Lateropulsion with active pushing in stroke patients : its link with lesion location and the perception of verticality: a systematic review

Lateropulsion with active pushing in stroke patients: its link with lesion location and the perception of verticality. A systematic review

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Abstract

Background: Lateropulsion with active Pushing (LwP) is characterized by impairments in postural control. Previous research suggests an association between LwP, lesion location and verticality misperception. This first-ever systematic review evaluates the association between LwP, lesion location and the perception of verticality (PROSPERO: CRD42020159248).

Methods: Pubmed, Web of Science, REHABDATA, Embase, Cochrane Library and PEDro were systematically searched on December 16th, 2021. Studies were included when examining lesion location or perception of verticality (Subjective Haptic, Visual or Postural Vertical) in supratentorial stroke patients showing LwP . Two reviewers independently screened and assessed risk of bias using the Newcastle Ottawa Scale. Data was qualitatively analysed and extracted.

Results: Nineteen studies were included, examining a total of 340 LwP patients. Lesions in: the thalamus, internal capsule, inferior parietal lobule at the junction of the postcentral gyrus, the posterior insula and the superior temporal gyrus, were associated with LwP. Whereas all studies examining the Subjective Postural and Haptic Vertical (haptic only examined once) reported a significant increased deviation in LwP patients, inconsistent results were found for the Subjective Visual Vertical. Furthermore, the Subjective Visual and Postural Vertical showed inconsistent results for magnitude, direction and variability of this deviation.

Discussion: A complex brain network, rather than only one brain region, seems responsible for body control with respect to gravity. A disruption within this network might lead to a bias in the construction of a correct internal reference frame, crucial for perceiving verticality. There was an association of LwP with verticality misperception in all three modalities.

Introduction

Postural control emerges from a complex interaction of sensory, motor and cognitive processes, and is often affected by stroke [1]. Postural orientation is key for postural control, referring to the active control of body alignment in relation to support surfaces, internal references and gravitational and visual environments. Besides postural orientation, postural equilibrium is essential, involving the coordination of sensorimotor strategies to stabilize the body's centre of mass [1]. However, some patients with a supratentorial stroke show a postural tilt (either towards ipsi- or contralesional), referred to as 'lateropulsion'. In clinical practice, this is seen as a patient who leans sideways [2, 3]. Some of them additionally push themselves with their non-paretic extremities and pelvis toward the contralesional side [4, 5]. As the postural orientation of these patients is severely impaired, they resist attempts of passive correction towards or over the midline [4]. In literature, various terms are used interchangeably to refer to this behaviour: (contraversive) lateropulsion, pushing or pusher behaviour/ syndrome [4, 6, 7]. In this study, the term lateropulsion with active Pushing (LwP) will be used. LwP occurs in 10-60% of stroke patients [8, 9]. It is suggested that this broad incidence rate is due to different definitions and assessment scales used to diagnose the disorder [10, 11].

LwP mainly occurs after right-sided lesions, which corresponds to the dominance of the right hemisphere for spatial orientation [1, 12-14]. In addition, LwP is strongly associated with spatial neglect, often seen in right-sided lesions as well. This visuospatial-orientation disorder is characterized by impaired awareness of stimuli in the contralesional hemispace and is also a negative determinant for postural control [15, 16]. Besides an apparent higher affinity with right-sided lesions, a diversity of lesion locations potentially associated with LwP have been documented. This review systematically investigates these lesion locations thoroughly to increase our understanding of LwP.

Evidence suggests that a processing deficit on the higher order neuronal levels, leading to disturbances in perceiving verticality, is associated with LwP [6]. Some of the regions associated with LwP, such as the superior temporal gyrus and the parieto-insular cortex, appear to be related to verticality perception as well [7, 13, 17]. Perceiving verticality is based on the individual's internal reference frame, established by the convergence of multisensory graviceptive information (e.g. somatosensory, visual, vestibular) [18, 19]. The accuracy of verticality perception is measured through different modalities, including the subjective visual, postural and haptic verticals (respectively the Subjective Visual Vertical (SVV), Subjective Postural Vertical (SPV) and Subjective

Haptic Vertical (SHV)) [20]. Previous research suggest that a disturbed perception of verticality impairs postural control [21] and correlates with the severity of LwP [2, 22, 23]. Additionally, an association between a misperception of verticality and spatial neglect is also suggested [15]. Even though the relationship between LwP and the perception of verticality is plausible, no study has yet systematically reviewed this.

An in-depth evaluation of the association between LwP, lesion locations involved and verticality misperception will improve our understanding of the (potentially contributing) mechanisms of LwP. For this reason, this review will provide a comprehensive overview and will integrate these topics. The aim of this first-ever systematic review is to examine whether LwP is related to lesions in specific brain regions (research question 1), and whether there is an association between a disturbed perception of verticality and LwP (research question 2).

Methods

This systematic review is PROSPERO (CRD42020159248) registered and written according the 'Preferred Reporting Items for Systematic Reviews and Meta-analysis' (PRISMA) guidelines (Appendix A, B) [24].

Data sources and search strategy

Two search strategies were determined, dedicated to the two research questions. Six electronic databases were systematically screened: Pubmed, Web of Science, REHABDATA, Embase, Cochrane Library and the Physiotherapy Evidence Database (PEDro). In Web of Science and Pubmed, two different search strategies were used based on each research question, formed by key-words and Medical Subject Heading terms (Pubmed) (table 1). For REHABDATA, Embase, Cochrane Library and PEDro, an adapted search strategy was used to fit the requirements of the databases. Final search was conducted on December 16th, 2021. Additionally, reference lists of the included studies were screened to retrieve missed literature.

[Insert table 1]

Study selection

Studies were included, if they 1) assessed patients with a unilateral supratentorial stroke (ischemic or hemorrhagic); 2) diagnosed patients with LwP using a validated scale (e.g. Burke Lateropulsion Scale (BLS) [25] or Scale for Contraversive Pushing (SCP) [26]);

3) assessed the association between LwP and lesion location, as a primary goal, or between LwP and perception of verticality; 4) evaluated this association either by comparing groups with and without LwP or with regression/correlation analyses; and 5) were written in English, Dutch or German. Studies were excluded if studies were case reports, meta-analyses, reviews or abstracts.

All studies were screened independently on eligibility criteria by two reviewers (CvdW, EE). First, titles and abstracts were screened using predefined in- and exclusion criteria. The remaining studies were screened based on full texts and a consensus meeting was organized in case of discrepancies.

Risk of bias

Methodological quality of the retrieved full-texts was assessed by two independent researchers (CvdW, EE). In case of discrepancies, a consensus meeting was organized. The Newcastle Ottawa Scale for case-control studies was used to assess the risk of bias of included studies. Studies were considered to have a high risk of bias with classification "poor", referring to methodological quality (following the Agency of Healthcare Research and Quality classification) [27]. The supplementary material provides an overview of the rating criteria (Appendix C). The Newcastle Ottawa Scale was also used for an interventional study, as only the pre-intervention characteristics of the participants were examined.

Data-analysis and extraction

Data were independently extracted by two reviewers (CvdW and EE) and manually summarized in evidence tables. Disagreements were resolved by discussion. The following data were extracted: patient characteristics (number of participants, age, lesion side, time post-stroke, LwP assessment), imaging method for research question 1, measurement tool for research question 2, main results and conclusions (tables 3-6). A qualitative data-analysis was conducted, respecting the methodological quality of the included studies.

Outcome measures

Relevant outcome measures for research question 1 included anatomical regions associated with LwP, e.g. provided by a subtraction method or voxel-based lesion behaviour mapping analysis. Concerning research question 2, the perception of verticality is a measure to indicate the accuracy of the perceived vertical in relation to the true

vertical (gravitational vector). This could refer to the SVV or SHV where the participant has to visually (SVV) or haptically (SHV) estimate a vertical position of an object. For the SPV, a participant sitting on a 'tilting' chair, has to indicate when perceiving his/ her body in an upright (vertical) position. A deviation of the SVV, SPV or SHV reflects the difference between the perceived vertical and the true vertical within the frontal plane. The direction of this deviation can be ipsi- or contralesional, with negative values indicating a contralesional/ anticlockwise direction and positive values an ipsilesional/ clockwise direction. Apart from this, the variability of deviation (in other words, the 'uncertainty') reflects the robustness of the internal reference of verticality [28]. Also the characteristics of the measurement methods were evaluated (e.g., type of measurement tool, test position, circumstances of testing, and calculation of variables).

