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Antwerp, 2023

GAINING INSIGHT INTO THE COGNITIVE-MOTOR RELATIONSHIP AFTER STROKE

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ATTENTIVELY MOVING REHABILITATION FORWARD

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Gaining insight into the cognitive-motor relationship after stroke:

Attentively moving rehabilitation forward

Inzicht verwerven in de cognitief-motorische relatie na een beroerte:

Met aandacht de revalidatie vooruit helpen

Dissertation submitted in fulfillment of the requirements for the degree of Doctor of Medical Sciences at the University of Antwerp

By

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Antwerp, 2023

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ENGLISH SUMMARY

The central focus of this thesis was on deepening the understanding of the relationship between cognitive and motor functions after stroke. To achieve this, we formulated three aims. The *first aim* was to evaluate the efficacy of combined cognitive-and-motor therapy for improving cognitive, motor and cognitive-motor outcomes after stroke. Cognitive-and-motor therapy engages individuals simultaneously in motor and cognitive behaviors. By doing so, it is suggested that greater therapeutic effects can be gained, as compared to isolated motor or cognitive interventions.

The *second aim* was to delve deeper into this relationship, by examining the association between specific cognitive and motor deficits after stroke. While stroke can lead to a wide spectrum of neurocognitive and motor deficits, our research specifically focused on the association between spatial neglect and postural control. This is particularly relevant, considering that spatial neglect is a very prevalent cognitive disorder after stroke. It is characterized by a lateralized attention deficit that predominantly affects one side of space or the body. We focused on two subtypes of spatial neglect: visuospatial neglect and personal neglect. In addition to these cognitive aspects, we have chosen to assess postural control as a critical aspect of motor functioning. Postural control refers to the control of the body's position in space, for the dual purpose of stability (controlling the center of mass in relation to the base of support) and orientation (controlling the body segments to each other, the task and the environment). This is a complex motor skill, derived from the interaction between multiple sensorimotor and cognitive processes. As its definition implies, postural control is significant for the performance of various daily-life activities, such as sitting, standing and functional mobility. Therefore, gaining a deeper understanding of the factors contributing to the restoration of postural control after stroke holds great significance.

The *third and final aim* was to evaluate the recovery time course of visuospatial and personal neglect, as this seems to be crucial to consider when studying the association of spatial neglect with postural control.

Chapter 1 of this thesis included a general introduction of stroke, its consequences, and its recovery. It introduces cognitive-motor relationships and puts forth why cognitive-and-motor therapy is hypothesized to be more beneficial, compared to isolated intervention. The chapter

also introduces a hypothesis that sheds light on the apparent limitations in the current efficacy of cognitive-and-motor therapy. Additionally, it proposes an investigation into the cognitive-motor relationship post-stroke by exploring how spatial neglect associates to postural control.

Chapter 2 examined the effects of cognitive-and-motor therapy on motor, cognitive and cognitive-motor outcomes after stroke through a meta-analysis of current literature. It revealed that cognitive-and-motor therapy provides a small yet statistically significant additional benefit for improving cognitive outcomes. These findings implied that motor training incorporating cognitive engagement can yield clinically relevant improvements for stroke patients. While current studies on cognitive-and-motor therapy offered valuable insights into the potential benefits and pitfalls of integrating cognitive and motor behaviors, a comprehensive understanding of the underlying mechanisms driving observed results, or lack thereof, remains unknown.

Chapter 3 examined the association of spatial neglect with postural control after stroke. **Chapter 3.1** reviewed the literature on how visuospatial neglect is associated with balance and mobility after stroke. Results indicated an association of visuospatial neglect with an increased need for assistance while *sitting*, with an asymmetric posture toward the affected body side. For *standing balance*, visuospatial neglect was associated with larger mediolateral instability during weight-shifting, and in some cases, also larger weight-bearing asymmetry during steady-state quiet stance. For *goal-directed walking*, people with visuospatial neglect laterally deviated from their path. Nevertheless, research evaluating the association between visuospatial neglect recovery and improvements in standing balance and mobility remains scarce. **Chapter 3.2** explored the association between personal neglect and motor function, daily activities, and participation outcomes after stroke. The chapter suggested that personal neglect was associated with decreased motor function, reduced functional mobility, and heightened dependency in daily activities. Stroke survivors with personal neglect had higher odds to experience extended hospital stays and a higher likelihood of non-home discharges. However, there is a significant lack of studies evaluating how the recovery of personal neglect associates to such rehabilitation outcomes over time. **Chapter 3.3** sought an explanation for the associations found in Chapter 3.1 and Chapter 3.2 (e.g., lateropulsion) and reviewed how spatial neglect was associated to verticality misperception after stroke. Spatial neglect was associated with Subjective Visual Verticality misperception in terms of line tilts and uncertainty measures. It was therefore suggested that such a misperception is a key feature of neglect. Modalities other than the visual one were poorly investigated or only yielded inconclusive results, as are longitudinal studies evaluating recovery of verticality misperception after stroke. In **Chapter 3.4**, a longitudinal observational cohort study evaluated the longitudinal association of egocentric and allocentric visuospatial neglect to the recovery of standing balance in the first 12 weeks after stroke. It showed that both egocentric and allocentric neglect were significantly associated with decreased standing independence, but not with larger postural instability or greater asymmetric weight-bearing. This chapter suggested that once a subject regains independent standing, visuospatial neglect (measured using a paper-and-pencil cancellation test) does not independently contribute to deficits in postural control or to greater weight-bearing asymmetry within the initial 12 weeks following a stroke.

In **Chapter 4**, the time course of visuospatial and personal neglect was evaluated. This chapter revealed significant improvements in egocentric visuospatial neglect scores within the first 5 weeks post-stroke, followed by a plateau. Body representation neglect improved significantly from week 3 to 12 post-stroke. No significant improvements over time were found for allocentric visuospatial neglect and tactile neglect.

The thesis contributed to our understanding of the relationship between cognitive and motor functions after stroke. It underscored the potential benefits of cognitive-and-motor therapy for stroke rehabilitation and shed light on the associations between spatial neglect and postural control. It highlighted important clinical implications, including the need for a holistic approach to rehabilitation that considers the relationship between cognitive and motor impairments. The potential benefits of cognitive-and-motor therapy were highlighted, particularly when tailored to individual. Additionally, the need for a multi-test approach to assess spatial neglect, especially in light of the time post-stroke, was emphasized. Recommendations for future research were made and included the need for refining cognitive-and-motor therapy methodologies, further research into specific neglect subtypes and their progression over time, and a deeper exploration of the association of personal neglect with motor function. The thesis also suggested that future studies should also examine how a misperception of verticality may play a role in the association between spatial neglect and postural control after stroke, and that future research should widen its scope to studying the cognitive and motor relationship by evaluating cognitive deficits beyond spatial neglect.

