independent gait after stroke.

Variables	aHR	95% CI	P-value
WMHs (moderate/severe vs no/mild)	0.56	0.37–0.85	0.007
Age (per year)	0.98	0.97–0.99	0.006
Initial NIHSS score (per point)	0.82	0.79–0.86	<0.001
Endovascular treatments (yes vs no)	1.78	1.24–2.55	0.002

WMHs, white matter hyperintensities; NIHSS, US National Institutes of Health Stroke Scale; aHR, adjusted hazard ratio; CI, confidence interval; Endovascular treatments, intravenous thrombolysis and/or thrombectomy.

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## STROBE checklist.

STROBE Statement—checklist of items that should be included in reports of observational studies (STROBE checklist for cohort, case-control, and cross-sectional studies [combined]).

	<b>Item No</b>	<b>Recommendation</b>
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract <b>Title and abstract</b>  (b) Provide in the abstract an informative and balanced summary of what was done and what was found <b>Abstract</b>
<b>Introduction</b>		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported <b>Introduction</b>
Objectives	3	State specific objectives, including any prespecified hypotheses <b>Introduction: fourth para</b>
<b>Methods</b>		
Study design	4	Present key elements of study design early in the paper <b>Methods: First para</b>
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection <b>Methods</b>
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <b>Methods: Participants</b>  Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants <b>Methods: Participants, Statistical analysis</b>
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable <b>Methods: Clinical assessments, Brain imaging</b>
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group <b>Methods: Clinical assessments, Brain imaging</b>
Bias	9	Describe any efforts to address potential sources of bias <b>Methods: Clinical assessments, Brain imaging; Discussion: Limitations</b>
Study size	10	Explain how the study size was arrived at <b>Methods: Participants</b>

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why <b>Methods: Statistical analysis</b>
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding <b>Methods: Statistical analysis</b>
		(b) Describe any methods used to examine subgroups and interactions <b>Methods: Statistical analysis</b>
		(c) Explain how missing data were addressed <b>Results: second para</b>
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed <b>Results: second para</b>
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy <b>Methods: Statistical analysis</b>
		(e) Describe any sensitivity analyses
<b>Results</b>		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed <b>Results: first two para</b>
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram <b>Figure 1</b>
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders <b>Tables 1 and 2</b>
		(b) Indicate number of participants with missing data for each variable of interest <b>Results: second para</b>
		(c) Cohort study—Summarise follow-up time (eg, average and total amount) <b>Table 1</b>
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time <b>Results, Table 2 and Figure 2</b>
		Cross-sectional study—Report numbers of outcome events or summary measures <b>Results, Table 2 and Figure 2</b>
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included <b>Results, Figure 2, Tables 3 and 4</b>

		(b) Report category boundaries when continuous variables were categorized <b>Results, Tables 1 and 2</b>
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses <b>Results, Tables 3 and 4</b>
<b>Discussion</b>		
Key results	18	Summarise key results with reference to study objectives <b>Discussion: first para</b>
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias <b>Discussion: Limitations</b>
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence <b>Discussion</b>
Generalisability	21	Discuss the generalisability (external validity) of the study results <b>Discussion: Limitations</b>
<b>Other information</b>		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based <b>Funding</b>

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.



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**Part II: White matter hyperintensities do not represent a critical lateropulsion determinant after stroke**

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**Declarations of interest: none.**

Title: 96 characters including spaces

Main text: 1093 words

References: 20

Figure 2

**Key words:** white matter hyperintensities, lateropulsion, balance, stroke recovery

**Abbreviations:** WMHs, white matter hyperintensities; SCP, Scale for Contraversive Pushing.

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Dear editor,

We recently demonstrated that white matter hyperintensities (WMHs), as a marker of small vessel disease, is critically detrimental to post-stroke balance and gait disorders, as well to their recovery (Dai *et al.*, 2021c). Post-stroke balance disorders are due either to an impaired orientation with respect to gravity, or to an impaired stabilization with respect to the base of support, or both (Pérennou, 2006; Dai *et al.*, 2021a). Do WMHs interact with balance disorders worsening the control of body orientation, the control of body stabilization or both? The literature suggests that the impaired body orientation in the frontal plane is due to some peculiar grey matter structures involving the thalamo-parieto-insular projections (Karnath *et al.*, 2000; Barra *et al.*, 2010; Brandt and Dieterich, 2017; Babyar *et al.*, 2019; Santos *et al.*, 2019; Lemaire *et al.*, 2020), and also the white matter structures which link them (Lemaire *et al.*, 2020). The damage of these structures induces lateropulsion (Pérennou *et al.*, 2008; An *et al.*, 2021; Dai *et al.*, 2021a; Dai *et al.*, 2021b), frequent after stroke (Pérennou *et al.*, 2008; Dai *et al.*, 2021a). In this monocentric observational study involving data from the cohort (Determinants of Balance Recovery After Stroke [DOBRAS]; ClinicalTrials.gov: NCT03203109), we hypothesized that when a hemisphere stroke occurs on a brain with WMHs, lateropulsion has a higher incidence and a poorer recovery.

This study extends a first one about the effect of WHMs on balance and gait recovery, with the same participants (Dai *et al.*, 2021c). Here we used clinical data collected on 30 ( $\pm 3$ ) days after a first unique hemisphere stroke (D30), then at discharge (within the last 3 days), and focused analyses on the influence of WHMs on lateropulsion, which represents the novelty. Lateropulsion was assessed with the Scale for Contraversive Pushing (SCP), the actual gold standard to quantify lateropulsion after hemisphere stroke (Karnath *et al.*, 2000). The total score

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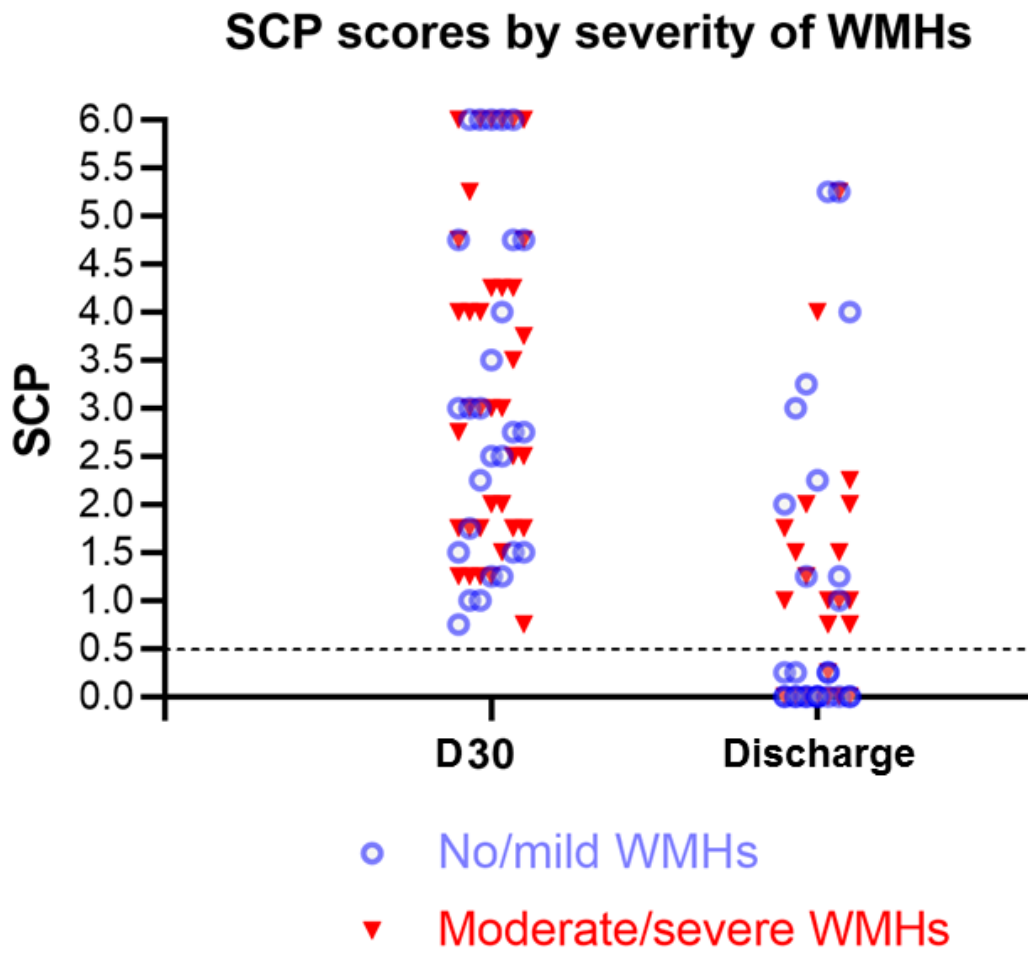
ranges from 0 (complete uprightness) to 6 (extreme lateropulsion). As proposed and validated previously (Pérennou *et al.*, 2008; Dai *et al.*, 2021a; Dai *et al.*, 2021b), we used a SCP cut-off  $> 0.5$  to classify individuals as having lateropulsion (upright otherwise). The presence of WMHs was sought on T2-FLAIR sequences from the first or second MRI (within the first 2 months after stroke) and graded with the Fazekas scale (Fazekas *et al.*, 1987). The scale simply grades WMHs in 4 levels: 0, no lesion; 1, focal lesions; 2, beginning lesions confluences; and 3, extended involvement with large confluent areas. According to recommendations (Georgakis *et al.*, 2019), we *a priori* planned to regroup grades 0 and 1 and grades 2 and 3. This approach takes into account the low frequency of grade 3 in individuals with a first hemisphere stroke and the fact that the difference between grades 0 and 1 may be tenuous. Its appropriateness was confirmed by our data (Dai *et al.*, 2021c).

Data are presented as n (%) or median (Q1–Q3), compared with Mann-Whitney and chi-square tests between two groups. Effect sizes were calculated for significant factors by using the  $X^2$  of the chi-square test,  $v = \sqrt{(X^2/n * \text{degree of freedom})}$ . Values 0.1, 0.3, and 0.5 represent a small, medium, and large effect. Two-sided  $p < 0.05$  was considered statistically significant. Statistical analyses involved using SPSS 24.0. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Characteristics of the 210 participants are detailed in our previous paper about WMHs. Median age was 67.3 years (57.4–72.7) and 68 (32%) were females. A total of 166 individuals (79%) presented WMHs graded 1 in 80 (38%), 2 in 71 (34%), 3 in 15 (7%), whereas 44 individuals (21%) did not show any WMHs (grade 0). We constituted 2 groups: no/mild WMHs ( $n=124$ , 59%) and moderate/severe WMHs with confluent lesions ( $n=86$ , 41%).

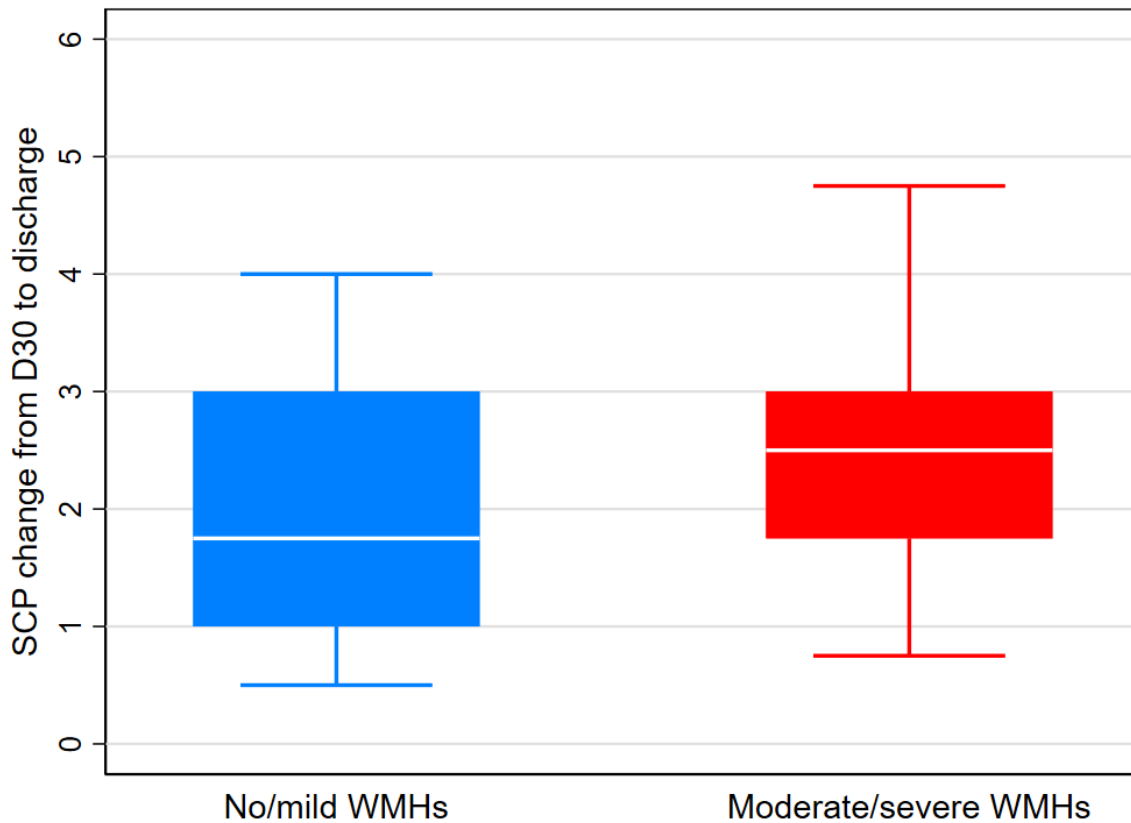
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On D30, there were 64/210 (30%) individuals showing lateropulsion, 27 with no/mild WMHs and 37 with moderate/severe WMHs. Moderate/severe WMHs was more frequent in individuals with lateropulsion than in upright individuals (37/64 [58%] vs 49/146 [34%],  $v=0.23$ ,  $p=0.001$ ). However, as shown in figure 1 in individuals showing lateropulsion on D30, lateropulsion severity was similar in the 27 individuals with no/mild WMHs (SCP=2.8 [1.5-4.8]) and in the 37 individuals with moderate/severe WMHs (SCP=3 [1.8-4.3];  $p=0.594$ ). We then investigated the effect of WMHs on lateropulsion recovery. Among the 64 individuals who showed lateropulsion on D30, at discharge 38 recovered and were considered upright whereas 26 still showed lateropulsion. Their lengths of hospitalization were comparable (no/mild WMHs: 148 [123-196] days vs moderate/severe WMHs: 151 [117-176] days,  $z= -0.1$ ,  $p=0.903$ ). No WMHs influence was found on this recovery pattern, the proportion of individuals with moderate/severe WMHs being comparable in individuals who did not recover and in those who recovered: 16/26 (62%) vs 21/38 (55%;  $p=0.618$ ). As shown in figure 2, the change score of the SCP was also comparable between 2 groups initially with lateropulsion ( $z= -1.6$ ,  $p=0.12$ ).



**Figure 1. SCP scores by severity of WMHs**

SCP scores on D30 and at discharge for 64 individuals showing lateropulsion on D30. The individuals under the dash line (SCP  $\leq 0.5$ ) at discharge are classified as upright.



**Figure 2. SCP change from D30 to discharge**

Comparison of SCP changes (presented as median [Q1–Q3] by boxplots) from D30 to discharge among the 64 individuals initially showing lateropulsion ( $z = -1.6$ ,  $p = 0.12$ ).

This study reveals that on D30 confluent WMHs (moderate/severe according to the Fazekas grading) were much more frequent in individuals showing lateropulsion than in upright individuals. However, the effect size was small which indicates that confluent WMHs do not represent a critical lateropulsion determinant. In addition, it seems that confluent WMHs do not alter lateropulsion recovery. These results are congruent with those of a pilot study with a small sample size, which failed to find an independent effect of WMHs on lateropulsion severity (Fujino *et al.*, 2017). This study did not analyze the effect of WMHs on lateropulsion recovery.

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Considering our previous results showing on one hand that WMHs is a key determinant altering post-stroke balance and gait disorders and their recovery (Dai *et al.*, 2021c), and on the other hand that balance control implies two components, body orientation with respect to gravity and body stabilization with respect to the base of support (Massion, 1992; Horak and Macpherson, 2011; Dai *et al.*, 2021a), our study strongly suggests that WMHs alter balance mainly by magnifying the impaired body stabilization. This is not surprising because body stabilization requires the whole brain, to ensure efficient postural control of the trunk and the four limbs, involving precise spatial representation and a coordinated sensori-motor control of body segments (Massion, 1992; Pérennou *et al.*, 2000; Horak and Macpherson, 2011). Therefore the risk is high that when present, WMHs damage white matters pathways involved in the postural stabilization, including the corticospinal tract, the damage of which magnifies balance and gait disorders and alter their recovery (Dai *et al.*, 2021c). In contrast, the more limited impact of WMHs on body orientation with respect to gravity strengthens the idea that body orientation with respect to gravity is mainly controlled from a core neural bases, involving a limited number of grey and white matter structures (Babyar *et al.*, 2019; Baier *et al.*, 2021; Piscicelli *et al.*, 2021 (in-press)). We used the Fazekas scale to quantify WMHs alterations, so we partly assessed MRI signs of small vessel disease and did not quantify WMHs in specific areas (periventricular or deep white matter) but rather hemisphere globally (side opposite the stroke). Finally, because WMHs were 1.7 time more frequent in individuals with lateropulsion than in upright individuals on D30, WMHs detection seems useful to interpret post-stroke lateropulsion. However, we failed to show any detrimental effect of WMHs on lateropulsion recovery from D30 to discharge.

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## ➤ **Chapter 9: Assessment of lateropulsion**

This is a narrative review to investigate the current tool of assessing lateropulsion after stroke. We run this review following the COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) guideline. We also introduce our novel scale of lateropulsion at the end. This paper is under preparation.

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## Why and how should we better assess lateropulsion

**S Dai, C Lemaire, A Odin, E Clarac, C Piscicelli, S Babyar, D Pérennou, in preparation**

The current theoretical model of balance control involves two domains, devoted to body orientation with respect to gravity and to body stabilization with respect to the base of support (Massion, 1992; Horak and Macpherson, 2011). This model might help in better understanding balance disorders in the clinic, in order to guide their rehabilitation. It could be especially useful after stroke (Pérennou, 2006; Pérennou *et al.*, 2008; Dai *et al.*, 2021a) owing to the devastating sequelae induced by balance disorders (Winstein *et al.*, 2016), which may be explained in terms of impaired body orientation or stabilization.

Postural balance is ensured when the projection of the center of mass on the ground is inside the base of support. To reduce the destabilizing effect of gravity, the body must be oriented vertical (body orientation) and the oscillations around this orientation controlled (body stabilization). In individuals with deficits of body orientation, the projection of the center of mass on the ground moves away the middle of the base of support, approaching the limit of stability as a function of the body tilt magnitude and so creates the condition to impair balance.

Lateropulsion referring to a deficit in body orientation with respect to gravity, in the frontal (roll) plane. It is related to biases in verticality representation (Pérennou *et al.*, 2008). This term initially introduced in the medical literature by the prominent French-Polish neurologist Joseph Babinski (Babinski and Nageotte, 1902).

The part played by deficits of body orientation on balance and gait disorders have been long overlooked so far. However, they are most detrimental on mobility (Bergmann *et al.*, 2019; An *et al.*, 2020; Dai *et al.*, 2021a). A recent paper has even showed that lateropulsion is the most

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important factor explaining balance and gait disorders at the subacute stage after stroke (Dai *et al.*, 2021a), encountering 90% of the information related to balance abilities after right hemisphere stroke (Dai *et al.*, 2021a). From a purely mechanical point of view, lateropulsion exposes people to a risk of falling on their side. Time has come to systematically detect and quantify lateropulsion and incorporate this assessment into more general battery of balance assessment. In this paper we strive to provide a useful resource to know how to assess lateropulsion in clinical practice, and also to highlight appropriate outcome measurements and endpoints for research.

## Lateropulsion

We define lateropulsion as a deficit of the active body orientation with respect to gravity, in the frontal plan. Lateropulsion was initially delineated as ipsilesional lateral body tilt with fall tendency after low brainstem stroke (Babinski and Nageotte, 1902), then further described by Thomas in 1940 who reported that individuals brain-damaged (also animals) may exhibit an active lateral body tilt, by pushing themselves away from the upright with sound limbs, and also resisted any corrections (Thomas, 1940). Lateropulsion was then variously named in different periods by different authors who focused more on the puzzling and spectacular additional postural signs than on the lateral body tilt itself. Most known denominations are listing phenomenon (Brunnstrom, 1970; Bohannon *et al.*, 1986), ease of falling (Fisher, 1982), thalamic astasia (Masdeu and Gorelick, 1988), pusher syndrome (Davies, 1985), terms comprising the word pushing, either ipsilateral pushing (Pedersen *et al.*, 1996); pushing behavior (Danells *et al.*, 2004; Pérennou *et al.*, 2008), contraversive pushing (Karnath *et al.*, 2000), and biased behavioral vertical (Pérennou *et al.*, 1998). In this paper we respect the original terms used by each author groups. These terms must be read as synonyms. Indeed, after

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a hemispherical stroke and as suggested by the research team at Burke Rehabilitation Hospital in New York (D'Aquila *et al.*, 2004; Babyar *et al.*, 2009; Babyar *et al.*, 2015; Babyar *et al.*, 2019) the 3 signs that Davies (Davies, 1985) had conceptualized and associated to constitute a syndrome (lateral body tilt, active pushing, resistance) were found to be consistently associated in moderate and severe forms of lateropulsion (Dai *et al.*, 2021b), thus representing a single dimension referring to verticality (Dai *et al.*, 2021b). In this paper we adopt the use of the word lateropulsion.

The association of the three signs becomes inconsistent in mild forms of lateropulsion (Dai *et al.*, 2021b). The degree of their association is influenced by the way assessment tools are devoted to detect and quantify rather one sign than another. Their respective prevalence (whatever their degree of severity) has recently been analyzed at one month post stroke in a series of 220 individuals consecutively admitted in a rehabilitation ward after a first hemisphere stroke: lateral body tilt 34%, resistance 26%, and active pushing 23%. Among the 220 individuals of this series, 145 (66%) presented no lateropulsion sign, 45 (20%) presented the three signs, 17 (8%) two signs (always body tilt, mostly associated with resistance), and 13 (6%) only one sign, almost constantly a lateral body tilt. The resistance is however found more frequently when assessed with a specific tool, reaching about 50% 2-3 weeks post-stroke (Danells *et al.*, 2004; Chow *et al.*, 2019). One week after the stroke, about two third of individuals exhibit at least one of the three sign (Danells *et al.*, 2004). The degree of association of the three lateropulsion signs might also depend on the type of the lateropulsion. For ipsilesional lateropulsion secondary to low brain stem lesions and characterized by a net lateral body tilt caused by a dysfunctioning on vestibulo-spinal pathways, pushing and resistance have never been described. However lateropulsion is a common problem after brain stem stroke and constitute a key sign of the Wallenberg syndrome. In low brain stem stroke the prevalence of the ipsilesional lateropulsion could be more than 50% (Amarenco *et al.*, 1990).

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To sum up lateropulsion is diagnosed if at least one of its three components is present, generally the lateral body tilt. Lateropulsion detection must be systematically part of clinical examination for balance and gait disorders. The lateral body tilt is the easiest lateropulsion component to be searched. This is very simple and lasts less than 1 min. The person is asked to stand upright, without support, or with human help if needed to avoid falling. A systematic lateral whole body tilt (always same side) signs the existence of the lateropulsion. The detection of light forms of lateropulsion may require a more challenging standing balance obtained with eyes closed or reduced base of support (feet together).

### **How to assess the lateropulsion?**

We consider the different tools to assess the lateropulsion frequently observed after stroke, which constitutes the human model. Several studies have attempted to develop devices allowing the lateropulsion to be quantified by instruments. The paradigm of the “rocking platform” makes it possible to raise awareness of the lateropulsion by asking patients to stand upright while sitting on a horizontal support mounted on an arc of a circle, itself placed on a support whose height is adjustable. Side devices prevent falls. The lower limbs hang freely, and the upper limbs are resting on the thighs, hands in each other. Only the trunk and the head are involved in postural orientation and stabilization. This paradigm of the "rocking platform" has the advantage of ecologically revealing the deficits of body orientation in the frontal plane and also of body stabilization. Ten seconds of recording is enough. This paradigm revealed that post-stroke lateropulsion is more linked to a problem relating to the treatment of somesthetic graviception (orientation of the trunk) than to a problem relating to vestibular graviception which controls the orientation of the head (Pérennou *et al.*, 1998; Pérennou *et al.*, 2002). A few seconds of recording is sufficient because this dynamic balance in a sitting position is difficult

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to achieve by patients with moderate to severe lateropulsion. This significant limitation of feasibility does not allow this device to be used in clinical routine. To date, none of the ways explored to quantify lateropulsion using motion analysis systems (Gissot *et al.*, 2007) has been validated. It would seem that when they are in a test situation in underwear with markers positioned on the trunk, patients correct or even over-correct their lateropulsion, which suggests the existence of an attentional component to post-stroke lateropulsion (Lafosse *et al.*, 2005).

The only tools that allow clinical evaluation of any type of lateropulsion regardless of the severity are either clinical scales providing both scores and categorizations in level of severity, or ordinal gradations immediately providing levels of severity. To go further and quantify lateropulsion for clinical routine or research, one must use one of the scales proposed since early 1990s, mostly by multidisciplinary teams constituted by medical doctors and physiotherapists, sometimes with neuropsychologists. Different types of scales have been designed to quantify lateropulsion according to its type, ipsilesional lateropulsion observed after low brain stem lesions due to an asymmetric vestibulo-spinal tone lesion, or contralesional lateropulsion observed after hemisphere lesions due to a biased internal model of verticality (Pérennou *et al.*, 2008). In this paper we examine main qualities of lateropulsion scales referenced in MEDLINE, including their clinimetric properties analyzed in the light of Cosmin guidelines ([www.cosmin.nl](http://www.cosmin.nl)). We focus on the two most frequently used scales (Babyar *et al.*, 2009; Koter *et al.*, 2017), the Scale for Contraversive Pushing (SCP) and the Burke Lateropulsion Scale (BLS), subsequently those with the best known clinimetric properties. Then we briefly overview other scales. Finally we present the rationale for a novel scale, the Scale for Lateropulsion (SCALA), conceived to meet better clinimetric properties than previous ones, and to be suited to assess both types of lateropulsion regardless their mechanisms, ipsilesional and contralesional.



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### **Scale for Contraversive Pushing (SCP)**

This is an ad hoc scale designed by the Tübingen group made of physiotherapists and neurologists, to diagnose the pusher syndrome caused by some hemisphere strokes, with a clear initial reference to the vertical orientation (Karnath *et al.*, 2000). The pusher syndrome was viewed as defined by Davies, i.e. an association of the 3 lateropulsion components described by Thomas (Thomas, 1940): contralesional body tilt, resistance to passive correction, active pushing from the non-impaired limbs to initiate or amplify the body tilt. The SCP has been elaborated both in German (Karnath *et al.*, 2001) and English languages (Karnath *et al.*, 2000). This is the most known and used lateropulsion scale, cited by more than 650 items (articles, books, congress abstracts) in Google scholar end 2020, now translated in numerous other languages, including French (Pérennou, 2005). Its success relies on its anteriority on others scales, its simplicity, and on the assessment of the three component of the pusher syndrome which makes it both concrete and comprehensive. The SCP is today the gold standard to assess post-stroke lateropulsion.

However, we did not find any trace of a cross-cultural validation between the initial German and English versions, which seems to differ on some points. In addition posterior to the two seminal publications (Karnath *et al.*, 2000; Karnath *et al.*, 2002), several adaptations were made by the authors (Karnath *et al.*, 2002; Karnath *et al.*, 2007). For instance the criterion B related to pushing was initially “use of non-affected extremities (leg or arm) to extend the area of physical contact to the ground” to become in 2002 “use of the non-paretic extremities (abduction & extension)“, then in 2007 “the use of the non-paretic extremities to bring about the pathological lateral tilt of the body axis”. Some instructions for the scoring of the contraversive pushing were also clarified at posteriori. These clarifications were important in

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particular regarding the term contraversive. Indeed it might be confusing to see that the same phenomenon, active pushing of the body with the strong side toward the paretic side, is called “ipsilateral pushing” in one study (Pedersen *et al.*, 1996), and “contraversive pushing” in another study (Karnath *et al.*, 2000), even if one knows that these papers refer one to the side of the active pushing and the other to the direction of the active pushing. These adaptations in the terminology and the instructions came relatively late several years after the first publication in English (Karnath *et al.*, 2000), from which have been translated most versions in other languages. Among these translations, only few have been subjected to the standard procedure with forward and backward translations (Martín-Nieto *et al.*, 2018).

Each criterion, the symmetry of spontaneous body posture (A), the use of non-affected extremities (leg or arm) to push the body laterally; (B), and the resistance to passive correction of the tilted posture (C) are scored from 0 to 1 in each of the two posture assessed, sitting and standing. The maximum score for each criterion is 2, and the total score ranges from 0 to 6. Patients are diagnosed as pushers if all three criteria are present, reaching a total score of at least 1 (sitting plus standing) for each criteria.

Many authors consider that the initial cut-off empirically determined (Karnath *et al.*, 2000; Karnath *et al.*, 2001) is irrelevant to constitute two groups (Danells *et al.*, 2004; Perennou, 2005; Baccini *et al.*, 2008; Pérennou *et al.*, 2008; Bergmann *et al.*, 2014; Dai *et al.*, 2021b), which often leads to misclassification (Baccini *et al.*, 2008; Bergmann *et al.*, 2014; Dai *et al.*, 2021b). This erroneously categorizes as non-Pushers many individuals associating lateral body tilt, resistance and pushing of various degrees under the cut off. In this perspective, Danells et al.(Danells *et al.*, 2004) proposed to adapt the SCP cut off value to the minimal possible value

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(SCP total score > 0, any of the 3 domains) as threshold to diagnose pushers (lateropulsion). This departs from the initial philosophy of the SCP considering as mandatory the presence of the three signs, body tilt, pushing, and resistance. This approach altered the agreement between raters (Bergmann *et al.*, 2014) and was not found suited to detect effect of interventions. To come back to the association of postural signs and avoid false-negative, Baccini, et al. (Baccini *et al.*, 2008) proposed to require a subscore > 0 for each domain, body tilt, pushing, and resistance, whatever the posture sitting or standing. This adaptation substantially improved the agreement between the categorization obtained with the SCP and expert's clinical judgment (Baccini *et al.*, 2008).

To not overlook intermediate group of individuals with moderate lateropulsion we propose to use the SCP beyond its initial objective and constitute three groups according to severity of the behavior against gravity (Pérennou *et al.*, 2008; Dai *et al.*, 2021a; Dai *et al.*, 2021b). A pusher group is defined using the same cut-off as that proposed in the seminal papers (Karnath *et al.*, 2000; Karnath *et al.*, 2001) . In addition as suggested by Danells et al (Danells *et al.*, 2004), we propose to use the SCP to differentiate individuals with an upright posture from those who were mildly tilted. To be conservative patients are considered upright for a total SCP score  $\leq 0.50$ . Indeed, values of 0.25 or 0.5 are clearly marginal, not allowing to state that the individual are not upright most of the time. Patients of the intermediate group with a moderate lateropulsion may be called Tilters because the body tilt is the only criteria always present, associated or not with light degrees of pushing or resistance not reaching conditions for a diagnosis of pusher. This approach is relevant because the three groups differ one from the other for all three criteria of the lateropulsion with a gradient of severity, frequency and magnitude of contralesional biases in verticality perception (Pérennou *et al.*, 2008; Dai *et al.*, 2021b), frequency and severity of spatial neglect, and also severity of balance and gait disorders (Dai *et al.*, 2021a).

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Beyond using the SCP to categorize lateropulsion in 2 or 3 groups of severity, it has also been proposed to quantify lateropulsion using the SCP as a quasi continuous variable. This is possible, on one hand because of the construction of the scale with 24 different levels from 0 to 6 thanks to a 0.25-point increment; and on the other hand because the three components represent a unique dimension referred to the vertical, body tilt pushing and resistance expressing different ways to contribute to the active behavior against gravity. This approach has been found valid, the SCP meeting conditions to be correlated with estimates of verticality perception or balance scores (Pérennou *et al.*, 2008; Dai *et al.*, 2021a; Dai *et al.*, 2021b), or in statistical analyses of brain imaging (Baier *et al.*, 2011). The total SCP score has also been used to analyze lateropulsion recovery (Danells *et al.*, 2004).

The clinimetric properties of the SCP have been well investigated. A key quality is its unidimensionality, referring only to behavior with respect to gravity. It has been recently showed by factorial analysis that the three signs had very high factor loadings (>0.90) on a same dimension, demonstrating that lateropulsion was effectively an entity comprising body tilt (cardinal sign), pushing and resistance, and also that the SCP is unidimensional (Dai *et al.*, 2021b). As a corollary the internal consistency is very good with very high alpha cronbach coefficient (Karnath *et al.*, 2002; Martín-Nieto *et al.*, 2018). A second important quality is that it has a satisfactory convergent validity with verticality perception, attested by very high concordances with biases of the postural and visual verticals (Pérennou *et al.*, 2008; Dai *et al.*, 2021b), except in several very small series with unexpected results difficult to interpret (Karnath *et al.*, 2000; Bergmann *et al.*, 2018). The SCP has a very good interrater reliability with very high interrater intraclass correlation (ICC) (0.97-0.99) on its total score (Karnath *et al.*, 2002; Martín-Nieto *et al.*, 2018). It has also good criterion validity with expert clinician diagnosis (Cohen  $\kappa = 0.93$ ) with  $> 0$  cutoff for each component (Baccini *et al.*, 2008). In addition to the lack of cross- cultural validation, an important flaw is the existence of several

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versions (non-formally referenced) with important changes made by the authors from 2000 to 2007 (Karnath *et al.*, 2000; Karnath *et al.*, 2001; Karnath *et al.*, 2002; Karnath *et al.*, 2007). This induces some haziness, amplified by an empirical way of grouping found a posteriori inappropriate, and enhanced by several groups of authors (see above). Another weak point is the absence of information regarding the smallest detectable change or the responsiveness. This represents a brake for using the SCP as main outcome in interventional studies, or more simply to follow lateropulsion recovery in clinical routine. Moreover the SCP shows very important floor and ceiling effects, defined as a percentage of patients with a minimal (floor) or a maximal (ceiling) score over 15% ([www.cosmin.nl](http://www.cosmin.nl)). In a recent series of 220 unselected patients tested in rehabilitation about one month after a first hemisphere stroke, the proportion of SCP scores at 0/6 was 66% attesting a very important floor effect (Dai *et al.*, 2021a). This makes the SCP insufficiently appropriate to detect and quantify mild forms of lateropulsion at any time after the stroke, and follow their recovery. This is annoying given that these forms are the most frequent. These flaws are likely due to a limited number of tasks assessed, reduced to two static postures (sitting and standing) tested without perturbation, and to a gross scoring especially for the resistance scored binary. Lastly the ranges of normality of the SCP have never been searched in a series of individuals without brain lesion.

Despite these important flaws, twenty years after the seminal publication the SCP is widely used in research and in clinics to categorize or quantify moderate and severe forms of lateropulsion, today mostly beyond its initial goal. It should be considered as a bed test appropriate for the acute stage, which indeed was the goal for what it was designed (Karnath *et al.*, 2000) and used by its inventors (Karnath *et al.*, 2002; Karnath *et al.*, 2005; Johannsen *et al.*, 2006b).