Results

Study selection

Searches resulted in 762 studies after the removal of duplicates. In total, 19 unique studies were retrieved (Figure 1). After screening on full-text, 8 relevant studies were selected to answer research question one and 12 for research question two. One study was relevant for both research questions [29].

Risk of bias

In total, three studies were of poor quality [26, 30, 31] and 16 of good quality [2, 7, 23, 29, 32-43] according the Newcastle Ottawa Scale. For research question 1, all studies had a good methodological quality with a score of 7 or 8 out of 9. Whereas for research question 2, scores ranged from 3 to 9 out of 9. None of the studies of research question 1 received a star for item 3 'selection of controls', as all participants were recruited within the same community. For research question 2, the majority of studies assessed healthy participants as well and received one star in this case. For the exposure part, the majority of studies of both research questions received three stars based on their description of the methodology. An overview of the risk of bias assessment can be found in table 2.

[Insert table 2]

Study characteristics

Of the 19 included studies, 2 studies were retrospective [32, 40] and 16 were prospective [2, 7, 23, 26, 29-31, 33, 35-39, 41-43] case-control studies. One study was a randomized

controlled trial [34]. A total of 182 LwP patients were examined for research question 1 and 158 for research question 2. To assess LwP, two studies used the BLS (score >2 out of 17 indicate LwP) [23, 32] and 17 studies the SCP [2, 7, 26, 29-31, 33, 35-40, 42-44]. However, different cut-off scores for the SCP were used, 12 studies used the original cut-off scores (>1 for each section: symmetry, use of non-paretic extremities and resistance to passive correction) [2, 7, 26, 29-31, 35, 38, 39, 42, 43] and 5 used modified cut-off scores (>0 for each component) [34, 36, 37, 40, 41]. Table 3 provides an overview of the demographic data of the included participants.

[Insert table 3]

Data-synthesis and analysis

Lesion location

All studies used spiral Computed Tomography or Magnetic Resonance Imaging with either fluid-attenuated inversion-recovery imaging [7, 29, 39, 40, 43] or diffusion-weighted imaging [7, 29, 32, 39, 40, 43]. A proportional difference map was used to compare the relative percentages of lesion overlap [32]. In addition, voxel-based lesion behaviour mapping analysis [29, 33] and lesion-symptom mapping using a multivariate statistical method (Sparse Canonical Correlation) [32] were performed to identify which lesion locations were associated with LwP. An overview of the extracted data can be found in table 4.

Regions associated with LwP in multiple studies were the thalamus [29, 38, 39, 43], inferior parietal lobule [7, 32, 43], pre- [40, 43] and postcentral gyrus [32, 40, 43] and its surrounding white matter [7], posterior insula [7, 29, 43], the superior temporal gyrus [7, 29, 43] and the internal capsule [29, 33, 38]. Some specific parts of the thalamus were reported: the posterior part [39], the ventral and lateral posterior nuclei of the posterolateral thalamus with extension to the internal capsule [38] and in the internal capsule reaching to the lateral thalamus [29]. Of the extra-thalamic regions, one study found that lesions of the inferior parietal lobule at the junction of the postcentral gyrus, were positively associated with severe LwP (according the BLS) [32]. The whole insula [40, 43] and specific regions of the insula, its posterior [7, 29] and anterior part [29], were related to LwP. The following tracts and regions associated to LwP were only reported once: corticospinal tract [43], inferior occipitofrontal [43], uncinate fasciculi [43], external capsule [33], subgyral parietal lobe [40], inferior frontal gyrus [40], and (frontal and Rolandic) parts of the operculum [29, 43].

[Insert table 4]

Perception of verticality

Table 5 and 6 provide an overview of respectively the protocol and set-up for the assessment and the results and raw values of the perception of verticality measurements.

Results of the SVV. Whereas four studies show that LwP patients have a higher [31] or a significantly higher deviation [2, 35, 42] of the SVV compared to non-LwP or healthy participants, five studies did not find a significant difference between groups if relative values were considered [26, 30, 34, 36, 41]. One study examined the absolute values of the SVV and reported a significant higher deviation in patients with right-sided lesions and LwP compared to non-LwP patients [29]. When the SVV was significantly deviated from the vertical, the direction was towards contralesional [2, 29, 31, 35] or ipsilesional [42]. For relative values, the magnitude of the deviation varied between studies from median -12.3° (Q1;Q3: -15.4; -8.5) to mean +4.8° (SD 5.1). Considering SVV variability, it was increased in LwP patients compared to non-LwP patients [35, 36, 41, 42]. Interestingly, patients with lateropulsion without pushing showed a significantly larger magnitude of deviation as well, compared to non-LwP patients [35]. Nevertheless, the magnitude of deviation of the patients with lateropulsion and pushing (LwP patients) was significantly larger compared to patients with only lateropulsion [35].

Results of the SHV. The SHV was only once examined: a significant higher deviation, in contralesional direction, was found in LwP patients compared to controls. The magnitude of the SHV deviation ranged from -9.5° to -5.6° in LwP patients [2].

Results of the SPV. All five studies show a significantly increased deviation of the SPV in LwP compared to non-LwP patients when assessed with closed eyes [2, 23, 26, 36], with the exception of a SPV measurement that was exclusively started in ipsilesional tilt direction [37]. The magnitude of the deviation varied between studies (mean 17.9 (SD 4.7) to -2.1 (SD2.0)) [23, 26]. Furthermore, consensus regarding its direction was not reached: two studies showed an ipsilesional deviation [23, 26] whereas the others showed a contralesional deviation [2, 36, 37]. Concerning the variability of SPV, a significant higher variability in LwP patients as compared to non-LwP patients was reported [23, 36]. However, in one study, the variability was only significant if the tilting chair started

from an ipsilesional tilt position [37]. If the SPV was examined with eyes open, no significant difference in mean deviation was found between LwP and non-LwP patients [26, 36], while the variability of deviation was still significantly higher in LwP patients [36].

[Insert table 5]

[Insert table 6]

Discussion

This systematic review investigates and integrates how LwP is associated with specific lesion locations and misperception of verticality.

Various lesion locations are associated with LwP: the thalamus, inferior parietal lobule, pre- and postcentral gyrus and its surrounding white matter, posterior insula, superior temporal gyrus and the internal capsule. This suggests that a network of brain regions is responsible for body orientation with respect to gravity, rather than one specific region.

This review shows alterations in verticality perception in LwP patients compared to non-LwP patients and patients with 'only' lateropulsion. No consensus was reached about the possible disturbance of the SVV [2, 26, 30, 31, 34-36, 41, 42]. All studies assessing the SPV reported a bias in LwP patients [2, 23, 26, 36], except for a SPV measurement which exclusively started in ipsilesional tilt direction [37]. However, the patients were able to compensate for this deviation using their vision when the SPV was assessed with eyes open [26, 36]. The magnitude of deviation, direction and variability (of both modalities) were inconclusive between studies. It is unclear how misperception of verticality exactly impacts LwP, but there is a link between them.