LIST OF ABBREVIATIONS

95% CI	95% Confidence Interval
AP	Anterior-Posterior
AR	Augmented Reality
BHT	Broken Hearts Test
BMI	Body Mass Index
C	Cohort study
Cm	Centimeter
CMT	Cognitive-and-Motor Therapy
CoM	Center of Mass
CoP	Center of Pressure
CoP_{vel}	Center of Pressure velocity
CS	Cross-sectional study design
EC	Eyes Closed
EO	Eyes Opened
F	Female
ICF	International Classification of Functioning, Disability and Health
IQD	Interquartile distance
LBT	Line Bisection Test
m	Meter
M	Male
Max	Maximum
Min	Minimum
ML	Medio-Lateral
mm	Millimeter
Mod	Moderate
n	Number of
NS	Not Significant
PEDro	Physiotherapy Evidence Database

PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PSN	personal space neglect
RCT	Randomized Controlled Trial
RMS	Root Mean Squared
s	Seconds
SCT	Star Cancellation Test
SD	Standard deviation
SHV	Subjective Haptic Vertical
SN	Spatial neglect
SPV	Subjective Postural Vertical
STROBE	Strengthening the reporting of observational studies in epidemiology
SVV	Subjective Visual Vertical
VR	Virtual Reality
VSN	Visuospatial neglect
VSTT	Visuospatial Search Time Test

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LIST OF A1 PUBLICATIONS THROUGHOUT THIS THESIS OBTAINED DURING PHD

CHAPTER 2 – COGNITIVE-AND-MOTOR THERAPY AFTER STROKE

- **Elissa Embrechts**, Thomas B. McGuckian, Jeffrey M. Rogers, Chris H. Dijkerman, Bert Steenbergen, Peter H. Wilson, Tanja C.W. Nijboer. Cognitive-and-Motor Therapy After Stroke Is Not Superior to Motor and Cognitive Therapy Alone to Improve Cognitive and Motor Outcomes: New Insights From a Meta-analysis. Archives of Physical Medicine and Rehabilitation, 2023, ISSN 0003-9993, https://doi.org/10.1016/j.apmr.2023.05.010.

CHAPTER 3 – THE RELATIONSHIP BETWEEN SPATIAL NEGLECT AND POSTURAL CONTROL AFTER STROKE

- **Elissa Embrechts**, Tamaya Van Criekinge, Jonas Schröder, Tanja Nijboer, Christophe Lafosse, Steven Truijen, Wim Saeys. The association between visuospatial neglect and balance and mobility post-stroke onset: A systematic review. Annals of Physical and Rehabilitation Medicine, Volume 64, Issue 4, 2021, 101449, ISSN 1877-0657, DOI: 10.1016/j.rehab.2020.10.003.
- **Elissa Embrechts**, Renata Loureiro-Chaves, Tanja C.W. Nijboer, Christophe Lafosse, Steven Truijen, Wim Saeys. The Association of Personal Neglect with Motor, Activities of Daily Living, and Participation Outcomes after Stroke: A Systematic Review. Archives of Clinical Neuropsychology, 2023, ISNN 1873-5843, DOI: 10.1093/arclin/acad063.
- **Elissa Embrechts**, Charlotte van der Waal, Dorine Anseeuw, Jessica van Buijnderen, Améline Leroij, Christophe Lafosse, Tanja CW Nijboer, Steven Truijen, Wim Saeys. Association between spatial neglect and impaired verticality perception after stroke: A systematic review. Annals of Physical and Rehabilitation Medicine, Volume 66, Issue 3, 2023, ISSN 1877-0657, DOI: 10.1016/j.rehab.2022.101700.
- **Elissa Embrechts**, Jonas Schröder, Tanja C.W. Nijboer, Charlotte van der Waal, Christophe Lafosse, Steven Truijen, Wim Saeys. Does visuospatial neglect contribute to standing balance within the first 12 weeks post-stroke? A prospective longitudinal cohort study. BMC Neurology. Accepted. DOI : 10.1186/s12883-023-03475-1.

CHAPTER 4 – TIME COURSE OF RECOVERY OF SPATIAL NEGLECT IN THE SUBACUTE PHASE POST-STROKE

- **Elissa Embrechts**, Jonas Schröder, Charlotte van der Waal, Christophe Lafosse, Steven Truijen, Wim Saeys, Tanja C.W. Nijboer. Time Course of Recovery of Visuospatial and Personal Neglect in the First 12 Weeks after Stroke: an Exploratory longitudinal Cohort Study. Neuropsychological Rehabilitation. *Under review.*

CHAPTER 1

GENERAL INTRODUCTION

1. Stroke

Stroke is one of the leading causes of disease burden worldwide, with an estimated 80.1 million stroke cases in 2016 [1]. In Belgium, approximately 19,000 people experience a stroke each year [2, 3], equivalent to 52 people a day. With aging populations, the prevalence of stroke is expected to increase substantially [4]. Not surprisingly, it is the second highest cause of death and a prominent contributor to long-term disability worldwide [5].

The term 'stroke' encompasses various stroke types, making its definition multifaceted and extensive. It includes central nervous system infarctions, intracerebral hemorrhages, subarachnoid hemorrhage and cerebral venous thrombosis [6]:

- **Central nervous system infarction** is characterized by death of brain, spinal cord, or retinal cells due to ischemia, based on pathological, imaging, and clinical evidence of permanent damage, with symptoms persisting for ≥24 hours or until death [6]. This category comprises **ischemic stroke**, denoting neurological dysfunction resulting from (multi)focal cerebral, spinal, or retinal infarction, accompanied by evident clinical symptoms. Additionally, central nervous system infarction encompasses **silent infarctions**, in which there are no evident clinical symptoms, while there is imaging or pathological evidence of an infarction [6]. In 2019, data reveals that ischemic strokes were the predominant type, encompassing 62.4% of all new stroke cases [7, 8].
- In case of an **intracerebral hemorrhage**, there is a (multi)focal accumulation of blood within the brain parenchyma or ventricular system, unrelated to trauma [6]. This leads to a rapid development of neurological dysfunction. Additionally, **silent cerebral hemorrhages** may occur, in which there is neuroimaging or pathological evidence without a history of acute neurological dysfunction. Intracerebral hemorrhages accounted for 27.9% of new stroke cases in 2019 [7, 8].
- **A subarachnoid hemorrhage** refers to a bleeding within the subarachnoid space (i.e., the space between the arachnoid membrane and the pia mater of the brain or spinal cord), not caused by trauma. There is a rapid development of neurological dysfunction and/or headache [6]. Subarachnoid hemorrhage, though less prevalent, still constituted 9.7% of new strokes in 2019 [7, 8].

- **Cerebral venous thrombosis** refers to an infarction or hemorrhage in the brain, spinal cord or retina that is due to a thrombosis of a cerebral venous structure [6].

In the current thesis, we focus on ischemic or hemorrhagic cerebral brain strokes that involve the brain arteries. Therefore, subarachnoid hemorrhages and cerebral venous thromboses are not considered.

Despite substantial advances in acute stroke treatment, such as thrombolysis and thrombectomy for ischemic stroke, the global stroke burden continues to rise due to the aging population and an increasing number of disability-adjusted life years in developing countries [7-9].