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## **Burke Lateropulsion Scale (BLS)**

The second most frequent used lateropulsion scale is the Burke Lateropulsion Scale (BLS), cited more than 180 times in Google scholar by the end of 2020 (articles, books, congress abstracts). The BLS has been designed by the research team at Burke Rehabilitation Hospital in New York, made of neurologists and physiotherapists, who reported to have worked on it since 1993, and having improved it several times before the publication in 2004 (D'Aquila *et al.*, 2004). The BLS is focused on the resistance offered by a patient when sustaining or changing position in the frontal plan, viewed as an important part of the lateropulsion. The resistance may be viewed as an indirect way to assess the deviation of the spontaneous posture from the true vertical. The research team at Burke Rehabilitation Hospital also hypothesized a muscular overactivity of lumbar paraspinal muscles in individuals with lateropulsion, which they could not confirmed (Babyar *et al.*, 2007). The BLS is assessed during the execution of 5 tasks: rolling in lying posture, sitting, standing, transferring, and walking. What is assessed is the amount of resistance encountered by the examiner when correcting tilted posture (table 2). Resistance is scored in 4 levels (from 0 to 3), except standing scored in 5 levels (from 0 to 4). The total score ranges from 0 to 17. The BLS has overall been conceived to give quasi continuous scores in order to quantify lateropulsion severity, and not to categorize individuals into groups of lateropulsion severity. The only cut-off values are those allowing to detect a lateropulsion:  $\geq 0$  or  $\geq 2$  if one wants to be conservative (D'Aquila *et al.*, 2004), or eventually  $\geq 3$  to better correspond with the classification obtained using the SCP and balance disorders (Bergmann *et al.*, 2019).

The BLS is increasingly used for several years and appears to be preferred to the SCP in interventional studies (Bergmann *et al.*, 2018; Yun *et al.*, 2018; An *et al.*, 2020), partly because of a better responsiveness (Clark *et al.*, 2012). It has been designed in English which limits the

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questions of its cross-cultural validity in English-speaking countries. Several translations in other languages have performed, including in French, but few have been subjected to a formal validation with forward and backward translation (Martin-Nieto *et al.*, 2019).

The clinimetric properties of the BLS have not been comprehensively investigated, which have to be done in the future. Assessing only resistance, the BLS is by nature unidimensional, which has been recently confirmed by a rasch analysis (Birnbaum *et al.*, 2020). This is an important quality, and it is true that lateropulsion in lying and lateropulsion in erect posture are often associated (Johannsen *et al.*, 2006a). However they might be underpinned by similar mechanisms (Barra *et al.*, 2007). This is why despite a very satisfactory internal consistency (Martin-Nieto *et al.*, 2019; Birnbaum *et al.*, 2020), further clarifications are needed to confirm the relevance of including a task not referred to verticality in a scale which assesses a behavior against gravity. The BLS has satisfactory reliability, with very high inter-rater and intra-rater ICC (D'Aquila *et al.*, 2004). Another important quality is its satisfactory responsiveness, allowing to detect change (recovery) every two weeks from admission to rehabilitation until discharge 8 weeks after (Clark *et al.*, 2012). This good responsiveness is attested by satisfactory standardized response mean (SRM) ranging from 1.48 for patients who stayed 4 weeks in the ward (admission to discharge) to 2.24 for more severe patients who stayed 8 weeks (Clark *et al.*, 2012). It also seems that the BLS has a substantial floor effect (Bergmann *et al.*, 2019; Chow *et al.*, 2019; An *et al.*, 2020). It does not assess the impaired body orientation with respect to gravity (body tilt), and its convergent validity with verticality perception has not been fully investigated in a large series of patients. On the bases of some studies with limited sample size, the relationship between BLS scores and magnitude of biases in verticality perception is not convincing (Bergmann *et al.*, 2016; Bergmann *et al.*, 2018). No measurement error has not been estimated so we don't know the smallest detectable change which limits the interpretation of interventional studies using the BLS.

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To sum up the BLS has been designed in a rehabilitation perspective. This is a simple test to be performed, rather in a gym, by a trained physiotherapist. It is a reliable unidimensional scale which assesses very carefully one component of the lateropulsion, the resistance to passive correction. As compared to the SCP, the BLS might have a better responsiveness. However, it does not directly refer to the orientation of the body with respect to gravity, and contains an item tested in lying. The smallest detectable change is unknown which limits the interpretation of clinical trials using the BLS as outcome.

### **Other lateropulsion scales**

Grading of Lateropulsion. To the best of our knowledge, the first grading of the lateropulsion was proposed by the Munich group in 1992 to categorize the severity of the ipsilesional lateropulsion of individuals with a Wallenberg syndrome (Dieterich and Brandt, 1992). It was named “Grading of Lateropulsion”, and followed a very simple grading: I, moderate head and body tilt without considerable imbalance; grade II, head and body tilt with considerable imbalance, but without falls; grade III, head and body tilt and lateral falls with eyes closed; grade IV, head and body tilt and falls with eyes open. Patients were well distributed according the four grades (Dieterich and Brandt, 1992). This scaling of a vestibulo-spinal impairment was parallel to indices of vestibulo-ocular impairment such ipsilesional tilt of the visual vertical and ocular torsion. To the best of our knowledge this ad hoc grading has never been subjected to a validation procedure, and is rarely mentioned in the literature despite its simplicity and relevance. Perhaps because the ipsilesional lateropulsion is not systematically graded in routine neither in research. Last and not the least this is the only lateropulsion scale which manipulate vision, and magnifies the lateral body tilt by asking subjects to close their eyes, a very common step in routine clinical examination of postural and vestibular disorders. This is even surprising



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that no scale designed for assessing the contralesional lateropulsion has ever used this procedure to increase sensitiveness and responsiveness.

Four-Point Pusher Scale. Two scales with same name grade lateropulsion in 4 levels, by evaluating the presence of the lateropulsion criteria already mentioned in different postures. These scales are based on the assumption that there is a gradient of increasing severity from the standing position (which alone can reveal mild lateropulsions) to the supine position (where only severe lateropulsions are evident). These evaluations were designed in the early 2000s or even before, which was before the discovery of the mechanisms underlying lateropulsion (Pérennou *et al.*, 2008). They were elaborated in parallel and independently by Belgian and Australian teams, but published in 2005 for one (Lafosse *et al.*, 2005) in 2019 for the other (Chow *et al.*, 2019). The Belgian assessment considers only 2 of the 3 components of lateropulsion, postural asymmetry and resistance to corrections. The number of postures (standing, sitting, lying) which present these two criteria determines the level of gradation. The authors postulate the same mechanism for the supine and erect lateropulsion, which remains to be proven (Barra *et al.*, 2007). The levels are: 0, no lateropulsion; 1, lateropulsion only when standing; 2, lateropulsion when standing and sitting; 3, lateropulsion including when lying down. It is an easy-to-achieve scale that has acceptable inter-rater agreement and good criterion validity in accordance with the SCP (Lafosse *et al.*, 2005). The Australian assessment detects and quantifies lateropulsion in three erect, static and dynamic posture tasks: walking, standing, sitting (Chow *et al.*, 2019). Each level corresponds to specific gradations which take into account the three criteria of lateropulsion (body inclination, spontaneous pushing and resistance), and is based on the hypothesis which remains to be proven that resistance to passive mobilization is detected more sensitive than other criteria. A rating guide (Chow *et al.*, 2019) qualifies lateropulsion as: 0, absence of any criteria; 1, slight with resistance to mobilization

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towards the ipsilesional side only when standing, without lateral tilt when standing or sitting; 2, moderate lateropulsion with presence of the 3 lateropulsion criteria in standing position, without body tilt in sitting position; 3, severe lateropulsion with the 3 lateropulsion criteria found in a sitting position. This evaluation has a good inter-rater agreement, but the distributions by level of the BLS and SCP scores show too much overlap, which questions the relevance of the gradation levels used to construct this scale and the postulates on which its construction is based. The main flaw of this scale is that it fails to correctly differentiate between mild and moderate lateropulsion levels. These scales make it possible to detect the existence of a lateropulsion, and to categorize it roughly into levels of severity that it would be appropriate to limit to 2 (rather than 3). They are based on a level of gradation designed a priori from unverified postulates, and leave a significant place for a certain subjectivity. They do not quantify lateropulsion and are not designed to assess ipsilesional lateropulsion. These reviews leave little room for clinical use, let alone in research.

### **Rational for a novel lateropulsion scale**

The criticisms addressed to the two lateropulsion scales (SCP and BLS) can be summarized as follows: 1. They have not been sufficiently validated from a conceptual basis since the mechanisms explaining contralesional and ipsilesional lateropulsion were discovered after their conception. These scales refer too much to the pusher syndrome empirically defined by Davies without interpretation about the origin of lateropulsion. 2. They completely forget the ipsilesional lateropulsion, which is common after stroke of the brainstem. 3. They were designed locally without being submitted to a panel of international experts to validate their design, in particular via a Delphi procedure as is the case today for the validation of new scales. 4. The corollary is a convergent validity with the lateropulsion mechanisms which have not

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been completely clarified, in particular concerning the contralesional lateropulsion the link between the BLS and the perception of the vertical, and concerning the ipsilesional lateropulsion the link between the BLS on the one hand and the SCP on the other hand with the measurements of vertical perception (visual vertical and postural vertical) as well as with the asymmetry indices of the vestibulo-spinal tone. 5. Their cross-cultural validation remains to be done in most languages. 6. Despite several studies on their reliability, the smallest detectable change remains insufficiently analyzed. 7. Their sensitivity to changes has not been sufficiently analyzed, and according to experts it does not seem appropriate for a satisfactory follow-up of lateropulsion recovery, at least in the case of SCP. Their added value as a score or as a threshold as a primary endpoint for randomized clinical trials remains questionable at this stage. 8. Their floor and ceiling effect limit the detection and quantification of mild forms of lateropulsion and the monitoring of moderate forms. 9. None of these scales assesses the patient's awareness of his lateropulsion or not, which is however frequent after right hemispherical stroke, and known for a long time (Fisher, 1982; Dieterich and Brandt, 1992) and which could be an additional risk factor for falls, and if present requires a specific rehabilitation approach. This area of lateropulsion awareness could also clearly differentiate ipsilesional lateropulsion (patients would be aware of their disorder) from contralesional lateropulsion (altered awareness of lateropulsion).

Experts agree on the need to develop a new scale designed to assess both ipsilesional and contralesional lateropulsion, with better properties than previous scales (Odin *et al.*, 2018). Our team in Grenoble has been working on such a scale for several years. This is a new scale called SCALe for LAteropulsion (SCALA). It is designed to assess lateropulsion after stroke, regardless of its ipsilesional or contralesional nature, clearly conceptualizing lateropulsion as a deficit in orientation from the vertical, regardless of the mechanism. The preliminary version (SCALA V0) was developed by our multidisciplinary team of MPR doctors, physiotherapists,

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neuropsychologists and scientists, all experts in the field. Its feasibility and suitability have been tested on a fairly large number of patients as part of clinical routine, resulting in improvement of the scale step by step. SCALA was developed simultaneously in French and English. Its content has been tested, improved and then validated with a Delphi procedure conducted with a panel of international experts, which has led to improved structure, scoring, and instructions (Odin *et al.*, 2018). The current version (SCALA V1) assesses four criteria relating to active maintenance of the erect position: 1-spontaneous body lateral tilt in different erect postures; 2-spontaneous lateral pushing in different erect postures; 3- resistance to postural corrections in different erect postures; 4-awareness of lateropulsion by patients in different erect postures. Thanks to a structure that understands dynamic tasks and conditions of vision (with and without vision) and positioning of the feet (normal and feet together) likely to amplify the lateropulsion to better detect it, we hope for a satisfactory sensitivity to changes with low floor and ceiling effects if they exist. The clinimetric properties of this version are currently being explored in a single-center study which will lead to improvements in the items that need to be improved. We intend to validate the final version with an international multicenter study on a large sample of people. We hope that SCALA will meet expectations.

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## ➤ Chapter 10: General discussion

### 1. Terminology

In contemporary literature, lateropulsion terminology is clouded by different terms proposed at different periods of time. In this thesis, we have mentioned them in several chapters, here we gather all terms together, as follows: lateropulsion, pusher/pushing syndrome/behavior, listing phenomenon, ease of falling, thalamic astasia, and biased postural vertical.

Lateropulsion is the term mostly used, since its first report in 1902 (Babinski and Nageotte, 1902). It is also the most general term among them, because it can represent different form of severity and different orientations (ispi- and contralateral). More details are given in the following chapter.

Other terms mentioned several times in this thesis are detailed as follows:

#### *Pusher/pushing syndrome/behavior*

Pusher syndrome is introduced by one of famous physiotherapists- Patricia Davies in 1985 (Davies, 1985). This term has been employed as “pusher behavior”, “pushing syndrome” and “pushing behavior” in last three decades. It is the second most frequent used term, particularly in early of 2000s, whose usage seemed more frequent than lateropulsion in that period. Our studies clearly indicate that pusher syndrome is just a severe form of lateropulsion, rather than an idiosyncratic disease (Dai *et al.*, 2021b). Pusher syndrome is not frequent and is found congruently in about 10% of hemisphere stroke cases (Pedersen *et al.*, 1996; Baccini *et al.*, 2008; Pérennou *et al.*, 2008; Abe *et al.*, 2012). Our studies used Karnath’s criteria (Karnath *et al.*, 2000). There are many other individuals with mild forms of lateropulsion without net pushing or resistance to correction. The detection of these individuals has been strongly suggested by several studies adopting a second SCP cut-off value (Danells *et al.*, 2004; Baccini

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*et al.*, 2008; Pérennou *et al.*, 2008; Dai *et al.*, 2021a; Dai *et al.*, 2021b) or using a different assessment tool such as the BLS (Bergmann *et al.*, 2018; Babyar *et al.*, 2019). These individuals with mild lateropulsion have a mild bias in their verticality perception (Pérennou *et al.*, 2008; Dai *et al.*, 2021b). The wide usage of “pusher syndrome” cover many light to moderate form of lateropulsion, which is much frequent, about 48.9% according to our meta-analysis. Owing to less use of the word “syndrome” in medical terms (Chen *et al.*, 2019), we propose to abandon the usage of “pusher/pushing syndrome/behavior”, a tree hides the forest.

### *Listing phenomenon*

The “listing phenomenon” was described in 1970 by Brunnstrom (Brunnstrom, 1970) who wrote “...In sitting... when the assistance is withdrawn, the patient’s trunk begins to list toward the affected side, as if drawn by a magnet ... cling onto something with their non-paretic hand to prevent listing”. This action to cling the surrounding was interpreted by Brunnstrom as an attempt to prevent falling to the listing side. The terminology “listing phenomenon” was retaken by Bohannon (Bohannon *et al.*, 1986), who emphasized on the postural imbalance in sitting posture. Interestingly the extension of the sound upper limb was interpreted oppositely by Brunnstrom and Davies (Davies, 1985), to limit the body tilt and prevent falls for Brunnstrom, to elicit and amplify the body tilt causing pusher syndrome for Davies. The lack of objective data on the lateral forces developed, makes difficult to definitively conclude about the possible coexistence of these two behaviors in same patients submitted to different tasks and surroundings.

### *Ease of falling*

The term ‘Ease of falling’ has been proposed by Charles Miller Fisher (1913-2012) in his review paper published in 1982 (Fisher, 1982) synthetizing a series of post-stroke cases dated from 1960s to 1970s (Fisher and Cole, 1965; Fisher, 1979). He wrote “slight weakness of one

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leg or of the leg and arm, combined with a remarkable tendency to fall toward the weak side in the absence of an adequate explanation.” The two key words of this term are ‘ease’ and ‘falling’. If a normal person is about to fall toward either right or left side, he should be aware of this falling tendency. Fisher emphasized several times this pathological ‘ease’ after stroke, which resembled the delusional unawareness of sensorial and motor deficits after brain lesions, termed as ‘Anton-Babinski syndrome’ or ‘Babinski’s anosognosia’ (Babinski, 1914). Through scarce publications around 90s, some authors portrayed this phenomenon as ‘a falling log’ (Labadie *et al.*, 1989), the ‘ease of falling’ has been out of usage in last three decades.

#### *Thalamic astasia*

Masdeu and Gorelick (Masdeu and Gorelick, 1988) employed the terminology “thalamic astasia” to describe and interpret the postural consequences of unilateral thalamic lesions (15 cases, strokes and tumors), by reference to astasia, a Greek word, referring to the inability to stand upright. They proposed this terminology to encounter for the inability to stand with a tendency to fall sideward (side opposite the damaged thalamus) and backward, in the absence of motor weakness or marked sensory loss. For similar clinical cases this terminology was then regularly retaken up to now (Amarenco *et al.*, 1990; Brandt and Dieterich, 2000; Karimi *et al.*, 2004; Brandt and Dieterich, 2017). Some authors explicitly claimed that the terminologies ‘thalamic astasia’ and ‘thalamic lateropulsion’ describe a same clinical picture (Amarenco *et al.*, 1990; Karimi *et al.*, 2004).

#### *Biased postural vertical*

Pérennou, et al. (Pérennou *et al.*, 1998) firstly used the terminology ‘biased postural vertical’ to depict several individuals after hemispheric stroke, who had contralesional tilt of the postural vertical in a rocking platform, varying with the severity of their spatial neglect and hemianaesthesia. Authors indicated that this behavior resulted from an asymmetric process of

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somatic graviceptive information due to some cerebral lesions. They further argued a relationship between the “biased postural vertical” and the well-known cerebral organization of spatial information processing, based on right hemisphere dominance for spatial attention and/or representation. The concept of “postural neglect” was proposed (Pérennou *et al.*, 1999). Here, all listed terms have similar clinical demonstrations. Some of them (listing phenomenon, ease of falling and biased postural vertical) are already scarcely used in current literature, some (pusher/pushing and thalamic astasia) are still in the usage. We consider that these terms are synonyms of lateropulsion.

However, there is still a discrepancy between the terminologies of “pusher/pushing syndrome/behavior” and “lateropulsion”. Some experts don’t agree that 2 terms mean the same phenomenon (Bergmann, *et al.* 2014; Bergmann, *et al.* 2018). They consider that lateropulsion is only due to infratentorial lesion, while pusher/pushing is only due to supratentorial lesion.

To elucidate this point, we first indicate the common point between 2 terms: both terms present the deficit of body orientation in frontal plane. In our previous study (Pérennou, *et al.* 2008; Dai, *et al.* 2021b), we clearly indicated that pusher was just a severe form of contralesional lateropulsion after supratentorial stroke, accompanied by pushing and resistance, the 2 additional postural signs. Lateropulsion itself could present the lateral body tilt with or without pushing and resistance (Dai, *et al.* 2021a; Dai, *et al.* 2021b). We consider that this discrepancy is mainly from the signs of pushing and resistance. The original description of pusher was from Davies, who emphasized both signs of pushing and resistance and called this phenomenon as “pusher syndrome”. However, the real pushers are only a small proportion, 12.5% according to our meta-analysis based on a population more than 3000 patients. In contrast, the contralesional lateropulsion could take up 50% of the same population. That is why we consider pusher covers the true lateropulsion in current literature.

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In addition, the lateropulsion after infratentorial stroke has been less investigated so far. One may misunderstand its true picture. According to some very old descriptions from Dejerine and Thomas (Thomas, 1940), lateropulsion after infratentorial lesion would sometimes also be accompanied by pushing and resistance. It is easy to imagine that whatever pathology and lesion, one has lateral body tilt and tendency to fall to the left side, he would extend spontaneously his right arm and abduct his right leg. Dejerine and Thomas examined many patients with lateropulsion like that, they always found resistance to push them to the contraversive side. Considering their pathologies and lesions, they could be peripheral vestibular lesions, infratentorial or supratentorial damage (stroke, tumor, infection, etc.), or even healthy people after vestibular modulation. If Dejerine and Thomas had acknowledged the contribution of Davies, they could also call these patients “pushers”.

We consider that the phenomenon “pusher/pushing” is not idiosyncratic, the action of pushing magnifies the lateropulsion, causing a spectacular picture and attracting tremendous attention in the last 2 decades. Indeed, given the high prevalence and detrimental consequences of lateropulsion, it should be merited more investigation in the future. We also encourage others to turn the page on “pusher/pushing” and to pay more attention on lateropulsion.

## **2. Understanding lateropulsion**

Today, lateropulsion is considered to have a vestibular origin with different mechanisms depending on lesion location.

After low-brainstem lesions, mostly in Wallenberg syndrome, lateropulsion is ipsilesional and mainly secondary to vestibulospinal disorders (Thomke *et al.*, 2005; Cnyrim *et al.*, 2007; Pérennou *et al.*, 2008; Brandt and Dieterich, 2017), inducing an asymmetric tone with a co-occurrence of vestibulo-ocular signs, which is quasi-consensus in neuro-otology.

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After hemispheric lesion, lateropulsion is contralesional, owing to an internal model of verticality abnormally tilted to the contralesional side (opposite the stroke) (Pérennou *et al.*, 2008; Dai *et al.*, 2021b). Individuals unconsciously align their body onto this erroneous reference of verticality, possibly in relation to a damaged multimodal vestibular network (Brandt and Dieterich, 2019).

Our two cohorts (Pérennou *et al.*, 2008; Dai *et al.*, 2021b) investigated the relationship between lateropulsion and verticality representation. Our findings, drawing on two studies led on a sample of 97 individuals with lateropulsion, show that contralesional visual vertical (VV) biases and contralesional lateropulsion are two inseparable criteria referring to a same dimension, the vertical orientation. VV is a physiological measure testing graviception and lateropulsion is a postural behavior leading to orientate the body against gravity. This means that their link cannot be just a co-occurrence. The only possibility is that lateropulsion is secondary to a biased verticality representation, presented by contralesional VV biases (Dai *et al.*, 2021b) and contralesional postural vertical (PV) biases (Pérennou *et al.*, 2008) in our 2 studies. Therefore, we conclude that lateropulsion is caused by an impaired graviception.

Among the current literature about lateropulsion after hemispheric lesion, a great ambiguity is how to understand the three relevant signs, which are frequently mentioned: “lateral body tilt/ asymmetry of spontaneous posture”, “pushing/ extension or abduction of non-affected limbs” and “resistance (to passive correction)”. Maybe the New York group (D'Aquila *et al.*, 2004; Babyar *et al.*, 2009; Babyar *et al.*, 2019) firstly considered the lateropulsion as a trilogy with the 3 signs, but the spontaneous pushing being not explicitly termed neither in these papers nor in the Burke Lateropulsion Scale. In addition, no previous study confirmed the associations of 3 signs, beyond the opinion that the 3 signs is an entity. The clear definition of lateropulsion as a lateral body tilt with tendency to fall sideward was proposed by Babinski (Babinski and Nageotte, 1902). However, the mechanisms underlying pushing and resistance are

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controversial, viewed as a way to adjust the body orientation onto a wrong reference of verticality or as a postural reflex reacting to a sensory conflict (Karnath *et al.*, 2000). Actions to push might even result from muscular over-activity (Thomas, 1940). Our finding clearly indicated that lateral body tilt should present in all lateropulsion, always accompanied by resistance, pushing, or both; in contrast, the famous “pushing” sign is the least frequent sign. Factorial analysis showed that the three signs represented a same dimension, lateral body tilt having the highest factor loading (0.98). All together, we firstly demonstrate that lateropulsion is an entity consisting of three postural components, lateral body tilt being the cardinal sign of an impaired body orientation against gravity.

Another question about lateropulsion in literature is its association with spatial neglect. Davis, maybe the first person suggested this association, although she didn't explicitly termed “spatial neglect” (Davies, 1985). In last century, the assessments of spatial neglect were underdeveloped, most of them based on pencil paper tests. That is why some famous precedent studies that couldn't conclude this association, such as the Copenhagen Stroke study (Pedersen *et al.*, 1996). Thanks to novel assessments to measure spatial neglect in multi-domains, the concept about lateropulsion and spatial neglect should evolve. Karnath and Dieterich (Karnath and Dieterich, 2006) not only demonstrated the clinical association of these behaviors, but also illustrated similar neuro-anatomical bases, located in parieto-insular vestibular cortex. The germen team then proposed both contralesional lateropulsion after hemispheric lesion and spatial neglect could attribute to higher vestibular dysfunctions which involve cognition and more than one sensory modality (Brandt *et al.*, 2014). In our DORBAS cohort, we assessed spatial neglect by multiple tests exploring all subdomains, as usually performed today (Azouvi, 2017; Rode *et al.*, 2017). We demonstrated solid association between lateropulsion and spatial neglect, the latter encompassing the former. This is not surprising, both are deficits of spatial cognition. Lateropulsion is a deficit of active body orientation with respect to gravity, expressed



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in the roll plane by a tilt with respect to the vertical axis. Spatial neglect is a deficit of spatial representation/attention mainly expressed in the horizontal plane by a right/left deviation. The strong similarity we congruently found between lateropulsion and spatial neglect suggests that some areas (multimodal thalamo-cortical network), when damaged, simultaneously induce both behaviors. Because we demonstrated that an impaired body orientation against gravity (lateropulsion) was inseparable from a physiological measure testing graviception (VV), lateropulsion might correspond to a kind of graviceptive neglect, bearing on vestibular and somesthetic graviception.

### **3. Lateropulsion and balance control**

In our manuscripts, we refer to the theoretic model of balance control conceptualized by Jean Massion (Massion, 1992), then by Fay Horak & Jane Macpherson in successive versions of physiology handbooks (Postural Orientation and Equilibrium, 1996 and 2011). This model which is now quasi-universally accepted in basic sciences, conceives balance control as a dual function supported by the control of body orientation with respect to gravity and the control of body stabilization with respect to the base of support. We consider lateropulsion as a sign of body misorientation with respect to gravity, therefore a cause of balance disorders. Balance control requires both components, orientation and stabilization. Indeed, postural balance is ensured when the projection of the center of mass on the ground is inside the base of support. To reduce the destabilizing effect of gravity, the body must be oriented vertical (body orientation) and the oscillations around this orientation controlled (body stabilization). In people with lateropulsion, the projection of the center of mass on the ground moves away the middle of the base of support, approaching the limit of stability as a function of the body tilt magnitude and so creates the condition for balance impairment. The scope of this thesis is to

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apply this theoretical concept of postural control to post-stroke balance and gait disorders. In this context, our results confirm that lateropulsion is the key.

We further demonstrate the effect lateropulsion on balance recovery in several longitudinal studies. We find that balance improvement is possible without substantial change in body orientation with respect to gravity, but better lateropulsion recovery amplifies balance improvement during the same period, particularly in acute and early subacute phase after stroke. In contrast, the effect of body stabilization maybe more important as post-stroke time increasing. It is noteworthy that the single limb stance (Dai *et al.*, 2021c), one part of body stabilization, is a remarkable sign for the balance recovery in the chronic phase after stroke.

#### **4. The novelties of this thesis**

A great novelty of this thesis is that we identify lateropulsion as a critical post-stroke deficit of lateral body orientation with respect to gravity, which had been so far overlooked (Gomes-Osman and Kloos, 2021). Lateropulsion is predominant after right hemisphere stroke, results from a biased representation of internal verticality, and corresponds to a kind of spatial neglect, thus we term it “graviceptive neglect”(Dai *et al.*, 2021b). Demonstrated as a deficit of body misorientation with respect to gravity, lateropulsion is the key element implicated in post-stroke balance and gait disorders. Therefore, we develop a novel theoretic model better explaining post-stroke mobility, which has been recently published as cover paper in Neurology (Dai *et al.*, 2021a; Dai *et al.*, 2021b). Concerning the post-stroke balance disorders, our works clearly present that two components – body orientation and body stabilization – function differently as a function of time. Body orientation, mainly referring to lateropulsion, high associated with balance capacity in acute and early subacute phases, while body stabilization, referring to the oscillations of body segments, play a more important role in the chronic phrase, such as the role

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of single limb stance (Dai *et al.*, 2021c). The different functions of two components also explain the recovery of balance disorders. We find a much better balance recovery between D30 and D60 than that between D60 and D90, strongly linked to better recovery of lateropulsion between D30 and D60. Our meta-analysis firstly investigates the epidemiologic data of lateropulsion, showing a very high lateropulsion in the acute phase (>50%). This finding, together with the detrimental effect of lateropulsion on balance and gait, appeals for its systematic detection to guide appropriate interventions as early as possible. Our new results reveal that there is an optimal window for lateropulsion recovery, which is from D15 to D70 after stroke when the patients are stable. Given our robust results, future clinical trials should fit that delay with a 4 to 6 weeks' follow-up. In addition, we analyzed the responsiveness of the SCP, which has been never explored in literature. Given poor responsiveness and strong ceiling effect of the current gold standard of assessment of lateropulsion, there is an urgent to establish a novel scale.

Overall, our studies give a renaissance of the terminology of lateropulsion. Now, the international network of lateropulsion tend to adopt our new definition, and the usages of other terms, such as “pusher syndrome/behavior” and “listing phenomenon” are sharply decreasing.

## 5. Perspectives

In our current works, one of the great difficulty is to choose a validated tool to assess the lateropulsion. Despite the majority of clinimetric properties validated, the SCP that we used hasn't cross-cultural validation, causing the ambiguity for the part of assessment of “pushing”. In addition, we find that the SCP has inadequate responsiveness and considerable floor effect, and its smallest detectable change remains missing. All these 3 deficits of clinimetric properties mean that the SCP couldn't monitor the lateropulsion recovery sufficiently. Concerning the

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other lateropulsion scales, none has soundly validated clinimetric properties and clearly conceptual basis.

What we urgently need in this domain is novel scale to bridge the gap. Our team in Grenoble has been working on such a scale for several years. This is a new scale called SCALe for LATERopulsion (SCALA). It is designed to assess lateropulsion after stroke, regardless of its ipsilesional or contralesional nature, clearly conceptualizing lateropulsion as a deficit in orientation from the vertical, regardless of the mechanism. Its feasibility and suitability have been tested on a fairly large number of patients as part of clinical routine, resulting in improvement of the scale step by step. SCALA was developed simultaneously in French and English. Its content has been tested, improved and then validated with a Delphi procedure conducted with a panel of international experts, which has led to improved structure, scoring, and instructions (Odin *et al.*, 2018). None of previous scales assesses the patient's awareness of his lateropulsion or not, which is however frequent after right hemispheric stroke, and known for a long time (Fisher, 1982; Dieterich and Brandt, 1992) and which could be an additional risk factor for falls. Thanks to the suggestions of experts in Delphi process, we will firstly add the item of “awareness of lateropulsion” into the SCALA, which is a great novelty to the assessment of lateropulsion. We also add dynamic tasks and conditions of vision (with and without vision) and positioning of the feet (normal and feet together) likely to amplify the lateropulsion to better detect it, we hope for a satisfactory sensitivity to changes with low floor and ceiling effects if they exist. Finally we will begin the single-center validation of the SCALA in front of multi-center validation this year.

Further to this, we have other two ongoing works. One refers to the neural bases of lateropulsion. The neural anatomic analysis is a fundamental research for innovative stimulation therapies, thus it is a priority in future works. The other one refers to a novel therapy

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to lateropulsion. We collaborate with a team of virtual reality and implicate the biased model of internal verticality in this technology. This work will be begun this autumn.

## 6. Conclusions

As a post-stroke deficit of body orientation with respect to gravity, lateropulsion is frequent, much more than the well-known severe form “pusher syndrome”. Lateropulsion is a trinity constituted by body tilt, pushing and resistance. It is a way to adjust the body orientation in the roll plane to a wrong reference of verticality. Referring to straight above, lateropulsion might correspond to a form of spatial neglect (referring to straight ahead), which would advocate for 3-D maps in the human brain involving the internal model of verticality. Concerning the consequences of lateropulsion, it is the primary factor altering post-stroke balance and gait at the subacute stage, especially after right hemisphere stroke where lateropulsion explained  $\geq 90\%$  of the information contained in balance disorders and  $\geq 66\%$  in gait disorders. Overall, high lateropulsion prevalence and detrimental effect on balance and gait, appeal for its systematic detection to guide appropriate interventions as early as possible. Post-stroke mobility rehabilitation should be rethought and should incorporate techniques devoted to misorientation with respect to gravity. As to the assessment of lateropulsion, the current tools are inadequate to quantify lateropulsion in follow-up, which calls for a novel scale to bridge the gap.

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## Annexes

### Annex 1. The Scale for Contraversive Pushing (SCP)

Examination Form Clinical Scale for Contraversive Pushing (SCP)			
Name.....		Date of birth.....	
Examination date.....		Ward.....	
Physician in charge.....		Diagnosis.....	
Physical therapist in charge.....			
(A) Spontaneous body posture		Sitting	Standing
Value 1 = severe contraversive tilt with falling to that side		<input type="checkbox"/>	<input type="checkbox"/>
Value 0.75 = severe contraversive tilt without falling		<input type="checkbox"/>	<input type="checkbox"/>
Value 0.25 = mild contraversive tilt without falling		<input type="checkbox"/>	<input type="checkbox"/>
Value 0 = inconspicuous		<input type="checkbox"/>	<input type="checkbox"/>
Sum total (max. = 2):			
(B) Use of the non-paretic extremities (abduction & extension)			
Value 1 = performed spontaneously, already when at rest		<input type="checkbox"/>	<input type="checkbox"/>
Value 0.5 = performed only on changing the position (e. g. on transferring from bed to wheelchair)		<input type="checkbox"/>	<input type="checkbox"/>
Value 0 = inconspicuous		<input type="checkbox"/>	<input type="checkbox"/>
Sum total (max. = 2):			
(C) Resistance to passive correction of tilted posture*			
Value 1 = resistance occurs		<input type="checkbox"/>	<input type="checkbox"/>
Value 0 = resistance does not occur		<input type="checkbox"/>	<input type="checkbox"/>
Sum total (max. = 2):			

\* Touch the patient at the sternum and the back. Instruction: "I will move your body sideways. Please permit this movement".

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## Annex 2. The Postural Assessment Scale for Stroke Patients (PASS)

### PASS Items and Criteria for Scoring

#### *Maintaining a Posture*

1. Sitting without support (sitting on the edge of an 50-cm-high examination table [a Bobath plane, for instance] with the feet touching the floor)

0= cannot sit

1= can sit with slight support, for example, by 1 hand

2= can sit for more than 10 seconds without support

3= can sit for 5 minutes without support

2. Standing with support (feet position free, no other constraints)

0= cannot stand, even with support

1= can stand with strong support of 2 people

2= can stand with moderate support of 1 person

3= can stand with support of only 1 hand

3. Standing without support (feet position free, no other constraints)

0= cannot stand without support

1= can stand without support for 10 seconds or leans heavily on 1 leg

2= can stand without support for 1 minute or stands slightly asymmetrically

3= can stand without support for more than 1 minute and at the same time perform arm movements above the shoulder level

4. Standing on nonparetic leg (no other constraints)

0= cannot stand on nonparetic leg

1= can stand on nonparetic leg for a few seconds

2= can stand on nonparetic leg for more than 5 seconds

3= can stand on nonparetic leg for more than 10 seconds

5. Standing on paretic leg (no other constraints)

Same scoring as item 4

#### *Changing Posture*

Scoring of items 6 to 12 is as follows (items 6 to 11 are to be performed with a 50-cm-high examination table, like a Bobath plane; items 10 to 12 are to be performed without any support; no other constraints):

0= cannot perform the activity

1= can perform the activity with much help

2= can perform the activity with little help

3= can perform the activity without help

6. Supine to affected side lateral

7. Supine to nonaffected side lateral

8. Supine to sitting up on the edge of the table

9. Sitting on the edge of the table to supine

10. Sitting to standing up

11. Standing up to sitting down

12. Standing, picking up a pencil from the floor

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## Annex 3. The Burke Lateropulsion Scale (BLS)

### Burke Lateropulsion Scale

**SOURCE:** D'Aquila MA, Smith T, Organ D, Lichtman S, Reding M. Validation of a lateropulsion scale for patients recovering from stroke. *Clin Rehabil.* 2004;18:102-109.

**SUPINE:** Use "log roll" technique to test patient's response. Roll first towards the affected side then towards the unaffected side. Circle the side to which the resistance is most prominent. Score below the maximum resistance felt and add one point if resistance is noted in both directions. (Patients with marked lateropulsion may resist rolling to either side; hence an extra point is added if resistance is noted with rolling both towards and away from the affected side).