Previous research noted the necessity of the internal reference frame for adjusting the sense of verticality [19]. It is suggested that the construction and update of this frame relies on the convergence and integration of vestibular, somatosensory and visual input using internal models [1, 18]. All regions associated with LwP are involved in the integration of multisensory and cognitive information [18, 19]. A stroke can affect sensory input or (re)weighting of this input [45]. Previous studies have also reported a relationship between the lesion size and misperception of verticality [32, 39]. Lesion size was reported to be significantly larger in LwP patients than without and, additionally, correlated with the BLS [2, 7, 32, 40]. This result might be related to the greater amount of brain regions affected in patients with larger lesion sizes, since several brain regions

are related to LwP. Therefore, the construction of a reference frame and perceiving verticality correctly seem to depend more on a neural network than on a specific brain region alone [19]. A stroke affecting the neural network that constructs the internal reference frame can lead to a bias of this frame (e.g. thalamo-parietal projections for somaesthetic graviception and thalamo-insular projections for vestibular graviception) [2, 19]. The neural network responsible for accurate perceiving verticality might be even bigger if also secondary lesion locations are considered (e.g. structural intact regions, but with abnormal perfusion after stroke) [43].

A biased reference frame might lead to lateropulsion when patients orient their body towards this frame. Lateropulsion could be accompanied by pushing in patients with a severely biased reference frame, as an attempt to align the body with the biased internal reference [2] or as a compensatory postural reaction to lateral imbalance due to the biased frame [26].

Results concerning verticality perception are inconclusive, so a definitive answer to the associated mechanisms is difficult. Heterogeneity in the included samples of patients might explain such inconsistency. First, severity of LwP varies between studies. Since a correlation was found between SPV deviation and severity of LwP (based on the BLS), this might explain differences in magnitude (e.g., 18° [26] vs 2.5° [26]). Second, LwP was diagnosed with different assessment scales [23, 26] and cut-off scores [10, 11]. The majority of included studies used the SCP (cut off >0 or >1). However, the BLS is recommended in English speaking countries, because it evaluates the condition across several functional tasks and might be more sensitive to reveal mild LwP [10, 46]. This heterogeneity might lead to contradictions: patients being diagnosed with LwP on the BLS but not on the SCP. Third, comorbidities could amplify the misperception of verticality, such as spatial neglect [36, 42, 47] and sensory loss [48]. Increased variability [36] and change in deviation direction [42] have been seen in patients with spatial neglect and LwP, as compared to those with solely LwP. Additionally, increased deviation of the SVV and SPV was found in stroke patients with more severe sensory problems [48].

There is also heterogeneity in experimental set-up for assessment of verticality perception. First, the amount of fixation of the patient could influence results. Previous research showed that head and trunk fixation during the SVV measurement resulted in difference in deviation and increased individual variability compared to conditions without trunk (and head) fixation [49]. As variability is considered a criterion for the validity of the measurement, this indicates that measurements without these fixations are

less valid [28, 49]. Head-to-body position could also influence the E-effect, indicating a deviation of the subjective vertical toward the opposite side of the starting head-on-body position. This phenomenon, seen in SVV and SPV measurements, could affect the results [50]. On the other hand, since LwP patients tend to turn and shift their head ipsilesional [4, 51], it must be considered that head and trunk fixation does not mimic the patients natural posture. Moreover, patients might use the additional sensory input provided by these fixations to realign the tilting chair to the vertical position. Second, body position (e.g. sitting/ standing) might also influence the results [42]. The internal reference frame might differ according to body position because of different somatosensory input [52]. Also LwP seems more severe if it occurs in positions with a decreased base of support: some patients (with mild LwP) only show these symptoms during standing, but not in a sitting or lying position [4, 44]. Third, the starting angles of both the line/object (SVV) and the patient (SPV) impacted results (e.g. increased starting angle resulted in increased magnitude of SPV deviation) [37, 50, 53]. This might have contributed to the difference in deviation of the SPV seen in the studies (e.g. starting angle 12°, deviation of 2.5° [23] vs starting angle 35°, deviation of 18° [26]). Fourth, the calculation of the variables differs across studies [28]. Deviation is frequently calculated as the mean value of the trials [2, 23, 26, 29, 30, 36, 37, 41, 42], however, sometimes median values are used [31, 35]. Variability is mostly expressed as the within-subject standard deviation [35, 36, 41, 42], however, the difference between maximum and minimal deviation is used as well [23].

Our results reflect the need for high-quality studies with sufficient statistical power to provide a definite answer concerning the role of verticality misperception in LwP. Longitudinal studies evaluating perception of verticality over time are lacking and little is known about recovery of misperception of verticality and its influence on LwP. Two studies examined verticality perception in patients with history of LwP (i.e., "recovered" from LwP), showing that the clinical characteristics of the condition (e.g. the pushing) and SPV were restored while the SVV was still impaired [30, 54]. This suggests that the SVV is not necessarily an influencing factor for LwP, whereas the SPV might be. This assumption should be examined in future research.

Recommendations for rehabilitation and future research

Consensus concerning LwP assessment is necessary, since the use of different scales led to heterogeneity between studies. Also spatial neglect and sensory dysfunction contribute

to postural control and perception of verticality [15, 16, 45, 47], and the presence of comorbidities should therefore be evaluated.

To decrease heterogeneity across studies, and also improve clinical assessment of verticality perception, consensus on how to assess this most accurately is needed. Previous research already gave recommendations for the SVV [28], but not for the SHV and SPV. General guidelines for assessment methods (e.g. position, fixation, starting positions, velocity of movement), test circumstances (e.g. amount of trials, darkness) and calculation of outcomes (e.g. deviation, direction and variability) should be developed. Longitudinal evaluation of the perception of verticality is recommended for clinical and research purposes, to track the (spontaneous) recovery of a misperception of verticality in LwP patients. Focus should be on the examination of the three modalities (SVV, SHV, SPV) and their mutual interaction. Furthermore, since disturbances in perceiving verticality and LwP are related, future therapies should examine the effect of relearning the true vertical position.

Conclusion

The thalamus, inferior parietal lobule, pre- and postcentral gyrus and its surrounding white matter, posterior insula, superior temporal gyrus and the internal capsule are associated with LwP, suggesting that a network of brain regions is responsible for body orientation with respect to gravity. There is evidence of an altered perception of verticality (SVV, SPV and SHV) in LwP patients. Results were inconsistent regarding the direction, magnitude and variability of deviation. Although it is plausible that a deviation in perceiving the postural vertical is associated with LwP, how this misperception exactly impacts the disorder is not yet clear.

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Declaration of interest

The authors report no conflicts of interest.

References

1. Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? Age Ageing. 2006;35 Suppl 2:ii7-ii11.
2. Perennou DA, Mazibrada G, Chauvineau V, Greenwood R, Rothwell J, Gresty MA, et al. Lateropulsion, pushing and verticality perception in hemisphere stroke: a causal relationship? Brain. 2008;131(Pt 9):2401-13.
3. An CM, Ko MH, Kim DH, Kim GW. Effect of postural training using a whole-body tilt apparatus in subacute stroke patients with lateropulsion: A single-blinded randomized controlled trial. Ann Phys Rehabil Med. 2020.
4. Davies P. Steps to Follow: a guide for the treatment of adulte hemiplegia. New York: Springer; 1985.
5. Perennou DA, Amblard B, Laassel el M, Benaim C, Herisson C, Pelissier J. Understanding the pusher behavior of some stroke patients with spatial deficits: a pilot study. Arch Phys Med Rehabil. 2002;83(4):570-5.
6. Lafosse C, Kerckhofs E, Troch M, Vereeck L, Van Hoydonck G, Moeremans M, et al. Contraversive pushing and inattention of the contralesional hemispace. J Clin Exp Neuropsychol. 2005;27(4):460-84.
7. Johannsen L, Broetz D, Naegele T, Karnath HO. "Pusher syndrome" following cortical lesions that spare the thalamus. J Neurol. 2006;253(4):455-63.
8. Danells CJ, Black SE, Gladstone DJ, McIlroy WE. Poststroke "pushing": natural history and relationship to motor and functional recovery. Stroke. 2004;35(12):2873-8.
9. Pedersen PM, Wandel A, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Ipsilateral pushing in stroke: incidence, relation to neuropsychological symptoms, and impact on rehabilitation. The Copenhagen Stroke Study. Arch Phys Med Rehabil. 1996;77(1):25-8.
10. Bergmann J, Krewer C, Riess K, Muller F, Koenig E, Jahn K. Inconsistent classification of pusher behaviour in stroke patients: a direct comparison of the Scale for Contraversive Pushing and the Burke Lateropulsion Scale. Clin Rehabil. 2014;28(7):696-703.
11. Baccini M, Paci M, Nannetti L, Biricolti C, Rinaldi LA. Scale for contraversive pushing: cutoff scores for diagnosing "pusher behavior" and construct validity. Phys Ther. 2008;88(8):947-55.
12. van der Ham IJM, Postma A, Laeng B. Lateralized perception: The role of attention in spatial relation processing. Neuroscience & Biobehavioral Reviews. 2014;45:142-8.
13. Saj A, Borel L, Honoré J. Functional Neuroanatomy of Vertical Visual Perception in Humans. Front Neurol. 2019;10:142.
14. Abe H, Kondo T, Oouchida Y, Suzukamo Y, Fujiwara S, Izumi S-I. Prevalence and Length of Recovery of Pusher Syndrome Based on Cerebral Hemispheric Lesion Side in Patients With Acute Stroke. Stroke; a journal of cerebral circulation. 2012;43:1654-6.
15. Pérennou D. Postural disorders and spatial neglect in stroke patients: a strong association. Restor Neurol Neurosci. 2006;24(4-6):319-34.
16. Embrechts E, Van Criekinge T, Schröder J, Nijboer T, Lafosse C, Truijen S, et al. The association between visuospatial neglect and balance and mobility post-stroke onset: A systematic review. Ann Phys Rehabil Med. 2020.
17. Rousseaux M, Honoré J, Vuilleumier P, Saj A. Neuroanatomy of space, body, and posture perception in patients with right hemisphere stroke. Neurology. 2013;81(15):1291.