1.1. Consequences of stroke

Stroke may include a wide range of physical [4], sensory [10], communication [11], emotional [12], and cognitive consequences [13]. Considering the majority of strokes are hemispheric brain strokes, the typical sensorimotor signs of a post-stroke individual include a sensorimotor hemiparesis or hemiplegia, contralateral to the side of the brain lesion [4].

The consequences described above may in turn lead to a reduction in everyday functional abilities, participation, and overall quality of life [14, 15]. Classically, the International Classification of Functioning, Disability and Health (ICF) provides a multidimensional framework for health and disability, used to classify the wide spectrum of impairments, limitations and restrictions post-stroke [16]. It provides an international, standardized framework to distinguish impairments in body functions and structures, which may affect the levels of activity and participation, and places it in the context of personal and environmental factors. An overview of common post-stroke consequences is presented in Figure 1.1.

On an ICF body function level, motor impairments may include, among others, muscle weakness, spasticity or loss of coordination [4], and altered sensation could lead to hyper -or hyposensitivity to sensory stimuli [10]. Cognition encompasses a wide range of mental abilities required for perceiving, processing, and interacting with the environment, and cognitive impairments may therefore include memory problems, trouble concentrating and attentional impairments [13]. Emotional impairments could result in mood fluctuations, post-stroke depression and heightened anxiety [12, 17]. Speech difficulties, such as word finding or production problems, might hinder effective communication, potentially causing difficulties

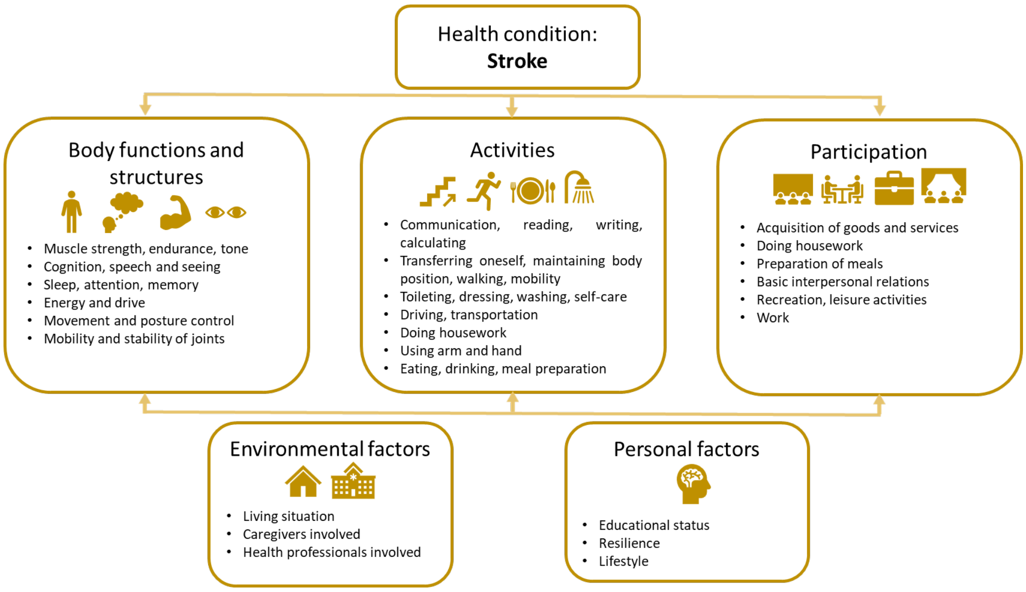


Figure 1.1. A visual representation of the International Classification of Functioning, Disability and Health for the health condition 'stroke'. It enables a holistic view on post-stroke consequences. Common consequences per domain have been added to aid interpretation.

in understanding instructions [11]. All of the above factors may affect the ability to perform activities of daily-living and may impact the individual's participation.

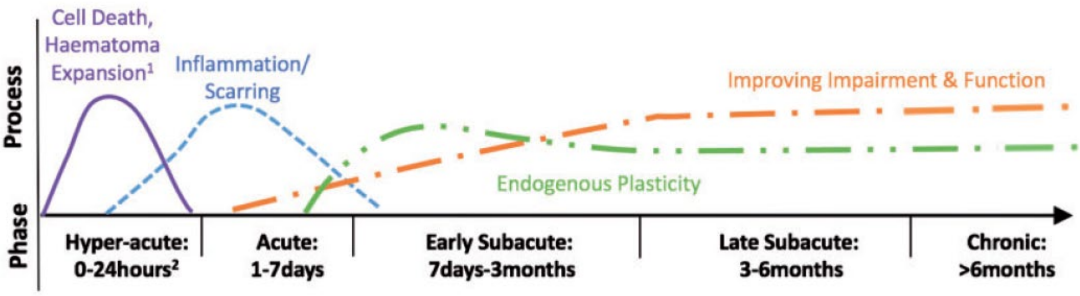
1.2. The path to recovery after stroke

1.2.1. Time course of recovery and prognosis

To facilitate a systematic understanding of the post-stroke recovery process, five time phases can be described: 1) Hyper-acute phase (0-24 hours after stroke), 2) Acute phase (1-7 days after stroke), 3) Early subacute phase (7 days - 12 weeks after stroke), 4) Late subacute phase (12 weeks - 24 weeks after stroke), and 5) Chronic phase (> 24 weeks after stroke) (Figure 1.2). This categorization provides a structured framework for studying stroke recovery systematically [18, 19]. The rationale behind this is that recovery post-stroke is time-dependent (Figure 1.2).

(Hyper)acute phase

In case of ischemic strokes, the faster blood flow to the brain is restored, the fewer brain cells will die, underscoring the critical principle that "time equals brain". Acute treatment of stroke focuses on early reperfusion of at-risk tissue with intravenous thrombolysis through two primary methods: (intravenous thrombolysis, which involves using medication to dissolve blood clots, or endovascular thrombectomy, a procedure to mechanically remove the blood clot [20]. In case of hemorrhagic strokes, the primary goal is to promptly stop the bleeding.



[1] Haemorrhagic stroke specific. [2] Treatments extend to 24 hours to accommodate options for anterior and posterior circulation, as well as basilar occlusion.

Figure 1.2. This figure is derived from *Bernhardt, Hayward and colleagues [18].* It is a visual representation of the critical timepoints post-stroke that relate to the currently known biology of recovery.

This involves the management of blood pressure and may, in some instances, necessitate neurosurgical procedures, such as a craniotomy [21].

Rehabilitation phase

As individuals transition into the rehabilitation phase, they have typically achieved medical stability. The phase is characterized by the implementation of rehabilitation programs that are essential to guiding recovery, restoring functional independence, and enhancing overall quality of life [22].

The term **recovery** refers to the improvement of outcomes between different timepoints after stroke. It encompasses both the measurable improvement in, for example, muscle strength, walking, and standing ability, as well as the underlying mechanisms driving this progress [23]. These mechanisms may involve behavioral restitution, which refers to the restoration of pre-stroke movement control, as well compensation strategies, which involve alternative approaches to achieve goals. **Restitution** emphasizes performance quality, usually situated on an ICF body function level. When studying the motor system, evaluating restitution this often requires instrumented assessment methods, such as biomechanical analysis to evaluate kinematics and kinetics. In contrast, **compensation** strategies involve task accomplishment and learning, without always necessitating neural repair [18, 24].