- 0= No resistance to passive rolling
- 1= Mild resistance
- 2= Moderate resistance
- 3= Strong resistance
- 1= Add one point if resistance noted in both directions

**SITTING:** Score with the patient seated, feet off floor, with both hands in lap. The expected hemiplegic response is for patient to carry his weight towards the unaffected side. Some patients will passively fall towards their paretic side when placed in true vertical position by the examiner. This will not be scored as "lateropulsion." Position the patient with their trunk 30 degrees off true vertical towards their affected side, then score the patient's response to your attempts to bring them back to vertical. The "lateropulsion" phenomenon is an active attempt by the patient to keep their center of gravity towards their impaired side as they are brought to true vertical.

- 0= No resistance to passive return to true vertical sitting position.
- 1= Voluntary or reflex resistive movements in trunk, arms or legs noted only in the last 5 degrees approaching vertical.
- 2= Resistive movements noted but beginning within 5 to 10 degrees of vertical.
- 3= Resistive movements noted more than 10 degrees off vertical.

**STANDING:** Score with the patient standing with whatever support is needed. The expected hemiplegic response is for the patient to carry their weight toward the unaffected side or to passively fall towards their paretic side when placed in true vertical position by the examiner. This will not be scored as "lateropulsion." Position the patient with their trunk 15 to 20 degrees off true vertical towards their affected side then score the patient's response to your attempts to bring them back to vertical, then 5 to 10 degrees past vertical toward the intact side. The "lateropulsion" phenomenon is a voluntary or reflexive response in the trunk or limbs to keep the center of gravity towards the impaired side, e.g., forced trunk curvature towards the paretic side, flexion of the affected hip or knee, shifting weight to the lateral aspect of the unaffected foot.

- 0= Patient prefers to place his center of gravity over the unaffected leg.
- 1= Resistance is noted when attempting to bring the patient 5 to 10 degrees past midline.
- 2= Resistive voluntary or reflex equilibrium responses noted, but only within 5 degrees of approaching vertical.
- 3= Resistive reflex equilibrium responses noted, beginning 5 to 10 degrees off vertical.
- 4= Resistive voluntary or reflex equilibrium responses noted, >10 degrees off vertical

**TRANSFERS:** Score this one by transferring the patient first to the unaffected side, then if possible, to the affected side. The expected hemiplegic response would be for the patient to require more assistance to transfer towards the affected side (use a sit-pivot, modified stand pivot, or stand pivot transfer, depending on the patient's functional level).

- 0= No resistance to transferring to the unaffected side is noted.
- 1= Mild resistance to transferring to the unaffected side.
- 2= Moderate resistance to transferring to the unaffected side is noted. Only one person is required to perform the transfer.
- 3= Significant resistance is noted with transferring to the unaffected side. Two or more people are required to transfer the patient due to the severity of pushing.

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**WALKING:** Score lateropulsion by noting active resistance by the patient to efforts by the therapist to support the patient in true vertical position. Do not score passive falling or leaning to the paretic side. Score lateropulsion as follows:

- 0= No lateropulsion noted.
- 1= Mild lateropulsion noted.
- 2= Moderate lateropulsion noted with walking,
- 3= Strong lateropulsion noted, takes two individuals to walk with the patient, or unable to walk because of severity of lateropulsion.

Circle most prominent direction of lateropulsion: left, right, posterior-left, posterior-right.

**Note:** Some patients may show such marked lateropulsion that they cannot be assessed while standing or walking. In such cases, they are scored as having a maximum deficit for those tasks not testable due to the severity of their lateropulsion.

TOTAL SCORE = SUM OF THE ABOVE \_\_\_\_ (Max = 17)

Kindly cite this source if reproducing this scoring system:

D'Aquila MA, Smith T, Organ D, Lichtman S, Reding M. Validation of a lateropulsion scale for patients recovering from stroke. *Clin Rehabil.* 204;18:102-107.

Burke Rehabilitation Hospital  
785 Mamaroneck Avenue  
White Plains, New York 10605



Annex 4. The SCALE for Lateropulsion (SCALA)

## Scale for Lateropulsion: SCALA-V1.1

<b>Name</b>				
<b>Date</b>				
<div style="border: 1px solid black; padding: 10px; width: fit-content; margin: auto;"> <p style="margin: 0;"><b>SCORING</b></p> <p style="margin: 0; color: red;"><b>TASKS</b></p> </div>	<b>Spontaneous lateral tilt</b>	<b>Self-initiated lateral pushing</b>	<b>Resistance to passive lateral tilting</b>	<b>Lateropulsion unawareness</b> <small>If situational disorders, cognitive troubles or aphasia prevent from evaluation, score "NA" for the whole section.</small>
	<p><b>Tilt side</b> L = Left R = Right</p>	<p><b>For item A,</b> 0 = no lateral tilt 1 = slight and possibly occasional lateral whole body tilt 2 = moderate (obvious) and permanent lateral whole body tilt 3 = severe lateral tilt, trunk is in abutment against the armrest to prevent lateral collapse</p> <p><b>For items B, to H,</b> 0 = no lateral tilt 1 = slight and possibly discontinuous lateral whole body tilt, stability easily preserved 2 = moderate (obvious) and permanent lateral whole body tilt leading to precarious balance 3 = severe lateral tilt leading to inevitable lateral fall if no intervention</p>	<p>0 = no active lateral pushing 1 = active pushing visually obvious and/or palpable, strong enough to move the body toward the affected side</p>	<p>0 = no resistance or no difference between sides 1 = slight resistance after midline when tilted to the side opposite to the lateropulsion 2 = slight resistance before midline when originated from the initial lateral tilt 3 = strong resistance implying great difficulty in realigning or tilting the patient.</p>
<p>If not feasible for reasons other than lateropulsion, specify "NA" and score NA for the item in the same column and just above.</p>				
<b>A. SPONTANEOUS SITTING IN WHEELCHAIR (or other armchair)</b>				
<b>B. SITTING</b>				
<b>C. LEANING FORWARD WHILE SITTING</b>				
<b>D. TRANSFER FROM SITTING TO STANDING</b>				
<b>E. TRANSFER FROM STANDING TO SITTING</b>				
<b>F. STANDING FEET APART</b>	Eyes open*			
	Without vision*			
<b>G. STANDING FEET TOGETHER</b>	Eyes open*			
	Without vision*			
<b>H. WALKING *</b>				
<b>Sub-sections scores</b>	<b>Sub-score 1</b> (sum the right or left scores, i.e. main tilt side only)		<b>Sub-score 2</b>	<b>Sub-score 3</b>
	Tilt side	/30	/8	/6
<b>Total is 1+2+3+4</b> If sub-score 4 is "NA", sum-up 1+2+3 and multiply by 50/44		/50		
<p><b>Comment on the level of assistance provided</b> (human or technical) Prosthetic device (rigid trunk support in wheelchair, handbar, tripod cane, etc) and items concerned</p>			<p>If tasks were not feasible for reasons other than lateropulsion, note here the reason why you scored "NA"</p>	
<p>Presence of associated retro-pulsion : <input type="checkbox"/> no <input type="checkbox"/> mild <input type="checkbox"/> severe</p>				

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## Annex 5. List of publications and communications related to the thesis

### Articles

#### *Published or in-press*

Shenhao Dai, Camille Lemaire, Céline Piscicelli, Marie Jaeger, Anne Chrispin, Patrice Davoine, Dominic Pérennou. White-matter hyperintensities do not represent a critical lateropulsion determinant after stroke. *Ann Phys Rehabil Med* 2021. *IF 2020 =4.919*

Shenhao Dai, Céline Piscicelli, Emmanuelle Clarac, Monica Baciú, Marc Hommel, Dominic Pérennou. Lateropulsion after hemispheric stroke, a form of spatial neglect involving graviception. *Neurology* 2021; 96:e2160-e2171. DOI: 10.1212/WNL.0000000000011826. *IF 2020 =9.91*

Shenhao Dai, Céline Piscicelli, Camille Lemaire, Adélie Christiaens, Michel Thiebaut de Schotten, Marc Hommel, Alexandre Krainik, Olivier Detante, Dominic Pérennou. Recovery of balance and gait after stroke is deteriorated by confluent white matter hyperintensities: Cohort study. *Ann Phys Rehabil Med*. 2021 DOI: 10.1016/j.rehab.2021.101488. *IF 2020 =4.919*

Camille Lemaire, Assia Jaillard, Irina Gornushkina, Céline Piscicelli, Shenhao Dai, Cédric Pichat, Olivier Detante, Marc Hommel, Monica Baciú, Dominic Pérennou. Functional connectivity within the network of verticality. *Ann Phys Rehabil Med*. 2020 DOI: 10.1016/j.rehab.2020.101463. *IF 2020 =4.919*

Shenhao Dai, Céline Piscicelli, Emmanuelle Clarac, Monica Baciú, Marc Hommel, Dominic Pérennou. Balance, lateropulsion, and gait disorders in subacute stroke. *Neurology*. 2020; 96:e2147-e2159. DOI: 10.1212/WNL.0000000000011152. *IF 2020 =9.91*

Caroline Jolly, Céline Piscicelli, Rémi Gimat, Claire Berenger, Eric Guinet, Laure Mathevon, Anne Chrispin, Shenhao Dai, Monica Baciú, Dominic Pérennou. Tilted writing after stroke, a sign of biased verticality representation. *Ann Phys Rehabil Med*. 2020;63(1):85-88. DOI: 10.1016/j.rehab.2019.12.001. *IF 2020 =4.919*

#### *Submitted or revised*

Shenhao Dai, Camille Lemaire, Céline Piscicelli, Dominic Pérennou. Lateropulsion prevalence after stroke: a systematic review and meta-analysis. Submitted to *Neurology*. *IF 2020 =9.91*

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Romain Gastaldi, Céline Piscicelli, Shenhao Dai, Nicolas Leroux, Valérie Fraix, Anna Castrioto, Patrice Davoine, Paul Krack, Dominic Pérennou. Falling backward whilst bending forward: an apparent contradiction resolved? Revised in *Ann Phys Rehabil Med*. *IF 2020 =4.919*

### ***Book chapters***

Céline Piscicelli, Shenhao Dai, Camille Lemaire, Dominic Pérennou. Le chapitre « La perception de la verticalité » du « L'équilibre en tous sens ». ELSEVIER MASSON 2021, Edit Pr A Yelnik.

Shenhao Dai, Emmanuelle Clarac, Céline Piscicelli, Dominic Pérennou. Le chapitre « Evaluation de la latéropulsion » du « L'équilibre en tous sens ». ELSEVIER MASSON 2021, Edit Pr A Yelnik

### ***In preparation***

Shenhao Dai, Dominic Pérennou. The renaissance of the terminology 'lateropulsion', a postural milestone.

Shenhao Dai, Camille Lemaire, Emmanuelle Clarac, Céline Piscicelli, Dominic Pérennou. Why and how should we better assess lateropulsion?

Adèle Chauvin, Shenhao Dai, Emmanuelle Clarac, Patrice Davoine, Anne Chrispin, Céline Piscicelli, Dominic Pérennou. Contributions and determinants of posturography indices to understand the standing posture after stroke.

David Gogo, Shenhao Dai, Charles Benaim, Dominic Pérennou. Postural Assessment Scale for Stroke: a systematic review for its 20 years old.

Camille Lemaire, Shenhao Dai, Monica Baciú, Céline Piscicelli, Dominic Pérennou. Neurological bases of lateropulsion after stroke.

Adelie Christieans, Camille Lemaire, Shenhao Dai, Adèle Chauvin, Michèle Thiebault de Schotten, Monica Baciú, Céline Piscicelli, Dominic Pérennou. Neurological correlates of weight bearing asymmetry.

Flora Diaine, Rémi Lafitte, Shenhao Dai, Patrice Davoine, Anne Chrispin, Marie Jaeger, Caroline Jolly, Monica Baciú, Céline Piscicelli, Dominic Pérennou. Are tilted writing and drawing after stroke related to a biased perception of the vertical?

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Rémi Lafitte, Marie Jaeger, Eve Dupeyrix, Shenhao Dai, Anne Chrsipin, Patrice Davoine, Monica Baciou, Céline Piscicelli, Dominic Pérennou. What is the relation between Unilateral Spatial Neglect and Verticality perception biases after stroke?

*Oral communications and posters (underlined name corresponding to the presented person)*

Shenhao Dai, Céline Piscicelli, Emmanuelle Clarac, Monica Baciou, Marc Hommel, Dominic Pérennou. Lateropulsion after hemisphere stroke, a form of spatial neglect involving graviception. Communication orale. Congrès de la Société Française de Médecine Physique et de Réadaptation (SOFMER). Lille, octobre 2021.

Shenhao Dai, Camille Lemaire, Céline Piscicelli, Dominic Pérennou. Lateropulsion prevalence after stroke: a systematic review and meta-analysis. Poster. Congrès de la Société Française de Médecine Physique et de Réadaptation (SOFMER). Lille, octobre 2021. Submitted.

Shenhao Dai, Céline Piscicelli, Camille Lemaire, Emmanuelle Clarac, Marie Jaeger, Anne Chrispin, Patrice Davoine, Dominic Pérennou. Within the first 3 months post-stroke, balance recovery is related to a better orientation with respect to gravity. Communication orale. Congrès de la Société Française de Médecine Physique et de Réadaptation (SOFMER). Lille, octobre 2021.

Shenhao Dai, Dominic Pérennou. Understanding lateropulsion after stroke. Communication orale au séminaire de Laboratoire Psychologie et NeuroCognition. Grenoble, mars 2021.

Shenhao Dai, Céline Piscicelli, Emmanuelle Clarac, Monica Baciou, Marc Hommel, Dominic Pérennou. Balance, lateropulsion, and gait disorders in subacute stroke. Oral communication at the 11th World Congress for Neurorehabilitation (WCNR). Lyon, octobre 2020.

Shenhao Dai, Céline Piscicelli, Emmanuelle Clarac, Monica Baciou, Marc Hommel, Dominic Pérennou. Lateropulsion after hemisphere stroke, a form of spatial neglect involving graviception. Communication orale. Congrès annuel de la Société Francophone Posture-Equilibre-Locomotion (SOFPEL). Lille, décembre 2021.

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Shenhao Dai, Céline Piscicelli, Dominic Pérennou. Lateropulsion is the cardinal sign of pusher syndrome. Poster at the 11th World Congress for Neurorehabilitation (WCNR). Lyon, octobre 2020.

Shenhao Dai, Klaus Dieterich, Marie Jaeger, Bernard Wuyam, Pierre-Simon Jouk, Dominic Pérennou. Handicap of adults with Arthrogyrosis Multiplex Congenita: severe, multifaceted and varying by genotype. Poster at the 11th World Congress for Neurorehabilitation (WCNR). Lyon, octobre 2020.

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Dominic Pérennou, Céline Piscicelli, Shenhao Dai. Oral communication at the international lateropulsion meeting. Perth, Grenoble, Sao Paulo, New York, janvier, 2020.

Shenhao Dai, Céline Piscicelli, Camille Lemaire, Emmanuelle Clarac, Anne Chrispin, Patrice Davoine, Monica Baciú, Dominic Pérennou. Is post-stroke lateropulsion a kind of graviceptive neglect? Communication orale. Congrès de la Société Française de Médecine Physique et de Réadaptation (SOFMER). Bordeaux, octobre 2019.

Shenhao Dai, Céline Piscicelli, Emmanuelle Clarac, Patrice Davoine, Anne Chrispin, Marie Jaeger, Olivier Detante, Monica Baciú, Marc Hommel, Dominic Pérennou. Leukoaraiosis, an invisible factor contributes to balance and gait disorders after stroke. Communication orale. Congrès de la Société Française de Médecine Physique et de Réadaptation (SOFMER). Bordeaux, octobre 2019.

Shenhao Dai, Céline Piscicelli, Camille Lemaire, Emmanuelle Clarac, Anne Chrispin, Patrice Davoine, Monica Baciú, Dominic Pérennou. Is post-stroke lateropulsion a kind of graviceptive neglect? Oral communication at the European Congress of NeuroRehabilitation. Budapest, octobre 2019.

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Shenhao Dai, Céline Piscicelli, Emmanuelle Clarac, Patrice Davoine, Anne Chrispin, Marie Jaeger, Olivier Detante, Monica Baciú, Marc Hommel, Dominic Pérennou.

Leukoaraiosis, an invisible factor contributes to balance and gait disorders after stroke. Oral communication at the European Congress of NeuroRehabilitation. Budapest, octobre 2019.

Shenhao Dai, Céline Piscicelli, Dominic Pérennou. The prevalence of pusher syndrome after a hemisphere stroke: a systematical review and meta-analysis. Poster at the European Congress of NeuroRehabilitation, Budapest, octobre 2019.

Shenhao Dai, Céline Piscicelli, Camille Lemaire, Emmanuelle Clarac, Anne Chrispin, Patrice Davoine, Monica Baciú, Dominic Pérennou. Is post-stroke lateropulsion a kind of graviceptive neglect? Oral communication at the 13th annual world congress 2019 of the International Society of Physical and Rehabilitation Medicine (ISPRM). Kobe, Juin 2019.

Shenhao Dai, Céline Piscicelli, Emmanuelle Clarac, Patrice Davoine, Anne Chrispin, Marie Jaeger, Olivier Detante, Monica Baciú, Marc Hommel, Dominic Pérennou.

Leukoaraiosis, an invisible factor contributes to balance and gait disorders after stroke. Oral communication at the 13th annual world congress 2019 of the International Society of Physical and Rehabilitation Medicine (ISPRM). Kobe, Juin 2019.

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2018.

Dominic Pérennou, Shenhao Dai, Camille Lemaire. Lateropulsion, une fenêtre de la cognition  
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Auvergnés-Rhône-Alpes. Lyon, mars 2018.

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Neurorehabilitation (WFNR). Mumbai, Inde, Février 2018.

Shenhao Dai, Emmanuelle Clarac, Anais Odin, Bastien Moineau, Céline Piscicelli, Marie  
Jaeger, Dominic Pérennou. Troubles de l'équilibre et de la marche à la phase subaigüe de  
l'AVC : la lateropulsion est la clé. Communication orale. Congrès annuel de la Société  
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Shenhao Dai, Emmanuelle Clarac, Anais Odin, Bastien Moineau, Céline Piscicelli, Marie  
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Jaeger, Dominic Pérennou. Troubles de l'équilibre et de la marche à la phase subaigüe de

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l'AVC : la lateropulsion est la clé. Communication orale. Congrès de la Société Française de Médecine Physique et de Réadaptation (SOFMER). Nancy, octobre 2017.



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## Annex 6. List of publications and communications unrelated to the thesis

### *Published*

Shenhao Dai, Klaus Dieterich, Marie Jaeger, Bernard Wuyam, Pierre-Simon Jouk, Dominic Pérennou. Author response: Disabilities of adults with arthrogryposis multiplex congenita: severe, multifaceted, partly invisible, and varying by genotype. *Neurology*. 2019;92:636. DOI: 10.1212/WNL.00000000000007169. *IF 2020 =9.91*

Shenhao Dai, Klaus Dieterich, Marie Jaeger, Bernard Wuyam, Pierre-Simon Jouk, Dominic Pérennou. Disabilities of adults with arthrogryposis multiplex congenita: severe, multifaceted, partly invisible, and varying by genotype. *Neurology*. 2018;90:e1596-e1604. DOI: 10.1212/WNL.00000000000005418. *IF 2020 =9.91*

### *Submitted*

Charles Benaim, Husam Alzuhairi, Hervé Devilliers, Anne Jambresic, Shenhao Dai, Camille Lemaire, Dominic Pérennou. Rasch analysis of the Aphasia Depression Rating Scale (ADRS). Revised in *Ann Phys Rehabil Med*. *IF 2020 =4.919*

### *In preparation*

Rémi Gimat, Shenhao Dai, Dominique Faletto, Emmanuelle Clarac, Dominic Pérennou. Fall risk factors after a stroke: mean follow up of two years.

Helena Favre, Margo Fradet, Shenhao Dai, Charles Benaim, Marc Hommel, Dominic Pérennou. Inability to walk, a predictor of post-stroke depression.

### *Oral communications and posters (underlined name corresponding to the presented person)*

Shenhao Dai, Klaus Dieterich, Marie Jaeger, Bernard Wuyam, Pierre-Simon Jouk, Dominic Pérennou. Handicap in adults with arthrogryposis is severe, partly invisible and varies by genotype. Poster at the 12th annual world congress 2018 of the International Society of Physical and Rehabilitation Medicine (ISPRM). Paris, Juillet 2018.

Shenhao Dai, Klaus Dieterich, Marie Jaeger, Bernard Wuyam, Pierre-Simon Jouk, Dominic Pérennou. Handicap of adults with arthrogryposis multiplex congenita: severe, partly

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invisible, and varying by genotype. Poster at 21st European Congress of Physical and Rehabilitation Medicine (ESPRM). Vilnius, Lithuania, Mai 2018.

Shenhao Dai, Klaus Dieterich, Marie Jaeger, Bernard Wuyam, Pierre-Simon Jouk, Dominic Pérennou. Handicap of adults with arthrogyrosis multiplex congenita: severe, multifaceted, partly invisible, and varying by genotype. Poster at the 10th World Congress for Neurorehabilitation (WFNR), Mumbai, Inde, Fevrier 2018.

Shenhao Dai, Klaus Dieterich, Marie Jaeger, Bernard Wuyam, Pierre-Simon Jouk, Dominic Pérennou. Arthrogyrosis multiplex congenita: what are the activity limitations in adulthood? Poster presented at the World Congress of the International Society of Physical and Rehabilitation Medicine (ISPRM), Buenos Aires, mai 2017.

Shenhao Dai, Klaus Dieterich, Marie Jaeger, Bernard Wuyam, Pierre-Simon Jouk, Dominic Pérennou. -Quelles sont les limitations d'activité et d'autonomie dans la vie quotidienne des adultes atteints d'arthrogrypose? Réunion des services universitaires de MPR de la région Auvergne-Rhône-Alpes. Lyon mars 2017.

Shenhao Dai, Klaus Dieterich, Marie Jaeger, Bernard Wuyam, Pierre-Simon Jouk, Dominic Pérennou. Quelles sont les limitations d'activité et d'autonomie dans la vie quotidienne des adultes atteints d'arthrogrypose? Communication orale. Congrès annuel de la Société Française de Médecine Physique et de Réadaptation (SOFMER). Saint-Etienne, octobre 2016.

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**Annex 7. Proofs of papers**

**7.1 Companion papers published in Neurology as cover**

**7.2 Paper of WMHs (in-press) in Ann Phys Rehabil Med**

**7.3 Paper of arthrogyryposis published in Neurology**

*Page numbers as original ones*



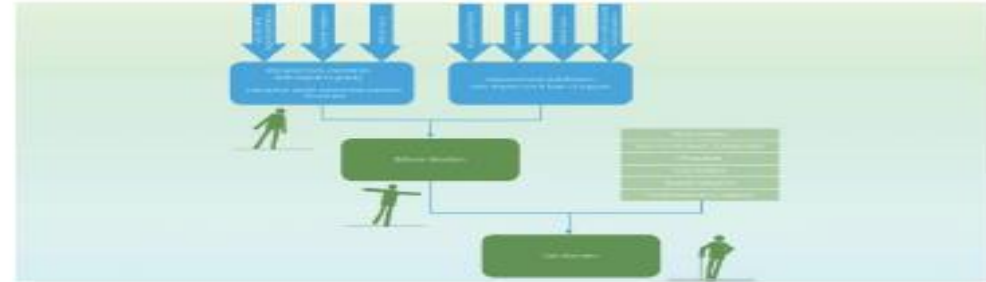
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Coverage with our theoretical model of balance and gait disorders after stroke (Dai et al DOI: 10.1212/WNL.0000000000011152)



## Cover Image

Theoretic model of balance and gait disorders after stroke. Stylized by Kaitlyn Aman Ramm, Digital Multimedia/Graphics Coordinator. See page 787

## Editorials

- 779 **Lateropulsion: An Overlooked Driver of Balance and Gait Deficits in Stroke?**  
J. Gomes-Osman and A. Kloos

## Articles:

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- 787 **Balance, Lateropulsion, and Gait Disorders in Subacute Stroke**  
S. Dai, C. Piscicelli, E. Clarac, M. Baciú, M. Hommel, and D. Pérennou  
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- 788 **Lateropulsion After Hemispheric Stroke: A Form of Spatial Neglect Involving Graviception**  
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➔ Video

Table of content showing that our 2 companion papers are the first of the issue, with an editorial

# Lateropulsion

## An Overlooked Driver of Balance and Gait Deficits in Stroke?

Joyce Gomes-Osman, PT, PhD, and Anne Kloos, PT, PhD, NCS

*Neurology*® 2021;96:779-780. doi:10.1212/WNL.0000000000011156

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### RELATED ARTICLE

Balance, Lateropulsion, and  
Gait Disorders in Subacute  
Stroke

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Lateropulsion after stroke limits a person's ability to sit, stand, and walk and delays or interferes with functional recovery.<sup>1,2</sup> Beyond contributing to significant disability in the individual, it creates safety challenges during rehabilitation and greater burden on caregivers and family. The neuroanatomic characterization of lateropulsion is in its early stages,<sup>3</sup> and thus, effective treatments are lacking.<sup>4</sup> This issue of *Neurology*® presents an elegant study<sup>5</sup> investigating a clinically important and underexamined question: what is the functional prognosis of patients who present with lateropulsion after subacute stroke?

Dai et al.<sup>5</sup> assessed the relationship between lateropulsion and recovery of balance and gait functions in 220 first-time patients with stroke over the course of an inpatient rehabilitation stay. This was the first study of its kind to investigate such relationships in the subacute stage after stroke in a longitudinal study of a moderate sample size. Lateropulsion as assessed by a clinical scale, the Scale for Contraversive Pushing, was found to be the primary cause of balance and gait disorders at the subacute stage after stroke. Specifically, multivariate regression models revealed that lateropulsion, weakness, and hypoesthesia were primary determinants of balance disorders and that lateropulsion and weakness were primary determinants of gait disorders. This was especially true after a right hemispheric stroke, wherein lateropulsion explained 90% of variance in balance initially and 92% at discharge. It also predicted 66% of variance in gait initially and 68% at discharge. For left hemispheric stroke, lateropulsion explained 59% of variance in balance and 43% of gait initially but was present in only 2% of the sample at discharge.

These data have important clinical implications. First, the finding that lateropulsion was strongly associated with the right hemisphere is novel, as is the longitudinal design that informs the clinical relevance not only at the initial assessment but also during discharge. Second, these findings challenge the idea that impaired body stabilization with respect to the base of support (sensorimotor deficits, spatial neglect) is the primary cause of balance and gait disorders after stroke.<sup>6</sup> It is important, however, to highlight considerations that limit generalizability of these findings to clinical rehabilitation settings in other parts of the world. All data collection was performed in 1 European rehabilitation hospital. The primary outcome of lateropulsion (Scale for Contraversive Pushing) has documented cross-cultural validity biases in the English language and thus is not the measure of choice in the United States.<sup>7</sup> Furthermore, the gait assessment is also performed with a scale that is not typically done in clinical rehabilitation settings in the United States, where the Functional Independence Measure is more often used. An important and exciting future research direction will be the cross-cultural replication of these findings.

In conclusion, the contribution of lateropulsion as an important driver of disability in subacute stroke is clearly established with the results of this innovative study. The results highlight the importance of considering lateropulsion as an impairment target in inpatient rehabilitation after stroke. Current literature on interventions targeting lateropulsion is emerging.<sup>8-10</sup> Therefore, in addition to further elucidating neurobiological underpinnings, it will be critical to establish whether lateropulsion responds to treatment.

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Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

## Study Funding

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## Disclosure

J. Gomes-Osman and A. Kloos report no disclosures relevant to the manuscript. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

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# Balance, Lateropulsion, and Gait Disorders in Subacute Stroke

Shenhao Dai, MD, Céline Piscicelli, PhD, Emmanuelle Clarac, PT, Monica Baciú, MD, PhD, Marc Hommel, MD, PhD, and Dominic Pérennou, MD, PhD

*Neurology*® 2021;96:e2147-e2159. doi:10.1212/WNL.00000000000011152

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## Abstract

### Objective

To test the hypothesis that impaired body orientation with respect to gravity (lateropulsion) would play a key role in poststroke balance and gait disorders.

### Methods

Cohort study of 220 individuals consecutively admitted to a neurorehabilitation ward after a first hemisphere stroke (DOBRAS cohort [Determinants of Balance Recovery After Stroke] 2012–2018, ClinicalTrials.gov: NCT03203109), with clinical data systematically collected at 1 month, then at discharge. Primary outcomes were balance and gait disorders, quantified by the Postural Assessment Scale for Stroke and the modified Fugl-Meyer Gait Assessment, to be explained by all deficits on day 30, including lateropulsion assessed with the Scale for Contraversive Pushing. Statistics comprised linear regression analysis, univariate and multivariate analyses, and receiver operating characteristic curves.

### Results

Lateropulsion was frequent, especially after right hemisphere stroke (RHS, D30, 48%; discharge 24%), almost always in right-handers. Among all deficits, impaired body orientation (lateropulsion) had the most detrimental effect on balance and gait. After RHS, balance disorders were proportional to lateropulsion severity, which alone explained almost all balance disorders at initial assessment (90%; 95% confidence interval [CI] [86–94],  $p < 0.001$ ) and at discharge (92%; 95% CI 89–95,  $p < 0.001$ ) and also the greatest part of gait disorders at initial assessment (66%; 95% CI 56–77,  $p < 0.001$ ) and at discharge (68%; 95% CI 57–78,  $p < 0.001$ ).

### Conclusion

Lateropulsion is the primary factor altering poststroke balance and gait at the subacute stage and therefore should be systematically assessed. Poststroke balance and gait rehabilitation should incorporate techniques devoted to misorientation with respect to gravity.

## RELATED ARTICLE

### Editorial

Lateropulsion: An Overlooked Driver of Balance and Gait Deficits in Stroke?

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Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

## Glossary

**AUC** = area under the receiver operating characteristic curve; **BLS** = Burke Lateropulsion Scale; **CI** = confidence interval; **D30** = day 30 after stroke; **DOBRAS** = Determinants of Balance Recovery After Stroke; **GLM** = generalized linear model; **LHS** = left hemisphere stroke; **Lw/oP** = lateropulsion without pushing; **mFMA** = modified Fugl-Meyer Assessment; **mRS** = modified Rankin Scale; **NPV** = negative predictive value; **PASS** = Postural Assessment Scale for Stroke; **PPV** = positive predictive value; **RHS** = right hemisphere stroke; **ROC** = receiver operating characteristic; **SCP** = Scale for Contraversive Pushing.

The current theoretical model of balance control involves 2 domains devoted to body orientation with respect to gravity and to body stabilization with respect to the base of support.<sup>1,2</sup> This model might help in better understanding balance disorders in the clinic, in order to guide their rehabilitation. It could be especially useful after stroke<sup>3,4</sup> owing to the devastating sequelae induced by balance disorders,<sup>5</sup> which may be explained in terms of impaired body orientation or stabilization.

As early as 1900, cases of brainstem<sup>6</sup> or hemisphere<sup>7</sup> stroke showing a lateral body tilt with fall tendency were described and initially termed lateropulsion,<sup>6</sup> then variously according to authors' consideration for additional postural signs and lesion location. Most known terms are listing phenomenon,<sup>8</sup> thalamic astasia,<sup>9,10</sup> ease of falling,<sup>11,12</sup> pusher/pushing syndrome/behavior,<sup>3,10,13–17</sup> and biased behavioral vertical.<sup>18</sup> Here we adopt lateropulsion, the most frequently used.<sup>3,6,19–25</sup>

Lateropulsion interpretation has long erred across mechanisms involving cerebellar and motor pathways. Today, lateropulsion is considered to have a vestibular origin with different mechanisms depending on lesion location.<sup>3,10,26</sup> After low-brainstem lesions, lateropulsion is ipsilesional and mainly secondary to vestibulospinal disorders, inducing an asymmetric tone with a co-occurrence of vestibulo-ocular signs.<sup>3,25,27</sup> After hemispheric lesion, lateropulsion is contralesional, owing to an internal model of verticality tilted to the contralesional side (opposite the stroke).<sup>3,28</sup> Individuals align their body onto this erroneous reference of verticality,<sup>3,18,28</sup> possibly in relation to a damaged multimodal network.<sup>26</sup> At the beginning, individuals are unaware of the lateropulsion,<sup>11,12</sup> which strengthens the interpretation of a biased internal model of verticality.<sup>3,29</sup>

Severe cases of lateropulsion jeopardize the ability to walk, stand, or sit,<sup>9,13,16,25,30</sup> with poor recovery.<sup>14,17,20,31</sup> Beyond these extreme forms, which represent only 10%,<sup>14,31</sup> the effect of lateropulsion on balance abilities has been little investigated. A few cross-sectional studies of limited sample size have ancillary reported a moderate correlation between lateropulsion indices and balance abilities.<sup>30,32</sup> To our knowledge, the effect of lateropulsion on balance capacity after stroke has never been investigated longitudinally in a large series. Our main hypothesis was that even mild forms of lateropulsion represent a key determinant of poststroke balance disorders. Indeed, any lateral body tilt generates a destabilizing effect of gravity, with a projection of the center of mass on the ground moving toward the limit of the base of support, which alters balance capacities.

For poststroke gait disorders, a common view is that they are mostly caused by sensorimotor deficits such as weakness,<sup>33</sup> muscular overactivity, and neuro-orthopedic complication of spasticity,<sup>33,34</sup> with an additional detrimental role of balance disorders.<sup>35,36</sup> We hypothesized that mild forms of lateropulsion also greatly affect gait abilities.

## Methods

### Study Design

This was a monocentric observational study of the DOBRAS cohort (Determinants of Balance Recovery After Stroke; NCT03203109). Participants were comprehensively assessed twice in routine care: initially in the first weeks after entry in the rehabilitation ward, then at discharge.

We assessed balance and gait abilities as well as sensory, motor, and cognitive deficits. Assessments were performed by trained and multidisciplinary examiners, with blinding to the study hypothesis. The sample size was planned to conduct multivariate analyses in a large series of individuals ( $\geq 200$  observations).