18. Dieterich M, Brandt T. Perception of Verticality and Vestibular Disorders of Balance and Falls. Front Neurol. 2019;10:172.
19. Barra J, Marquer A, Joassin R, Reymond C, Metge L, Chauvineau V, et al. Humans use internal models to construct and update a sense of verticality. Brain. 2010;133(Pt 12):3552-63.
20. Perennou D, Piscicelli C, Barbieri G, Jaeger M, Marquer A, Barra J. Measuring verticality perception after stroke: why and how? Neurophysiol Clin. 2014;44(1):25-32.
21. Bonan IV, Hubeaux K, Gellez-Leman MC, Guichard JP, Vicaut E, Yelnik AP. Influence of subjective visual vertical misperception on balance recovery after stroke. J Neurol Neurosurg Psychiatry. 2007;78(1):49-55.
22. Baggio J, Mazin S, Alessio-Alves F, Barros C, Carneiro AA, Leite J, et al. Verticality Perceptions Associate with Postural Control and Functionality in Stroke Patients. PLOS ONE. 2016;11:e0150754.
23. Bergmann J, Krewer C, Selge C, Muller F, Jahn K. The Subjective Postural Vertical Determined in Patients with Pusher Behavior During Standing. Top Stroke Rehabil. 2016;23(3):184-90.
24. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Bmj. 2009;339:b2700.
25. D'Aquila M, Smith T, Organ D, Lichtman S, Reding M. Validation of a lateropulsion scale for patients recovering from stroke. Clinical rehabilitation. 2004;18:102-9.
26. Karnath HO, Ferber S, Dichgans J. The origin of contraversive pushing: evidence for a second graviceptive system in humans. Neurology. 2000;55(9):1298-304.
27. Hartling L, Hamm M, Milne A, Vandermeer B, Santaguida PL, Ansari M, et al. AHRQ Methods for Effective Health Care. Validity and Inter-Rater Reliability Testing of Quality Assessment Instruments. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.
28. Piscicelli C, Perennou D. Visual verticality perception after stroke: A systematic review of methodological approaches and suggestions for standardization. Ann Phys Rehabil Med. 2017;60(3):208-16.
29. Baier B, Janzen J, Muller-Forell W, Fechir M, Muller N, Dieterich M. Pusher syndrome: its cortical correlate. J Neurol. 2012;259(2):277-83.
30. Fraser LE, Mansfield A, Harris LR, Merino DM, Knorr S, Campos JL. The Weighting of Cues to Upright Following Stroke With and Without a History of Pushing. Can J Neurol Sci. 2018;45(4):405-14.
31. Snowdon N, Scott O. Perception of vertical and postural control following stroke: a clinical study. Physiotherapy. 2005;91(3):165-70.
32. Babyar SR, Smeragliuolo A, Albazron FM, Putrino D, Reding M, Boes AD. Lesion Localization of Poststroke Lateropulsion. Stroke. 2019;50(5):1067-73.
33. Baier B, Cuvenhaus HS, Müller N, Birklein F, Dieterich M. The importance of the insular cortex for vestibular and spatial syndromes. Eur J Neurol. 2021;28(5):1774-8.
34. Bergmann J, Krewer C, Jahn K, Muller F. Robot-assisted gait training to reduce pusher behavior: A randomized controlled trial. Neurology. 2018;91(14):e1319-e27.
35. Dai S, Piscicelli C, Clarac E, Baciu M, Hommel M, Pérennou D. Lateropulsion After Hemispheric Stroke: A Form of Spatial Neglect Involving Graviception. Neurology. 2021;96(17):e2160-e71.

36. Fukata K, Amimoto K, Fujino Y, Inoue M, Inoue M, Takahashi Y, et al. Influence of unilateral spatial neglect on vertical perception in post-stroke pusher behavior. Neurosci Lett. 2020;715:134667.
37. Fukata K, Amimoto K, Fujino Y, Inoue M, Inoue M, Takahashi Y, et al. Starting position effects in the measurement of the postural vertical for pusher behavior. Exp Brain Res. 2020;238(10):2199-206.
38. Karnath HO, Ferber S, Dichgans J. The neural representation of postural control in humans. Proc Natl Acad Sci U S A. 2000;97(25):13931-6.
39. Karnath HO, Johannsen L, Broetz D, Kuker W. Posterior thalamic hemorrhage induces "pusher syndrome". Neurology. 2005;64(6):1014-9.
40. Lee KB, Yoo SW, Ji EK, Hwang WS, Yoo YJ, Yoon M-J, et al. Is Lateropulsion Really Related with a Specific Lesion of the Brain? Brain sciences. 2021;11(3):354.
41. Paci M, Matulli G, Megna N, Baccini M, Baldassi S. The subjective visual vertical in patients with pusher behaviour: a pilot study with a psychophysical approach. Neuropsychol Rehabil. 2011;21(4):539-51.
42. Saj A, Honore J, Coello Y, Rousseaux M. The visual vertical in the pusher syndrome: influence of hemispace and body position. J Neurol. 2005;252(8):885-91.
43. Ticini LF, Klose U, Nagele T, Karnath HO. Perfusion imaging in Pusher syndrome to investigate the neural substrates involved in controlling upright body position. PLoS One. 2009;4(5):e5737.
44. Bergmann J, Krewer C, Mueller F, Jahn K. A new cutoff score for the Burke Lateropulsion Scale improves validity in the classification of pusher behavior in subactue stroke patients. Gait & Posture. 2018;68.
45. Saeys W, Herssens N, Verwulgen S, Truijen S. Sensory information and the perception of verticality in post-stroke patients. Another point of view in sensory reweighting strategies. PLoS One. 2018;13(6):e0199098.
46. Koter R, Regan S, Clark C, Huang V, Mosley M, Wyant E, et al. Clinical Outcome Measures for Lateropulsion Poststroke: An Updated Systematic Review. J Neurol Phys Ther. 2017;41(3):145-55.
47. Utz KS, Keller I, Artinger F, Stumpf O, Funk J, Kerkhoff G. Multimodal and multispatial deficits of verticality perception in hemispatial neglect. Neuroscience. 2011;188:68-79.
48. Saeys W, Vereeck L, Truijen S, Lafosse C, Wuyts FP, Van de Heyning P. Influence of sensory loss on the perception of verticality in stroke patients. Disability and Rehabilitation. 2012;34(23):1965-70.
49. Piscicelli C, Barra J, Sibille B, Bourdillon C, Guerraz M, Pérennou DA. Maintaining Trunk and Head Upright Optimizes Visual Vertical Measurement After Stroke. Neurorehabil Neural Repair. 2016;30(1):9-18.
50. Saeys W, Vereeck L, Bedeer A, Lafosse C, Truijen S, Wuyts FL, et al. Suppression of the E-effect during the subjective visual and postural vertical test in healthy subjects. Eur J Appl Physiol. 2010;109(2):297-305.
51. Lafosse C, Kerckhofs E, Vereeck L, Troch M, Van Hoydonck G, Moeremans M, et al. Postural abnormalities and contraversive pushing following right hemisphere brain damage. Neuropsychol Rehabil. 2007;17(3):374-96.
52. Bergmann J, Kreuzpointner MA, Krewer C, Bardins S, Schepermann A, Koenig E, et al. The subjective postural vertical in standing: reliability and normative data for healthy subjects. Atten Percept Psychophys. 2015;77(3):953-60.
53. Baccini M, Paci M, Del Colletto M, Ravenni M, Baldassi S. The assessment of subjective visual vertical: comparison of two psychophysical paradigms and age-related performance. Atten Percept Psychophys. 2014;76(1):112-22.