Functional recovery after stroke involves a comprehensive approach that is aimed at helping the individual with stroke regain as much independence and quality of life as possible. This can encompass various aspects of a person's life, from physical mobility to cognitive and emotional well-being. The primary goal is to enable the individual to perform everyday activities and participate in social and recreational activities, while managing and adapting to any disabilities or limitations resulting from the stroke. Functional recovery varies between individuals and is depended upon various factors. These may include, among others, the type and severity of the stroke, time post-stroke, baseline clinical status (e.g., consciousness, level of physical impairment, cognitive status, …), individual characteristics (e.g., age, comorbidities, …), and the available resources and support [25-27].

The time course of recovery is, in most cases, characterized by a natural logistic pattern of improvement in functions, with the majority of recovery occurring within the first 12 weeks post-stroke with recovery rapidly levelling off afterwards [18, 19, 28-30]. This seems to be irrespective of the impairment being assessed.

Chronic phase

While the majority of recovery occurs within the first few weeks after a stroke, ongoing improvements and behavioral changes can persist for years [31]. The impact of a stroke can be lifelong, underscoring the importance of maintaining functional abilities and monitoring post-stroke quality of life on the long term.

2. Cognitive-and-motor therapy after stroke: moving rehabilitation forward?

2.1. Cognition interacts with movement, and vice versa

Generally, engaging in physical activity is widely recognized for its health benefits, including the prevention of chronic diseases, improved fitness, and enhanced quality of life [32, 33]. Apart from this, physical activity can have positive effects on cognition [34]. This is not surprising, given that activities such as playing soccer or basketball necessitate decision-making and strategic planning, involving cognitive processes such as attention, visuospatial skills, and problem-solving [35-37]. Consequently, optimal cognitive function is vital for participating in and sustaining physical activity [35-37].

The nuanced coordination involved in planning and governing our movements might not have crossed our minds, yet it is evident that activities such as playing sports, typing, tossing a ball, or even just drawing, go beyond mere reflexes. Unlike the automatic response of retracting a hand upon touching a hot surface, these actions stem from more than external triggers and rather emerge through a series of cognitive processes [38]. There is thus a clear relationship between cognitive and motor functions.

2.2. Standalone cognitive or motor therapy vs. combined cognitive-and-motor therapy

In stroke rehabilitation, evidence shows beneficial effects of physical therapy to improve motor [39-41] and even cognitive outcomes after stroke [42]. However, no single approach to physical rehabilitation is any more (or less) effective in promoting recovery of function and mobility [40, 41]. Besides this, intervention effects are often restricted to the period of intervention alone and are mainly related to the functions and activities specifically trained by the intervention [39, 40]. Similarly, cognitive interventions show only modest benefits for cognition [43-45], indicating that there is a lack of generalization of effects which seem to be non-lasting.

The growing recognition of the relationship between cognitive and motor functions has sparked the development of combined cognitive-and-motor therapy (CMT) [34]. This integrated approach aims to engage individuals simultaneously in motor and cognitive behaviors [34]. By incorporating such multimodal therapies, it is suggested that a synergistic effect on brain plasticity can be achieved, resulting in greater therapeutic gains compared to isolated motor or cognitive interventions [34]. Stroke rehabilitation serves as an excellent example where CMT may gain prominence, as stroke consequences may involve impairments in both motor and cognitive functions [13, 46].

While research into CMT's efficacy is expanding, recent meta-analyses have predominantly concentrated on gait and balance outcomes within the chronic phase of stroke recovery, showcasing moderate positive effects compared to motor-only therapies [47-50]. However, questions persist regarding CMT's broader impact on a range of motor, cognitive, and cognitive-motor outcomes, especially within the subacute phase of stroke recovery (within six months) – despite this period being the most intensive for rehabilitation [51]. Furthermore, the durability of CMT's benefits beyond immediate post-treatment remains uncertain.

A potential reason for the limited magnitude of effects observed in prior studies could be an incomplete understanding of the relationship between cognitive and motor functions post-stroke. To gain a more profound insight into this relationship, we focused on exploring the relationship between spatial neglect, a common cognitive disorder after stroke, and postural control.

3. Spatial neglect and its relationship with motor function after stroke

3.1. Attention and awareness after stroke

Attention plays a fundamental role in the ability to understand, and engage within, our surrounding environment. It allows us to focus on specific aspects of the environment, while filtering out irrelevant or distracting stimuli [52]. It acts as a spotlight, directing our mental resources towards relevant stimuli or tasks [53] and can therefore be considered the gateway to our conscious awareness [52-54].

Spatial neglect is a prevalent cognitive post-stroke disorder characterized by a lateralized attention deficit. This translates itself into a reduced attention towards (usually) the contralesional hemispace and an increased capture of information in the (usually) ipsilesional hemispace, which cannot be attributed to sensorimotor or memory impairments [55-57]. Neglect in general is considered a syndrome consisting of multiple spatial and non-spatial components that affect various aspects of attention [58].

3.1.1. Neglect heterogeneity

The nature of neglect is inherently heterogeneous. It may encompass a diverse range of symptoms that could involve different reference frames (egocentric/viewer-centered or allocentric/object-centered), processing stages (perceptual/sensory, representational, and motor), and physical spaces (personal/body, peri-personal/reaching distance, and extra-personal/beyond reaching distance) [59]. Consequently, a range of assessment tools has been developed, resulting in varying reported prevalence rates (from 18% to 80%), depending on the tool, constructs evaluated, and evaluation timing [59, 60].

The current thesis primarily addresses two main types of spatial neglect: visuospatial neglect and personal neglect. These two types will be explained in more detail within the following sections.

Visuospatial neglect

Visuospatial neglect, the most commonly studied form of spatial neglect, involves neglect for visual stimuli [61]. Among other observations, individuals with visuospatial neglect may bump into objects on their neglected side during locomotion, may eat only the food on the non-neglected side of their plate, or only attend to the non-neglected side of a page when reading a book [62]. It can manifest in different physical spaces (personal/body space, peri-personal/within reach, extra-personal/beyond reach) and reference frames. In terms of reference frames, two main types of visuospatial neglect are recognized: egocentric (or viewer-centered) and allocentric (or object-centered). Egocentric visuospatial neglect is defined with respect to an individual's trunk or head position. Here, individuals may only attend to targets on one side (e.g., the right side) while ignoring targets on the other side. In case of allocentric visuospatial neglect, there is an impaired spatial coding of objects relative to each other. Therefore, one side of an object is neglected (e.g., the left side), regardless of its position relative to their body's center [61] (Figure 1.2).

During clinical evaluation, visuospatial neglect is typically assessed using conventional paper-and-pencil tests, such as cancellation tasks or line bisection tasks [51].