### Standard Protocol Approvals, Registrations, and Patient Consents

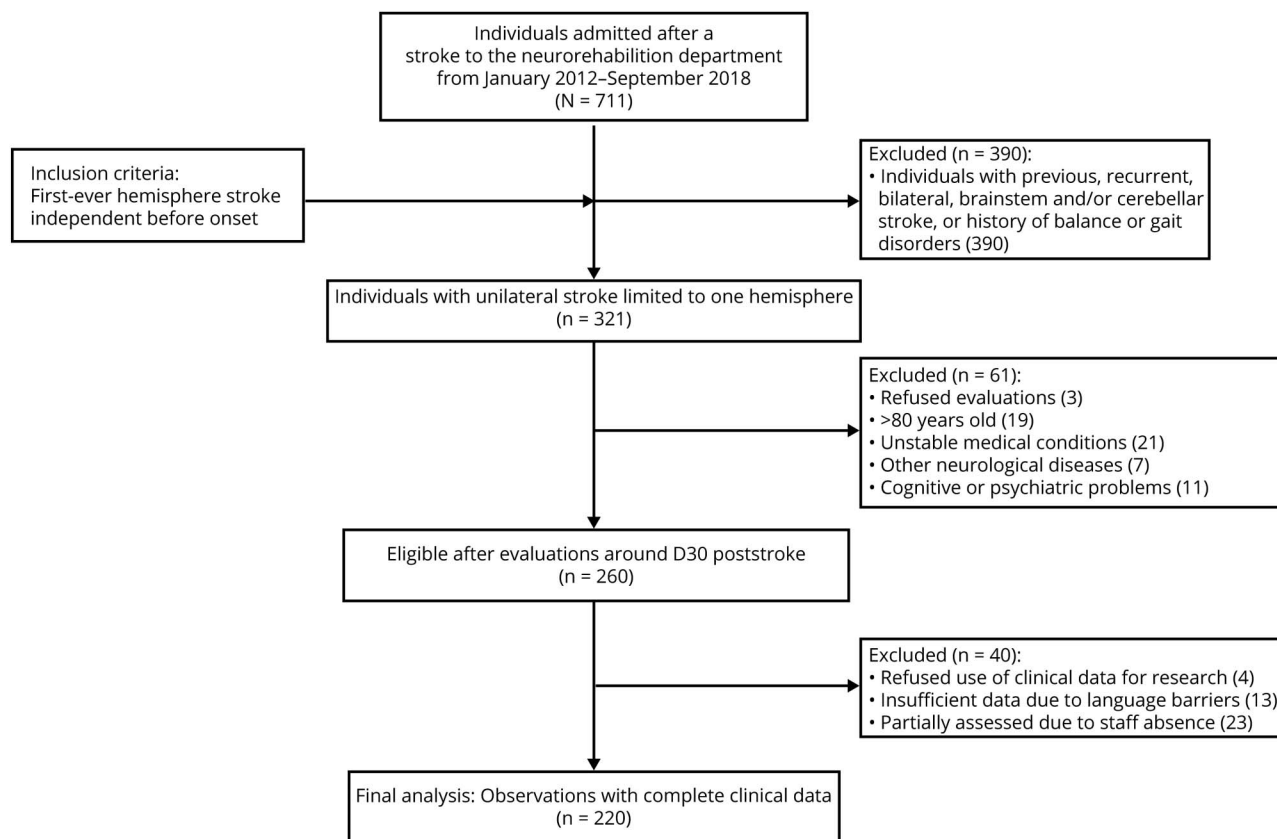
The DOBRAS cohort was approved by our institutional review board (CHU Grenoble Alpes) who validated the ClinicalTrials.gov registration (NCT03203109). The study was also registered at the National Committee for Informatics and Freedom (Commission Nationale Informatique et Liberté; CNIL-No.2014874-v1) 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

From January 2012 to September 2018, we included 220 consecutive individuals (figure 1). Inclusion criteria were age  $\geq 18$ –80 years and a first-ever unilateral stroke limited to one hemisphere (right hemisphere stroke [RHS] or left hemisphere stroke [LHS]). Exclusion criteria were recurrent stroke; complication at the acute stage (malignant infarct, cerebral herniation, subarachnoid hemorrhage, hydrocephalus); dementia;



**Figure 1** Flow of Participants in the Study



previous disability interfering with balance, gait, or vestibular disorders; unstable medical condition or psychiatric problems; or not French-speaking. These conditions were obtained from the hospital electronic file describing the history of every patient, by interviewing patients and relatives, and by a systematic clinical examination. Patients followed a personalized rehabilitation program, taking into account deficits and activity limitations. According to their abilities, individuals had 2 physiotherapy and 1 occupational therapy sessions per day (total 1 hour 30 minutes), plus, if needed, sessions with a speech therapist, neuropsychologist, psychologist, or orthoptist.

## Assessments

We conducted the initial assessments at about day 30 after stroke (D30) with a window of 3 days before and after to start and complete assessments. This date is a compromise between the desire to collect data as early as possible after the stroke and the need for sufficient medical stability and attentional resources to afford a battery of comprehensive assessments performed during several days, at a time when almost all individuals have been admitted to the rehabilitation ward. Among the 220 participants, 207 (94%) were admitted during the first month poststroke and so were assessed on D30. For the 13 others admitted after D30 (6%), the initial assessment was also performed in due time, on day 60 (window of 3 days before and after). These initial assessments collected information about handedness, all deficits, postural

and gait disorders, and disability. All variables collected are listed below. The second assessment was performed at discharge and only focused on postural and gait disorders.

Global disability was estimated by the modified Rankin Scale (mRS).

Handedness before stroke was assessed by interview (patient, relatives) by using a French translation of the Edinburgh inventory. Right-handedness was considered with a score  $>0.4$ .

To assess body orientation with respect to gravity in the frontal plane, we used the Scale for Contraversive Pushing (SCP).<sup>15</sup> The SCP assesses the 3 components of the pusher syndrome defined by Davies,<sup>13</sup> that is, contralesional lateral body tilt (while sitting and standing), active pushing of the unaffected arm or leg to the contralesional side (while sitting and standing), and resistance to passive correction of posture (while sitting and standing). The total score ranges from 0 to 6. As defined in the original article,<sup>15</sup> individuals who met these 3 criteria with at least 1 point for each were considered pushers. As proposed previously,<sup>3</sup> we also used the SCP to differentiate individuals with an upright posture from those who were mildly tilted. To be conservative, we used the same SCP cut-off  $>0.5$  as in a previous article,<sup>3</sup> which classifies as having a lateropulsion without pushing (Lw/oP) according to the SCP scoring only individuals who showed net lateral body

tilt at least in one posture, sitting or standing, but without pushing or resistance. So constituted, the 3 groups corresponded to individuals differently oriented with respect to gravity: individuals upright were correctly oriented, individuals showing Lw/oP presented a moderate deficit in orientation with respect to gravity, and pushers presented a severe deficit in orientation with respect to gravity. We also used SCP scores to test relationships with balance and gait scores. Details on the validity of these approaches are given in the study limitations.

Balance disorders were assessed with the Postural Assessment Scale for Stroke (PASS),<sup>32</sup> the most appropriate balance scale at the subacute stage after stroke.<sup>37,38</sup> The total score ranges from 0 to 36 (satisfactory balance), and a score  $\geq 28$  indicates the ability to stand independently without any help.<sup>32</sup>

Gait disorders were assessed with the modified chart of the Fugl-Meyer Assessment (mFMA), designed to classify post-stroke gait with 7 levels of mobility.<sup>39</sup> The mFMA ranges from 0 (no mobility) to 6 (normal gait), and a score  $\geq 5$  indicates the ability to walk independently without a cane (or rollator).

Deficits were assessed by means of a comprehensive battery of tests. Spatial neglect (body and nonbody domains) was assessed with a battery of 6 tests: ecological Catherine Bergego Scale,<sup>40</sup> thumb finding,<sup>40</sup> Fluff (since 2014)<sup>41</sup> and Bells tests,<sup>40</sup> line bisection,<sup>40</sup> and drawing copy.<sup>40</sup> The Catherine Bergego Scale result was considered normal with score  $< 2$ , moderately altered with score  $\geq 2$ , and markedly altered with score  $\geq 15$ . The thumb finding test result was considered abnormal with score  $> 0$ . The Fluff test result was considered normal with  $\geq 13$  targets detached, moderately altered with  $\geq 9$  targets detached, and markedly altered with  $< 9$  targets detached. The Bells test result was considered normal with  $\leq 6$  omissions, moderately altered with  $\leq 15$  omissions, and markedly altered with  $> 15$  omissions. The line bisection (20 mm) result was considered normal at  $\leq 7$  mm, moderately altered at  $\leq 10$  mm, and markedly altered at  $> 10$  mm. The Gainotti copy result was considered abnormal if  $> 0$  omissions. A few individuals with severe comprehension (aphasia) or executive troubles were not able to complete the whole neglect battery but had to perform at least 3 tests to not be considered with missing data. Spatial neglect was considered absent if all test results were normal or slight if only one test result was marginally altered, severe with results of least 2 tests markedly altered (altered if binary categorized), or moderate otherwise.

The presence of aphasia was evaluated by the gravity section of the Boston Diagnostic Aphasia Examination; a score  $< 5$  was considered aphasia. Apraxia was assessed by the Apraxia Screen of Tulia<sup>42</sup> and participants with a score  $< 9$  had a diagnosis of upper limb apraxia.

Motor weakness was assessed by a standardized examination of muscle strength adapted for participants with central neurologic disorders.<sup>18,32</sup> Eight muscle groups of both the upper and

lower limb were tested, and the final score was then adjusted to range from 0 to 80 (normal strength). Light weakness was considered a score  $> 64/80$  (every muscle had a motor command of 4/5, on average), severe weakness a score  $\leq 32$  (every muscle had a motor command of  $\leq 2/5$ , on average), and moderate weakness otherwise. Spasticity was assessed with the Ashworth Scale.<sup>18,32</sup> Five muscle groups of both the upper and lower limb were tested, and the final score was adjusted to range from 0 to 40 (extremely severe and diffused spasticity). Participants were classified as follows in terms of spasticity: no or light (0–4), moderate or severe ( $> 4$ ).

Hypoesthesia was manually tested on both contralesional upper and lower limbs by trained physicians who assessed tactile and pain sensibility.<sup>18,32</sup> Participants were classified as having no or light hypoesthesia if errors were seldom, moderate hypoesthesia if detection errors were frequent, and deep hypoesthesia if they did not perceive any stimuli. Hemianopia was manually tested by trained physicians.

Depression was assessed by the Aphasia Depression Rating Scale<sup>43</sup>; participants with scores  $> 8$  were considered depressed.

## Statistical Analysis

Continuous data are presented as median with interquartile range (Q1–Q3) and dichotomized and categorical data as number (%). When useful, 95% confidence intervals (CIs) are given.

Data for upright, Lw/oP, and pusher groups were compared by the Mann-Whitney *U* test or  $\chi^2$  test (Fisher exact test). Effect sizes were calculated by using the *Z* values of the Mann-Whitney test,  $r = Z/\sqrt{n}$ , and the  $X^2$  of the  $\chi^2$  test,  $v = \sqrt{(X^2/n \times \text{degree of freedom})}$ . With  $p < 0.05$ , effect sizes are given; values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both the Mann-Whitney test and  $\chi^2$  test.

The relationship of balance and gait was analyzed by linear regression. Our primary hypothesis was that lateropulsion would be the most detrimental determinant on balance and gait disorders. All the clinical features related to balance and gait disorders were first analyzed by nonparametric univariate analysis (Kruskal-Wallis or Mann-Whitney *U* test). The significant *p* values for univariate analyses were adjusted to 0.004 (0.05/12) owing to multiple comparisons. Variables with  $p < 0.004$  on univariate analysis were selected for the multivariate regression model. Because PASS and mFMA scores followed a Poisson distribution, we used a generalized linear model (GLM, Poisson regression).

Then we analyzed the consequences of a misorientation with respect to gravity on balance and gait abilities by using linear regression on initial and discharge data. Owing to the well-known RHS predominance for postural control,<sup>3,4,17,18,31,32</sup> we separately analyzed RHS and LHS.

**Table 1** Clinical Data for Participants as a Function of Lateropulsion in 3 Categories

Characteristics	All (n = 220)	Upright (n = 158)	Lw/oP (n = 32)	Pushers (n = 30)	Upright vs Lw/oP	Upright vs pushers	Lw/oP vs pushers
Female	73 (33%)	49 (31)	11 (34)	13 (43)	$v = 0.03$	$v = 0.1$	$v = 0.09$
Age, y	66.9 (58–73)	66.2 (54–72)	66 (60–71)	70.4 (64–76)	$r = -0.03$	$r = -0.21$	$r = -0.28$
Right-handers	198 (90)	138 (87)	30 (94)	30 (100)	$v = 0.07$	$v = 0.15$	$v = 0.18$
<b>Stroke features</b>							
Test date, D30	207 (94)	151 (96)	29 (91)	27 (90)	$v = 0.08$	$v = 0.09$	$v = 0.01$
Stroke type, infarct	183 (83)	133 (84)	26 (81)	24 (80)	$v = 0.03$	$v = 0.04$	$v = 0.02$
Stroke side, right hemisphere	94 (43)	49 (31)	20 (63)	25 (83)	$v = 0.24$	$v = 0.39$	$v = 0.23$
Modified Rankin scale score (0–6)	3 (2–4)	3 (2–3)	4 (4–4)	5 (4–5)	$r = -0.58$	$r = -0.65$	$r = -0.56$
Length of hospital stay, d, onset to discharge	81 (51–138)	64 (45–91)	151 (113–180)	169 (143–202)	$r = -0.47$	$r = -0.55$	$r = -0.19$

Abbreviations: D30 = day 30 (others were tested at day 60); Lw/oP = lateropulsion without pushing; pusher = lateropulsion with pusher syndrome;  $r$  = effect size of the Mann-Whitney test;  $v$  = effect size of  $\chi^2$  test. Data are n (%) or median (Q1–Q3), unless stated otherwise.

We further investigated these relationships and tested the value of initial SCP scores to predict the ability to stand (PASS  $\geq 28$ ) or walk independently (mFMA  $\geq 5$ ) at discharge. We plotted receiver operating characteristic (ROC) curves and calculated areas under the ROC curve (AUC). Optimal cutoff values were determined by the Youden Index. From the SCP cutoff values, we calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Missing data were few, so imputation was not performed. As recommended,<sup>44</sup>  $p$  values were limited to the main hypothesis, with 2-sided  $p < 0.05$  considered statistically significant. Only CIs and effect sizes were given for analyses of secondary endpoints. Statistical analysis involved using SPSS 21.0.

### Data Availability

Anonymized data that support the findings of this study are available from the corresponding author, upon reasonable request.

## Results

Clinical data for the 220 individuals investigated are presented in table 1. Their median age was 66.9 years (Q1–Q3 58–73), 147 were male (67%), and most were right-handed (90%) and with infarcts (83%). The median mRS score was 3 (2–4); 150 (68%) individuals had moderate or severe disability (mRS score  $> 2$ ). The median hospital stay in the rehabilitation ward was 81 days (range 51–138).

Missing initial data concerned spatial neglect ( $n = 2$ ), apraxia ( $n = 5$ ), hemianopia ( $n = 1$ ), and depression ( $n = 9$ ). Discharge data could not be collected for 3 (1%) individuals (2 deaths, 1 urgent transfer).

In this series, 158 individuals (72%) were considered upright, with 2 scenarios: 146 (66%) sat and stood perfectly upright (including 1 who exhibited pushing when changing positions in standing), and 12 (6%) showed some degree of isolated body tilt in sitting or standing, without fall tendency. The 62 others (28%) were considered misoriented with respect to gravity in erect posture; among them, 32 (14%) showed Lw/oP and 30 (14%) were pushers. Individuals with lateropulsion were almost all right-handed (97%), and pushers were all right-handed, which indicates that the orientation of the self with respect to gravity relies on a lateralized brain function. Lateropulsion (with or without pushing) prevalence was much greater after RHS than LHS (45/94 [48%] vs 17/126 [13%];  $v = 0.38$ ), which indicates a strong right-hemisphere predominance for the upright orientation (lateropulsion 3.7 times more frequent after RHS than LHS).

### Relationship Between Gait and Balance Disorders

Balance and gait scores were highly correlated, both initially ( $r = 0.89$ ,  $p < 0.001$ ) and at discharge ( $r = 0.86$ ,  $p < 0.001$ ), which indicates that balance capacities highly explained the information contained in gait capacities: 79% (95% CI 75–84) initially (about 1 month) and 74% (95% CI 68–80) at discharge.

### Determinants of Balance and Gait Abilities

We sought determinants of balance and gait disorders from initial data. On univariate analyses, only 2 variables did not affect balance or gait (stroke type and aphasia), and 2 did not affect gait (age and stroke side) (table 2). All other variables were kept in the multivariate analyses (table 2).

For balance disorders, the GLM revealed only 3 deficits with an independent detrimental role: lateropulsion, weakness, and hypoaesthesia when severe. The model was sound with

**Table 2** Univariate and Multivariate Analysis of Effect of Clinical Features on Balance Disorders and Gait Disorders

	Balance				Gait			
	PASS, median (Q1–Q3)	<i>p</i> Value <sup>a</sup> (univariate)	Exp (β) (95% CI)	<i>p</i> Value (multivariate)	mFMA, median (Q1–Q3)	<i>p</i> Value <sup>a</sup> (univariate)	Exp (β) (95% CI)	<i>p</i> Value (multivariate)
<b>Age, y</b>								
≤60 (n = 67)	33 (28–36)	0.003	1		5 (3–6)	0.012		
>60 (n = 153)	32 (19–34)		1 (0.9–1)	0.161	3 (0–6)			
<b>Stroke type</b>								
Infarct (n = 183)	32 (22–35)	0.374			4 (1–6)	0.97		
Hemorrhage (n = 37)	30 (24–34)				3 (2–5)			
<b>Stroke side</b>								
Left (n = 126)	33 (29–36)	<0.001	1		4.5 (3–6)	0.012		
Right (n = 94)	29 (16–34)		1 (1–1.1)	0.831	3 (0–6)			
<b>Lateropulsion</b>								
Upright (n = 158)	34 (31–36)		1		5 (3–6)		1	
Lw/oP (n = 32)	20.5 (18–25)	<0.001	0.9 (0.8–1)	0.037	0.5 (0–2)	<0.001	0.6 (0.3–0.9)	0.014
Pushers (n = 30)	8 (3–15)		0.4 (0.3–0.5)	<0.001	0 (0–0)		0.1 (0–0.2)	<0.001
<b>Spatial neglect</b>								
No or light (n = 120)	34.5 (32–36)		1		5 (4–6)		1	
Moderate (n = 54)	30 (21–33)	<0.001	1 (0.9–1.1)	0.912	3 (1–5)	<0.001	1 (0.8–1.2)	0.942
Severe (n = 44)	14 (6–19)		1 (0.9–1.2)	0.94	0 (0–0)		0.9 (0.5–1.7)	0.838
<b>Aphasia</b>								
No (n = 131)	32 (21–35)	0.801			4 (1–6)	0.951		
Yes (n = 89)	32 (24–35)				4 (2–6)			
<b>Apraxia</b>								
No (n = 169)	33 (26–36)	<0.001	1		5 (2–6)	0.003	1	
Yes (n = 46)	26.5 (13–32)		1 (0.9–1.1)	0.419	3 (0–5)		0.9 (0.7–1.2)	0.484

Continued

**Table 2** Univariate and Multivariate Analysis of Effect of Clinical Features on Balance Disorders and Gait Disorders (continued)

	Balance				Gait			
	PASS, median (Q1–Q3)	<i>p</i> Value <sup>a</sup> (univariate)	Exp (β) (95% CI)	<i>p</i> Value (multivariate)	mFMA, median (Q1–Q3)	<i>p</i> Value <sup>a</sup> (univariate)	Exp (β) (95% CI)	<i>p</i> Value (multivariate)
<b>Weakness</b>								
<b>Light (n = 109)</b>	35 (33–36)		1		6 (5–6)		1	
<b>Moderate (n = 61)</b>	29 (24–33)	<0.001	0.9 (0.8–1)	0.001	3 (2–3)	<0.001	0.6 (0.5–0.8)	<0.001
<b>Severe (n = 50)</b>	13 (7–20)		0.7 (0.6–0.7)	<0.001	0 (0–0)		0.2 (0.1–0.3)	<0.001
<b>Spasticity</b>								
<b>No or light (n = 156)</b>	33.5 (30–36)	<0.001	1		5 (3–6)	<0.001	1	
<b>Moderate or severe (n = 64)</b>	21 (12–30)		1 (0.9–1.1)	0.694	1 (0–3)		1 (0.8–1.2)	0.793
<b>Hypoesthesia</b>								
<b>No or light (n = 57)</b>	35 (34–36)		1		6 (5–6)		1	
<b>Moderate (n = 103)</b>	32 (29–35)	<0.001	1 (0.9–1)	0.404	4 (3–6)	<0.001	0.9 (0.8–1.1)	0.234
<b>Severe (n = 60)</b>	17 (8–26)		0.9 (0.8–1)	0.002	0 (0–3)		0.8 (0.6–1)	0.086
<b>Hemianopia</b>								
<b>No (n = 146)</b>	33 (29–36)	<0.001	1		5 (3–6)	<0.001	1	
<b>Yes (n = 73)</b>	26 (15–33)		1 (0.9–1)	0.257	2 (0–5)		1 (0.8–1.2)	0.983
<b>Depression</b>								
<b>No (n = 87)</b>	34 (30–36)	<0.001	1		5 (3–6)	<0.001	1	
<b>Yes (n = 124)</b>	30 (19–34)		1 (0.9–1)	0.54	3 (0–5)		1 (0.8–1.1)	0.524

Abbreviations: CI = confidence interval; Lw/oP = lateropulsion without pushing; mFMA = modified Fugl-Meyer Assessment gait scale; PASS = Postural Assessment Scale for Stroke. Data are median (Q1–Q3). Missing data: spatial neglect (n = 2), apraxia (n = 5), hemianopia (n = 1), and depression (n = 9).

<sup>a</sup> Significant *p* value for univariate analyses adjusted as 0.004 (0.05/12) owing to multiple comparisons.

**Table 3** Initial and Discharge Data of Balance and Gait for Participants as a Function of Lateropulsion in 3 Categories

	All (n = 220)	Upright (n = 158)	Lw/oP (n = 32)	Pushers (n = 30)	Upright vs Lw/oP	Upright vs Pushers	Lw/oP vs Pushers
<b>D30</b>							
Body orientation against gravity, SCP (0–6)	0 (0–1.3)	0 (0–0)	1.8 (1.3–2.4)	4.8 (4–6)	$r = -0.87$ $p < 0.001$	$r = -0.86$ $p < 0.001$	$r = -0.86$ $p < 0.001$
Balance, PASS (0–36)	32 (22–35)	34 (31–36)	20.5 (17–24)	8 (3–15)	$r = -0.57$ $p < 0.001$	$r = -0.63$ $p < 0.001$	$r = -0.74$ $p < 0.001$
Gait, mFMA (0–6)	4 (1–6)	5 (3–6)	0.5 (0–2)	0 (0–0)	$r = -0.58$ $p < 0.001$	$r = -0.64$ $p < 0.001$	$r = -0.49$ $p < 0.001$
<b>Discharge</b>							
Body orientation against gravity, SCP (0–6)	0 (0–0)	0 (0–0)	0 (0–0)	1.6 (0.4–3.1)	$r = -0.22$ $p = 0.003$	$r = -0.79$ $p < 0.001$	$r = -0.66$ $p < 0.001$
Balance, PASS (0–36)	34 (32–36)	35 (34–36)	32 (29–33.5)	24.5 (16.5–31)	$r = -0.42$ $p < 0.001$	$r = -0.57$ $p < 0.001$	$r = -0.53$ $p < 0.001$
Gait, mFMA (0–6)	5 (4–6)	6 (5–6)	4 (3–5)	2 (0.5–4)	$r = -0.43$ $p < 0.001$	$r = -0.53$ $p < 0.001$	$r = -0.39$ $p = 0.003$

Abbreviations: Lw/oP = lateropulsion without pushing; mFMA = modified Fugl-Meyer Assessment gait scale; PASS = Postural Assessment Scale for Stroke; pusher = lateropulsion with pusher syndrome; SCP = Scale for Contraversive Pushing.  $r$  = effect size of the Mann-Whitney test. Data are median (Q1–Q3).

strong likelihood ( $X^2 = 806.2$ ,  $p < 0.001$ ). Lateropulsion was the strongest determinant of balance disorders, with PASS scores multiplied by a  $\beta$  coefficient of 0.4 (95% CI 0.3–0.5,  $p < 0.001$ ) for pushers or 0.9 (95% CI 0.8–1,  $p = 0.037$ ) with Lw/oP, everything being equal as compared with upright individuals. Weakness also had a negative effect on balance ability, with PASS scores multiplied by a  $\beta$  coefficient of 0.7 (95% CI 0.6–0.7,  $p < 0.001$ ) with severe weakness and 0.9 (95% CI 0.8–1,  $p = 0.001$ ) with moderate weakness. Severe hypoesthesia was an independent factor affecting balance, with PASS scores multiplied by 0.9 (95% CI 0.8–1,  $p = 0.002$ ).

For gait disorders, the GLM revealed only 2 deficits with an independent detrimental role: lateropulsion and weakness. The model was sound with strong likelihood ( $X^2 = 390.4$ ,  $p < 0.001$ ). Gait scores were multiplied by a  $\beta$  coefficient of 0.1 (95% CI 0–0.2,  $p < 0.001$ ) for pushers, so no participant was able to walk independently, and 0.6 (95% CI 0.3–0.9,  $p = 0.014$ ) for individuals with Lw/oP. Beyond the pusher feature, gait ability was affected by mild forms of lateropulsion, whereas 92% of upright individuals could walk without human aid. Weakness had also a strong independent effect on gait ability, with a  $\beta$  coefficient of 0.2 (95% CI 0.1–0.3,  $p < 0.001$ ) with severe weakness and 0.6 (95% CI 0.5–0.8,  $p < 0.001$ ) with moderate weakness.

### Postural, Balance and Gait Recovery

Table 3 shows that individuals who were initially tilted with respect to gravity were better oriented at discharge, with a large effect size both with Lw/oP ( $r = -0.62$ ) and for pushers ( $r = -0.61$ ). The predominance of lateropulsion after RHS was even greater than initially: RHS (22/92 [24%]) vs LHS (2/125 [2%],  $v = 0.35$ ). At discharge, lateropulsion was 12

times more frequent after RHS than LHS, in which the prevalence became negligible.

At discharge, balance ( $r = -0.49$ ) and gait ( $r = -0.46$ ) abilities were both much better in the whole series and in each group (with moderate to large effect sizes).

### Mobility Limitation as a Function of Body Orientation With Respect to Gravity

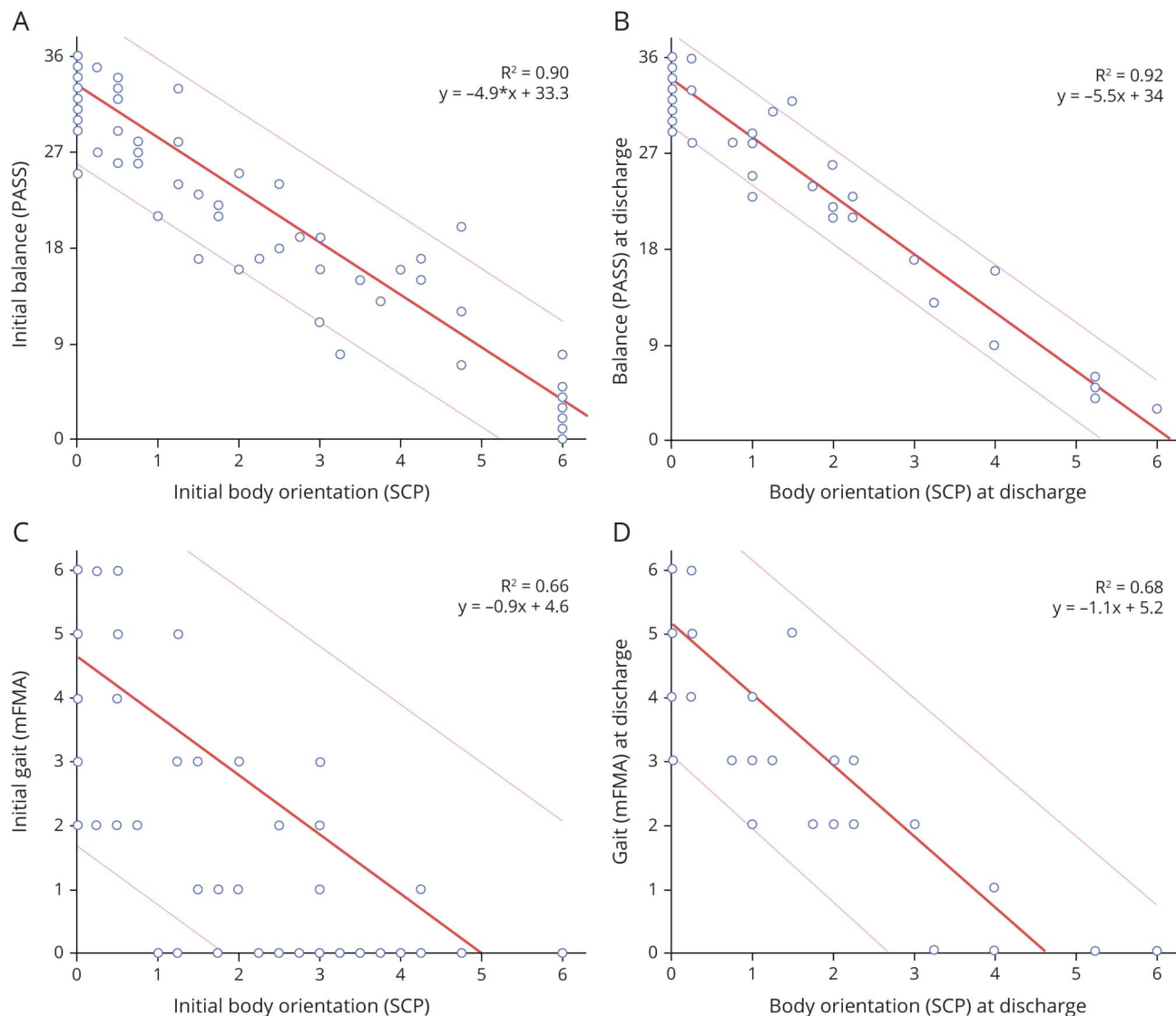
Balance and gait capacities greatly depended on body orientation against gravity (table 3). Upright individuals had much better balance and gait capacities than others. Individuals with Lw/oP had much better balance and gait capacities than pushers. All differences had  $p$  values  $\leq 0.003$  with moderate to large effect sizes, both initially and at discharge. As a corollary, the length of hospital stay (stroke onset–discharge of the rehabilitation ward) for individuals with lateropulsion was much longer than that of upright individuals (164 days [126–192] vs 64 days [45–91];  $r = -0.62$ ).

### Body Orientation With Respect to Gravity Explains Mobility Limitation

After RHS, lateropulsion explained almost all the information contained in balance disorders: 90% (95% CI 86–94,  $p < 0.001$ ) initially (about 1 month after onset) (figure 2A) and 92% (95% CI 89–95,  $p < 0.001$ ) at discharge (figure 2B) and also the greatest part of gait disorders: 66% (95% CI 56–77,  $p < 0.001$ ) initially (figure 2C) and 68% (95% CI 57–78,  $p < 0.001$ ) at discharge (figure 2D).

After LHS, lateropulsion also explained a substantial part of mobility limitation initially: 59% (95% CI 48–69,  $p < 0.001$ ) of balance disorders and 43% (95% CI 30–56,  $p < 0.001$ ) of gait

**Figure 2** Relationship Between Body Orientation With Respect to Gravity and Balance/Gait Capacities After Right Hemisphere Stroke



(A, C) Initial data (about 1 month after onset). (B, D) Data collected at discharge. All the linear regressions were valid because of high  $R^2$  and fit Durbin-Watson statistics ranging from 1.8 to 2.2 (Durbin-Watson A = 2; B = 1.9; C = 2; D = 2.2). mFMA = modified Fugl-Meyer Assessment gait scale; PASS = Postural Assessment Scale for Stroke; SCP = Scale for Contraversive Pushing.

disorders. No analysis was performed at discharge for LHS because only 2/125 (2%) individuals still presented lateropulsion.

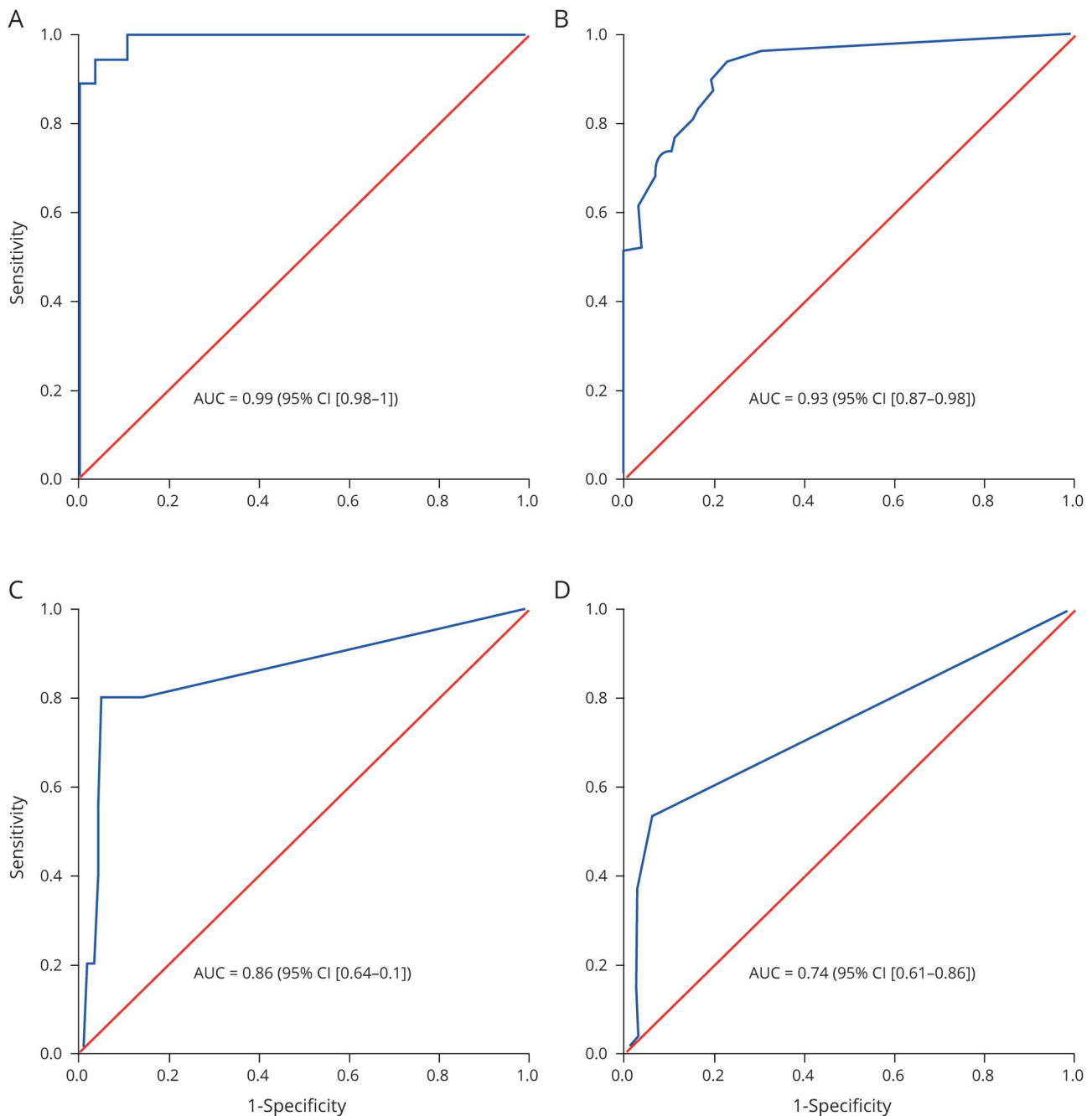
### Initial Body Orientation Predicts Balance and Gait at Discharge

ROC curves were plotted from initial SCP scores and dichotomized balance (erect stance) and gait (independent walking) abilities at discharge (figure 3) for RHS and LHS.

For RHS, the AUC was 0.99 (95% CI 0.98–1) for balance (figure 3A) and 0.93 (95% CI 0.87–0.98) for gait (figure 3B). The SCP cutoff values calculated from the Youden Index were 3.5 for balance (sensitivity 0.94, specificity 0.96, PPV 0.86, NPV 0.99) and 1 for gait (sensitivity 0.9, specificity 0.8, PPV 0.67,

NPV 0.95). Low values of these indices were satisfactory predictors of good recovery. Specifically, individuals with an initial SCP score <3.5 would be able to stand independently at discharge (probability 99%, 95% CI 92–100), and individuals with an initial SCP score <1 (upright or light lateropulsion) would be able to walk without any help at discharge (probability 95%, 95% CI 87–98). For LHS, the AUC was 0.86 (95% CI 0.64–0.1) for balance and only 0.74 (95% CI 0.61–0.86) for gait. For balance, the SCP cutoff value calculated from the Youden Index was 2 (sensitivity 0.8, specificity 0.95, PPV 0.45, NPV 0.99), so that individuals with an initial SCP score <2 would be able to stand independently at discharge (probability 99%, 95% CI 95–100). No other robust prediction was possible with LHS (figure 3, C and D).

**Figure 3** Initial Body Orientation Predicts Balance and Gait at Discharge



Scale for Contraversive Pushing (SCP) score predicts balance and gait abilities in individuals after a right hemisphere stroke (RHS, A [balance] + B [gait]) (n = 92 at discharge) and a left hemisphere stroke (LHS, C [balance] + D [gait]) (n = 125 at discharge). Receiver operating characteristic (ROC) curves predicting, from the initial SCP score, the inability to stand without assistance (Postural Assessment Scale for Stroke [PASS] score <28) at discharge after RHS (A) and LHS (C). ROC curves predicting, from the initial SCP score, the inability to walk independently without a cane or rollator (modified Fugl-Meyer assessment [mFMA] score <5) after RHS (B) and LHS (D). AUC = area under the ROC curve; CI = confidence interval.