54. Mansfield A, Fraser L, Rajachandrakumar R, Danells CJ, Knorr S, Campos J. Is perception of vertical impaired in individuals with chronic stroke with a history of 'pushing'? Neurosci Lett. 2015;590:172-7.

Tables

Table 1. Search strategy used in Pubmed* based on the PICO-strategy.

	Research question 1	***Research question 2***
P	((stroke OR ("stroke"[MeSH Terms]) OR cerebrovascular* OR hemiplegia OR ("hemiplegia"[Mesh Terms]) OR paresis OR ("paresis"[MeSH Terms)) AND (pusher AND (behavi* OR syndrome)) OR lateropulsion OR (contraversive pushing) OR (lateral AND propulsion))	
I	X	X
C	X	X
O	(location OR lesion OR cortical OR anatomy OR (diagnostic imaging) OR MRI OR CT OR scan OR (lesion mapping))	((perception of verticality) OR (subjective visual vertical) OR ((postural AND control) OR balance) OR postural OR (internal model) OR ((postural OR visual OR haptic*) AND vertical*) OR sensory OR proprioception OR vestibular OR somatosensory OR perception OR graviceptive OR sensory OR processing OR spatial OR contralesional OR tilt OR listing OR leaning OR thrusting OR pushing OR (lateral inclination) OR (reference frame))
**For the other databases, this search strategy was adapted to fit the requirements of the specific database.*		
C = control, I = intervention, O = outcome, P = patient, PICO = patient, intervention, comparison and outcome		

Table 2. Risk of bias assessed with the Newcastle Ottawa Scale

Case control studies	Selection				Comparability	Exposure				
Author	**1**	**2**	**3**	**4**	**1**	**1**	**2**	**3**	**Total score**	**Methodological quality**
Research question 1										
Babyar et al., 2019 [32]	*	*		*	**	*	*	*	8	Good
Baier et al., 2021 [33]	*	*		*	*	*	*	*	7	Good
Johanssen et al., 2006 [7]	*	*		*	**	*	*	*	8	Good
Karnath et al., 2000 [38]	*	*		*	**		*	*	7	Good
Karnath et al., 2005 [39]	*	*		*	*	*	*	*	7	Good
Lee et al., 2021 [40]	*	*		*	**	*	*	*	8	Good
Ticini et al., 2009 [43]	*	*		*	*	*	*	*	7	Good
Research question 1 + 2										
Baier et al., 2012 [29]	*	*		*	*	*	*	*	7	Good
Research question 2										
Bergmann et al., 2016 [23]	*	*	*		**	*	*	*	8	Good
Bergmann et al., 2018 [34]	*	*		*	**	*	*	*	8	Good
Dai et al., 2021 [35]	*	*		*	**	*	*	*	8	Good
Fraser et al., 2018 [30]			*			*	*		3	Poor
Fukata et al., 2020 [36]	*		*	*	**	*	*	*	8	Good
Fukata et al., 2020 [37]	*	*		*	**	*	*	*	8	Good
Karnath et al., 2000 [26]	*		*	*		*	*	*	6	Poor
Paci et al., 2011 [41]	*	*	*	*	**	*	*	*	9	Good
Perennou et al., 2008 [2]	*	*	*	*	**	*	*	*	9	Good
Saj et al., 2005 [42]	*	*	*	*	*	*	*	*	8	Good
Snowdon et al., 2005 [31]			*		*	*	*	*	5	Poor

Table 3. Data-extraction research question 1 and 2 – demographic data.

Author, year	Groups, N	Mean age in years ± SD	Lesion side (L/R)	Time post-stroke	LwP assessment (cut-off score)
		Research question 1			
Babyar et al., 2019 [32]	LwP = 50 non-LwP = 50	76.5 ± 10.4 76.7 ± 9.9	28/22 28/22	9.1 ± 5.5 d 8.5 ± 5.6 d	BLS (≥2)
Baier et al., 2021 [33]	LwP = 25 non-LwP = 57	65.1 ± 12.5	R	5.8 ± 1.9 d	SCP (>1)
Johannsen et al., 2006 [7]	LwP = 21 non-LwP = 24	L: 67.8 ± 8.3, R: 68.0 ± 9.4 L: 65.7 ± 9, R: 60.6 ± 13.2	10/11 12/12	L: 6.5 ± 5.4, R: 5.7 ± 4.2 d L: 5.0 ± 3.7, R: 4.8 ± 3.8 d	SCP (>1)
Karnath et al., 2000 [38]	LwP = 23 non-LwP = 23	L: 68, R: 71 L: 63.5, R: 65	8/15 8/15	NR NR	SCP (>1)
Karnath et al., 2005 [39]	LwP = 14 non-LwP = 26	L: 63.9 ± 9.7, R: 66.1 ± 7.5 L: 61.8 ± 18.0, R: 62.2 ± 12.2	5/9 12/14	L: 9.4 ± 3.8, R: 6.2 ± 2.5 d L: 3.8 ± 2.9, R: 4.7 ± 4.1 d	SCP (>1)
Lee et al., 2021 [40]	LwP = 17 non-LwP = 33	69.21 ± 11.42 68.82 ± 16.45	R	10.59 ± 7.57 d 6.39 ± 5.51 d	SCP (>0)
Ticini et al., 2009 [43]	LwP = 9 non-LwP = 10	TL: 67.8 ± 6.1, HL: 64.5 ± 16.6 TL: 56.6 ± 9.6, HL: 64.7 ± 13.8	3/6 1/9	TL: 9.6 ± 6.1, HL: 3.5 ± 4.7 d TL: 7.2 ± 7.9, HL: 3.0 ± 4.1 d	SCP (>1)
		Research question 1 and 2			
Baier et al., 2012 [29]	LwP = 23 non-LwP = 43	64 ± 12	7/16 21/22	L: 5 ± 2, R: 7 ± 3 d L: 6 ± 2, R: 7 ± 3 d	SCP (>1)
		Research question 2			
Bergmann et al., 2016 [23]	LwP = 8 non-LwP = 10 H = 10	*72.5* *71.1* *70.5*	2/6 3/7 NA	66 d 61 d NA	BLS (>2)
Bergmann et al., 2018 [34]	LwP_EG = 15 LwP_CG = 15	72 ± 9 71 ± 10	4/11 3/12	7.5 ± 2.6 w 8.0 ± 3.8 w	SCP (>0)
Dai et al., 2021 [35]	LwP = 30 LP = 32 non-LwP = 158	70.4 (64; 76) 66 (60; 71) 66.2 (54; 72)	5/25 12/20 109/49	± 30 d	SCP (>1, LP 0.5-1)
Fraser et al., 2018 [30]	LwP = 1 non-LwP = 8 H = 12	67 *62* *65*	L 3/5 NA	1 m *10* NA	SCP (>1)
Fukata et al., 2020 [36]	LwP(SN+) = 11 LwP(SN-) = 10 non-LwP = 12 H = 15	70.1 ± 10.4 66.3 ± 12.4 65.4 ± 10.8 67.0 ± 8.0	R R R NA	14.0 ± 8.3 12.1 ± 4.7 15.2 ± 5.0 NA	SCP (>0)
Fukata et al., 2020 [37]	LwP = 24 non-LwP = 29	67.8 ± 11.6 65.2 ± 10.5	2/22 10/19	16.2 ± 11.0 15.2 ± 5.7	SCP (>0)
Karnath et al., 2000 [26]	LwP = 5 non-LwP = 5 H = 5	73.6 53.4 NR	R R NA	13.2 110;6 NA	SCP (>1)
Paci et al., 2011 [41]	LwP = 3 non-LwP = 5 H = 10	*74.6* *77.6* *77.4*	2/1 2/3 NA	*17 d* *20.8 d* NA	SCP (>0)
Perennou et al., 2008 [2]	LwP = 6 non-LwP Contra-LP H = 33	62.7 ± 11.3 52.7 ± 13.4 58 ± 12.3 48.8 ± 10.8	1/5 NR 6/23 NA	8.8 ± 7.4 w 10.7 ± 7.4 w 13.8 ± 8.7 w NA	SCP (>1, LP 0.5-1)
	LwP(SN+) = 4	67	R	*39.3 d*	SCP (>1)