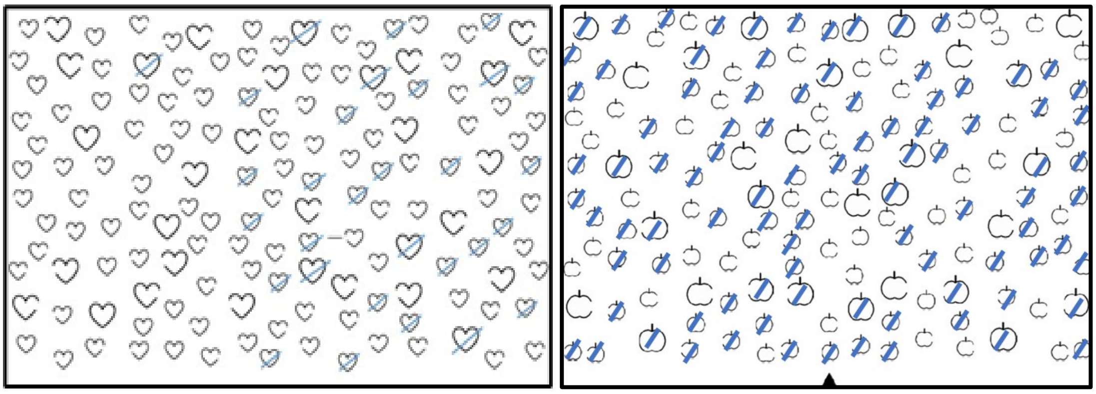


Figure 1.2. In the presented figure, two cancellation tasks are illustrated: the Broken Hearts Test (left) and the Apple Test (right). In both assessments, individuals are instructed to mark or cross out fully drawn hearts or apples. In the Broken Hearts Test, evidence of egocentric visuospatial neglect is apparent, as the individual only marked full hearts on the right side of the page. Conversely, the Apple Test reveals indications of allocentric visuospatial neglect. The individual attends to stimuli on both sides of the paper, however, also marked incomplete apples (in this case, those with a left-opening).

Personal neglect

Personal neglect involves a lateralized attention deficit to on one side of the body, usually contralesional. Despite the potential impact on daily life through the presentation of specific clinical observations, such as individuals only grooming the non-neglected facial side, “forgetting” to dress the neglected body side, or disregarding the neglected arm [61, 63], personal neglect remains a highly understudied disorder, and its systematic consideration in scientific and clinical studies is limited [63].

Within the spectrum of personal neglect, different subtypes exist, each with its unique characteristics [64]. The subtypes falling under the umbrella term of personal neglect include:

- Body representation neglect: involves a reduced body exploration related to a distorted self-body representation [61, 63-65].
- Somatosensory neglect: encompasses errors in perceiving tactile or proprioceptive stimuli occurring on the neglected body side, in the absence of primary somatosensory deficits [61, 63, 64].
- Motor neglect: manifests as a reduced spontaneous utilization of the contralesional body side [61, 63, 64, 66].
- Premotor neglect: involves a decreased tendency to initiate movements of non-neglected limbs towards the neglected side of the body [61].

3.2. Recovery of spatial neglect vs. recovery of motor function after stroke

3.2.1. The recovery of spatial neglect

Spatial neglect recovery is understudied as compared to the recovery of motor function after stroke. Few studies have examined the time course of spatial neglect recovery, revealing a period of significant improvement during the first 12-14 weeks post-stroke onset. This improvement is then quickly followed by a plateau [29, 67-72]. These longitudinal studies have primarily focused on visuospatial neglect, and particularly on its spatial characteristics (such as, omissions and deviations), while the recovery of its temporal aspects (such as, search times in contra- versus ipsilesional hemispace) have not been evaluated. Additionally, the time course of recovery of personal neglect, remains unknown.

3.2.2. Association of spatial neglect and motor function

A study by Nijboer et al. [62] investigated the association between the recovery of visuospatial neglect and the recovery of upper limb motor function following stroke. Their findings revealed that more severe visuospatial neglect was associated with less improvements in upper limb motor function [73]. The authors suggested the possibility of an inhibitory effect of visuospatial neglect on the recovery of upper limb motor function. Furthermore, other studies have highlighted the significance of spatial neglect severity as an independent predictor of upper limb motor recovery [74, 75].

However, our understanding of how spatial neglect may relate to other motor activities, such as sitting, standing, and functional mobility, remains limited. While these activities may seem effortless for individuals in good health, they are, in fact, governed by a well-functioning postural control system [76]. Consequently, among the various sensorimotor consequences following a stroke, impaired postural control is likely to have the most substantial impact on an individual's ability to engage in daily-life activities [77, 78]. As a result, it is not surprising that the recovery and treatment of balance and mobility rank among the top 10 research priorities in the context of life after stroke [79]. Therefore, gaining a deeper understanding of the factors contributing to the recovery of postural control after stroke holds great relevance.

4. How and why would spatial neglect associate with postural control deficits after stroke?

4.1. Our postural control system

Postural control refers to the control of the body’s position in space, for the dual purpose of stability and orientation [76]. Postural stability is the ability to control the center of mass in relationship to the base of support [76]. Postural orientation refers to the relationship of the body’s segments to each other, to the task, and to the environment. For most functional tasks, we maintain a vertical body orientation.

Postural control is a complex motor skill, derived from the interaction of multiple sensorimotor and cognitive processes. The functioning of our postural control system can be described in light of the input – processing – output model [80]. The input level encompasses the afferent information coming from various senses, such as our vision, vestibular system and somatosensory system (e.g., proprioception, touch) [76, 80]. This afferent information arrives at the central nervous system, where it undergoes higher-order cognitive processing. These processes ensure perception and interpretation of the sensory input, as well as the conceptualization and buildup of a strategy/plan for balance and/or movement [80]. One important aspect of this process is the construction of a coherent internal model that represents the body's position and orientation in space, around which postural control can be organized [80]. Some cognitive functions involved in this process include attention, planning, executive functioning, motivation as well as emotional aspects. After processing, neural commands are sent towards the end-effectors (i.e., muscles for postural control), which subsequently produce a motor output. The generated output (e.g., standing) is dependent upon the biomechanical degrees of freedom (or constraints) of the individual [76, 80]. A disorder in any one, or a combination, of these steps may thus induce problems with postural control.

4.2. Spatial neglect and postural control

Spatial neglect is characterized by an attentional bias, leading to a decreased awareness of and attention for the neglected hemispace [61, 81]. Consequently, the processing of sensory information related to that hemispace is compromised. This may lead to incomplete or distorted interpretations of the environment, as well as to an impaired body representation [61, 81]. As a result, the internal models used for generating the neural commands that ensure postural control, may be affected in terms of their accuracy. Individuals with spatial neglect could therefore experience challenges with maintaining postural control (i.e., postural stability and/or orientation) (Figure 1.3).