## Discussion

To reduce the destabilizing effect of gravity, the body must be oriented vertical, which corresponds to 1 of the 2 domains of postural control.<sup>1,2</sup> Here we analyzed the contribution of an impaired body orientation in the frontal plane (known as lateropulsion) on daily life balance and gait disorders after stroke. Our findings reveal that lateropulsion is the primary

cause of balance and gait disorders at the subacute stage after stroke. This finding contradicts a general feeling that the key problem deals with the stabilization component of balance control. It is of major importance for poststroke balance and gait rehabilitation, which should be rethought.

In a series of 220 nonselected individuals with a first hemisphere stroke, we found that at initial assessment (D30), most



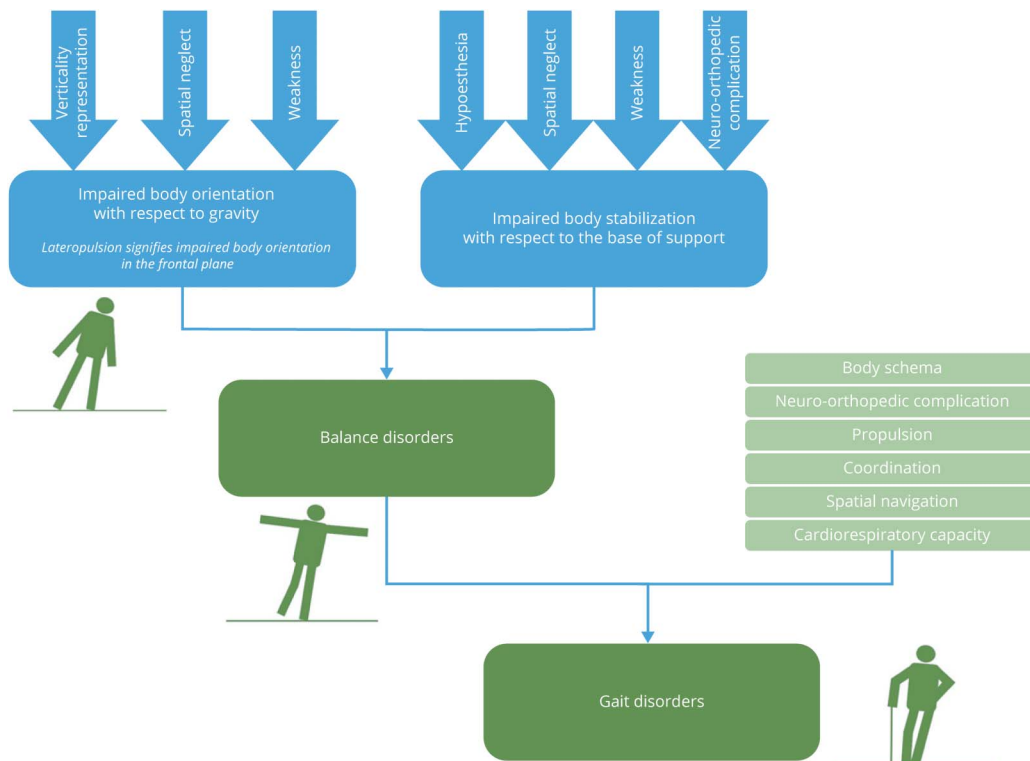
individuals with an LHS remained upright (87%), whereas half with RHS showed lateropulsion (48%), almost always in right-handers (97%). Therefore, the control of uprightness is a highly lateralized brain function, mainly located in the right hemisphere, which justifies our approach to separately analyze RHS and LHS. This analysis requires 4 subgroups of individuals, therefore a large series. Only 2 studies have addressed this question in a large series (>200) of consecutive individuals.<sup>14,31</sup> When individuals were assessed early in the acute stroke unit, no significant RHS predominance was found,<sup>14</sup> whereas an RHS predominance was found when individuals were assessed later at entry in the rehabilitation unit.<sup>31</sup> Together with these 2 studies, ours clearly demonstrates that the gradient RHS/LHS for lateropulsion increases as a function of time after stroke: lateropulsion 1.3 times more frequent after RHS than LHS a few days poststroke,<sup>14</sup> 1.8 times more frequent at admission to rehabilitation,<sup>31</sup> 3.7 times more frequent on D30 (our study), and 12 times more frequent at rehabilitation discharge (our study). We assume that this finding might be related to a possible diaschisis,<sup>45</sup> altering the functioning of both hemispheres during the days following the stroke, whatever the side, because lateropulsion may result from similar lesions of both hemispheres.<sup>22</sup> The release of the diaschisis should increase the predominance of the right hemisphere for processing spatial information, including control of the upright. This suggestion remains to be demonstrated by further studies. Beyond the

underlying mechanisms, our findings explain why the recovery of balance and gait disorders is worse after RHS than LHS, a well-known finding.<sup>4</sup>

Lateropulsion plays a primary role in balance and gait disorders during the subacute phase after hemisphere stroke. In RHS, balance disorders were quasi-proportional to lateropulsion severity, which explained them almost entirely in initial and discharge assessments. This novel finding has a major scope because of the high lateropulsion prevalence and the great impact of balance disorders on autonomy.

These results bring new insights into how to conceive post-stroke balance and gait disorders (figure 4), so far considered to result from motor and tone deficits<sup>4,33</sup> and from spatial neglect,<sup>4,32,46,47</sup> thus leading to impaired postural stabilization and walking propulsion.<sup>36,46,47</sup> An interesting result of our study is that at the subacute stage, gait disorders are mainly due to balance disorders. Overall, from a comprehensive battery of deficits and appropriate multivariate analyses, our study shows that sensory-motor deficits and spatial neglect are less determinant than are deficits in body orientation to generate postural and gait disorders. Thus, lateropulsion is a key determinant of balance and gait disorders at the subacute phase after stroke. Our results advocate for better considering lateropulsion as a rehabilitation target and the need to design

**Figure 4** Theoretic Model of Balance and Gait Disorders After Stroke



We considered the clinical application of the theoretical model of balance control.<sup>1,2</sup> At the subacute stage after stroke, body misorientation (lateropulsion) is the primary cause of balance disorders, which mostly explains gait disorders.

and validate novel techniques and programs partly supported by modulations of the internal model of verticality.<sup>3,29</sup>

Predicting recovery is of great importance for patients and their relatives. It has been repeatedly shown that balance capacity in the first weeks after the stroke is a good indicator of final gait ability and falls occurrence.<sup>35,48</sup> Our study goes further by showing that a satisfactory orientation with respect to gravity (no lateropulsion) predicts a good balance and gait recovery, with very high accuracy. After an RHS, individuals with an initial SCP score <3.5 would be able to stand independently at discharge (probability 99%). In other words, lateropulsion severity at D30 determines the long-term walking prognosis.

Data were collected by a multidisciplinary team that was well-trained and motivated, with few missing data given the large sample size and the study duration. Evaluators were therapists, and blinding was not possible or beneficial in this observational study. To ensure nonbiased assessments, therapists and patients were not informed of the study hypothesis.

How we assessed the orientation with respect to gravity might be viewed as a limitation. Lateropulsion is currently assessed with the Burke Lateropulsion Scale (BLS)<sup>19,23,24</sup> or the SCP.<sup>23,24</sup> The BLS assesses lateropulsion in erect and also recumbent postures. Because we wanted to focus on behaviors against gravity, we used the SCP, which is also reliable,<sup>24,49</sup> despite the lack of cross-cultural validation<sup>24</sup> and several reformulations of items by authors. If we categorized pushers using the seminal cutoff,<sup>15</sup> we also used the SCP beyond its initial objective, to objectively distinguish individuals upright from those showing lateropulsion without being pushers. The appropriateness of this approach, already adopted in some studies,<sup>3,17</sup> was confirmed by the fact that the 3 groups (upright, Lw/oP, pushers) differed in their behavior with respect to gravity (all 3 domains differed, body tilt, pushing, and resistance) and in the severity of other deficits. With an SCP score increment of 0.25 from 0 to 6, the construction of the SCP<sup>15</sup> allows for quantifying the magnitude of the body tilt and the intensity of additional signs (pushing and resistance), thus, lateropulsion severity, which is strongly correlated with magnitudes of biases in the postural perception of the vertical.<sup>3</sup> Therefore, it is appropriate to test relationships between SCP, balance, and gait scores, with good statistical fit. In our care pathways, only one third of individuals admitted to acute stroke units are then referred to rehabilitation units,<sup>50</sup> the others having too slight or too severe disabilities. These criteria, which correspond to those adopted in most European countries,<sup>50</sup> condition the generalizability of our results. However, our findings may be generalized to the rehabilitation context, which is overall important because lateropulsion is a major rehabilitation challenge. One cannot even exclude that the scope of the study might have been reduced by the inclusion criteria (first-ever hemisphere stroke without the cerebral complications listed in Methods) and the time of the initial assessment (D30). Indeed, lateropulsion prevalence and severity are greater earlier after stroke<sup>17,19,49</sup> and likely in cases of

preexisting altered brain functions, recurrent strokes, or neurologic complications.

Body misorientation with respect to gravity is the primary factor altering balance and gait during the poststroke subacute stage. Thus, lateropulsion should be systematically assessed. We suggest that poststroke balance and gait rehabilitation incorporate techniques specifically devoted to lateropulsion.

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## Disclosure

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## Appendix Authors

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<b>Céline Piscicelli, PhD</b>	Grenoble Alpes University Hospital, France	Acquisition of data, revised the manuscript for intellectual content
<b>Emmanuelle Clarac, PT</b>	Grenoble Alpes University Hospital, France	Acquisition of data, material support
<b>Monica Baci, MD, PhD</b>	Grenoble Alpes University, France	Revised the manuscript for intellectual content
<b>Marc Hommel, MD, PhD</b>	Grenoble Alpes University, France	Interpreted the data, revised the manuscript for intellectual content
<b>Dominic Pérennou, MD, PhD</b>	Grenoble Alpes University Hospital, France	Designed and conceptualized study, study supervision, interpreted the data, drafted the manuscript for intellectual content, obtained funding

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# Lateropulsion After Hemispheric Stroke

## A Form of Spatial Neglect Involving Graviception

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## Abstract

### Objective

To test the hypothesis that lateropulsion is an entity expressing an impaired body orientation with respect to gravity in relation to a biased graviception and spatial neglect.

### Methods

Data from the DOBRAS cohort (ClinicalTrials.gov: NCT03203109) were collected 30 days after a first hemisphere stroke. Lateral body tilt, pushing, and resistance were assessed with the Scale for Contraversive Pushing.

### Results

Among 220 individuals, 72% were upright and 28% showed lateropulsion (tilters [14%] less severe than pushers [14%]). The 3 signs had very high factor loadings ( $>0.90$ ) on a same dimension, demonstrating that lateropulsion was effectively an entity comprising body tilt (cardinal sign), pushing, and resistance. The factorial analyses also showed that lateropulsion was inseparable from the visual vertical (VV), a criterion referring to vertical orientation (graviception). Contralesional VV biases were frequent (44%), with a magnitude related to lateropulsion severity: upright  $-0.6^\circ$  ( $-2.9$ ;  $2.4$ ), tilters  $-2.9^\circ$  ( $-7$ ;  $0.8$ ), and pushers  $-12.3^\circ$  ( $-15.4$ ;  $-8.5$ ). Ipsilesional VV biases were less frequent and milder ( $p < 0.001$ ). They did not deal with graviception, 84% being found in upright individuals. Multivariate, factorial, contingency, and prediction analyses congruently showed strong similarities between lateropulsion and spatial neglect, the latter encompassing the former.

### Conclusions

Lateropulsion (pusher syndrome) is a trinity constituted by body tilt, pushing, and resistance. It is a way to adjust the body orientation in the roll plane to a wrong reference of verticality. Referring to straight above, lateropulsion might correspond to a form of spatial neglect (referring to straight ahead), which would advocate for 3D maps in the human brain involving the internal model of verticality.

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## Glossary

**AUC** = area under the receiver operating characteristic curve; **BAG** = behavior against gravity; **CI** = confidence interval; **DOBRAS** = Determinants of Balance Recovery After Stroke; **FIM** = Functional Independence Measure; **OR** = odds ratio; **PV** = postural vertical; **ROC** = receiver operating characteristic; **SCP** = Scale for Contraversive Pushing; **VV** = visual vertical.

Thomas<sup>1</sup> first reported cases of individuals (and animals) with brain damage who showed active lateral body tilt, pushed themselves away from the upright with sound limbs, and resisted any corrections. Davies<sup>2</sup> carefully detailed these striking signs observed after stroke, empirically combined in the so-called pusher syndrome, confirmed later by the Copenhagen Stroke Study.<sup>3</sup> The term syndrome lacks accuracy and its usage is decreasing.<sup>4</sup> Simply using “lateropulsion” has been proposed.<sup>5,6</sup>

To what extent lateropulsion signs are associated remains to be investigated. Mechanisms underlying pushing and resistance are controversial, viewed as a way to adjust the body orientation to a wrong reference of verticality<sup>7</sup> or as a postural reflex reacting to a sensory conflict.<sup>8</sup> Actions to push or resist might even result from inappropriate muscular overactivity.<sup>1</sup>

For hemisphere stroke, we hypothesized that signs of contralesional lateropulsion would represent a same dimension corresponding to an impaired orientation of the body against gravity, in relation to an altered graviception. We tested this unidimensionality by analyzing data collected in a large series of consecutive individuals covering the whole range of lateropulsion severity.

Spatial neglect is frequently associated with lateropulsion, sometimes systematically.<sup>8-10</sup> Is it a co-occurrence<sup>11</sup> or rather the result of a process underpinning an impaired spatial referential linking straight above (verticality) and straight ahead (left/right gradient)? Lateropulsion might be considered a form of spatial neglect bearing on graviception.<sup>9,11</sup> We addressed this question.

## Methods

### Study Design

This was a monocentric observational study using the data of the DOBRAS (Determinants of Balance Recovery After Stroke) cohort, with participants comprehensively assessed in routine care, initially during the first weeks after entry in the rehabilitation ward. The sample size was planned to conduct multivariate analyses in a large series of individuals ( $\geq 200$  observations). Sensory, motor, and cognitive deficits were assessed at a fixed date by trained and multidisciplinary examiners, with blinding to other data and the study hypotheses. The reporting follows the STROBE statement.

### Participants and Assessment Timing

From January 2012 to September 2018, we included 220 consecutive individuals (figure 1) with a first-ever unilateral

stroke limited to one hemisphere. Details on inclusion and exclusion criteria are given in the companion article.<sup>12</sup>

Initial assessments were performed if possible on about day 30 after stroke (D30) with a 3-day window before and after. The rationale for this timing is explained in the companion article.<sup>12</sup> Among the 220 participants, 207 (94%) were admitted during the first month poststroke and were assessed on D30. For the 13 others admitted after D30 (6%), the initial assessment was performed on day 60 (D60, window of 3 days before and after).

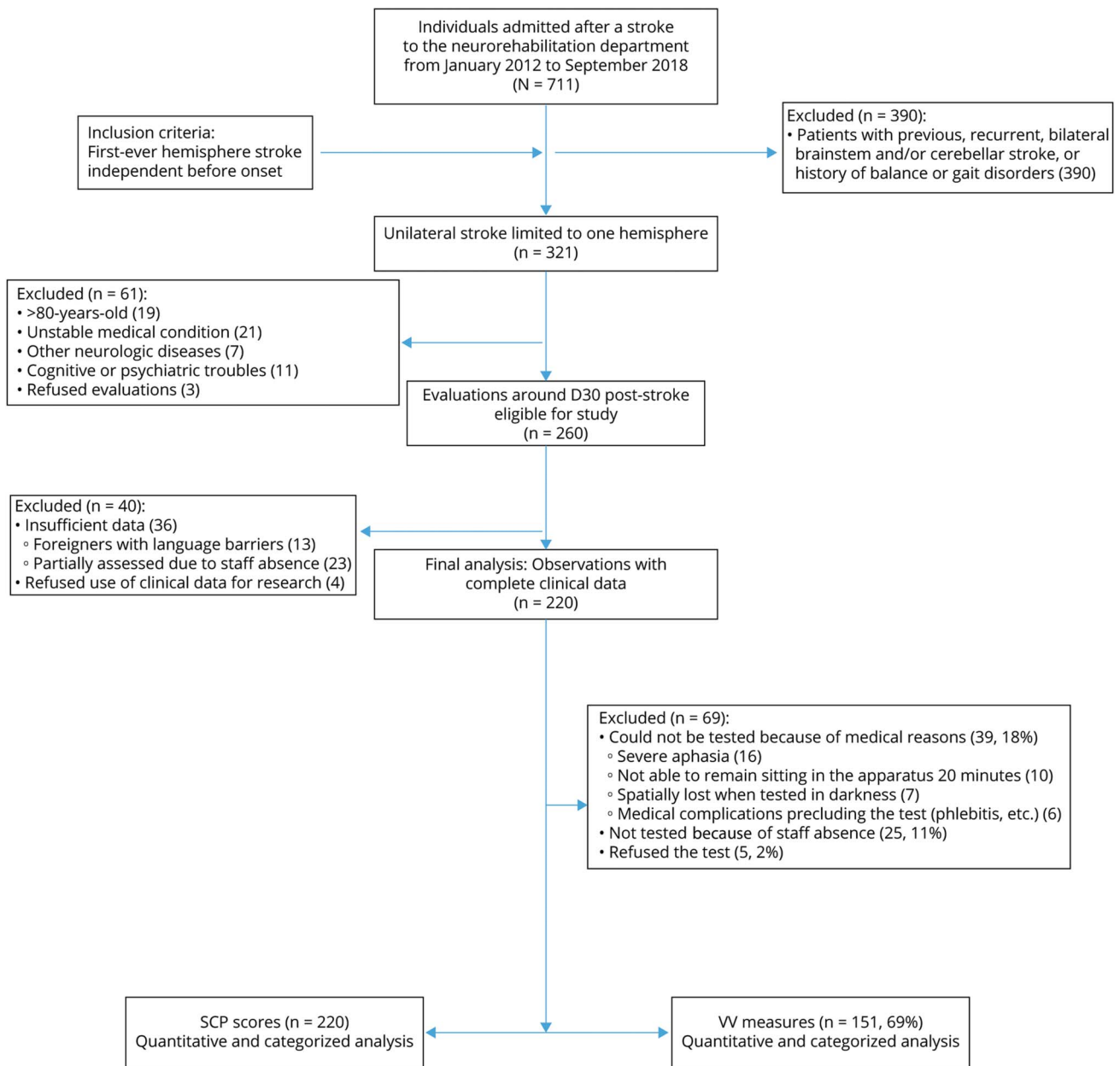
### Behavior Against Gravity

Behavior against gravity (BAG) was assessed by the Scale for Contraversive Pushing (SCP), with increments of 0.25 and total score from 0 to 6.<sup>8</sup> The SCP has been designed to categorize individuals according to scores of the 3 signs defined by Davies<sup>2</sup>: active lateral body tilt, spontaneous action of abduction/extension of the ipsilesional upper or lower limb to push the body away from the upright,<sup>3,7</sup> and resistance to passive correction making the body upright. As defined in the original method,<sup>8</sup> individuals who met these 3 criteria with at least 1 point for each component were considered pushers. They represent a small part of consecutive individuals, limited to severe lateropulsion.<sup>3,7,13</sup> Only considering pushers would overlook individuals with moderate lateropulsion. As proposed previously,<sup>7</sup> we also used the SCP to differentiate individuals with an upright posture from those who were mildly tilted. To be conservative, we used the total SCP cutoff  $\leq 0.50$  to define the upright group. Indeed, values of 0.25 or 0.5 were clearly marginal, not allowing us to state that the individual was not upright most of the time. In this study, we called tilters individuals of the intermediate group. They showed net lateral body tilt at least in one posture, sitting or standing, regardless of the 2 other lateropulsion signs, but did not show the criteria to be pushers. In line with our hypothesis, this approach had the advantage of constituting a priori an intermediate group with individuals in whom mild degrees of body tilt, pushing, and resistance could be associated or not. To summarize, upright individuals had a total SCP score  $\leq 0.5$ ; tilters had a total SCP score  $> 0.5$  and a score for at least 1 of the 3 components (body tilt, pushing, or resistance)  $< 1$ , so were not pushers; and pushers had a total SCP score  $\geq 3$  and scores for all 3 components  $\geq 1$ .

### Verticality Perception

We used the visual vertical (VV) test and a procedure well described and validated<sup>17,14-17</sup> for testing individuals with postural disorders,<sup>16-18</sup> with reliability<sup>15</sup> and low measurement error.<sup>15</sup> VV tests were performed by trained examiners

**Figure 1** Flowchart of Participants in the Study



Flow diagram of the study, explaining the processing of inclusion and assessments. We enrolled 220 participants for analyses of the postural behavior (n = 220) and visual vertical (VV) measures (n = 151). D30 = day 30; SCP = Scale for Contraversive Pushing.

(C.P. and S.D.). To avoid any error due to the setting,<sup>15</sup> individuals were seated with their head and trunk maintained upright and straight by using lateral cushioning blocks in complete darkness (room without window, thick curtain over the door). Participants were asked to verbally adjust the line to the vertical, for 10 trials. We calculated 2 indices: VV orientation and VV uncertainty. VV orientation corresponded to the average of trials with negative values indicating a contralesional rotation, classified as follows<sup>7,18</sup>: normal VV  $-2.5^\circ$  to  $2.5^\circ$ ; contralesional VV bias  $<-2.5^\circ$ ; and ipsilesional VV bias  $>2.5^\circ$ . VV uncertainty corresponded to within-subject variability (SD of the trials).

## Spatial Neglect

Body and nonbody neglect were assessed with a battery of 6 tests: ecological Catherine Bergego Scale,<sup>19,20</sup> thumb finding,<sup>19,20</sup> Fluff<sup>21</sup> (since 2014) and Bells tests,<sup>19,20</sup> the bisection of 2 successive 200-mm lines,<sup>19,20</sup> and the copy of Gainotti drawing.<sup>19,20</sup> They were classified according to cutoffs proposed in seminal articles or revised later,<sup>20</sup> and detailed in the companion article.<sup>12</sup> A few individuals with severe comprehension (aphasia) or executive troubles were not able to complete the whole neglect battery but had to perform at least 3 tests to not be considered with missing data. Grouping for spatial neglect was as follows: no or light if all test results were normal or if only one test was

**Table 1** Demographic Data and Stroke Features as a Function of Behaviors Against Gravity

	All (n = 220)	Upright (n = 158)	Tilters (n = 32)	Pushers (n = 30)	Omnibus test	Group comparisons <sup>a</sup>		
						Upright vs tilters	Upright vs pushers	Tilters vs pushers
Age, y	66.9 (58; 73)	66.2 (54; 72)	66 (60; 71)	70.4 (64; 76)	$\eta^2 = 0.03$ $p = 0.013$	$r = -0.03$ $p = 0.707$	$r = -0.21$ $p = 0.004$	$r = -0.28$ $p = 0.027$
Sex, male	147 (67)	109 (69)	21 (66)	17 (57)	$v = 0.06$ $p = 0.417$			
BMI, kg/m <sup>2</sup>	25 (22; 28)	26 (23; 28)	24 (22; 27)	25 (21; 29)	$\eta^2 = 0.01$ $p = 0.196$			
Right-handers	198 (90)	138 (87)	30 (94)	30 (100)	$v = 0.11$ $p = 0.072$			
Stroke type, infarct	183 (83)	133 (84)	26 (81)	24 (80)	$v = 0.03$ $p = 0.813$			
Stroke side, RH	94 (43)	49 (31)	20 (63)	25 (83)	$v = 0.28$ $p < 0.001$	$v = 0.24$ $p < 0.001$	$v = 0.39$ $p < 0.001$	$v = 0.23$ $p = 0.066$

Abbreviations: BMI = body mass index; RH = right hemisphere.

Data are n (%) or median (Q1; Q3).  $\eta^2$  = effect size of the Kruskal-Wallis test.  $r$  = effect size of the Mann-Whitney test.  $v$  = effect size of the  $\chi^2$  test. The values 0.01, 0.06, and 0.14 represent a small, medium, and large effect for the Kruskal-Wallis test. The values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both the Mann-Whitney  $U$  test and  $2 \times 2 \chi^2$  test. For the  $2 \times 3 \chi^2$  test, effect sizes of 0.07, 0.21, and 0.35 represent small, medium, and large effect, respectively.

<sup>a</sup> The significant  $p$  values for group comparisons were adjusted to 0.013 (0.05/4) owing to multiple comparisons.

marginally altered, severe with results of at least 2 tests markedly altered (altered if binary categorized), or moderate otherwise.

## Other Assessments

We also assessed handedness, aphasia, apraxia, motor weakness, spasticity, hypoesthesia, hemianopia, and depression. Details are given in the companion article.<sup>12</sup> Disability was assessed by the Functional Independence Measure (FIM).

## Statistical Analysis

Continuous data are presented as median with interquartile range (Q1; Q3) and dichotomized and categorical data as number (%). When useful, 95% confidence intervals (CIs) are given. Demographics of BAG groups were compared by using omnibus tests (Kruskal-Wallis or  $\chi^2$ ); then, when significant, Mann-Whitney  $U$  or  $\chi^2$  test. Corrected  $p$  values were set at 0.013 (0.05/4).

To test the first part of our hypothesis that body tilt, pushing, and resistance represent the same dimension of trouble corresponding to an impaired orientation of the body against gravity, we performed a factorial analysis to determine the number of dimensions they represented. We also analyzed their gradient of severity as a function of BAG, and sought their dissociations. To test the second part of our hypothesis that this impaired body orientation was related to an altered graviception, we added VV orientation in the factorial analysis and also analyzed VV abnormalities as a function of BAG. BAG groups were compared by using omnibus tests (Kruskal-Wallis or  $\chi^2$ ); then, when significant, Mann-Whitney  $U$  or  $\chi^2$  test. Because multiple comparisons for VV indices were supposed to be dependent on each other, corrected  $p$  values were set at 0.0025 (0.05/5 variables  $\times$  4 comparisons). Because VV

could not be tested in all individuals (reasons explained in figure 1), VV was analyzed after multiple imputations.

The question of the link between lateropulsion and spatial neglect was comprehensively investigated and addressed by means of multivariate, factorial, contingency, and prediction analyses. We first analyzed the clinical profiles of the 3 BAG groups by comparing their deficits using omnibus tests (Kruskal-Wallis or  $\chi^2$ ); then, when significant, Mann-Whitney  $U$  or  $\chi^2$  test. Because of multiple comparisons, corrected  $p$  values (deficits independent of each other) were set at 0.013 (0.05/4 tests for each deficit). Variables found significant were included in a multivariate ordinal regression to further explore their association with BAG; odds ratios (ORs) were calculated. Then, similarities between clinical profiles of BAG groups and spatial neglect severity were sought by a principal component analysis with varimax rotation and Kaiser normalization. Contingency analyses with Venn diagrams further explored how lateropulsion and spatial neglect nested. Finally, receiver operating characteristic (ROC) curves were plotted, and the area under the ROC curve (AUC) was calculated to predict one deficit from the other.

Unless otherwise indicated (corrections), 2-tailed  $p < 0.05$  was considered statistically significant. Effect sizes were calculated by using the  $H$  values of the Kruskal-Wallis test ( $\eta^2 = H - k + 1/n - k$ ), the  $Z$  values of the Mann-Whitney test ( $r = Z/\sqrt{n}$ ), and the  $\chi^2$  values of the  $\chi^2$  test ( $v = \sqrt{\chi^2/n}$  \* degree of freedom).<sup>22</sup> Statistical analysis involved using SPSS 21.0.

## Standard Protocol Approvals, Registrations, and Patient Consents

The DOBRAS cohort was approved by our institutional review board (CHU Grenoble Alpes), who opened and

**Table 2** Lateropulsion Signs and Verticality Perception as a Function of Behaviors Against Gravity (BAG)

	All (n = 220)	Upright (n = 158)	Tilters (n = 32)	Pushers (n = 30)	Omnibus test	Group comparisons <sup>a</sup>		
						Upright vs tilters	Upright vs pushers	Tilters vs pushers
<b>Behavior against gravity</b>								
<b>Lateral body tilt (0-2)</b>	0 (0; 0.3)	0 (0; 0)	0.5 (0.3; 0.8)	1.3 (1; 2)	$\eta^2 = 0.83$ $p < 0.001$	$r = -0.82$ $p < 0.001$	$r = -0.87$ $p < 0.001$	$r = -0.8$ $p < 0.001$
<b>Pushing (0-2)</b>	0 (0; 0)	0 (0; 0)	0.5 (0; 0.5)	1.5 (1; 2)	$\eta^2 = 0.83$ $p < 0.001$	$r = -0.71$ $p < 0.001$	$r = -0.98$ $p < 0.001$	$r = -0.87$ $p < 0.001$
<b>Resistance (0-2)</b>	0 (0; 1)	0 (0; 0)	1 (1; 1)	2 (2; 2)	$\eta^2 = 0.92$ $p < 0.001$	$r = -0.92$ $p < 0.001$	$r = -0.99$ $p < 0.001$	$r = -0.68$ $p < 0.001$
<b>Total SCP score (0-6)</b>	0 (0; 1.3)	0 (0; 0)	1.8 (1.3; 2.4)	4.8 (4; 6)	$\eta^2 = 0.87$ $p < 0.001$	$r = -0.87$ $p < 0.001$	$r = -0.86$ $p < 0.001$	$r = -0.86$ $p < 0.001$
<b>VV: estimated values after multiple imputations for untested VV<sup>b</sup></b>								
<b>VV orientation, °</b>	-1.6 (-5.4; 1.7)	-0.6 (-2.9; 2.4)	-2.9 (-7; 0.8)	-12.3 (-15.4; -8.5)	$\eta^2 = 0.32$ $p < 0.001$	$r = -0.24$ $p = 0.001$	$r = -0.58$ $p < 0.001$	$r = -0.66$ $p < 0.001$
<b>VV uncertainty, °</b>	1.5 (1; 2.8)	1.3 (1; 2)	1.9 (1.4; 2.7)	4.5 (3.4; 5.7)	$\eta^2 = 0.28$ $p < 0.001$	$r = -0.22$ $p = 0.003$	$r = -0.55$ $p < 0.001$	$r = -0.63$ $p < 0.001$
<b>VV biases</b>								
<b>Contralesional</b>	96 (44)	48 (30)	19 (59)	29 (97)	$v = 0.33$ $p < 0.001$	$v = 0.23$ $p = 0.002$	$v = 0.49$ $p < 0.001$	$v = 0.45$ $p < 0.001$
<b>No bias</b>	75 (34)	69 (44)	6 (19)	0 (0)	$v = 0.24$ $p < 0.001$	$v = 0.19$ $p = 0.009$	$v = 0.33$ $p < 0.001$	$v = 0.32$ $p = 0.024$
<b>Ipsilesional</b>	49 (22)	41 (26)	7 (22)	1 (3)	$v = 0.13$ $p = 0.024$	$v = 0.03$ $p = 0.629$	$v = 0.2$ $p = 0.006$	$v = 0.28$ $p = 0.054$

Abbreviations: SCP = Scale for Contraversive Pushing; VV = visual vertical.

Data are n (%) or median (Q1; Q3).  $\eta^2$  = effect size of the Mann-Whitney test.  $v$  = effect size of the  $\chi^2$  test. The values 0.01, 0.06, and 0.14 represent a small, medium, and large effect for the Kruskal-Wallis test. The values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both the Mann-Whitney  $U$  test and  $2 \times 2 \chi^2$  test. For the  $2 \times 3 \chi^2$  test, effect sizes of 0.07, 0.21, and 0.35 represent small, medium, and large effect, respectively.

<sup>a</sup> The significant  $p$  values for group comparisons were adjusted to 0.003 (0.05/4\*4) for BAG and 0.0025 (0.05/5\*4) for VV owing to multiple comparisons.

<sup>b</sup> Among 220 observations, 151/220 (69%) individuals tested the VV. Owing to few missing data of other variables (0.4% of the whole dataset), we applied multiple imputations to those untested VV values.

validated the ClinicalTrials.gov declaration (NCT03203109). The study was also registered at the National Committee for Informatics and Freedom (CNIL-No.2014874-v1) and performed in accordance with the Helsinki Declaration. According to French law, eligible individuals were informed of the DOBRAS study (orally and in writing) and those who did not want to participate signed an opposition form. Authorization was obtained from patients (or families) for disclosure of any recognizable persons in videos.

## Data Availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

## Results

The demographic characteristics and stroke type of the 220 individuals (median age 66.9 [58; 73] years, 147 [67%] male) are listed in table 1. Most were right-handed (90%) and with infarcts (83%). Most stood upright (158/220, 72%; video 1, links.lww.com/WNL/B352), 32 (14%) were tilters (video 2,

links.lww.com/WNL/B353), and 30 (14%) were pushers (video 3, links.lww.com/WNL/B354). Disability was greater (lower FIM scores) in pushers than tilters (45 [37; 56] vs 62 [50; 76];  $r = 0.37$ ,  $p = 0.004$ ), and greater in tilters than upright individuals (62 [50; 76] vs 107 [85; 118];  $r = 0.45$ ,  $p < 0.001$ ).

## Missing Data

The total missing data represented only 4.5% of the dataset. No missing data concerned the SCP, and few missing data concerned clinical deficits: spatial neglect ( $n = 2$ , with left hemisphere stroke and severe aphasia), apraxia ( $n = 5$ ), hemianopia ( $n = 1$ ), and depression ( $n = 9$ ). Most missing data concerned VV, mainly because of the procedure requiring precise instructions in darkness, which precluded testing every patient (see details in figure 1). This explained why VV data decreased with deficit severity: 114/158 (72%) for upright individuals, 22/32 (69%) for tilters, and 15/30 (50%) for pushers. However, we could assess VV in 151/220 individuals (69%), mostly on D30 (123/151, 81%) and otherwise on D60 (28/151, 19%). Owing to very few missing data for other variables (0.4% of the whole dataset) and no missing data on the primary outcome



**Table 3** Clinical Deficits as a Function of Behaviors Against Gravity

	All (n = 220)	Upright (n = 158)	Tilter (n = 32)	Pusher (n = 30)	Omnibus test	Group comparisons <sup>a</sup>		
						Upright vs tilters	Upright vs pushers	Tilters vs pushers
<b>Spatial neglect</b>								
No or light	120 (55)	120 (77)	0	0				
Moderate	54 (25)	35 (22)	16 (50)	3 (10)	$v = 0.45$ $p < 0.001$	$v = 0.5$ $p < 0.001$	$v = 0.59$ $p < 0.001$	$v = 0.3$ $p < 0.001$
Severe	44 (20)	1 (1)	16 (50)	27 (90)				
Aphasia, yes	89 (41)	70 (44)	13 (41)	6 (20)	$v = 0.16$ $p = 0.003$	$v = 0.09$ $p = 0.702$	$v = 0.18$ $p = 0.009$	$v = 0.22$ $p = 0.078$
Apraxia, yes	46 (21)	28 (18)	6 (19)	12 (40)	$v = 0.13$ $p = 0.028$	$v = 0.01$ $p = 0.952$	$v = 0.19$ $p = 0.009$	$v = 0.24$ $p = 0.066$
<b>Weakness</b>								
Light	109 (50)	106 (67)	3 (9)	0				
Moderate	61 (28)	44 (28)	10 (31)	7 (23)	$v = 0.36$ $p < 0.001$	$v = 0.39$ $p < 0.001$	$v = 0.47$ $p < 0.001$	$v = 0.17$ $p = 0.18$
Severe	50 (23)	8 (5)	19 (59)	23 (77)				
Spasticity, yes	64 (29)	25 (16)	18 (56)	21 (70)	$v = 0.33$ $p < 0.001$	$v = 0.36$ $p < 0.001$	$v = 0.47$ $p < 0.001$	$v = 0.14$ $p = 0.263$
<b>Hypoesthesia</b>								
No or light	57 (26)	55 (35)	2 (6)	0				
Moderate	103 (47)	85 (54)	12 (38)	6 (20)	$v = 0.3$ $p < 0.001$	$v = 0.31$ $p < 0.001$	$v = 0.43$ $p < 0.001$	$v = 0.19$ $p = 0.088$
Severe	60 (27)	18 (11)	18 (56)	24 (80)				
Hemianopia, yes	73 (33)	34 (22)	19 (59)	20 (67)	$v = 0.29$ $p < 0.001$	$v = 0.31$ $p < 0.001$	$v = 0.36$ $p < 0.001$	$v = 0.08$ $p = 0.553$
Depression, yes	124 (59)	77 (51)	25 (81)	22 (73)	$v = 0.17$ $p = 0.002$	$v = 0.22$ $p = 0.003$	$v = 0.16$ $p = 0.027$	$v = 0.09$ $p = 0.497$

Data are n (%) or median (Q1; Q3).  $v$  = effect size of the  $\chi^2$  test. The values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both the  $2 \times 2 \chi^2$  test. For the  $2 \times 3 \chi^2$  test, effect sizes of 0.07, 0.21, and 0.35 represent small, medium, and large effect, respectively. For the  $3 \times 3 \chi^2$  test, effect sizes of 0.05, 0.15, and 0.25 represent small, medium, and large effect, respectively.