Saj et al., 2005 [42]	LwP(SN-) = 1	77	R	*30 d*	
	non-LwP(SN+) = 6	55.5	R	*54.2 d*	
	non-LwP(SN-) = 6	50.7	R	*61.3 d*	
	H = 6	51.2	NA	NA	
Snowdon et al., 2005 [31]	LwP = 2	*82.7*	R	14, 28 d	SCP (>1)
	non-LwP = 10	*70.2*	4/6	62.1* d	

BLS = Burke Lateropulsion Scale; d = days; H = healthy participants; HL = hemispheric lesion; L = left; LP = lateropulsion; LwP = (group) stroke patients with Lateropulsion with active Pushing; LwP-CG = control group with patients with LwP; LwP-EG = experimental group with patients with LwP; LwP(SN+) = patients with LwP and spatial neglect; LwP(SN-) = patients with LwP without spatial neglect; m = months; N = number of patients; NA = not applicable; non-LwP = stroke patients without LwP; R = right; SCP = Scale for Contraversive Pushing; SD = standard deviation; TL = thalamic lesion; w = weeks. Italics: indicates self-calculated mean values, underlined: indicates median values (Q1-Q3).

Table 4. Data-extraction research question 1: lesion location associated with LwP.

	Material & procedure		
Author, year	**Imaging, analysis and software method**	**Region of interest**	**Results**
Babyar et al., 2019 [32]	T2 MRI, LESYMAP - SCCAN, Lesion to symptom mapping and Proportional Difference Map	HL	Region associated with highest BLS: inferior parietal lobule at the junction of the **PCG** and **Brodmann Area 40**. Overall model was significant, cross validation correlation of $p<0.001$* ($r=0.32$).
Baier et al., 2012 [29]	MRI (DWI/ FLAIR/ T1/ T2), VLBM-based regression analysis	HL	VLBM-based regression analysis with score of SCP, lesion size and neglect: no significant voxels ($p>0.05$). Key areas related to extent of LwP: Right sided lesions uncorrected regression analysis: **posterior insular cortex, STG, operculum** and **white matter**. Left sides lesions uncorrected regression analysis: **anterior insular cortex** reaching to the **operculum, IC** reaching to **lateral thalamus**.
Baier et al., 2021 [33]	MRI (DWI/ FLAIR/ T1/ T2), VLBM-based regression analysis	HL	VLBM-based regression analysis: in patients with LwP: significant association between the score of the SCP and the **IC, external capsule** and **the white matter**.
Johannsen et al., 2006 [7]	MRI (DWI/ FLAIR/ T1/T2)/ CT, Subtraction technique	HL sparing the thalamus	Center of overlap: lesion locations in LwP patients with right/ left-sided lesions: **posterior insula, PCG** and surrounding **white matter**. Subtraction method, specific for LwP: small regions at left **posterior insula** and **STG**, left **IPL** and right **PCG**
Karnath et al., 2000 [38]	T1 MRI/ CT	HL	Center of overlap, LwP vs non-LwP patients: **ventral posterior and lateral posterior nuclei of the posterolateral thalamus** into the **posterior crus of the IC**, **dorsally** also slightly into the **corpus of the caudate nucleus**
Karnath et al., 2005 [39]	MRI (FLAIR/ DWI /T1 /T2)/ CT, Subtraction technique	TL	Subtraction method, lesion overlap centered: in LwP patients in **posterior thalamus**, and for non-LwP patients in **anterior thalamus**.
Lee et al., 2021 [40]	MRI (DWI/ FLAIR/ T1 /T2), VLSM-based analysis	HL	VLBM method combined with statistical non-parametric mapping: **precentral gyrus, PCG, inferior frontal gyrus, insula** and **subgyral parietal lobe** of the right hemisphere were associated with SCP scores ($p<0.05$). However, when the lesion volume is adjusted as nuisance covariate, no lesion locations were significantly associated with SCP.
Ticini et al., 2009 [43]	T2 MRI (DWI / FLAIR), Subtraction technique	TL, HL sparing the thalamus	Center of overlap: TL: in LwP and non-LwP patients: located on the **thalamus**. HL sparing the thalamus: in LwP patients: **insula, frontal** and **rolandic operculum**, **IPL**, **PCG**, **pre central gyrus,** part of **CST**, **inferior occipitofrontal** and **uncinate fasciculi**. In non-LwP patients: **insula, rolandic operculum, STG,** part of **CST.**

BLS = Burke Lateropulsion Scale; CST = cortico-spinal tract; CT = computed tomography; DWI = diffusion-weighted imaging; FLAIR = Fluid-attenuated inversion recovery; HL = hemispheric lesions; IC = internal capsule; IPL = Inferior Parietal Lobule; MRI = Magnetic Resonance Imaging; non-LwP = (group) stroke patients without lateropulsion with active pushing; LwP = (group) stroke patients with lateropulsion with active pushing; PCG = Postcentral gyrus; SCP = Scale for Contraversive Pushing; STG = Superior Temporal Gyrus; TL = thalamic lesions; VLBM = voxel-based lesion behaviour mapping; VLSM = voxel-based symptom mapping.

Table 5. Characteristics of measurement tools to assess the SVV, SHV and SPV.