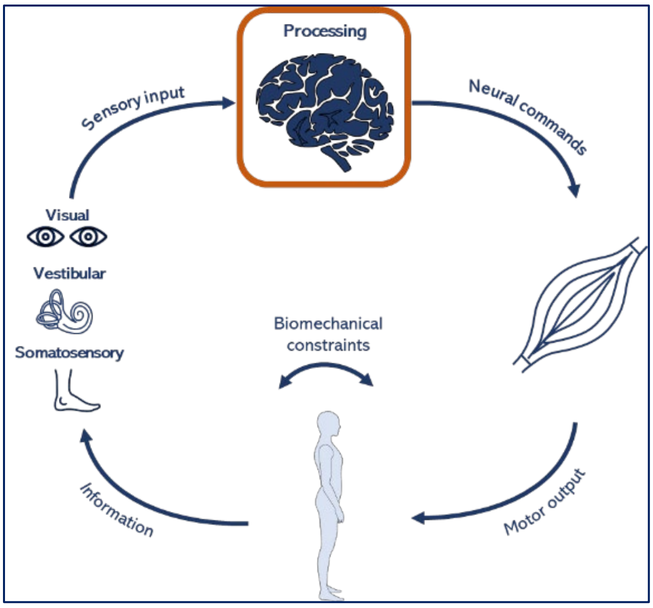


Figure 1.3. A visual representation of the input-processing-output model. Spatial neglect may impair the processing of sensory information related to the neglected hemispace or body side, and is thus situated at the processing level (orange square).

In the context of the spatial neglect types central to the framework presented in this thesis, visuospatial neglect may be related to difficulties with planning, orientation, execution, and coordination, given the crucial role of visual feedback in motor tasks. Regarding personal neglect, motor neglect could directly impair motor task execution by reducing involvement of the neglected body side. Activities requiring bilateral coordination—such as walking, standing, and object manipulation—might be particularly affected. Premotor neglect's reduced initiation of movements toward the neglected side could also disrupt these activities.

Also the distorted self-body representation that characterizes body representation neglect could lead to challenges with body orientation and directing movements in space. Somatosensory neglect, characterized by errors in perceiving tactile and proprioceptive stimuli, may disrupt the feedback loop essential for refining motor actions, further contributing to postural control challenges.

While previous studies have suggested a potential association between spatial neglect and impaired sitting balance, standing balance and gait, our understanding of this relationship remains limited [82, 83]. To which extent spatial neglect is associated with impairments in different areas of balance and mobility remains unknown [82]. Moreover, prior studies evaluating this relationship focused mainly on visuospatial neglect, whereas other types of neglect, such as personal neglect, have not been addressed. Finally, there is a lack of longitudinal studies that evaluate the underlying mechanisms of a potential relationship, for example with regards to changes in underlying postural control, especially within the subacute phase post-stroke.

4.3. Perception of verticality, postural control and spatial neglect

Verticality perception refers to the ability to perceive and maintain an accurate sense of the true vertical position, which is parallel to the gravitational vector at 0° [84]. Accurate verticality perception is considered essential for postural control through the maintenance of a correct postural orientation, that is, an upright posture with respect to gravity and a correct estimation of the orientation of objects in the surrounding environment [84, 85]. It relies on an internal model of verticality, which integrates information from multiple sensory inputs [86-88].

In spatial neglect, afferent information processing may be impaired, thus hampering the spatial representation of the gravitational vector. Prior studies already proposed a link between spatial neglect and verticality misperception [82, 83, 86]. However, the specific nature of this association remains unclear, especially in light of time post-stroke. Understanding this relationship would increase insight into underlying mechanisms that may contribute to potential deficits in postural control in individuals with spatial neglect.

5. Aims and outline

The primary focus of this dissertation is to evaluate cognitive-motor relationships after stroke. The overarching aim to enhance our understanding of these relationships by looking into a specific cognitive post-stroke disorder, spatial neglect, and how it associates with postural control.

The *first sub-aim* is to assess CMT efficacy for improving cognitive, motor, and cognitive-motor outcomes after stroke, all time phases post-stroke considered. This will be discussed in **Chapter 2**.

The *second sub-aim* is to investigate the cognitive-motor relationship after stroke by examining the association between spatial neglect and postural control. This will be discussed in **Chapter 3**. In **Chapter 3.1**, emphasis will be placed on visuospatial neglect, a widely studied subtype of spatial neglect. By systematically reviewing prior research, this chapter will shed light onto the association between visuospatial neglect and sitting and standing balance, as well as functional mobility post-stroke. **Chapter 3.2** will focus on personal neglect. Given the limited research on this particular subtype of neglect, this chapter will review prior studies that assess how personal neglect relates to motor function, activities of daily living, and overall participation outcomes following stroke. This broader scope is necessary to comprehensively understand the implications of personal neglect, despite its relative lack of attention in previous research. **Chapter 3.3** delves into the relationship between spatial neglect and the perception of verticality after a stroke, a potentially important factor to consider when studying the association of spatial neglect with postural control. **Chapter 3.4** builds upon findings of Chapter 3.1 and encompasses a longitudinal cohort study to evaluate the longitudinal association between visuospatial neglect and standing balance within the first 12 weeks post-stroke onset.

The *third sub*-aim is to evaluate the time course of visuospatial and personal neglect throughout the first 12 weeks post-stroke. This will be prospectively investigated in **Chapter 4**. This knowledge may improve our understanding of spatial neglect and how it recovers, and may shed light onto the results of previous chapters.

Finally, **Chapter 5** of this dissertation contains the synthesis and discussion of the results.

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CHAPTER 2

COGNITIVE-AND-MOTOR THERAPY AFTER STROKE

CHAPTER 2.1

COGNITIVE-AND-MOTOR THERAPY AFTER STROKE IS NOT SUPERIOR TO MOTOR AND COGNITIVE THERAPY ALONE TO IMPROVE COGNITIVE AND MOTOR OUTCOMES: NEW INSIGHTS FROM A META-ANALYSIS

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Published in Archives of Physical Medicine and Rehabilitation (2023):
Elissa Embrechts*, Thomas B. McGuckian*, Jeffrey M. Rogers, Chris H. Dijkerman, Bert Steenbergen, Peter H. Wilson, Tanja C.W. Nijboer. Cognitive-and-motor therapy after stroke is not superior to motor and cognitive therapy alone to improve cognitive and motor outcomes: new insights from a meta-analysis. Archives of Physical Medicine and Rehabilitation (2023). DOI: https://doi.org/10.1016/j.apmr.2023.05.010.

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Abstract

Objective: Cognitive-and-motor therapy is suggested to be more effective than single motor or cognitive therapy in stroke rehabilitation. Two CMT approaches exist: CMT Dual-task ("classical" dual-task where the secondary cognitive task has a distinct goal) and CMT Integrated (where cognitive components of the task are integrated into the motor task). This study evaluates whether CMT is more effective than no/mono-therapies on motor and/or cognitive outcomes, whether effects are lasting and which approach is effective.

Data sources: AMED, EMBASE, MEDLINE/PubMed, and PsycINFO databases were searched in October, 2022.

Study selection: Twenty-six studies fulfilled the inclusion criteria: randomized controlled trials published in peer-reviewed journals since 2010, that investigated adults with stroke, delivered CMT, and included at least 1 motor, cognitive or cognitive-motor outcome.