<sup>a</sup> The significant  $p$  values for group comparisons were adjusted to 0.013 (0.05/4) owing to multiple comparisons.

Missing data: spatial neglect (n = 2), apraxia (n = 5), hemianopia (n = 1), depression (n = 9).

(SCP), we performed multiple imputations (bearing exclusively on VV values) and compared the 2 datasets: one with estimated values and the original one with VV measurements. The comparison revealed no difference in VV values ( $-1.1^\circ$  [ $-4.8$ ;  $1.9$ ] vs  $-1.6^\circ$  [ $-5.4$ ;  $1.7$ ]) or bias frequency (contralateral: 36% vs 44%; ipsilateral: 21% vs 22%). Sensitivity indices were high: 0.82 (95% CI [ $0.73$ ;  $0.89$ ]) and 0.96 (95% CI [ $0.86$ ;  $0.99$ ]) for frequencies of contralateral and ipsilateral biases, respectively. Therefore, all analyses involving VV were performed with a complete dataset obtained by multiple imputations.

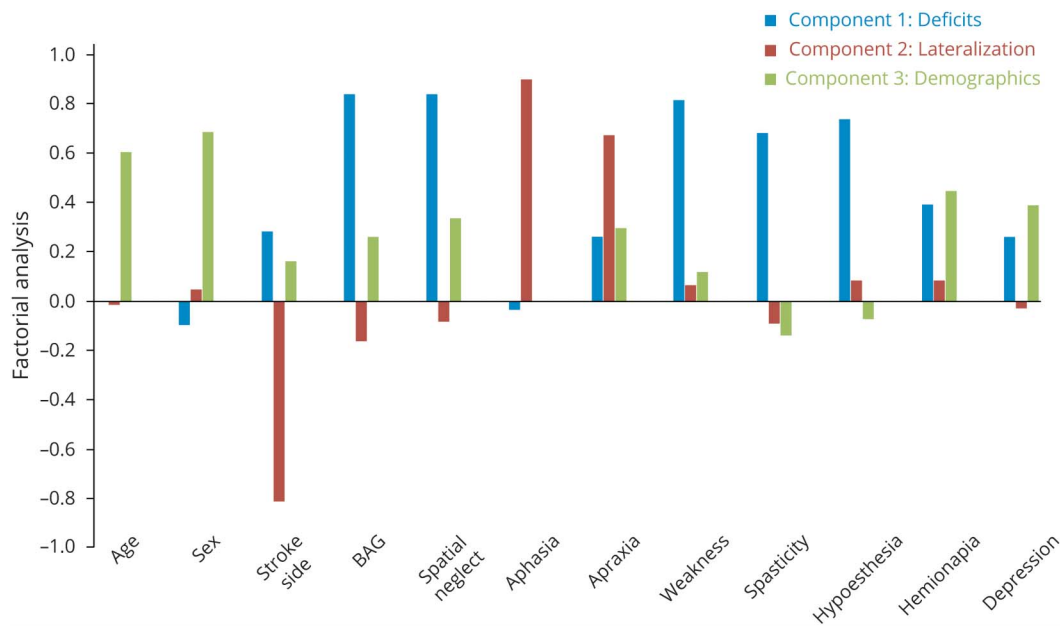
### Behavior Against Gravity

Table 2 shows that body tilt, pushing, and resistance were not only more severe in pushers than in tilters and upright individuals but were also more severe in tilters than upright individuals. Therefore, the construction of our intermediate group was relevant.

Among the 158/220 (72%) individuals considered upright, most sat and stood perfectly upright (146/158, 95%). Only 12 (5%) showed some degree of isolated body tilt in sitting or standing without fall tendency. One (perfectly upright) exhibited mild pushing only when changing positions in standing. None showed any sign of resistance. When isolated, body tilts were always slight and in the upright group. All tilters exhibited a lateral body tilt in sitting or standing, always accompanied by resistance (13/32, 41%), pushing (4/32, 12%), or both (15/32, 47% with signs insufficiently pronounced to be a pusher). These data confirm the appropriateness to call this intermediate group tilters.

Among the 220 individuals of the series, 145 (66%) presented no lateropulsion sign, 45 (20%) presented the 3 signs, 17 (8%) 2 signs (always body tilt, mostly associated with resistance), and 13 (6%) only one sign, almost constantly a

**Figure 2** Factorial Analysis of Clinical and Demographic Features



The 12 features that comprehensively described the 220 individuals of the study were analyzed by factorial analysis. This figure displays how every feature analyzed is determined by the 3 components resulting from the factorial analysis: demographics in green, deficits in blue, and brain lateralization in red. Behavior against gravity (BAG) and spatial neglect have similar clinical profiles in terms of demographics, deficits, and brain lateralization.

lateral body tilt. Among individuals who showed at least one sign, lateral body tilt was almost always present (74/75, 99%), whereas resistance (58/75, 77%) and pushing (50/75, 67%) were less frequent.

Factorial analysis of the 3 signs revealed that they represented a same dimension. The lateral body tilt had the highest factor loading: 0.98 vs 0.96 for pushing and 0.95 for resistance.

### Verticality Perception

Table 2 shows that BAG was greatly influenced by biases of VV orientation, both in magnitude and frequency. VV orientation was mostly distributed within the normality range in upright individuals, mostly tilted to the contralesional side, with a moderate magnitude in tilters and strongly tilted to the contralesional side in pushers. The effect size was medium between the first 2 groups and large between the last 2 groups. The prevalence of contralesional VV biases reached 97% in pushers. About half of upright individuals showed a normal VV and half a mild bias, either contralesional or ipsilesional.

Several results indicated that contralesional and ipsilesional VV tilts corresponded to different mechanisms. Most tilters and pushers (77%) had contralesional VV biases (quasisystematic in pushers), and half of the 44% of individuals with a contralesional VV bias were tilters and pushers. In contrast, ipsilesional VV biases were poorly related to BAG, individuals showing ipsilesional VV biases being mostly upright (84%, except for 7 tilters and 1 pusher). Ipsilesional VV biases were less frequent and

with lesser magnitudes than contralesional biases (22%; 3.7° [2.6; 5.6] vs 6° [3.9; 9.1];  $r = -0.81$ ,  $p < 0.001$ ).

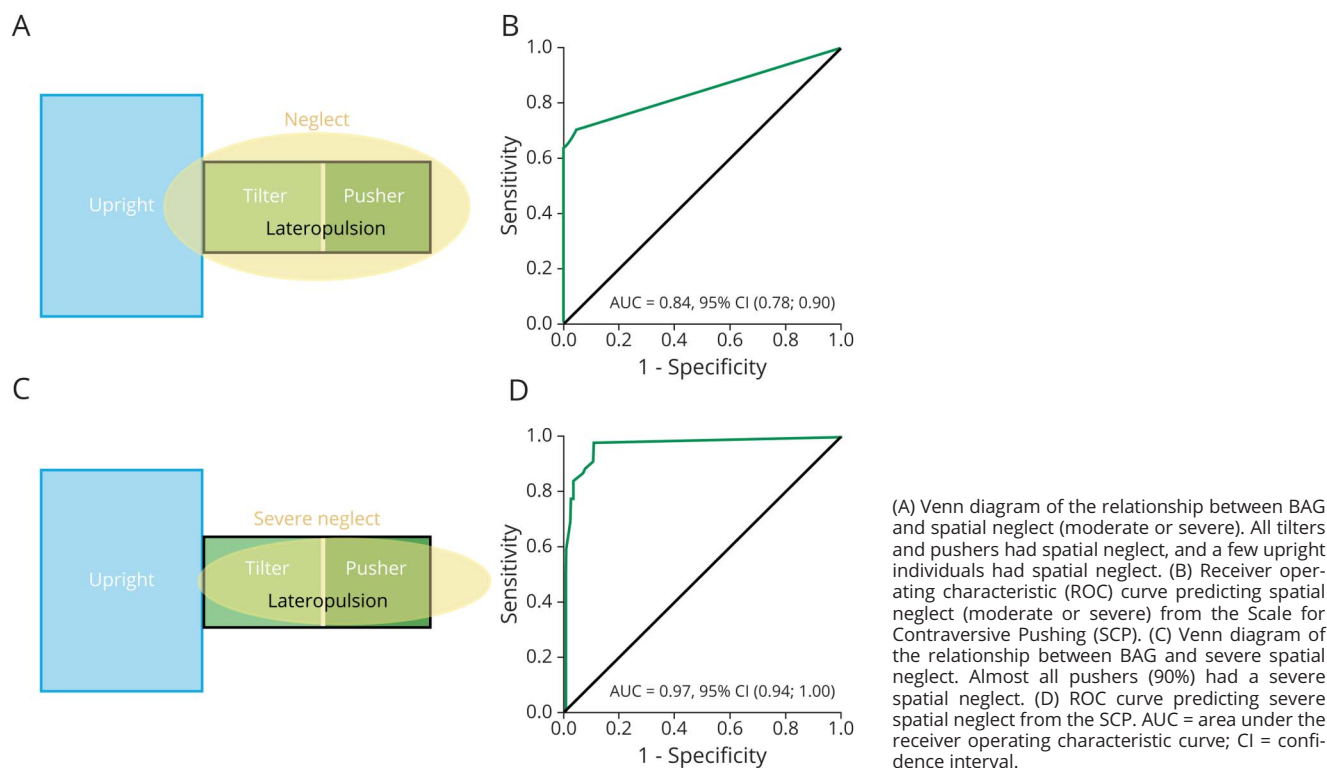
Adding VV orientation in the previous factorial analysis demonstrated that lateropulsion and VV orientation were 2 criteria of a same dimension (i.e., the vertical orientation). The 0.78 factor loading of VV orientation was less high than others (which became 0.96 for body tilt, 0.95 for pushing, and 0.94 for resistance) because of some ipsilesional biases.

### Clinical Profile as a Function of BAG

Table 3 shows that pushers differed from tilters only by more severe spatial neglect, and that most clinical deficits were more severe in tilters than in upright individuals (except aphasia and apraxia).

Ordinal regression of clinical deficits on the 3 categories of BAG revealed that only spatial neglect and weakness were independently associated with lateropulsion. The model was sound (likelihood:  $\chi^2 = 160.1$ ,  $p < 0.001$ ), without interaction between the 2 variables (parallel test:  $\chi^2 = 2.9$ ,  $p = 0.561$ ), and explained much information on the orientation of the body against gravity (Nagelkerke:  $R^2 = 0.66$ ). Spatial neglect was the strongest determinant of lateropulsion (severe spatial neglect: OR 15.4, 95% CI [4.5; 52.3],  $p < 0.001$ ; moderate spatial neglect: OR 5.1, 95% CI [1.8; 14.6],  $p = 0.002$ ). Severe weakness was a secondary determinant of lateropulsion (OR 5.6, 95% CI [2; 15.6],  $p = 0.001$ ).

**Figure 3** Association of Behavior Against Gravity (BAG) and Spatial Neglect



### Relationship Between Lateropulsion and Spatial Neglect

We first ran a principal component analysis with main demographics, stroke side, and all deficits including BAG. This dataset was organized in 3 components corresponding to demographics, brain lateralization supporting functions, and deficits per se. Figure 2 shows their contribution to each variable, pointing out a similarity in the construction of lateropulsion and spatial neglect, both sharing similar levels of components.

Contingency analyses displayed in table 3 show that spatial neglect was found in 23% of upright individuals but in 100% of tilters and pushers. Severe spatial neglect was found in 90% of pushers but only 1% of upright individuals. Conversely, lateropulsion prevalence increased with spatial neglect: 0% if no neglect, 35% with moderate neglect, and 98% with severe neglect. Figure 3, A and C schematizes how lateropulsion was nested in spatial neglect.

Finally, we plotted ROC curve analyses (figure 3, B and D). SCP scores predicted spatial neglect (moderate or severe), with high AUC (0.84; 95% CI [0.78; 0.9],  $p < 0.001$ ), for a cutoff of 0.25 (sensitivity 0.7, specificity 0.95, positive predictive value 0.94, negative predictive value 0.75). Hence, individuals with a net lateral body tilt in standing or sitting, even without risk of falling,<sup>8</sup> had a 94% probability (95% CI [88; 97]) of showing spatial neglect. SCP scores also

predicted severe spatial neglect with high AUC (0.97; 95% CI [0.94; 1],  $p < 0.001$ ), for a cutoff of 0.75 (sensitivity 0.98, specificity 0.89, positive predictive value 0.68, negative predictive value 0.99).

### Discussion

Our study is the first to analyze the 3 signs of the contralesional lateropulsion in a large series of individuals examined after a hemisphere stroke, in parallel with careful assessments of verticality perception and spatial neglect. We hypothesized that the 3 signs of contralesional lateropulsion represent a same dimension corresponding to an impaired orientation of the body against gravity in relation to an altered graviception. We also addressed the issue that lateropulsion might be considered a form of spatial neglect bearing on graviception.

Resistance and pushing were almost constantly associated with lateral body tilt, which was present in 99% of individuals showing at least one sign and also could be found in isolation. Factorial analysis showed that the 3 signs represented a same dimension, lateral body tilt having the highest factor loading (0.98). All together, these results demonstrate that lateropulsion is an entity consisting of 3 postural components, lateral body tilt being the cardinal sign of an impaired body orientation against gravity.

Group comparisons and factorial analysis demonstrated that contralesional VV biases and contralesional lateropulsion were 2 inseparable criteria referring to the vertical orientation, one dealing with graviception (VV) and the other being a postural behavior aiming to orient the body against gravity. Hence, lateropulsion is a way to adjust the body orientation in the roll plane to a wrong reference of verticality. Ipsilesional VV biases were not negligible, found overall in upright individuals and in some tilters.

Multivariate, factorial, contingency, and prediction analyses clearly showed similarities between lateropulsion and spatial neglect, the latter encompassing the former.

Lateropulsion was first described by Babinski and Nageotte in the early 1900s,<sup>23</sup> as a lateral body tilt caused by ipsilateral low-brainstem lesions (details in companion article<sup>12</sup>). Lateropulsion was then described after contralateral hemisphere lesions, with several additional signs not clearly delineated, until the pusher syndrome definition by Davies.<sup>2</sup> The term “syndrome” introduced the idea of a singular behavior. Progressively pushing and resistance became predominant in the literature, leading to a search for their origin in motor and tone disorders. In fact, in our study, we found that only severe motor weakness played a role, in agreement with previous studies.<sup>24</sup> Weakness does not trigger the body tilt but intervenes in magnifying it. Spasticity and apraxia did not play any role in our study, so lateropulsion is not plausibly elicited by a peculiar movement disorder.

In contrast, we show that pushers and tilters responded to a gradient of severity found not only for the 3 postural signs (lateral body tilt, pushing, resistance) but also for VV and spatial neglect. We demonstrate that tilters and pushers belong to the same entity, which may be called lateropulsion, with lateral body tilt as a cardinal sign of an impaired body orientation against gravity. This finding confirms the assumption made 2 decades ago that the term lateropulsion could encompass all 3 signs.<sup>5,6,25-28</sup> By showing that a contralesional body tilt or even pushing may be isolated and that the 3 signs are not always associated, our study provides a unified view of the different terminologies. We suggest that together or in isolation, these signs constitute lateropulsion. Another argument for using the term lateropulsion is the analogy with the term retro-pulsion, also related to a bias in verticality perception, this time backward in the pitch plane.<sup>29</sup> In our study, pushers were diagnosed according to the original criteria,<sup>8</sup> focused on most severe forms of lateropulsion, as attested by a median SCP score of 4.8 (maximum 6) and severe disability (median FIM score 45/126). They represented 14% of the series, which corresponds to the literature<sup>3,13</sup> and hence allows for generalizing our findings. These individuals are known to not recover well<sup>3,13,24,26</sup> and are those who do not benefit most from intensive rehabilitation. We recommend no longer focusing on pusher syndrome, the tree that “hides the forest.”

Our study shows that contralesional VV biases and contralesional lateropulsion are 2 inseparable criteria referring to a same dimension, the vertical orientation. VV is a physiologic measure testing graviception<sup>18,30</sup> and lateropulsion is a postural behavior leading to orient the body against gravity. The frequency and magnitude of contralesional VV biases increased as a function of lateropulsion severity, which cannot be just a question of co-occurrence. The procedure to test VV excludes that VV biases result from an abnormal BAG. The only possibility is that abnormal lateropulsion is secondary to an impaired graviception, quantified by contralesional VV biases. The 3 lateropulsion signs constitute a way to adjust the body orientation in the roll plane to a wrong reference of verticality. Stroke often affects core structures involved in construction of the internal modal of verticality<sup>14,31-36</sup> leading to lateropulsion.<sup>28</sup> This novel finding, supported by a factorial analysis, goes beyond studies having shown that lateropulsion is the rule in individuals with an abnormal contralesional VV tilt.<sup>7,37,38</sup> However, the VV factor loading was less high than for lateropulsion signs. We assume that this is likely due to some ipsilesional VV biases, dealing with something else than verticality (see below).

Our current study and the previous one<sup>7</sup> (same testing) included 97 patients showing lateropulsion. The magnitude of their contralesional VV biases, which increased with lateropulsion severity, was twice greater than that found in 2 series of pushers tested early.<sup>37,38</sup> Conversely, they occasionally showed normal (10/97, 10%) and ipsilesional (9/97, 9%) VV. This clear pattern obtained in almost 100 patients contradicts studies claiming that normal VV is the rule in pushers.<sup>8,39,40</sup> Such discrepancies might have been marred by technical differences in VV tests,<sup>18</sup> concerning settings, procedures, number of trials, parameters, and eventually level of training of examiners. The reliability of VV tests in individuals with stroke strongly depends on the quality of procedures.<sup>15-18</sup> As recommended by experts when VV tests entered the clinic,<sup>30,32,41</sup> we test VV in a black room in complete darkness, without any visual clues. This is not the case for all studies. We install individuals in a device maintaining the head and trunk upright during the test. Together with the number of trials considered sufficient,<sup>16</sup> this procedure led to robust data, as attested by a satisfactory within-subject variability.<sup>14,42</sup> Results are less reliable otherwise in pushers.<sup>17</sup> However, these constraints do not allow for testing all patients. In addition to participants who had medical complications, 33 (15%) had not been able to complete the VV test because of the procedure: inability to remain sitting in the apparatus 20 minutes, lost in darkness (8%), or severe aphasia (7%). Conditions were met to perform multiple imputations and we conducted analysis with complete VV data.

Ipsilesional VV biases may be somewhat frequent after some hemisphere strokes (9%–21%),<sup>7,17,31-33,40</sup> especially after inferior and median thalamic lesions.<sup>33</sup> Of note, 5 individuals in our series had an ipsilesional VV bias despite a contralesional body tilt. All had relatively limited lesions encroaching the basal

ganglia: 2 the thalamus, totally (7.9°) or small posterior part (2.6°), and 3 the putamen, with internal and medial temporal lobe (9.8°), with adjacent insula (5.1°), or caudate nuclei (4.6°). The pathophysiology of these puzzling ipsilesional VV biases remains to be elucidated. They are not associated with a vestibulo-ocular sign,<sup>33</sup> which argues against an ipsiversive cyclo-ocular torsion and furthermore are not so frequent after hemisphere stroke.<sup>32</sup> Anatomical and functional imaging studies of the vestibular network in normal individuals and patients have revealed complex ipsilateral and contralateral vestibular pathways running from both vestibular nuclei to both parieto-insular junctions, one bypassing the thalamus.<sup>33,34</sup> Depending on the precise lesion location, VV tilts might be contralesional or ipsilesional,<sup>31,33,34</sup> which would explain the frequency of both modalities. However, this interpretation does not take into account the lack of ipsilesional bias when the lesion damages somesthetic graviception<sup>7</sup> or the different functional effect of ipsicontralesional VV tilts discovered in our study. Indeed, individuals with ipsilesional VV biases (many of low magnitude) were mostly upright, sometimes tilters, rarely pushers. None had an ipsilesional lateropulsion.

When discarding ipsilesional VV biases, we found a strong parallel severity gradient between VV biases and BAG, with a large VV increment between groups: upright individuals, median -0.6°; tilters, -2.9°; pushers, -12.3°. This association was much greater than that previously reported without discarding ipsilesional VV biases.<sup>7</sup> With this precaution, the VV test would become relevant to guide and monitor a specific rehabilitation of the sense of upright after stroke, by detecting and quantifying contralesional biases in the internal model of verticality. Since we showed that contralesional VV tilts represent a biased verticality representation, it was not necessary to analyze other modalities of verticality perception. Data obtained with a visuo-haptic test must be interpreted with caution, pushers being inclined to push the rod away, which may induce some ipsilesional tilts.<sup>43</sup> The literature reports opposite results for the postural vertical (PV),<sup>7,8</sup> and in our experience VV is much easier to test than PV.

In addition to pusher syndrome, the clinical picture described by Davies<sup>2</sup> comprised signs of spatial neglect (not explicitly termed). Since then, spatial neglect has been repeatedly found in series investigating lateropulsion, reaching even 100% prevalence in several studies by several groups.<sup>8-10</sup>

With a battery of 6 well-validated tests assessing body and nonbody neglect (with an ad hoc grouping in 3 categories) and by means of complementary analyses (multivariate, factorial, contingency, prediction), we clearly showed similarities between lateropulsion and spatial neglect, the latter encompassing the former.

Both are deficits of spatial cognition. Lateropulsion is a deficit of active body orientation with respect to gravity, expressed in the roll plane by a tilt with respect to the vertical axis. Spatial neglect is a deficit of spatial representation/attention mainly

expressed in the horizontal plane by a right/left deviation. How can one link these 2 forms of impaired spatial cognition, one referring to straight ahead in a frontal plane (lateropulsion) and the other straight ahead in the horizontal plane (spatial neglect)? The strong similarity we congruently found between lateropulsion and spatial neglect suggests that some areas, when damaged, simultaneously induce both behaviors.<sup>11</sup> They might be centered on the multimodal thalamo-cortical network coding space in 3 dimensions and often viewed as the vestibular cortex.<sup>35,44</sup> Because we demonstrated that the postural behavior leading to an impaired body orientation against gravity (lateropulsion) was inseparable from a physiologic measure testing graviception (VV), lateropulsion might correspond to a kind of graviceptive neglect, bearing on vestibular and somesthetic graviception.<sup>11,45</sup> Rather than using a mosaic of 2D representations,<sup>46,47</sup> the human brain might use 3D maps<sup>46,47</sup> involving the internal model of verticality.

We found that spatial neglect encompassed lateropulsion. This may be explained by the fact that spatial neglect is not solely the consequence of a distorted spatial referential but also relies on other components such as attentional bias, impaired disengagement of attention, or defective arousal,<sup>48</sup> which contribute to altering clinical test results.<sup>21</sup>

The association of lateropulsion and spatial neglect raises the question of the right hemisphere predominance for both deficits. In our companion article,<sup>12</sup> we show that the ratio of the lateropulsion prevalence between right and left hemisphere stroke increases with time since stroke. A similar pattern is well known for spatial neglect,<sup>49</sup> which is another similarity between both deficits.

Karnath et al.<sup>8</sup> invented the SCP to diagnose PS, and lateropulsion assessment with this scale may be considered as a limitation. Our study shows that the original criteria are not relevant to constitute 2 groups: pushers vs nonpushers.<sup>8</sup> This would categorize as nonpushers many individuals associating lateral body tilt, resistance, and pushing to various degrees. To avoid overlooking individuals with moderate lateropulsion, we used the SCP beyond its initial objective and constituted 3 BAG groups, as previously advocated.<sup>7,12</sup> The appropriateness of this approach is again confirmed by our study. The novelty is the demonstration that the SCP is unidimensional, referring to body orientation with respect to gravity. This property allows for using the SCP to quantify lateropulsion.

A second limitation concerns VV data. We did not examine ocular torsion and therefore cannot exclude that some VV tests might have underestimated or overestimated the part played by verticality representation. If any, this error should be weak given the substantial magnitude of contralesional tilts we found and the low prevalence of ocular torsions after hemisphere stroke.<sup>32</sup> In 15% of individuals, the VV test could not be completed because of the procedure. Multiple imputation giving a complete data set comprising some estimated

values confirmed the results obtained with measured data. However, this diminishes the generalizability of the study, which will need external validity.

In most European countries, as in our practice, only one third of individuals admitted to stroke units are then referred to rehabilitation.<sup>50</sup> Lateropulsion is a major rehabilitation challenge, so it is important that our findings be generalized to the rehabilitation context.

Our study shows that lateral body tilt, resistance, and pushing effectively constitute an entity, better termed lateropulsion than pusher syndrome. Body tilt is its cardinal sign. Contralesional VV biases and contralesional lateropulsion are 2 inseparable criteria referring to the vertical orientation, one dealing with graviception (VV) and the other being a postural behavior aiming to orient the body against gravity. Ipsilesional VV biases were not negligible, found overall in upright individuals and in some tilters. Weakness played a minor role in magnifying the lateropulsion, without triggering it. Several analyses congruently found similarities between lateropulsion and spatial neglect. Spatial neglect encompasses lateropulsion, which might be considered a form of spatial neglect, bearing on graviceptive information (graviceptive neglect). Overall, these findings suggest that the human brain uses 3D maps involving the internal model of verticality and not just a mosaic of 2D representations.

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## Disclosure

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## Appendix Authors

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<b>Shenhao Dai, MD</b>	Grenoble Alpes University Hospital, France	Analyzed and interpreted the data, drafted the manuscript for intellectual content
<b>Céline Piscicelli, PhD</b>	Grenoble Alpes University Hospital, France	Acquisition of data, revised the manuscript for intellectual content

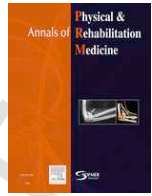
## Appendix (continued)

Name	Location	Contribution
<b>Emmanuelle Clarac, PT</b>	Grenoble Alpes University Hospital, France	Acquisition of data, material support
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<b>Marc Hommel, MD, PhD</b>	Grenoble Alpes University, France	Interpreted the data, revised the manuscript for intellectual content
<b>Dominic Pérennou, MD, PhD</b>	Grenoble Alpes University Hospital, France	Designed and conceptualized study, study supervision, interpreted the data, drafted the manuscript for intellectual content, obtaining funding

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## Original article

## Recovery of balance and gait after stroke is deteriorated by confluent white matter hyperintensities: Cohort study

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## ABSTRACT

White matter hyperintensities (WMHs) are well known to affect post-stroke disability, mainly by cognitive impairment. Their impact on post-stroke balance and gait disorders is unclear. Objectives We aimed to test the hypothesis that WMHs would independently deteriorate post-stroke balance and gait recovery. This study was performed in 210 individuals of the cohort Determinants of Balance Recovery After Stroke (DOBRAS), consecutively enrolled after a first-ever hemisphere stroke. Clinical data were systematically collected on day  $30 \pm 3$  (D30) post-stroke and at discharge from the rehabilitation ward. WMHs were searched on MRI, graded with the Fazekas scale, and dichotomized as no/mild (absence/sparse) or moderate/severe (confluent). The primary endpoint was the recovery of the single limb stance, assessed with the Postural Assessment Scale for Stroke (PASS). The secondary endpoint was the recovery of independent gait, assessed with the modified Fugl-Meyer Gait Assessment (mFMA). The adjusted hazard ratios (aHRs) of achievements of these endpoints by level of WMHs were estimated by using Cox models, accounting for other relevant clinical and imaging factors. Individuals with moderate/severe WMHs ( $n = 86$ , 41%) had greater balance and gait disorders and were more often fallers than others ( $n = 124$ , 59%). Overall, they had worse and slower recovery of single limb stance and independent gait ( $P < 0.001$ ). Moderate/severe WMHs was the most detrimental factor for recovery of balance (aHR 0.46, 95% confidence interval [CI] 0.32–0.68,  $P < 0.001$ ) and gait (0.51, 0.35–0.74,  $P < 0.001$ ), along with age, stroke severity, lesion volume and disrupted corticospinal tract. With cerebral infarct, endovascular treatments had an independent positive effect, both on the recovery of balance (aHR 1.65, 95% CI 1.13–2.4,  $P = 0.009$ ) and gait (1.78, 1.24–2.55,  $P = 0.002$ ). WMHs magnify balance and gait disorders after stroke and worsen their recovery. They should be better accounted for in post-stroke rehabilitation, especially to help establish a prognosis of mobility. ClinicalTrials.gov registration: NCT03203109.

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## 1. Introduction

After a stroke, predicting the functional prognosis is of major importance. With mobility limitation as one of the most frequent complaints [1] and one of the most severe causes of disability [1], patients and relatives ask about the prognosis of mobility and express their hope of a good recovery. Although recovering balance control is a

prerequisite for an independent gait and a satisfactory mobility [2], the recovery of balance and gait disorders after stroke has been little modelled so far [2–6]. There is a pressing need to acquire specific and in-depth knowledge in this domain, both for establishing individual prognosis and improving clinical trials focused on mobility [2,4,7,8].

Several factors may affect balance and gait recovery after stroke: stroke volume [9] and severity [3], the disruption of the corticospinal tract (CST) [10], as well as the nature of clinical deficits [6,11,12]. Although highly suspected [13,14], the detrimental role of preexisting

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brain alterations related to small vessel disease remains to be established for balance and gait recovery, as it has been for the recovery of generally disability [13,15] and cognitive functions [16–18]. Small vessel disease alters the whole brain, thus especially deteriorating functions such as balance control, which involve numerous areas distributed in both hemispheres, the cerebellum and the brain stem, interconnected in networks [19–21]. Overall, after a stroke, the reorganization of these networks supporting brain plasticity should be greatly altered by diffused brain alterations caused by small vessel disease. For example, the reorganization might alter the retuning of interhemispheric balance, involved in the sensorimotor recovery [22].

White matter hyperintensities (WMHs) constitute the most striking marker of small vessel disease [13,23], associated with worse balance and gait capacities in older people [24–26]. If any, WMHs may be sparse or confluent [13,27], which represents an indicator of severity, with greater and more diffuse whole brain alteration [13,27].

This study analyzed the effect of WMHs (dichotomized as no/mild or moderate/severe) on balance and gait recovery in a large cohort of individuals followed at the subacute phase after a first hemisphere stroke. The primary endpoint was the recovery of the single limb stance, a challenging task requiring an efficient postural control of the trunk and the four limbs that involves precise spatial representation and a coordinated sensori-motor control of body segments, thus the whole brain [28]. The second endpoint was independent gait, which involves a single limb stance. We used multivariate analyses dedicated to the follow-up to detect the possible effects of several other relevant clinical or imaging factors. We hypothesized that individuals with a stroke and preexisting confluent WMHs not only have greater balance disorders than others but also exhibit overall worse recovery of their balance abilities, especially the capacity to regain the single limb stance and to re-walk without a cane.

The reporting of the study follows the STROBE statement (checklist in Online material).

## 2. Methods

### 2.1. Study design

This was a monocentric observational study involving data from the cohort Determinants of Balance Recovery After Stroke [DOBRAS]; ClinicalTrials.gov: NCT03203109) with participants comprehensively assessed in routine care in the rehabilitation ward [2]. For this study, we used balance and gait data collected at 30 ( $\pm 3$ ) days after stroke (D30), then at discharge (within the last 3 days) in the neurorehabilitation ward. Assessments were performed by trained and multidisciplinary examiners, with blinding to other data and the study hypothesis. We also used demographic data and main clinical and imaging features. The sample size of the DOBRAS cohort was planned to conduct multivariate analyses focused on balance and gait recovery in a large series of individuals ( $\geq 200$  observations), including multivariate ( $\geq 3$  variables) Cox models performed in this study.

### 2.2. 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 a na-

tional 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.

### 2.3. Participants

From January 2012 to October 2019, we included 210 consecutive individuals (age 18 to 80 years), with a first-ever unilateral hemisphere stroke analyzed by MRI. Exclusion criteria were recurrent stroke, complications at the acute stage (malignant infarct, cerebral herniation, severe subarachnoid hemorrhage and hydrocephalus), dementia, previous disability interfering with balance or vestibular disorders, and unstable medical condition or psychiatric problems jeopardizing data reliability (Fig. 1). These conditions were obtained from the hospital electronic file describing the history of every patient, by interviewing patients and relatives, and by a systematic clinical examination. Participants followed a personalized rehabilitation program, taking into account deficits and activity limitations, capacities to face intensive rehabilitation (fatigue or transitory medical problems), individual recovery, and the most appropriate guidelines. According to their abilities, participants had at least 2 physiotherapy and 1 occupational therapy sessions per day (each session lasting at least 30 min for a total daily time of sensori-motor rehabilitation over  $\geq 1.5$  hr per patient), plus sessions with a speech therapist, neuropsychologist, psychologist, or orthoptist if needed. The length of hospitalization of our participants was measured from stroke onset to discharge of the rehabilitation ward.

### 2.4. Risk factors related to WMHs

The categorical diagnosis of hypertension, diabetes, and dyslipidemia and information on consumption of tobacco and of alcohol were retrieved from hospital records for each participant. Thresholds were all those internationally recommended (details in Online material) [29].

### 2.5. Clinical assessments

Balance disorders were assessed with the Postural Assessment Scale for Stroke (PASS), the most appropriate balance scale at the subacute stage after stroke [30,34]. The total score ranging from 0 to 36 (satisfactory balance) assesses balance abilities in daily life. The last 2 items assess single limb stance on paretic and non-paretic sides, which are independent of other items because of their difficulty [30]. According to the scoring of these items, an individual who is able to maintain a single limb stance for  $> 5$  sec (whatever the side) has a total PASS score  $> 32/36$  [30], which we used as endpoint in this study. The 5-sec duration is the usual cutoff considered to indicate that this task is achieved [30,31]. The side of the single limb stance is almost always the non-paretic side in individuals with stroke [31].