Assessment method and circumstances						Calculating outcome		
Author, year	**Type of method**	**Position, darkness**	**Fixation**	**Distance in m, speed, order**	**Control of object/ tilting chair**	**n°**	**Deviation/ direction**	**Varia-bility**
			SVV					
Baier et al., 2012 [29]	Hemispherical dome method	Sitting, surface of dome covered	No fixation	1.0	P manually adjusts object to vertical position	7	Mean	NA
Bergmann et al., 2018 [34]	Bucket Test	Sitting, NR	No fixation	NR	P verbally adjusts object to vertical position	6	Mean	NA
Dai et al., 2021 [35]	15-cm luminous line projected on computer screen	Sitting, dark room	Head, trunk and feet fixated	1.2	P verbally adjusts object to vertical position	10	Median	SD
Fraser et al., 2018 [30]	Line projected on screen	Sitting, NR	Head, trunk and feet fixated	NR	P verbally adjusts object to vertical position	30	Mean	NA
Fukata et al., 2000 [36]	Cylindrical tube with visual indicator	Sitting, bright room	Head not fixated, trunk fixated, feet flat on the floor	0.5, 5°/s	P verbally adjusts object to vertical position	8	Mean	SD
Karnath et al., 2000 [26]	7.5-cm luminous rod	Sitting, dark room	Trunk fixated, head and legs not fixated	NR	P verbally adjusts object to vertical position	10	Mean	NA
Paci et al., 2011 [41]	40-cm gabor patch, displayed for 250 ms	Sitting, dark room	Arms lying on table, head fixated	NR	P verbally adjusts object to vertical position	80	Mean	SD
Perennou et al., 2008 [2]	15-cm luminous line projected on computer screen	Sitting, dark room	Head, trunk and feet fixated	1.2	P verbally adjusts object to vertical position	10	Mean	NA
Saj et al., 2005 [42]	25-cm metal rod rotated a front of black panel	Sitting with legs extended and supine, dark room	Head and trunk fixated	NR	P manually adjusts object to vertical position	6	Mean	SD

Snowdon et al., 2005 [31]	2-cm line across circle	Sitting, goggles to restrict surrounding	Head fixated	2.5	P verbally adjusts object to vertical position	10	Median	NA
			SHV					
Perennou et al., 2008 [2]	15-cm rod pivoting about a horizontal axis	Upright sitting, blindfolded in dark room	Head and feet fixated, trunk and arm wedges were released	0.4-0.5	P had to manually set the object to vertical position (non-paretic hand)	10	Mean	NA
			SPV					
Bergmann et al., 2016 [23]	Spacecurl ® (Physio Boerse, Wittlich, Germany)	Passively standing, blindfolded	Head and trunk not restrained, fixation of legs and feet	Unpredictable order: 12, 15 or 18°, 1.0-1.5°/s	P verbally adjusts chair to vertical position	6	Mean	Range
Fukata et al, 2020 [36, 37]	Vertical board	Sitting, bright room	Head and legs were free, trunk fixated, arms folded across chest	Unpredictable order, 15° or 20°, 1.5°/s	P verbally adjusts chair to vertical position	8	Mean	SD
Karnath et al., 2020 [26]	Motor-driven padded chair	Sitting, bright room	Trunk fixated, head and legs not fixated	Random offset of at least 35°	P verbally adjusts chair to vertical position	10	Mean	NA
Perennou et al., 2008 [2]	Druk-like tilting apparatus	Sitting, darkened room	Head, trunk and feet fixated	Random tilt between 15-45°, 1.5°/s	P verbally adjusts chair to vertical position	10	Mean	NA

cm = centimeter; m = meter; n° = number of trials; NA = not applicable; NR = not reported; P = participant, s = seconds, SD = standard deviation; SHV = subjective haptic vertical; SPV = subjective postural vertical; SVV = subjective visual vertical. .

Table 6. Data-extraction research question 2: perception of verticality.

Author, year	Outcome	Mean deviation and variability (SD) in °	Conclusion
		SVV	
Baier et al., 2012 [29]	Deviation	Absolute values: LwP: R: 3.3 ± 1.5, L: 2.0 ± 1.4 non-LwP: R: 2.0 ± 1.4, L: 1.9 (1.0)	Absolute values: for R-lesion: LwP vs non-LwP patients no significant difference in mean deviation (p=0.091, F=2.334). In L-lesion: LwP vs non-LwP patients no significant difference in mean deviation (p=0.241, F(4.23)=0.241). R+L-lesion: LwP patients with right sided lesion showed a significant larger deviation of SVV (p=0.010*, F=7.354). Relative values: **significant main effect for lesion side**, indicating a **contralesional deviation** (p=0.004*, F(1.62)=8.875)
Bergmann et al., 2018 [34]	Deviation	LwP-experimental group: *0.3 (Q1-Q3: -2.0 - 1.7),* LwP-control group: *1.2 (Q1-Q3: -1.3 to 3.9)*	**SVV at baseline within ranges of normality** (-2.5 to 2.5), based on healthy participants of the study of Perennou et al. 2008 [2], indicating no significant bias of SVV in LwP patients.
Dai et al., 2021 [35]	Variability	LwP: 4.5 (Q1;Q3: 3.4; 5.7), LP: 1.9 (Q1;Q3: 1.4; 2.7), non-LwP: 1.3 (Q1;Q3: 1; 2)	Significant difference between groups: **significant higher variability in LwP vs LP** (p<0.001) **and non-LwP patients** (p<0.001). LP patients significant higher variability compared to non-LwP patients (p=0.003).
	Deviation	LwP: -12.3 (Q1;Q3: -15.4;-8.5), LP: -2.9 (Q1;Q3: -7;0.8), non-LwP: -0.6 (Q1;Q3: -2.9; 2.4)	Significant difference between groups: **significant higher deviation in LwP compared to LP** (p<0.001) **and non-LwP patients** (p<0.001). LP patients significant higher deviation compared to non-LwP patients (p=0.001). Deviation was in **contralesional direction**.
Fraser et al., 2018 [30]	Deviation	LwP participant: 0, non-LwP participant: -5, H: -1, 95% CI [-2,0]	**No bias of the SVV** in the patient with LwP
Fukata et al., 2020 [36]	Variability	LwP(SN+): 7.6 (6.3), LwP(SN-): 1.9 (0.5), non-LwP: 1.4 (0.6), H: 1.3 (0.6)	Significant difference between groups (p<0.001*, F=8.086). **Significant higher variability of the SVV in LwP(SN+) compared to LwP(SN-), non-LwP and H participants** (p<0.05*).
	Deviation	LwP(SN+): -1.4 (5.1), LwP(SN-): 1.5 (5.7), non-LwP: -0.6 (2.2), H: -0.7 (1.8)	**No significant difference in mean deviation** of the SVV between groups (p=0.252, F=1.385).
Karnath et al., 2000 [26]	Deviation	LwP: -0.4 (2.5), non-LwP: -0.4 (1.7), H: 95% CI [-1.7, 0.8]	Mean SVV was within CI of H participants.
Paci et al., 2011 [41]	Variability	LwP: 6, non-LwP: NR, H: NR	**Significant difference in median** variability in LwP compared to non-LwP patients (p=0.036*, U=0.000) and controls (p=0.007*, U=0.000)
	Deviation	NR	**No significant difference in bias of SVV in LwP patients** compared to controls (p=0.547, $\chi 2$ =1.206).
Perennou et al., 2008 [2]	Deviation	SVV ranges: LwP: -8.2 to -3.3, CL-LP: -18 to 3.2, non-LwP: NR, H: -2.2 to 2.2 (mean H: -0.04 (1.1)).	Significant higher deviation in **contralesional direction** in LwP patients compared to CL-LP, non-LwP and H participants (p<10^-6*, F=321.7). In all stroke patients (including patients with brainstem stroke): positive correlation between magnitude of mean deviation of **SVV and SCP** (p=0.003, r=-0.003*).
Saj et al., 2005 [42]	Variability	LwP: 6.8 (3.3), non-LwP(SN+): 2.1 (0.3), non-LwP(SN-): 1.3 (0.4), H: 0.9 (0.2)	**Significant variability** of SVV between groups (p<0.001*, F(3.18)=17.96), with an increased variability in LwP patients.