Data extraction: Data on study design, participant characteristics, interventions, outcome measures (cognitive/motor/cognitive-motor), results and statistical analysis were extracted. Multi-level random-effects meta-analysis was conducted.

Data synthesis: CMT demonstrated positive effects compared to no therapy for motor outcomes (g=0.49 [0.10, 0.88]) and cognitive-motor outcomes (g = 0.29 [0.03, 0.54]). CMT showed no significant effects compared to motor therapy for motor, cognitive and cognitive-motor outcomes. A small positive effect of CMT compared to cognitive therapy for cognitive outcomes (g=0.18 [0.01, 0.36]) was found. CMT demonstrated no follow-up effect compared to motor therapy (g=0.07 [-0.04, 0.18]). Comparison of CMT Dual-task and Integrated revealed no significant difference for motor ($F_{1,\,141}$=0.80, P= .371) or cognitive outcomes ($F_{1,\,72}$=0.61, P=.439).

Conclusions: CMT was not superior to mono-therapies to improve outcomes after stroke. CMT approaches were equally effective suggesting that training that enlists a cognitive load per se, may benefit outcomes. (PROSPERO CRD42020193655).

Keywords: Stroke, Meta-Analysis, Cognitive-and-motor therapy, motor therapy, cognitive therapy

Introduction

Stroke is one of the leading causes of disease burden worldwide, with an estimated 80.1 million stroke cases in 2016 [1]. With aging populations, the prevalence of stroke is expected to increase 20% over the next 10 years [2]. Motor and cognitive deficits after stroke are frequent and enduring, and are central to the activity limitations and participation restrictions that make stroke a leading cause of disability worldwide [3]. While the specific signs and symptoms after stroke vary with the location and extent of brain injury, cognitive consequences may include deficits in attention and information processing, language, visuo-spatial, memory and executive function [4]. Common motor consequences include motor impairments such as paresis and spasticity, and restrictions in upper limb activities, balance and mobility [5, 6]. These frequent consequences affect multiple levels of the International Classification of Functioning, Disability and Health (ICF) [7], which highlights the need for therapies that target various domains of functioning [8].

Recovery of functional abilities after stroke remains extremely challenging. In clinical practice, rehabilitation typically addresses motor and cognitive consequences as discrete and distinct domains resulting in the creation of divergent theoretical frameworks, with more attention typically given to physical and occupational (i.e., mainly motor) rather than cognitive therapy [9-11]. Evidence shows beneficial effects of physical therapy to improve motor [12-14] and even cognitive outcomes [15]. However, no single approach to physical rehabilitation is any more (or less) effective in promoting recovery of function and mobility after stroke [13, 14]. Besides this, intervention effects are often restricted to the period of intervention alone and are mainly related to the functions and activities specifically trained by the intervention [12, 13]. Similarly, cognitive interventions show only modest benefits for cognition [16-18], indicating that there is a lack of generalisation and effects seem to be non-lasting.

Therapies requiring simultaneous performance of motor and cognitive behaviours (cognitive-motor therapy (CMT)) more accurately reflect the demands of daily-life and are therefore considered more ecologically valid. Such multimodal therapies, targeting a range of functions (i.e., cognitive and motor), could produce a synergistic effect on brain plasticity that would induce greater therapy gains than standalone mono-therapies [19-21]. These additive synergistic effects could be explained by the neurophysiological mechanisms related to the "facilitation effects" of motor exercises and "guidance effects" of cognitive exercises [21]. The facilitation effect is an exercise-induced release of neurotrophic factors associated with synaptogenesis and neurogenesis, promoting neuroplasticity and improved cognition [21]. Cognitive stimulation may then guide these neuroplastic processes, and contributes to the functional integration of new neuronal cells in the respective brain circuits to stabilize the neuroplastic changes [21].

CMT can be further classified according to the demands of the cognitive task. The first approach is a "classical" dual-task approach in which the secondary cognitive task has a distinct goal, and is typically used as an additional distractor of the motor task (e.g. subtracting 7 from 100 while walking; *CMT Dual-task*). In the second approach, the cognitive task is incorporated into the motor task and is a prerequisite for successful performance of the motor-cognitive task as a whole (e.g., dancing or walking to objects in a certain order; *CMT Integrated*) [21].

Previous meta-analyses have predominantly focused on evaluating the effectiveness of CMT in improving gait and balance outcomes after stroke [22-25]. These studies generally demonstrated positive effects compared to motor therapy [22-25]. However, there has been limited evaluation of the effectiveness of CMT on other outcomes by prior meta-analyses. Only one explored the effects of CMT on other motor outcomes, such as motor strength and upper limb outcomes, which demonstrated an overall positive effect [26]. Another examined the effects of CMT on dual-task outcomes (i.e., gait speed under dual-task conditions), however, their analysis was limited by the inclusion of only three studies [27]. Similarly, the available evidence regarding the efficacy of CMT on cognitive functions is scarce, with only one previous meta-analysis which showed unclear effectiveness of CMT [22]. Moreover, these latter studies were limited to the chronic post-stroke phase (>6 months post-stroke) [22, 26, 27]. Taken together, it remains unknown whether CMT would be effective in improving a wide range of motor, cognitive, and cognitive-motor outcomes within the subacute phase post-stroke (<6 months), despite this being the period in which most rehabilitation is typically provided [28]. Additionally, so far, only one meta-analysis has evaluated whether the effects of CMT are long-lasting (i.e., whether they persist at follow-up) [23], and none have evaluated whether a CMT Dual-task or CMT Integrated approach provides greater benefits.

Therefore, the current systematic review and meta-analysis evaluates whether CMT is more effective compared to no therapy or mono-therapies (only cognitive or motor therapy) on a broad range of motor and/or cognitive outcomes after stroke, and whether effects remain at follow-up. We also evaluate which CMT approach is most effective (*CMT Dual-task* or *CMT Integrated*) in improving motor and/or cognitive outcomes after stroke. Finally, we investigate a range of additional factors as potential moderators of the therapy effectiveness, such as time post-stroke, therapy intensity, type of outcome and risk of bias.

Methods

The current systematic literature review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [29-31]. Protocol details for the review were registered with the online International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42020193655).

Eligibility criteria

To evaluate contemporary research, the review included original research studies published in English in peer-reviewed journals since 2010. Studies were included if they: (i) investigated an adult (>18 years) stroke sample; (ii) delivered a CMT intervention; (iii) included a '*no therapy', 'motor therapy*' or '*cognitive therapy*' control group; (iv) included at least one standardized motor, cognitive or cognitive-motor outcome, and (v) were a randomized controlled trial (RCT). Exclusion criteria were: (i) studies reporting animal or child research (<18 years old); (ii) studies including mixed populations with no separate reporting of stroke only data; (iii) studies including participants with non-specified neurological conditions; (iv) studies where the intervention consisted of a single treatment session or a multitude of intervention approaches; and (v) case series or studies.