Gait disorders were assessed with the modified Fugl-Meyer Assessment of gait (mFMA-gait), designed to classify post-stroke gait in 7 levels of mobility [32]. The mFMA-gait score ranges from 0 (no possibility to walk) to 6 (indicating a [quasi] normal gait) [35]. The 7 levels are as follows: 0, cannot walk at all; 1, can walk with the help of two persons; 2, can walk with the help of one person; 3, walk with the help of a walker, crutches or quadripod cane; 4, walk with the help of a simple cane or a crutch; 5, walk without any help but slowly or with lameness; 6, walk with normal speed for age. We used as the

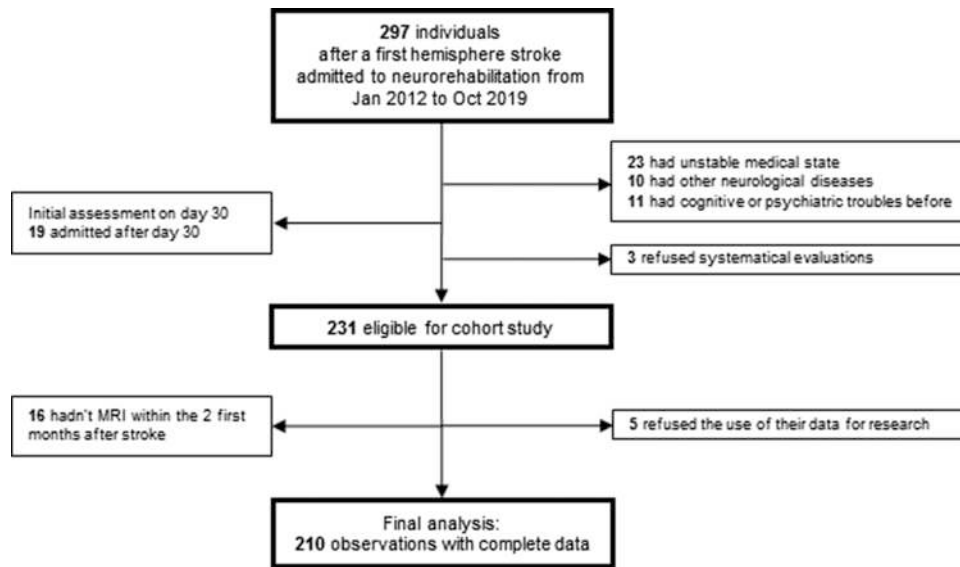


Fig. 1. Flow of participants in the study.

endpoint a score  $> 4$  indicating the ability to walk independently without a cane (or walker).

A fall was defined as an event that results in a person coming to rest inadvertently on the ground [33]. Falls during the rehabilitation ward (wherever the room and the time of occurrence) were monitored by the multidisciplinary team all during the rehabilitation stay. Any fall was declared on a specific hospital register and recorded in the patient's electronic file. The presence and number of falls were counted at the end of the stay. A faller was defined as a person who fell at least once.

Global disability was estimated with the modified Rankin Scale (mRS).

Clinical features of stroke comprised the initial stroke severity estimated by the US National Institutes of Health Stroke Scale (NIHSS) at 24 hr post-stroke (range 0–42, higher scores indicating greater stroke severity), stroke type (ischemic or hemorrhagic) and side (right or left hemisphere) as well as cortical or subcortical stroke location. Intravenous thrombolysis and/or thrombectomy were also considered for ischemic strokes.

## 2.6. Brain imaging

The presence of WMHs was sought on T2-FLAIR sequences from the first or second MRI (within the first 2 months after stroke) and graded with the Fazekas scale [27]. The scale simply grades WMHs in 4 levels: 0, no lesion; 1, focal lesions; 2, beginning lesions confluences; and 3, extended involvement with large confluent areas [32]. Two trained independent examiners (SD, CP), carefully examined the absence, presence, and severity of WMHs in the hemisphere spared by the stroke. If any, their differences of grading were resolved by consensus [23].

According to recommendations [15,34], we *a priori* planned to re-group grades 0 and 1 and grades 2 and 3. This approach takes into account the low frequency of grade 3 in individuals with a first hemisphere stroke and the fact that the difference between grades 0 and 1 may be tenuous. Its appropriateness was confirmed by our data.

Complementary analyses were performed to control for possible confounders, such as stroke volume and CST disruption, known to affect balance and gait disorders [9,10,35,36]. These imaging confounders were analyzed in the second MRI, with a reasonable interval

that is recommended to avoid overestimating stroke volume [37]. Details about the machine and acquisition parameters are given in Online material. Lesion volume, determined as the percentage of hemisphere encroached on by the lesion (number of voxels for the lesion/number of voxels for the hemisphere  $\times 100$ ) was measured by using MRIcron after a manual lesion delineation from axial slices acquired with T2-FLAIR sequences. All drawings involved 2 trained operators, the first from a panel of three (CL, SD, AC) and the second always the same and with blinding to behavioral data (CP). Any disagreements were resolved by consensus. Drawings were performed on axial slices of a T1-weighted MRI template from the Montreal Neurological Institute (<https://www.mcgill.ca/bic/neuroinformatics/brainatlases-human>) normalized to Talairach's space. CST disruption was analyzed with the "Tractotron" tool of the BCBToolkit software (<http://toolkit.biclab.com/>), which determines the disruption induced at the level of a given lesion. Each participant's lesion was compared with an atlas of white matter tracts for each voxel. As suggested, we analyzed both the proportion and probability of the ipsilesional CST disrupted by the stroke [38]. The proportion corresponds to the number of damaged voxels in the CST divided by the total volume of this tract. The probability corresponds to the lesioned voxel with the highest percentage value. The CST was considered disrupted when an estimated proportion or probability was  $> 50\%$  [38].

For clarity reasons and length constraint, the effect of stroke location on balance and gait recovery was not analyzed in this study focused on the effects of WMHs as a marker of small vessel disease.

## 2.7. Statistical analysis

The two groups of WMH severity were compared with Mann–Whitney and  $\text{Chi}^2$  tests. Effect sizes were calculated for significant factors by using the  $Z$  values of the Mann–Whitney test,  $r = Z/\sqrt{n}$ , and the  $X^2$  of the  $\text{Chi}^2$  test,  $v = \sqrt{(X^2/n \times \text{degree of freedom})}$ . Values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both tests [39]. Factors found significant on univariate analysis were entered into a binary logistic regression to determine independent factors associated with moderate/severe WMHs. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated.

Cox proportional-hazard regression was used to determine factors independently associated with the achievement of the single limb

stance and the achievement of the independent gait. We adopted this type of model because it determines independent factors involved in the recovery of these endpoints, taking into account individual timelines for this recovery (from D30 to discharge). Cases were censored as follows: recovery of single limb stance regardless of supporting lower limb with PASS score  $>32/36$ , recovery of independent gait with mFMA-gait score  $>4/6$ . We used backward Cox models to estimate the adjusted hazard ratios (aHRs) of these endpoints (with 95% CIs). Two Cox models were run, for the recovery of balance (primary criteria) and gait, a primary model with relevant clinical factors (age, stroke severity and type, sex, BMI and endovascular treatments limited to infarcts), and a complementary model with imaging factors being potential confounders (stroke volume, CST disruption).

In addition, Kaplan–Meier survival tests were performed to compare the timeline of the achievement of single limb stance (and independent gait) between individuals with no/mild WMHs and those with moderate/severe WMHs. Differences between participants with no/mild and moderate/severe WMHs were compared by the log-rank test.

The relationships between balance and gait disorders (at D30 and discharge) were tested by linear regression. Continuous data are presented as median (Q1–Q3) and categorical data as number (percentage, %). Two-sided  $P < 0.05$  was considered statistically significant. Statistical analyses involved using SPSS 24.0 and Stata 15.1. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### 3. Results

The median age of the 210 participants was 67.3 years (57.4–72.7); 68 (32%) were females. In total, 172/210 (82%) had a brain infarct; 65 (38%) received thrombolysis and/or thrombectomy. The initial stroke severity was moderate to severe (median NIHSS on D1 12 [7–16]).

No data were missing for the primary analyses. Complementary analyses with stroke volume and CST disruption were conducted on the 182/210 observations of participants who had a second MRI (87%). To ensure the validity of the complementary cox model for imaging data, we analyzed the data sensitivity within the frame of the whole series. Sensitivity was high: 0.88 and 0.87 for the endpoints of single limb stance and independent gait, respectively. These results indicated that missing data for brain imaging were randomly distributed, inducing no bias.

#### 3.1. Features of individuals with WMHs

A total of 44 (21%) participants did not show WMHs (grade 0); 166 (79%) presented WMHs graded as follows: grade 1, 80 (38%); 2, 71 (34%); and 3, 15 (7%). We constituted 2 groups: no/mild WMHs ( $n = 124$ , 59%) and moderate/severe WMHs with confluent lesions ( $n = 86$ , 41%). Characteristics are compared in Table 1. The latter group was older, more often female, more often hypertensive, and with more hematomas than the former group. When these 4 variables were analysed by binary logistic regression, sex did not remain significant, in contrast to hematoma (aOR 2.5, 95% CI 1.12–5.73,  $P = 0.025$ ), hypertension (2.17, 1.1–4.28,  $P = 0.025$ ), and age (1.08, 1.04–1.12,  $P < 0.001$ ). The 2 groups did not differ in brain imaging, including stroke volume or proportion/probability of CST disruption. Disability was greater with moderate/severe than no/mild WMHs, both at D30 and discharge. The length of hospitalization since stroke (acute/subacute neurological units, then neurorehabilitation ward) was longer in the moderate/severe than no/mild WMHs group.

**Table 1**

Demographic and clinical features of individuals with no/mild or moderate/severe white matter hyperintensities (WMHs).

	No/mild WMHs ( $n = 124$ )	Moderate/severe WMHs ( $n = 86$ )	P-value	Effect size
<b>Demographics</b>				
Age (years)	63.6 (53–69)	70.9 (66–74)	$< 0.001$	r
Sex, female (%)	32 (26)	36 (42)	0.014	v
BMI ( $\text{kg}/\text{m}^2$ )	24.5 (22–28)	26.2 (23–28)	0.134	
<b>WMH risk factors</b>				
Hypertension (%)	62 (50)	66 (77)	$< 0.001$	v
Diabetes (%)	21 (17)	22 (26)	0.127	
Dyslipidemia (%)	56 (45)	42 (49)	0.6	
Tobacco smoking (%)	77 (62)	44 (51)	0.115	
Alcohol drinking (%)	32 (26)	17 (20)	0.309	
<b>Stroke features</b>				
Stroke type: infarct (%)	108 (87)	64 (74)	0.019	v
Thrombolysis and/or thrombectomy (%)	42 (39)	23 (36)	0.7	
Stroke side: right hemisphere (%)	56 (45)	39 (45)	0.979	
Stroke location (%)	34 (27)	30 (35)	0.284	
Subcortical	47 (38)	24 (28)		
Cortical	43 (35)	32 (37)		
Subcortical + cortical				
Initial NIHSS score (0–42)	12 (7–16)	11 (7–16)	0.948	
<b>Imaging features<sup>a</sup></b>				
Delay of MRI (in rehabilitation) after stroke onset (days) <sup>b</sup>	62 (59–74)	63 (58–76)	0.673	
Lesion volume <sup>a</sup>	17,353	9,720	0.497	
In voxels	(3,781–40,600)	(2,061–38,202)		
In %	2.3 (0–5)	1.3 (0–5)		
Disrupted CST <sup>a</sup>	62 (59)	48 (62)	0.654	
Proportion $> 50\%$ (%)	104 (99)	77 (100)	1	
Probability $> 50\%$ (%)				
<b>Disability</b>				
mRS on D30 (0–6)	3 (2–3)	3 (3–4)	$< 0.001$	r
mRS at Discharge (0–6)	2 (1–2)	2 (2–3)	0.001	r
Length of hospitalization since stroke (days) <sup>b</sup>	69 (48–111)	107 (61–166)	0.001	r

BMI: body mass index; NIHSS: US National Institutes of Health Stroke Scale; CST: corticospinal tract; D30: day 30; mRS: modified Ranking Scale. Data are  $n$  (%) or median (Q1–Q3). Effect sizes are given as “r” for the Mann–Whitney test and “v” for  $\text{Chi}^2$  test. With  $P < 0.05$ , effect sizes are given; values 0.1, 0.3, and 0.5 represent a small, medium, and large effect for both the Mann–Whitney and  $\text{Chi}^2$  tests.

<sup>a</sup> Imaging features were analyzed in 182 individuals with control MRI around day 60.

<sup>b</sup> Duration from stroke onset to discharge from the rehabilitation ward.

#### 3.2. Balance and gait disorders

Balance and gait scores were highly correlated, both at D30 ( $r = 0.89$ ,  $P < 0.001$ ) and at discharge ( $r = 0.86$ ,  $P < 0.001$ ), so balance

ca-

capacity highly explained the information contained in gait capacity: 79% (95% CI 75–84,  $P < 0.001$ ) at D30 and 73% (67–79,  $P < 0.001$ ) at discharge. Balance and gait disorders were worse with moderate/severe than no/mild WMHs, both at D30 and discharge (Table 2).

Fallers more frequently had moderate/severe than no/mild WMHs (Table 2). The mean (SD) incidence of falls during rehabilitation was 0.6 (0.1) per person for 100 days with moderate/severe WMHs and 0.2 (0.1) per person for 100 days in others.

### 3.3. Balance recovery

In the first Cox model with clinical features (Table 3, upper part), moderate/severe WMHs had an independent detrimental role in balance recovery (aHR 0.46, 95% CI 0.32–0.68,  $P < 0.001$ ), along with age and initial NIHSS score. The aHR value of 0.46 meant that the chance to achieve the single limb stance (> 5 sec) at discharge for individuals with moderate/severe WMHs was 0.46-fold that of individuals of the same age and stroke severity but with no/mild WMHs. Stroke type, sex, and BMI were not independently associated with poor balance recovery. This model limited to infarcts to include endovascular treatments (Online material) showed thrombolysis and/or thrombectomy with an independent beneficial effect on balance recovery (aHR 1.65, 95% CI 1.13–2.4,  $P = 0.009$ ). In the second model with imaging factors (Table 3, lower part), WMHs also played a primary detrimental role in balance recovery (aHR 0.46, 95% CI

**Table 2**

Balance and gait between groups with no/mild versus moderate/severe white matter hyperintensities (WMHs).

	No/mild WMHs (n = 124)	Moderate/severe WMHs (n = 86)	P-value	Effect size
<b>D30</b>				
Balance (PASS, 0-36)	33 (27–36)	29 (16–33)	< 0.001	$r = -0.28$
Gait (mFMA-gait, 0-6)	5 (3–6)	3 (0–5)	< 0.001	$r = -0.26$
<b>Discharge</b>				
Balance (PASS, 0-36)	35 (33–36)	33 (31–34)	< 0.001	$r = -0.36$
Gait (mFMA-gait, 0-6)	5 (5–6)	5 (3–6)	0.013	$r = -0.25$
Fallers (%)	20 (16)	32 (36)	0.001	$v = 0.23$

D30: day 30; PASS: Postural Assessment Scale for Stroke; mFMA-gait: modified Fugl–Meyer Assessment of gait. Data are n (%) or median (Q1–Q3).

**Table 3**

Multivariate Cox regression models<sup>a</sup> of factors associated with achieving single limb stance after stroke.

Variables	aHR	95% CI	P-value
<b>Model 1 with clinical features (n = 210)</b>			
WMHs (moderate/severe vs. no/mild)	0.46	0.32–0.68	< 0.001
Age (per year)	0.98	0.97–0.99	0.005
Initial NIHSS score (per point)	0.84	0.81–0.87	< 0.001
<b>Model 2 with imaging features (n = 182)</b>			
WMHs (moderate/severe vs. no/mild)	0.46	0.31–0.67	< 0.001
Lesion volume (per 1% of hemisphere)	0.94	0.91–0.98	0.003
Disrupted CST (proportion > 50% vs. ≤ 50%)	0.59	0.4–0.89	0.01

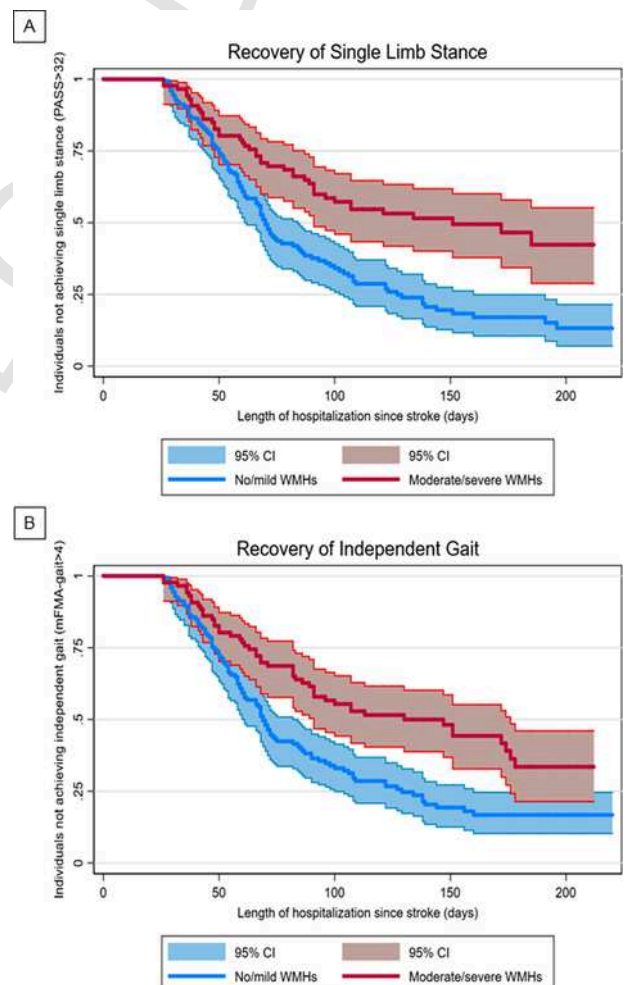
WMHs: white matter hyperintensities; NIHSS: US National Institutes of Health Stroke Scale; CST: corticospinal tract; aHR: adjusted hazard ratio; CI: confidence interval.

<sup>a</sup> Two models were tested. Model 1 involved clinical features of the 210 individuals with follow-up from day 30 post-stroke to discharge from the rehabilitation ward. Model 2 involved imaging features analyzed on MRI performed about 2 months after the stroke (182 individuals).

0.31–0.67,  $P < 0.001$ ), along with disrupted ipsilesional CST and stroke volume. The aHR value of 0.46 meant that the chance to achieve the single limb stance (> 5 sec) at discharge of individuals with moderate/severe WMHs was 0.46-fold that of individuals of the same lesion volume and CST disruption but with no/mild WMHs. The Kaplan–Meier survival test showed that the achievement of single limb stance was less frequent and delayed with moderate/severe than no/mild WMHs (Fig. 2A;  $X^2 = 19.2$ ,  $P < 0.001$ ). The single limb stance was achieved with a median delay of 151 (66–196) days with moderate/severe WMHs and 70 (50–127) days for others. At discharge, 49% of participants with moderate/severe WMHs could not maintain the single limb stance for 5 sec versus 19% of those with no/mild WMHs ( $X^2 = 20.5$ ,  $v = 0.31$ ,  $P < 0.001$ ).

### 3.4. Gait recovery

In the first Cox model with clinical features (Table 4, upper part), moderate/severe WMHs had an independent detrimental role in gait recovery (aHR 0.51, 95% CI 0.35–0.74,  $P < 0.001$ ), along with age and initial NIHSS score. Stroke type, sex, and BMI were not independently associated with poor gait recovery. This model limited to infarcts to include endovascular treatments (Online material) showed



**Fig. 2.** Recovery of balance and gait. Time to achieve: A) single limb stance (Postural Assessment Scale for Stroke score > 32); and B) independent gait (modified Fugl–Meyer Assessment of Gait score > 4) for 2 groups of white matter hyperintensities (WMHs).

**Table 4**  
Multivariate Cox regression models<sup>a</sup> of factors associated with achieving independent gait after stroke.

Variables	aHR	95% CI	P-value
Model 1 with clinical features ( <i>n</i> , 210)			
WMHs (moderate/severe vs. no/mild)	0.51	0.35–0.74	< 0.001
Age (per year)	0.98	0.97–1	0.006
Initial NIHSS score (per point)	0.83	0.8–0.86	< 0.001
Model 2 with imaging features ( <i>n</i> = 182)			
WMHs (moderate/severe vs. no/mild)	0.52	0.36–0.75	0.001
Lesion volume (per 1% of hemisphere)	0.94	0.91–0.98	0.002
Disrupted CST (proportion > 50% vs. ≤ 50%)	0.61	0.42–0.9	0.013

WMHs: white matter hypertensities; NIHSS: US National Institutes of Health Stroke Scale; CST: corticospinal tract; aHR: adjusted hazard ratio; CI: confidence interval.

<sup>a</sup> Two models were tested. Model 1 included clinical features of the 210 individuals with a follow-up from day 30 post-stroke to discharge from the rehabilitation ward. Model 2 included imaging features analyzed by MRI performed about 2 months after the stroke (182 individuals).

that thrombolysis and/or thrombectomy had an independent beneficial effect on gait recovery (aHR 1.78, 95% CI 1.24–2.55,  $P = 0.002$ ). In the second model with imaging factors (Table 4, lower part), WMHs played a detrimental role in gait recovery (aHR 0.52, 95% CI 0.36–0.75,  $P = 0.001$ ), along with disrupted ipsilesional CST and stroke volume. The Kaplan–Meier survival test showed that the achievement of independent gait was less frequent and delayed with moderate/severe than no/mild WMHs ( $X^2 = 15.1$ ,  $P < 0.001$ ) (Fig. 2B). Independent gait was achieved at a median delay of 130 (63–176) days with moderate/severe WMHs versus 69 (47–129) days with no/mild WMHs. At discharge, 43% of participants with moderate/severe WMHs could not regain independent gait versus 19% of those with no/mild WMHs ( $X^2 = 13.8$ ,  $v = 0.26$ ,  $P < 0.001$ ).

#### 4. Discussion

Our study confirms that gait disorders after stroke are more severe with confluent WMHs [14,40], reveals that this is due to balance disorders, and extends this finding to the risk of being a faller. Using multivariate Cox regression models and Kaplan–Meier survival tests to master possible confounding variables and rank independent effects, we confirm our hypothesis that WMHs independently alter the recovery of balance and gait, regardless of other clinical and imaging factors. The study goes even beyond our hypothesis, discovering that the presence of confluent WMHs plays a primary detrimental role on the recovery of endpoints such as the ability to maintain the single limb stance for 5 sec or the ability to walk without a cane, achieved roughly twice less frequently than for other patients of same age, stroke severity and volume, and disruption of CST. The single limb stance appears to be a key milestone, which should deserve more attention in balance and gait rehabilitation after stroke. These findings were obtained in a large series of consecutive individuals admitted to rehabilitation after a first hemisphere stroke ( $n = 210$ ), with stroke severity (NIHSS, lesion volume, disability) comparable to that reported in the literature.

##### 4.1. WMHs

Described 3 decades ago, under the terms leukoaraiosis and WMHs [27], altered brain white matter has become a major topic in gerontology and in vascular and neurological sciences. The literature is abundant and congruent about the detrimental effects of WMHs on cognitive functions [16–18]. However, the literature is more limited

but still consensual about the detrimental effect of WMHs on mobility [24–26], most cohorts involving older people or people with neurodegenerative diseases [16,41].

WMHs and stroke share common risk factors [34,42], and WMHs increase the risk of stroke [15]. We found WMHs associated with usual demographic, cardiovascular and clinical factors (i.e., age, hypertension, and hemorrhagic stroke).

##### 4.2. Balance disorders and their recovery after stroke

Balance ability refers to a dual control: for body orientation with respect to gravity and body stabilization with respect to the base of support [43]. Balance disorders combine both types of impairments [2], especially after stroke, and are globally assessed in daily life by the PASS, used in our study. We showed that individuals with moderate/severe WMHs have worse balance disorders than others at the subacute phase after stroke but did not analyse the specific effect of WMHs or body orientation with respect to gravity or body stabilization with respect to the base of support. This remains to be investigated.

Single limb stance is considered one of most challenging balance tests in the general population [43,44], a predictor of age-related decline [44] and also a milestone of satisfactory balance after stroke [30,31]. For these reasons, the single limb stance would represent a particularly relevant aspect to investigate the impact of diffused brain alterations related to small vessel disease on balance recovery after stroke.

Using comprehensive multivariate analyses (Cox models), we showed that moderate/severe WMHs was one of the most detrimental factors affecting recovery of the single limb stance, whose achievement in individuals with confluent WMHs (grades 2 and 3) was twice less frequent than in individuals without or with sparse WMHs (grades 0 and 1), regardless of other clinical and imaging factors. We do not exclude that the preexistence of the WMHs might have affected the capacity of some individuals to balance on one leg before the stroke, particularly in the oldest participants. Although preexisting balance disorders was an exclusion criterion for this study, balance abilities had not been quantified before the stroke, which leads us to remain cautious with this assumption. However, several studies have indicated that abnormal single limb stance would be a marker of pathological cognitive and motor decline, a predictor of severe falls (with lesion) in older adults [44]. Given its simplicity, the single limb stance deserves wider utilization in medicine, to detect the consequence of general vascular risk factors on the brain.

Our study also underlines the detrimental effects of age, stroke severity, lesion volume, and disruption of CST, mainly taken into account in our models as possible confounders. There is a rich literature on the detrimental effect of CST disruption on the functional ability of upper and lower limbs after stroke [45], but the literature is more sparse on the effect of disrupted CST on post-stroke balance disorders [10]. Our study revealed that achieving the ability to maintain the single limb stance for 5 sec is greatly affected by an important disruption of CST.

Age [4], stroke severity and lesion volume [9,36,46] are well-known factors affecting post-stroke balance abilities. Our study is one of the first to reveal the independent detrimental effect of these factors on the recovery of balance after stroke, especially on the achievement of the single limb stance.

In our study, the probability to recover the ability to stand on one leg (for > 5 sec) was 65% greater for individuals who underwent recanalization than others with a cerebral infarct but no endovascular treatment, regardless of other factors. This finding supports the view

that individuals with confluent WMHs may be considered for endovascular treatments [47,48].

#### 4.3. Gait disorders and their recovery after stroke

In our series of individuals examined at the subacute stage after stroke, gait ability was mainly linked to balance ability, so gait and balance were similarly affected by WMHs. WMHs predicted the recovery of an independent gait (walking without any assistance), considered an endpoint for recovery of satisfactory gait in the context of post-stroke rehabilitation. The single stance is the critical event of a gait without technical aid, requiring the ability to bear the body's weight on a single lower limb (alternatively non-paretic and paretic) and to master the control of a dynamic balance on this narrow base of support. This challenging task involves both hemispheres, which explains the detrimental role of moderate/severe WMHs on regaining independence of gait. This result was obtained with multivariate analyses, which again revealed the negative effect of age, stroke severity, lesion volume, and also marked disruption of the ipsilesional CST. These findings confirm previous results of studies of gait recovery after stroke, reporting the negative effect of age [3,5], stroke severity [3] and lesion volume [46]. The effect of disrupted CST on gait ability [35] has been more recently demonstrated. Of note, our study also showed a beneficial effect of endovascular therapy on gait recovery.

#### 4.4. Falls

WMHs are a well-known determinant of falls in older people [24] and also a factor increasing the risk of falls after stroke [49]. We confirmed these findings, fallers being twice more frequent with moderate/severe than no/mild WMHs, which call for better fall prevention in stroke individuals showing moderate/severe WMHs. The analysis of brain imaging should be more systematic for assessing the individual risk of fall after stroke.

#### 4.5. Impact of these results to the field

Predicting functional prognosis is of major importance after a stroke, and our study revealed that individuals with confluent WMHs had 2-fold less chance than others to recover an independent gait (without a cane), other things being equal, likely because of difficulty mastering the single limb stance [50]. Preexistence of severe comorbidity [3], stroke severity including severe weakness [12] and spatial neglect [19], together with the presence of a net lateropulsion [2] are the principle indicators of poor functional prognosis, jeopardizing the recovery of an efficient or even independent gait several months after the stroke. Our study reveals that whole brain alteration by small vessel disease is another major indicator raising fears of poor gait recovery, found the primary one in our study. The patient and the relatives must be informed, and solutions found to ensure, if possible by other ways, an independent mobility (wheelchair), with a house adapted as early as possible to prepare for discharge (to not inappropriately extend the length of stay). More positively, a reasonable short length of stay may be expected for individuals with no or sparse WMHs. An intact brain parenchyma outside the stroke should facilitate brain plasticity and recovery. We do not know whether a rigorous mastering of small-vessel disease risk factors might have a positive effect on long-term balance and gait recovery. With this hope at least for individuals with moderate forms, a systematic detection of WMHs after stroke is useful to treat the accessible risk factors. With a therapeutic education leading to appropriate lifestyle modification

[42], this should be a major challenge during the stay in the rehabilitation ward.

For research, our study suggests that stratifying trials of post-stroke balance and gait rehabilitation by level of WMH severity could be relevant. This stratification has been performed rarely, which might contribute to the high rate of negative trials in the field. MRI should be more systematically considered in this context. CST disruption is an important factor increasingly being taken into account to explain a poor recovery [45,51]. Our study suggests adding WMHs as another possible brain imaging biomarker of post-stroke recovery, at least for balance and gait.

#### 4.6. Limitations

We used the Fazekas scale to quantify WMHs alterations, so we partly assessed MRI signs of small vessel disease and did not quantify WMHs in specific areas (periventricular or deep white matter) but rather hemisphere globally (side opposite the stroke). The Fazekas scale classifies individuals into 4 grades. Because of the limited number of individuals in grades 0 and 3, we merged grades 0 and 1 (no/mild WMHs) and grades 2 and 3 (moderate/severe WMHs). With this procedure that is frequently adopted [15,34], sample sizes were satisfactory in both groups (124 vs. 86), ensuring clear and robust conclusions. However, the specific impact of grades 0 and 3 on balance and gait recovery remained unanswered. We do not frequently admit individuals > 80 years old in our ward for rehabilitation after stroke, which explains why individuals of our series are among the youngest in the literature, with a relatively low prevalence of Fazekas grade 3. The ceiling effects of PASS and mFMA scores might be considered another limitation of the study. This is why we did not use scores but rather endpoints, analyzed with Cox regression models and Kaplan–Meier survival tests. The generalizability of our findings is limited to post-stroke rehabilitation [1,52]. In this context, the results seem generalizable because participants had the usual demographic, cardiovascular and clinical factors associated with WMHs.

### 5. Conclusions

After stroke, WMHs alter balance and gait recovery and increase the number of fallers. These findings appeal for a systematic detection of WMHs in post-stroke rehabilitation, both in routine practice and research. In routine practice, knowing the existence and severity of WMHs should help establish the prognosis in terms of mobility recovery. For research, our study highlights the interest of a stratification by WMH grades for trials of balance and gait rehabilitation.

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#### Disclosure of interest

The authors declare that they have no competing interest.

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**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.rehab.2021.101488>.

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# Disability in adults with arthrogryposis is severe, partly invisible, and varies by genotype

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## Abstract

### Objective

To understand the disability of adults with arthrogryposis multiplex congenita (AMC), a rare disease spectrum characterized by at least 2 joint contractures at birth in different body areas.

### Methods

This is a retrospective analysis of data for unselected persons with AMC referred to the French center for adults with AMC from 2010 to 2016. All underwent a pluriprofessional systematic and comprehensive investigation of deficits, activity limitation, and participation restriction according to the International Classification of Functioning, Disability and Health and genetic analysis when indicated. Participants were divided by amyoplasia and other AMC types.

### Results

Mean (SD) age of the 43 participants (27 female) was 33.2 (13.4) years; 28 had amyoplasia and 15 other types of AMC. Beyond joint stiffness, deformities, and muscle weakness, the well-known core symptoms that we quantified and for which first-line treatment involved technical aids, other less visible disorders that could contribute to severe participation restriction were particularly pain and psychological problems including anxiety, fatigue, difficulty in sexual life, altered self-esteem, and feelings of solitude. Severe respiratory disorders were infrequent and were linked to *PIEZO2* mutations. Gait disorders were not due to respiratory impairment but to skeletal problems and were always associated with amyoplasia when severe. Functional independence was worse but respiratory and swallowing capacities were better with amyoplasia than other AMC types.

### Conclusion

This study describes disability patterns of a cohort of adults with AMC by genotype. The disability of adults with AMC is influenced by genotype, with important invisible disability.

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Coinvestigators are listed at [links.lww.com/WNL/A499](https://links.lww.com/WNL/A499)

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## Glossary

**6MWT** = 6-minute walk test; **AMC** = arthrogryposis multiplex congenita; **DA** = distal arthrogryposis; **FAC** = Functional Ambulation Classification; **FIM** = Functional Independence Measure; **FVC** = forced vital capacity; **HADS** = Hospital Anxiety and Depression Scale; **ICF** = International Classification of Functioning, Disability and Health; **PROM** = passive range of motion.

Arthrogryposis multiplex congenita (AMC) refers to a rare disease spectrum characterized by the presence of at least 2 joint contractures at birth in different body areas. Causes of AMC are numerous and imply the neuromuscular system or CNS or connective or bone tissue.<sup>1</sup> Amyoplasia, a sporadic condition occurring in 1/10,000 live births,<sup>2</sup> is the most frequent type, followed by neuromuscular causes presenting mainly as distal arthrogryposes of genetic origin.<sup>3</sup> Most apparent clinical deficits are joint deformities and muscle weakness or wasting, responsible for activity limitations and disabilities. Disability patterns have almost exclusively been reported in early age,<sup>4–6</sup> and little is known about disability during adulthood, despite recent interest.<sup>7–9</sup>

We present an extensive study investigating disability in a cohort of adults with AMC, analyzed according to the International Classification of Functioning, Disability and Health (ICF) by phenotype and genotype.

## Methods

### Design

This was a retrospective study of a cohort of people with AMC referred to the French reference center for adults with AMC (Genetic and Neurorehabilitation Departments, University Hospital Grenoble-Alpes, France), in whom deficits, activity limitations, and participation restrictions were systematically analyzed according to the ICF. Details on the study design are given in figure 1.

### Standard protocol approvals, registrations, and patient consents

The study was performed in compliance with the Helsinki Declaration. All participants provided informed consent. According to French law, as a noninterventional (observational) study, this research did not require approval by an ethics committee.

### Participants

If no theoretical sample size was calculated, we decided a priori to wait for a sufficient recruitment of 40 participants with AMC to retrospectively analyze their data. In total, 46 participants with AMC were assessed from 2010 to 2016 (figure 1), and retrospective data analysis was conducted in 43 (3 medical files unexploitable). They lived in France and had many ethnic origins. They were divided into 2 subgroups according to clinical signs and molecular diagnosis: 28 with amyoplasia and 15 with other types of AMC, including 10 with distal arthrogryposis (DA), 1 multiple pterygium

syndrome (compound heterozygous *CHRNA2* mutation), 2 dominant Larsen syndrome (heterozygous *FLNB* mutation), and 2 neurogenic without clinical or molecular diagnosis. Among participants with DA, 5 had heterozygous mutations in *PIEZO2*, 2 a homozygous mutation in *ECEL1*, and 2 heterozygous mutations in *TNNT3* and *MYH3*, respectively. One participant with DA did not show any pathogenic variant in the currently known genes involved in DA.

### Disability assessments

All participants underwent a 4-day multidisciplinary evaluation involving physicians (geneticist, physical medicine and rehabilitation physician, pulmonologist), a psychologist, physiotherapists, occupational and speech therapists, and nurses. Systematic assessments involved free and semi-structured interviews, analysis of the medical history in available medical records, clinical examination, and a battery of tests. These assessments were guided by the ICF<sup>10</sup> and aimed at analyzing participation restriction, activity limitations, and deficits.<sup>11</sup> All details are presented in the supplemental Methods ([links.ww.com/WNL/A408](https://www.ww.com/WNL/A408)).