	Deviation	Sitting position, central rod: LwP: 4.8 (5.1), non-LwP(SN+): -4.6 (3.2), non-LwP(SN-): -1.4 (1.7), H: -0.3 (0.6), 95% CI [-1.4, 0.9]	**Significant difference between groups** (p<0.001*, F=12.22), LwP and LwP(SN+) differed significantly with the other groups (p<0.05*). While the non-LwP(SN-) and non-LwP(SN+) patients showed a contralesional deviation, LwP patients showed an **ipsilesional deviation.** Body position (sitting/ lying) affected the performance of the SVV (p<0.001*) with significant group effect (p=0.003*). Significant decrease of ipsilesional deviation in supine position compared to sitting position in LwP patients (p<0.01). Significant interaction of rod location x group, with increased ipsilesional deviation in LwP patients when the rod was located in the left or right hemispace vs central (p<0.01*).
Snowdon et al., 2005 [31]	Deviation	LwP participants: -9.75 and -3.75	**Contralesional deviation** of SVV as compared to non-LwP patients.
			SPV
Bergmann et al., 2016 [23]	Variability	LwP: 13.5 (5.2), non-LwP: 5.6 (3.7), H: 4.0 (1.9)	Significant **higher variability** in LwP patients compared to non-LwP (p<0.001*) and H participants (p<0.001*).
	Deviation	LwP: 2.5 (2.5), non-LwP: 0.3 (1.0), H: -0.6 (0.8)	Significant higher deviation, in **ipsilesional direction,** of SPV in LwP compared to non-LwP (p=0.015*) and H participants (p<0.001*). Significant positive correlation between mean SPV and BLS (p=0.037*, r=0.663), but not significant with the SCP (p=0.068, r=0.575).
Fukata et al., 2020 [36]	Variability	Eyes closed: LwP(SN+): 6.6 (2.0), LwP(SN-): 6.3 (1.4), non-LwP: 3.5 (1.0), H: 3.3 (1.4). Eyes open: LwP(SN+): 7.6 (2.9), LwP(SN-): 5.3 (1.5), non-LwP: 2.7 (1.0), H: 3.0 (0.8).	Eyes closed: Significant difference between groups (p<0.001*, F=12.267), with **higher variability** of the SPV in LwP(SN+) compared to LwP(SN-), non-LwP and H participants (p<0.05*). Eyes open: significant **higher variability** of the SPV in LwP(SN+) and LwP(SN-) compared to non-LwP and H participants (p<0.05).
	Deviation	Eyes closed: LwP(SN+): -2.1 (2.0), LwP(SN-): -2.2 (1.1), non-LwP: -0.4 (1.0), H: -0.2 (1.1). Eyes open: LwP(SN+): -7.6 (2.9), LwP(SN-): 5.3 (1.5), non-LwP: 2.7 (1.0), H:3.0 (0.8).	Significant higher **contralesional deviation** of SPV in LwP compared to non-LwP and H participants (p<0.001*, F=6.943) with eyes closed. In the eyes open condition, no significant group effect (p=0.284, F=12.267).
Fukata et al., 2020 [37]	Variability	CL-Start position = LwP: 2.6 (1.2), non-LwP: 2.0 (1.2), IL-Start position = LwP: 4.8 (2.0), non-LwP: 2.2 (1.3)	CL-Start position = **variability not significant** different between groups (p=0.132). No correlation between variability and SCP or BLS (resp. p=0.787, r=− 0.046; p=0.849, r=− 0.027). IL-Start position = **variability significantly higher** in LwP compared to non-LwP patients (p<0.001). Variability was significantly positively correlated with SCP 5p<0.001, r=0.631) and BLS (p<0.001, r=0.616)
	Deviation	CL-Start position = LwP: -6.3 (1.6), non-LwP: -2.2 (1.8), IL-Start position = LwP: 2.0 (3.7), non-LwP: 1.5 (3.0)	CL-Start position = c**ontralesional deviation** of SPV in LwP patients, significantly different from non-LwP patients (p<0.001). Mean deviation was negatively correlated with SCP (p<0.001, r=-0.732) and BLS (p<0.001, r=-0.702). IL-Start position = **no significant difference** between groups in mean deviation (p=0.593). Mean deviation not significantly correlated with SCP (p=0.228, r=0.168) or BLS (p=0.157, r=0.197),

Karnath et al., 2000 [26]	Deviation	Eyes closed: LwP: 17.9 (4.7), non-LwP: 0.4 (0.9), H: 95% CI: -0.2 to 1.0. Eyes open: LwP: 0.9 (1.6), non-LwP: 0.3 (0.8), H: 95% CI: -0.2 to 0.9	Eyes closed: **Ipsilesional deviation** of the SPV in patients with LwP compared to non-LwP and H participants. SPV mean deviation outside CI. Eyes open: **Mean deviation within CI** in eyes open-condition.
Perennou et al., 2008 [2]	Deviation	SPV ranges: LwP: -18.2 to -5.6, CL-LP: -18.7 to 1.2, non-LwP: NR, H: -1.9 to 2.2 (mean H: 0.03 (0.9)).	Significant higher deviation in **contralesional direction** in LwP patients compared to CL-LP, non-LwP and H participants (p<10^-6*, F=321.7). In all stroke patients (including patients with brainstem stroke): **positive correlation between magnitude of mean deviation of SPV and SCP** (p<10^-6*, r=-0.71). Within patients with LwP, significant greater differences between modalities (SVV, SHV, SPV) (p=0.001*, F(2.111)=7.1) with a higher deviation in SPV compared to SVV and SHV.
			SHV
Perennou et al., 2008 [2]	Deviation	SHV ranges: LwP: -9.5 to -5.6, CL-LP: -17.1 to 3.8, non-LwP: NR, H: -3.1 to 3.5 (mean H: 0.25 (1.7)).	Significant higher deviation in **contralesional direction** in LwP patients compared to CL-LP, non-LwP and H participants (p<10^-6*, F=321.7). In all stroke patients (including patients with brainstem stroke): **positive correlation between magnitude of mean deviation of SHV and SCP (p<10^-3, r=-0.49*).**

*BLS = Burke Lateropulsion Scale; CI = confidence interval; CL-LP: group with contralesional lateropulsion, without pushing; H = healthy participants; L = left; LwP = (group) stroke patients with Lateropulsion with active Pushing; LwP(SN+) = (group) with LwP and spatial neglect; LwP(SN-) = (group) with LwP but without spatial neglect; non-LwP: (group) stroke patients without LwP; NR = not reported; R = right; SCP = Scale for Contraversive Pushing; SD = standard deviation; SHV = subjective haptic vertical; SPV = subjective postural vertical; SVV = subjective visual vertical. Underlined = indicates median values; italics = indicates self-calculated mean values, deviation = positive value indicate ipsilesional/ clockwise direction, negative value contralesional/ anticlockwise direction of deviation; * = significant (p<0.05).*

Appendix A. PRISMA Checklist. *(Page numbers based on title page followed by abstract and main document)*

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	17
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13-14

Appendix B. PRISMA Checklist for abstracts.

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	Yes

Appendix B. Rating criteria NOS scale for case control studies with additional criteria regarding research question.

	Criteria	RQ	Rating criteria
Selection	*Adequate case definition*	1, 2	- The patient(s) has/have a diagnosis of a stroke - LwP is diagnosed by a validated scale (SCP or BLS)
	Representatives of cases	1, 2	- The number of patients is more than one - Patients were consecutively admitted OR - Inclusion and exclusion criteria are described - Inclusion and exclusion criteria are reasonable and not too strict - Heterogeneity between group (lesion location and gender) - Exclusion criteria of study are not based on lesion location and/or gender
	Selection of controls	1 2	- Control participants were recruited from a community (Control participants recruited from hospital or rehabilitation center: no star) - Stroke patients without LwP and healthy participants were recruited
	Definition of controls	1, 2	- Controls are stroke patients with LwP as measured by validated scale - Controls are stroke patients without history of LwP as measured by a validated scale (BLS or SCP) - The authors show predefined criteria concerning LwP and divide patients in groups based on the criteria - The outcome of the LwP assessment for controls is also mentioned in the article
Compare-bility	*Comparability of cases and controls (max 2 stars possible)*	1, 2	- Author compares both groups to determine comparability of age - Author compares both groups to determine comparability of time after stroke OR gender OR lesion location
Exposure	*Ascertainment of exposure*	1 2	- Lesion mapping is applied using a well-described and validated method - Perception of verticality is measured by a validated tool or the tool is well described and reasonable
	Same method for cases and controls	1, 2	- Control group was exposed by the same measurement or treatment method as the experimental group
	Non response rate	1, 2	- All the recruited patients were evaluated - Data of all recruited patients were reported

BLS = Burke Lateropulsion Scale; RQ = research question; SCP = Scale for Contraversive Pushing;