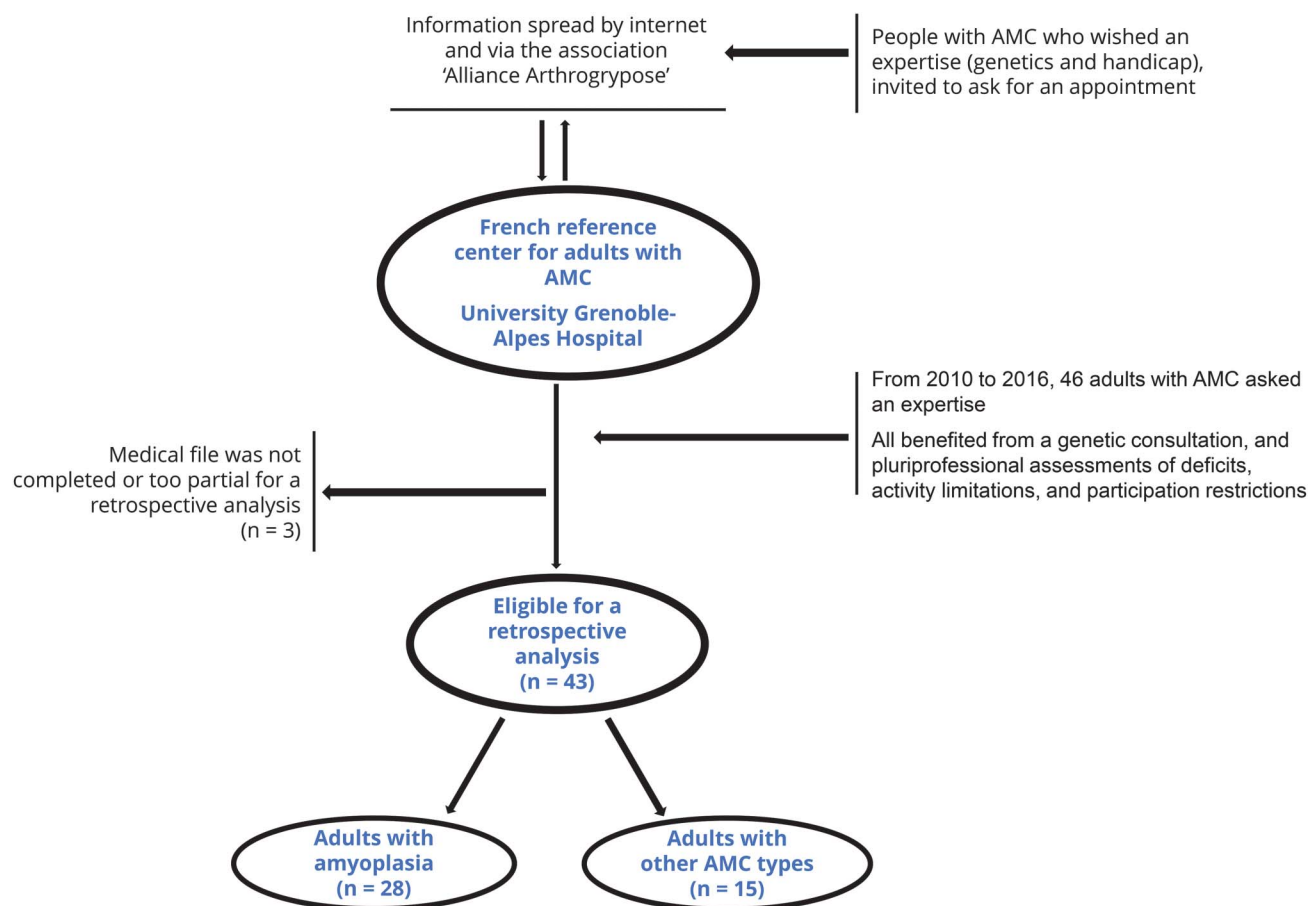
Muscular deficits of all main muscles of the 4 limbs were assessed by the Medical Research Council scale (0–5) for muscle strength<sup>12</sup> and a JAMAR dynamometer (Sammons Preston, UK) for grip strength.<sup>13</sup> For the latter test, participants were instructed to hold the dynamometer and apply maximal grip force. Three trials were performed for each hand, then averaged.

Passive range of motion (PROM) was investigated for all main joints by conventional clinical examination and quantified in degrees. To build a clear picture of joint stiffness, range of motion was classified into 4 grades for each joint: 1, normal range; 2, moderate limitation <50% of normal PROM; 3, major limitation ≥50% of normal PROM; and 4, ankylosis (almost no movement).

Respiratory impairment was evaluated. Spirometry involved standardization of the European Respiratory Society.<sup>14</sup> Briefly, maximal lung volume (forced vital capacity [FVC]) and mean forced expiratory volume in 1 second were derived from 3 reproducible maneuvers. Measured values were expressed in percentage of normative value for sex, height, and age. One participant was unable to perform spirometry because of tracheostomy. For 3/40 participants (7.5%), spirometry data were not available.

Frequency and nature of pain were both assessed by the physicians and the psychologist. When required, the

**Figure 1** Flowchart of the study



AMC = arthrogyposis multiplex congenita; ICF = International Classification of Functioning, Disability, and Health.

psychologist also quantified psychological problems by the Hospital Anxiety and Depression Scales (HADS).<sup>15</sup>

Functional Independence Measure (FIM)<sup>16</sup> was used to assess activity in daily living. Total FIM scores (range 18–126) were analyzed together with the cognitive and motor domains.

In addition to specific FIM items, mobility was assessed by the 6-minute walk test (6MWT)<sup>17</sup> and the Functional Ambulation Classification (FAC), with classes from 0 to 5, 5 being independent walking anywhere.<sup>18</sup> The normative values were from the American Thoracic Society.<sup>19</sup> In addition to specific FIM items, prehension was assessed by ad hoc reaching and grasping tests (supplemental Methods, [links.lww.com/WNL/A408](https://links.lww.com/WNL/A408)).

### Statistical analysis

Statistical analysis involved use of SPSS 20.0. Continuous data with normal distribution were analyzed by Student *t* test and otherwise by Mann-Whitney *U* test. Categorical data were analyzed by  $\chi^2$  or Fisher exact test. Data are presented as mean (SD) for Gaussian distributions and median (quartile 1–3 [Q1–Q3]) otherwise. Significance level was set at  $p < 0.05$ .

Chi-square test was used to compare FIM items by dependence rank, regrouped as independence (score 7, complete independence, and score 6, modified independence) and dependence (score 5, need supervision, and score 1–4, need human help).

### Data availability statement

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

## Results

Forty-three individuals with AMC (27 female; 28 with amyoplasia) were assessed from 2010 to 2016. Age was 33.2 (13.4) years. Height, weight, and body mass index were 156.5 (7.5) cm, 57.7 (12.5) kg, and 23.5 (5.0) kg/m<sup>2</sup>, respectively.

### History of surgery

All participants except one had a history of surgery, especially foot–ankle functional surgery (including 2 who had ankle arthrodesis). Two participants had spine arthrodesis. The other surgical sites concerned elbows, wrists, hands, hips, and

knees, with a functional objective or after a fracture. Ptosis surgery was noted in one participant with *ECEL1* mutation.

## Impairments

### Muscle weakness

Data for muscular testing are presented in figure 2. All main muscles showed some degrees of weakness, with a mean grade of testing of 3–4/5. Muscular deficits were greater with amyoplasia than other AMC types, especially ankle muscles, which were very weak ( $p < 0.001$ ). In participants with amyoplasia, about half of the muscles were not functional (score <3). Grip strength score measured by a hand dynamometer was weaker with amyoplasia than other AMC types (12 [0–20] vs 29 [9–36];  $p = 0.03$ ).

### Joint stiffness and deformities

Data are presented in figure 3. Passive movements were limited at all joints, with major limitations (stiffness) more frequent in the lower limbs (hips, knees, ankles), where joint stiffness was more severe with amyoplasia than other AMC types. Ankylosis (impossible passive movement) was found mostly on more distal joints: fingers, ankle, and toes. Joint limitations were symmetrical.

### Respiratory impairment

Respiratory function was variable. Three participants, all with *PIEZO2* mutations, needed night ventilation (1 invasive with tracheotomy, 2 noninvasive with a mask). Respiratory impairment, defined as FVC <80% predicted, was of mixed origin, neuromuscular and orthopedic (scoliosis). Five participants showed exertional dyspnea: 3 with amyoplasia and 2 with other

types (1 with *CHRNA3* mutation and 1 *FLNB* mutation). In all 35 participants explored, ventilatory measures were generally satisfactory. FVC was 3.1 L (2.4–4.1) (i.e., 95% of predicted values, for sex, age, and height). Only 2 participants with heterozygous *PIEZO2* mutation had limitations in vital capacity (0.47 and 0.5 L), both with severe kyphoscoliosis requiring noninvasive ventilation. Respiratory function was better with amyoplasia than other AMC types (FVC 3.8 [3–4.3] vs 2.2 [1.4–2.7],  $p < 0.001$ ).

### Disorders in bladder and bowel control

Seven participants (16%) had urinary disorders, 4 with amyoplasia and 3 with other AMC types. Urinary incontinence was the most frequent syndrome. Other problems were chronic urinary infection and dysuria. Three participants (7%) with amyoplasia had bowel control disorders: 1 was totally incontinent and needed permanent garments and 2 required frequent washing because of constipation. We were not able to assess any relationship between these symptoms and the existence of gastroschisis or bowel atresia, especially in participants with amyoplasia in whom these malformations have been described.<sup>2</sup>

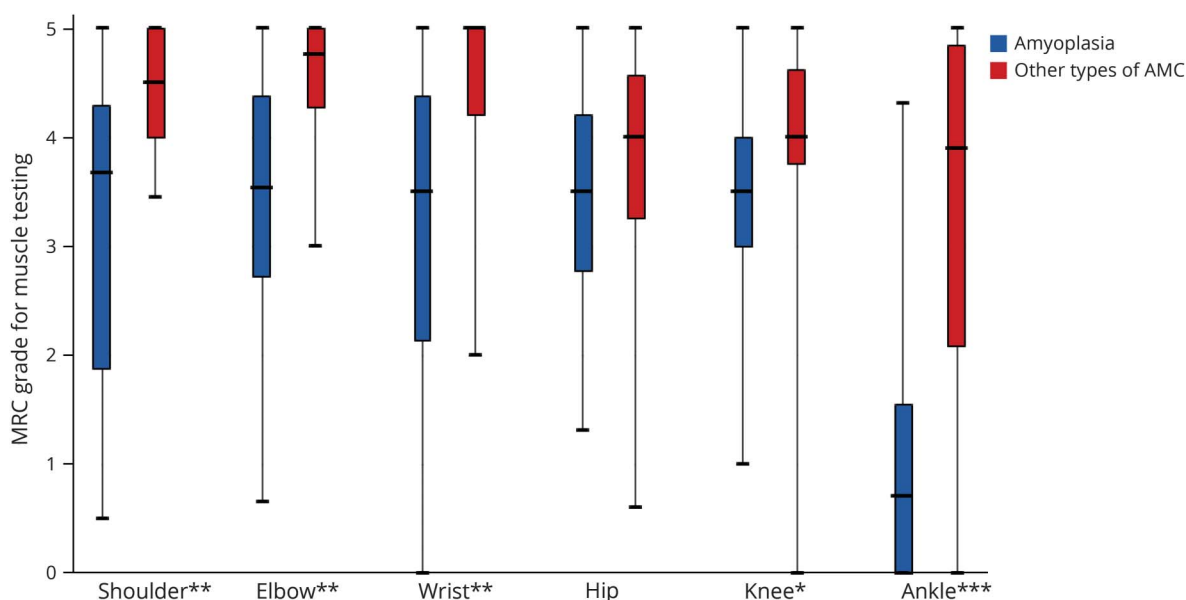
### Swallowing and speech disorders

Data are presented in table 1. Many participants showed chewing, swallowing, or articulation problems or hypophonia. Almost 1 in 3 participants had limited mouth opening. Swallowing and speech disorders were less frequent with amyoplasia than other AMC types.

### Pain and psychological problems

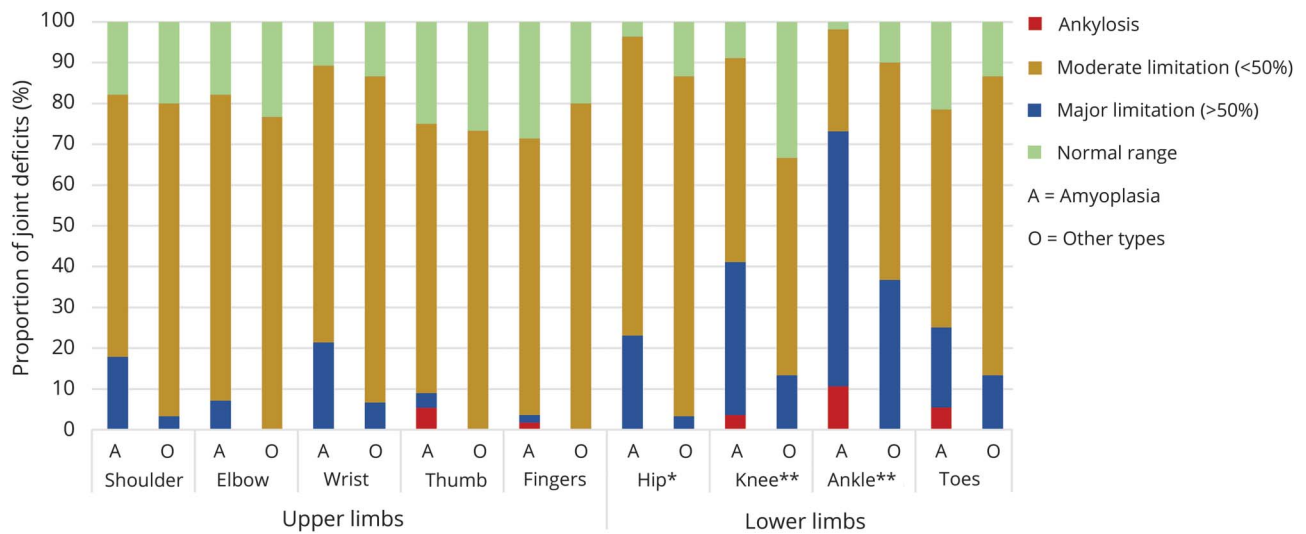
Overall, 39 participants complained of pain (91%). Pain was chronic (sometimes since childhood), with psychological

**Figure 2** Muscular deficits



Muscular deficits in participants with amyoplasia and other arthrogryposis multiplex congenita (AMC) types. MRC grade: Medical Research Council scale for muscle strength. Box plots are median, quartiles 1 to 3, and extreme values. \* $p < 0.05$ ; \*\* $p < 0.01$ , \*\*\* $p < 0.001$  between amyoplasia and other AMC types.

**Figure 3** Joint deficits



Proportion of joint deficits in participants with amyoplasia and other arthrogryposis multiplex congenita (AMC) types. Joint mobility was assessed passively, for both body sides, in all participants. \* $p < 0.05$ , \*\* $p < 0.01$  between amyoplasia and other AMC types.

consequences (half of participants), and often reported as an activity-limiting factor. Pain had muscular and articular origins, was magnified by exercise, and especially was located in the trunk (spine area) and lower limbs, less often in the upper limbs. Pain prevalence and location did not differ between groups (table 2).

In addition to the psychological dimension of pain, the main psychological problems were anxiety (43% with HADS >10 for anxiety subscore; with a median 9 [6–19]), fatigue (34%), difficulty in sexual life (24%), altered self-esteem (17%), and a feeling of solitude (15%). These difficulties affected work or study for 17% of participants and planning parenthood for 7%. The prevalence of depression was low, with HADS depression subscore 3 (1–6). The 2 groups did not differ in psychological problems (table 2).

### Activity limitations

#### Independence in daily life

As shown in figure 4, most participants had modified independence, with mean FIM score 113 (13.9), out of 126 possible. FIM scores were lower with amyoplasia than other

AMC types (110.4 [16.3] vs 118.1 [4.8],  $p = 0.026$ ), for less independence in daily life. Nearly all participants had high scores for the cognitive component of the FIM (34.8 [0.6], out of 35 possible). The mean motor component of the FIM was altered (78.3 [13.4], out of 91 possible) and lower with amyoplasia than other AMC types (75.6 [15.8] vs 83.2 [4.6],  $p = 0.024$ ). Figure 4 is the conventional representation of independence for all FIM items, showing that tasks dealing with personal care and mobility (especially climbing stairs) were the most affected. These are further analyzed below.

#### Mobility

Most participants with AMC (88%) could walk independently. However, the 5 (12%) who were not independent in ambulation all had amyoplasia (3 were not able to walk at all, and 2 could walk with help from one person). However, the FAC score did not differ with and without amyoplasia: 4.5 (4–5) vs 5 (4–5). The analysis of FIM items (tables e-1 and e-2, [links.lww.com/WNL/A407](https://www.lww.com/WNL/A407)) showed that only 37% of participants were totally independent in ambulation (walk or wheelchair). Transfers required a technical aid

**Table 1** Swallowing and speech deficits in participants with amyoplasia and other types of arthrogryposis multiplex congenita (AMC; 41 participants were assessed, data for 2 with amyoplasia were missing)

	All AMC, n (%)	Amyoplasia, n (%)	Other AMC types, n (%)	<i>p</i> Value
Limited mouth opening (<3 fingers ≈40 mm)	13 (31.7)	7 (26.9)	6 (40)	0.386
Chewing problems	13 (31.7)	7 (26.9)	6 (40)	0.386
Swallowing problems	6 (14.6)	2 (7.7)	4 (26.7)	0.157
Hypophonia	7 (17.1)	1 (3.8)	6 (40)	0.006
Articulation	5 (12.2)	3 (11.5)	2 (13.3)	1.000

**Table 2** Pain and psychological problems in participants with amyoplasia and other types of arthrogryposis multiplex congenital (AMC)

	All AMC, n (%)	Amyoplasia, n (%)	Other AMC types, n (%)	p Value
<b>Pain<sup>a</sup></b>	39 (90.7)	25 (89.3)	14 (93.3)	1.000
<b>Location</b>				
<b>Trunk</b>	31 (72.1)	21 (75.0)	10 (66.7)	0.561
<b>Lower limbs</b>	24 (55.8)	17 (60.7)	7 (46.7)	0.377
<b>Upper limbs</b>	8 (18.6)	5 (17.9)	3 (20.0)	1.000
<b>Psychological problems<sup>b</sup></b>				
<b>Anxiety</b>	10 (43.5)	7 (53.8)	3 (30.0)	0.402
<b>Depression</b>	1 (4.3)	0 (0)	1 (10.0)	0.435
<b>Fatigue</b>	14 (34.1)	10 (37.0)	4 (28.6)	0.734
<b>Difficulty in sexual life</b>	10 (24.4)	5 (18.5)	5 (35.7)	0.224
<b>Altered self-esteem</b>	7 (17.1)	5 (18.5)	2 (14.3)	1.000
<b>Feeling of solitude</b>	6 (14.6)	3 (11.1)	3 (21.4)	0.393
<b>Work or study affection</b>	7 (17.1)	4 (14.8)	3 (21.4)	0.673
<b>Difficulty in planning parenthood</b>	7 (7.3)	2 (7.4)	1 (7.1)	1.000

<sup>a</sup> All participants were assessed.

<sup>b</sup> 41 Participants were assessed with a structured interview, and 23 quantitatively using the Hospital Anxiety and Depression Scale.

for more than one-third of participants. The greatest difficulties were in climbing stairs: only 19% were completely independent, 58% had modified independence (technical aid), and 23% required human help. Of note, all participants requiring human help had amyoplasia, and independence in climbing stairs was lower with amyoplasia than other AMC types. The walking distance assessed with the 6MWT was lower than expected for this age (450 meters), without significant difference between amyoplasia and other AMC types (300 [120–414] vs 350 [337–375] meters). The 8 participants with respiratory impairment had a limited walking distance (268 [208–356] meters), comparable to that for other participants (317 [210–428] meters;  $p = 0.45$ ).

### Prehension and personal care

Assessing reaching and grasping abilities with ad hoc tests showed that the reaching function was altered, especially with amyoplasia (13 [6–16] vs 16 [15–16];  $p = 0.037$ ), whereas grasping function was relatively preserved (20.5 [15.8–22] with amyoplasia vs 22 [20.5–22] with other AMC types;  $p = 0.087$ ). The analysis of FIM items (supplemental Methods, [links.lww.com/WNL/A408](https://links.lww.com/WNL/A408)) showed that fewer than half of participants had complete independence for different items, and only 30%–50% reached modified independence with a technical aid. The proportion of participants who needed human help was relatively high (15%–30%). Participants with amyoplasia tended to be more dependent than those with other AMC types, significantly for eating and bathing (supplemental Methods).

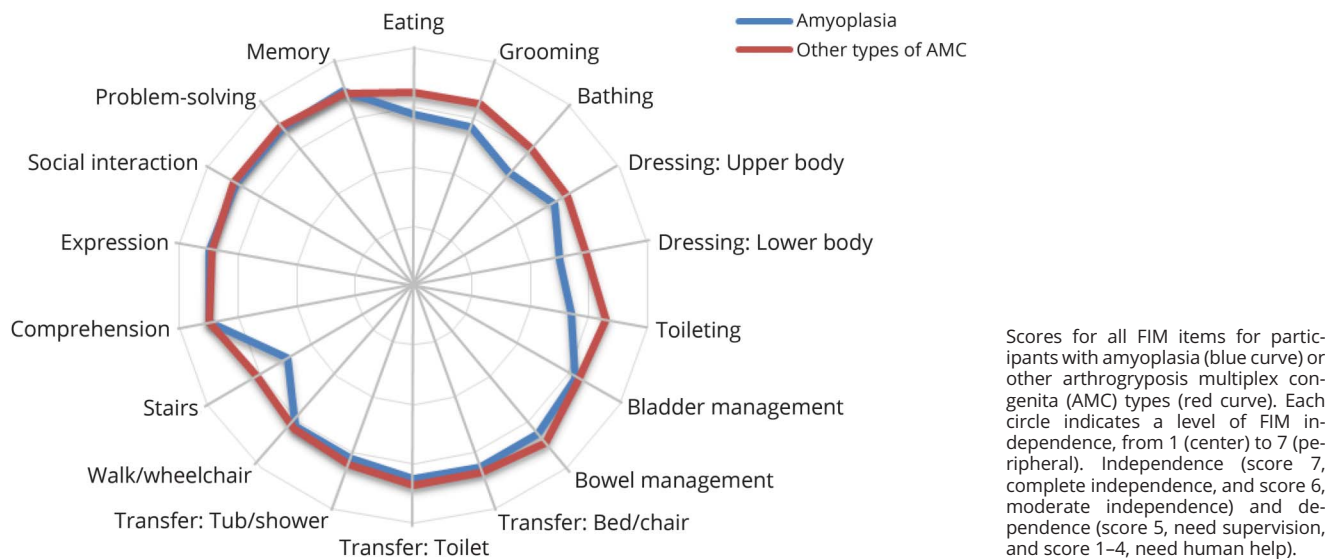
### Participation restriction

All but one participant lived at home, and only one lived in a residence for disabled persons; 23% were students. The ability to work was much altered by the disease, similarly with amyoplasia and other AMC types: 26% could not find a suitable job because of their disabilities, and among the 51% who had a job, most (60%) needed an arrangement of the workplace or time. Only 23% were able to work normally. About one-third (35%) were unable to drive a car, with higher prevalence with amyoplasia than other AMC types (46% vs 13%,  $p = 0.03$ ). Aids were required for most participants: technical aids for 50% (wheelchair for 35%, electrical wheelchair 28%, manual wheelchair 7%, crutches or orthopedic shoes 14%) and human aid for 40%. Requiring technical aids was more frequent with amyoplasia than other AMC types (61% vs 27%,  $p = 0.05$ ).

### Discussion

Despite a recent interest to define the consequences of AMC in terms of disorders and disability in adulthood,<sup>7–9</sup> cohort studies have mainly focused on the genetics or surgery for skeletal deformations in childhood until now. Our study extensively investigates the disability of adult people with arthrogryposis in terms of phenotypes and genotypes. We retrospectively analyzed data for 43 participants followed at the French reference center for adults with AMC, from 2010 to 2016 (unselected participants except for AMC diagnosis):

**Figure 4** Representation of Functional Independence Measure (FIM) scores



28 with amyoplasia and 15 with other AMC types. Assessments were performed according to a protocol that followed the ICF, with the view of quantifying deficits and activity limitations in all health domains, and participation restriction.

Frequent history of surgery was stressed in an international survey,<sup>9</sup> reporting between 5 and 10 surgeries for one-quarter of adults with AMC and more than 9 for one-third. We showed that the ankles and feet were mostly operated on (79%). Few adults with AMC have not had surgery: 7% in recent research<sup>9</sup> and 2% in ours. We found a proportion of unemployed participants similar to that previously reported,<sup>9</sup> and few participants were able to work full-time without adaptation. Almost all lived at home, but 40% required a human aid, overall for toileting, bathing, and eating. Half required a technical aid, overall for mobility, and almost one-third needed an electric wheelchair. However, participants with amyoplasia and other AMC types did not differ in the need for technical help. One-third were unable to drive an adapted car (mostly those with amyoplasia), a little less than the 44% previously reported in an orthopedic clinic.<sup>7</sup>

Our study revealed that the invisible part of the disability was severe. First, chronic pain seemed to be more prevalent (9/10 participants via structured interviews) than in a previous study assessing pain with the Medical Outcomes Study Short Form 36 (75% of participants).<sup>9</sup> Both studies reported the spine region as the most frequently concerned, with consequences on daily life remaining to be investigated. Second, psychological difficulties of many participants were discovered: anxiety (43%), fatigue (34%), difficult sexual life (24%), altered self-esteem (17%), and feeling of solitude (15%). These findings are similar to the social difficulties already reported.<sup>9</sup> Specific supports, care, and follow-up should be more systematically

proposed with AMC, ideally from childhood. Depression prevalence was low, presumably because the disease was congenital and participants had come to terms with it. Many other troubles contribute to the invisible part of the disability of adults with AMC, especially the speech and swallowing disorders found more frequently with other AMC types than amyoplasia, as well as incontinence. These troubles were well-reported in children with AMC<sup>20–22</sup> but rarely reported in adults.

Our study systematically assessed all aspects of the most visible part of the disability of adults with AMC, and compared muscle weakness and joint stiffness by AMC types, finding greater deficits with amyoplasia than other types, particularly in the lower limbs. This finding explained why mobility and participation were more altered with amyoplasia than other types.

Because participants with and without ventilatory impairments showed comparable walking distance, the limitations in walking distance we found were not due to respiratory impairment but rather to weakness, pain, stiffness, and related skeletal deformities. These findings agree with a former study,<sup>4</sup> which found in 35 children with amyoplasia (age 5 years) that the strongest predictor of walking ability was muscle strength (better than limitations in joint range of motion). In our study, 5 participants (12% AMC) were not able to walk without human help. This proportion is comparable to the 15% nonambulant children with AMC found in a series of 38 children reported precendently.<sup>23</sup> Our study also reveals that almost 1 in 5 participants with amyoplasia is nonambulant in adult age. This is a major source of disability in people with amyoplasia.

We point out a specific difficulty in climbing and descending stairs. All participants with other AMC types were independent

in negotiating stairs, whereas more than one-third (36%) with amyoplasia needed human help with stairs (supervision or help). This ability should be a specific target for intervention at home to help with autonomy. This greater activity limitation with amyoplasia than other AMC types was also found for prehension, which explained the more severe restriction of participation discussed previously.

Ventilatory deficits had never been investigated in adults with AMC. Overall, 23% of participants showed respiratory disorders, without a clear-cut difference between amyoplasia and other types. These findings highlight that respiratory impairment is far from negligible in adults with AMC and requires further attention and systematic assessment. Causes likely combine severe trunk deformity, sedentary lifestyle, and respiratory muscle contractile dysfunction. However, the median FVC was high (95% predicted), which excludes respiratory muscle weakness in most participants. The existence of hypophonia and wheeziness in some participants is likely linked to respiratory impairment and needs to be systematically investigated. The 3 participants (9%) who required night ventilation all had heterozygous *PIEZO2* mutations. Severe restrictive respiratory disease has been described in participants with *PIEZO2* mutations.<sup>24–26</sup> It occurs even in the absence of spinal deformities and therefore is an intrinsic feature of *PIEZO2*-related AMC.

The main limitation is related to the retrospective analysis of data obtained by participant reports, even if participants were prospectively assessed with a battery of systematic tests set with the activity of the French reference for AMC. With this procedure and the weak turnover of examiners, results were reliable, with few data missing (ventilatory assessment in 35/43 participants). An important difficulty was in assessing muscle weakness and joint stiffness when joints had severe deformities or had undergone surgery. The great experience of therapists involved in the assessments limited this problem, which was also attenuated by a choice of adapted indices in view of statistical analyses. However, because of this retrospective approach focused on the disability, we were not able to draw any relationship between bowel symptoms and possible malformation. One may question the generalizability of these findings. The results might be biased by entry in the study, individuals with the most severe forms of AMC being possibly more inclined than others to consult the National Center for AMC to obtain solutions to their problems. This would thus overestimate the disability of people with AMC living in the community. In contrast, this disability would have been underestimated by the fact that people with most severe forms of AMC die in childhood, or that it would be especially difficult for them to come for a consultation. These possible biases should be counterbalanced, and the findings should have satisfactory generalizability, at least at the scale of one European country.

In adults with AMC, beyond muscle weakness and joint stiffness, the well-known core symptoms precisely assessed

here and for which the first-line treatment was technical aids to improve autonomy, we show that other less visible disorders contribute to severe activity limitations and participation restriction. Particularly, pain and psychological difficulties should be better assessed and treated. Overall, we underscore the need to consider specific phenotypes and genotypes in managing disability in adults with AMC.

## Author contributions

Shenhao Dai: data collection (neurorehabilitation part), analysis and interpretation of data, writing of the first draft of the paper. Klaus Dieterich: study concept and design, data acquisition and collection (genetic part), writing of the manuscript. Marie Jaeger: acquisition of data (neurorehabilitation part), revision of manuscript for intellectual content. Bernard Wuyam: data acquisition and collection (respiratory part). Pierre-Simon Jouk: study supervision. Dominic Pérennou: study concept and design, data interpretation, writing of the manuscript.

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## Disclosure

The authors report no disclosures relevant to the manuscript. Go to [Neurology.org/N](http://Neurology.org/N) for full disclosures.

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**Disability in adults with arthrogyrosis is severe, partly invisible, and varies by genotype**

Shenhao Dai, Klaus Dieterich, Marie Jaeger, et al.  
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# Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

## Editors' note: Disability in adults with arthrogryposis is severe, partly invisible, and varies by genotype

In "Disability in adults with arthrogryposis is severe, partly invisible, and varies by genotype," Dai et al. reported that disability patterns in a cohort of adults with arthrogryposis multiplex congenita were influenced by genotype, with important invisible disability. In response, Drs. Sawatzky et al. contend that the data emphasized the patients' "negatives" and that such language may lead readers, including the general public, to underestimate patients' capabilities to lead meaningful lives. In their rebuttal, the authors contend that they followed international recommendations for unbiased reporting of their findings, and argue that it is the role of physicians to translate such findings into appropriate and personalized terms for patients and their families.

Aravind Ganesh, MD, and Steven Galetta, MD  
*Neurology*® 2019;92:635. doi:10.1212/WNL.0000000000007167

## Reader response: Disability in adults with arthrogryposis is severe, partly invisible, and varies by genotype

Bonita Sawatzky (Vancouver, Canada) and Judith G. Hall (Vancouver, Canada)  
*Neurology*® 2019;92:635. doi:10.1212/WNL.0000000000007168

Dai et al.<sup>1</sup> published a report of a long-term comprehensive follow-up of adults with arthrogryposis from their specialized clinic, perhaps the first such clinic in the world. They published valuable information, but emphasized the patients' negatives rather than their strengths, which raised a red flag about how we, as researchers, write and publish findings. Language and tone that we use in our literature makes a difference. In modern clinical literature, it must inspire physicians to use positive language with their patients, encouraging patients to become healthier and independent, despite their disabilities. How patient data are portrayed in our literature matters since more patients and families access our work. Dai et al. writes about impairment rather than function. If a parent were to read this article, he or she would think his or her child will become a miserable adult not able to do much, but other arthrogryposis studies refute this.<sup>2-4</sup> Adults with disabilities must be encouraged to get an education and live as independently as possible, joint limitations or not. If negative attitudes continue in health care literature, our patients will have little hope in their future or faith in us who are supposedly working on their behalf.

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## Author response: Disability in adults with arthrogryposis is severe, partly invisible, and varies by genotype

Shenhao Dai (Grenoble, France), Klaus Dieterich (Grenoble, France), Marie Jaeger (Grenoble, France), Bernard Wuyam (Grenoble, France), Pierre-Simon Jouk (Grenoble, France), and Dominic Pérennou (Grenoble, France)

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In their comment on our article,<sup>1</sup> Drs. Sawatzky and Hall discuss how to positively or negatively describe a handicap, in terms of either ability or disability, and how to inform patients. We refer to the International Classification of Functioning, Disability and Health,<sup>2</sup> edited with the aim to provide a unified and standard language for describing health and health-related states. Medical writing is also subject to international recommendations to ensure clear, ethical, and unbiased reporting of scientific findings,<sup>3</sup> and this is also true for rare diseases. We followed these recommendations and reject any allegation of a negative attitude in our article.<sup>1</sup>

Although patients and families easily access medical literature these days, it is our role to assist them, translate what is too technical in simple words, and give all explanations they need and request, with the help of a psychologist. The time is past to not deliver comprehensive information. This is what is called a “handicap announcement,” which helps patients adapt their life. In our arthrogryposis clinic, the main demand is for appropriate and personalized information. In the end, the degree of satisfaction of these individuals is very high, and this is more important to us than publishing an article.

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### Editors' note: A family-based study into penetrance in facioscapulohumeral muscular dystrophy type 1

In “A family-based study into penetrance in facioscapulohumeral muscular dystrophy type 1,” Wohlgenuth et al. identified many asymptomatic mutation carriers by careful examination of facial and shoulder muscles, noting that such recognition is essential for participant selection for future trials. In response, Drs. Brignol and Urtizberea suggest that examining for often-asymptomatic retinal vasculopathy using techniques like optical coherence tomography angiography may help further characterize genotype–phenotype correlations in facioscapulohumeral muscular dystrophy. They call for greater collaboration between neurologists and ophthalmologists in this regard. In their reply, the authors express agreement and note that they are currently pursuing an observational study of retinal abnormalities in another cohort.

Aravind Ganesh, MD, and Steven Galetta, MD  
*Neurology*® 2019;92:636. doi:10.1212/WNL.0000000000007170

## Reader response: A family-based study into penetrance in facioscapulohumeral muscular dystrophy type 1

Tuy Nga Brignol (Evry, France) and J. Andoni Urtizberea (Marseille, France)  
*Neurology*® 2019;92:637. doi:10.1212/WNL.00000000000007172

We read with interest the article reporting on facioscapulohumeral muscular dystrophy (FSHD) type 1 probands and their relatives. Penetrance of FSHD, based on muscle symptoms, depends on D4Z4 repeat size and continues to increase in adulthood.<sup>1</sup> It would be interesting to study the penetrance of retinal vasculopathy in this family by using optical coherence tomography angiography, a noninvasive imaging technique that acquires volumetric angiographic information without the use of a dye. Indeed, according to the existing literature, only a systematic examination of eye fundus can detect telangiectasia and aneurysms, which may be present early in life before evidence of muscle disease.<sup>2</sup> Very few complaints related to retinal alteration have been reported by patients with FSHD, as retinal lesions rarely affect the macula. A more severe retinal vasculopathy, known as Coats-like retinopathy, is observed by fluorescein angiography in 40%–75% of patients with FSHD. However, retinal findings prior to the diagnosis of FSHD are only detected in very rare cases.<sup>3–5</sup>

In lieu of these data, interdisciplinary collaborations between neurologists and ophthalmologists are important—not only for diagnostic and counseling viewpoints, but also to better understand the relation between genotype and phenotype, and mechanisms that regulate expression.

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## Author response: A family-based study into penetrance in facioscapulohumeral muscular dystrophy type 1

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We thank Drs. Brignol and Urtizberea for the comment on our article.<sup>1</sup> We agree that retinal abnormalities are an interesting additional mode to study the penetrance of facioscapulohumeral dystrophy (FSHD). Indeed, we are currently performing an observational study on retinal abnormalities in another cohort of patients with FSHD. We acknowledge that a family-based approach would offer additional insights. Also, we agree that interdisciplinary collaborations enhance our understanding of the pathophysiology and optimal care for patients.

1. Wohlgenuth M, Lemmers RJ, Jonker M, et al. A family-based study into penetrance in facioscapulohumeral muscular dystrophy type 1. *Neurology* 2018;91:e444–e454.

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