In order for an intervention to be classified as CMT, it had to involve the simultaneous performance of motor and cognitive tasks, either by integrating the cognitive load into the motor task (CMT Integrated) or delivering the cognitive load additionally to the motor task (CMT Dual-task) [21]. The motor or cognitive demands of CMT had to be higher compared to stand-alone cognitive or motor therapy, respectively. For example, interventions that used Wii Fit or Kinect exercises (e.g., skiing, bowling and weight-bearing) without incorporating additional cognitive tasks, were not considered CMT, since the cognitive demands associated with such exercises are minimal and similar to that of solely motor therapy.

Search strategy

The electronic AMED, EMBASE, MEDLINE/PubMed, and PsycINFO, indexing databases were systematically searched. Combinations of subject headings and key words were used relating to the concepts of motor function, cognition, motor-cognitive integration, rehabilitation, and stroke. To illustrate, the full MEDLINE search strategy is presented in Appendix 1. Databases were searched in October, 2022. Reference lists from recent reviews and included articles were also hand searched to identify other potentially relevant publications.

Identification of relevant studies and data extraction

After deleting duplicate papers, three researchers (EE, TM, JR) screened each title and abstract to assess the suitability for inclusion based on the inclusion and exclusion criteria outlined above. Disagreements between reviewers were resolved by a fourth independent reviewer. Those considered potentially eligible were uploaded to Rayyan (https://rayyan.qcri.org) [32] and reviewed in full text by three researchers (EE, TM, JR). Disagreement was resolved by a fourth independent reviewer.

For full-text articles deemed eligible for inclusion, data on study design, participant characteristics (sample size, gender, age, stroke type, time post-stroke), interventions (type and intensity), outcome measure types (cognitive/motor/cognitive-motor), outcome measure classifications (ICF body function or activity level), results and statistical analysis were extracted (EE, TM, JR) (Table 2.1 and 2.2). Pre- and post-intervention as well as follow-up results (means and *SDs*) were extracted for both intervention and control groups (Appendix 2). *SE* values were converted to *SD* when these were reported.

Interventions were classified as either CMT Dual-task or CMT Integrated (for definitions, see Introduction). In cases where a study included an intervention that exhibited characteristics of both CMT dual-task and CMT integrated, the decision was made to classify it as CMT integrated. This was due to the intervention no longer conforming to the characteristics of a "classical" dual-task approach. Nonetheless, this classification was contingent on the study adhering to the established criteria for CMT integrated.

Outcome measures were cognitive, motor, or cognitive-motor outcomes. Cognitive outcomes evaluate cognitive functions and could include aspects of executive function, attention, memory, cognitive screening and language. Motor outcomes evaluated motor functions and activities, and included balance, synergy control, strength, spasticity, upper-limb function and abilities, and walking/gait (Table 2.1).

Quality assessment

The risk of bias of each included study was assessed using the Physiotherapy Evidence Database (PEDro) Scale [33], completed by two of EE, TM, JR, CD, BS, TCWN and PW. The 11-item PEDro Scale rates methodological quality across the domains of Selection, Performance, Detection, Information, and Attribution biases [34]. Studies with PEDro total scores six and above are typically considered *high* quality [35]. The current review adopted a slightly more stringent threshold of nine or above, while papers with a rating > 5 and < 9 were classified as *some concerns*, and papers rated five and below were classified as *low* quality.

Meta-Analysis

Statistical analyses were conducted using *R version 4.0.5 [36]* and *RStudio [37]*. Pre-post/post-follow-up change scores were calculated for each outcome for both intervention and control groups. Pre-post/post-follow-up change SD was imputed using Cochrane formula with an r-value of 0.5 [38]. Using pre-post/post-follow-up change score and SD for intervention and control groups, Hedges' *g* effect size was calculated to quantify the magnitude of pre-post/post-follow-up change difference between groups. Effect sizes were calculated such that improved performance post-intervention would always be signified by a positive value.

Multi-level random-effects meta-analysis was conducted using the *metaphor* package [39, 40]. Multi-level meta-analyses were chosen as they account for non-independence of effect sizes, which is needed to synthesize results when multiple effect sizes are extracted from each study, such as in the present review [41-44]. The Hartung-Knapp-Sidik-Jonkman method was used to estimate the variance of the pooled effect as it outperforms other methods when there are few studies or substantial heterogeneity [45]. Using the *dmetar* package [46], heterogeneity was assessed at both the effect size (i.e., level-2) and study (i.e., level-3) levels with I^2 statistics. Effect size and study heterogeneity was interpreted as low, medium, and high at 25%, 50%, and 75%, respectively [47].

For all analyses, pooled effects were calculated separately for motor and cognitive outcomes. First, meta-analyses were conducted to compare combined therapies (i.e., CMT Dual-task *and* CMT Integrated therapies) with no therapy, motor therapy, and cognitive therapy control groups. The same analysis was conducted for the post-follow-up comparison. Second, outcomes were grouped by combined therapy type (i.e., CMT Dual-task *or* CMT Integrated) and compared to no therapy or single therapies, and Wald-type tests were used to directly compare model coefficients for CMT Dual-task and CMT Integrated outcomes. Finally, a range of other relevant factors were assessed as potential moderators of the effectiveness of CMT therapy on stroke. These moderators included the outcome types, ICF level, the total hours of therapy, stroke phase, and study risk of bias. Pooled estimates with 95% confidence intervals that did not cross zero were used to indicate significance, and pooled estimates were interpreted according to standard conventions: 0.3 (small), 0.5 (moderate), 0.8 (large), >1.0 (very large) [48].

Results

Study selection

In total, 566 unique articles were retrieved (557 from database search and 9 from citation search). After screening of 'title and abstract', 74 studies were considered of which 26 were included after full-text screening. A PRISMA flow diagram of the study screening process is outlined in Figure 2.1.

Study characteristics

Study intervention characteristics are summarised in Table 2.1. Participant demographic and lesion characteristics are summarised in Table 2.2. For the experimental groups, 13 studies used a CMT Dual-Task approach [9, 49-60] and 13 a CMT Integrated approach [61-73]. CMT Dual-task approaches consisted of treadmill gait training while performing cognitive exercises either without virtual reality (VR) (e.g., mathematical subtraction) [49, 50, 59, 60] or with VR (e.g., memory task) [51, 57, 58], sitting/standing balance/walking training while performing cognitive exercises either without [52, 53, 55, 56] or with VR [9, 54]. The CMT Integrated approaches included music-supported therapy, where participants performed rhythmic- and cognitively-demanding upper/lower limb movements in time to the beat in various sequences and combinations [61], or where they played musical instruments following a modular approach with stepwise increase of cognitive and motor complexity [63, 64]. CMT Integrated also included a recreational exercise program that included activities that emphasize planning, strategy, decision making, and learning (e.g., playing billiards, making crafts, arts and cooking [67]). Upper limb motor and cognitive training using VR (e.g., arm reaching training during attention and memory exercises) [62, 66, 68, 69, 71-73], or a Cognitive Orientation to daily Occupational Performance training was also regarded as CMT Integrated [70]. The latter involves a form of meta-cognitive strategy training, that enables (motor) skill acquisition

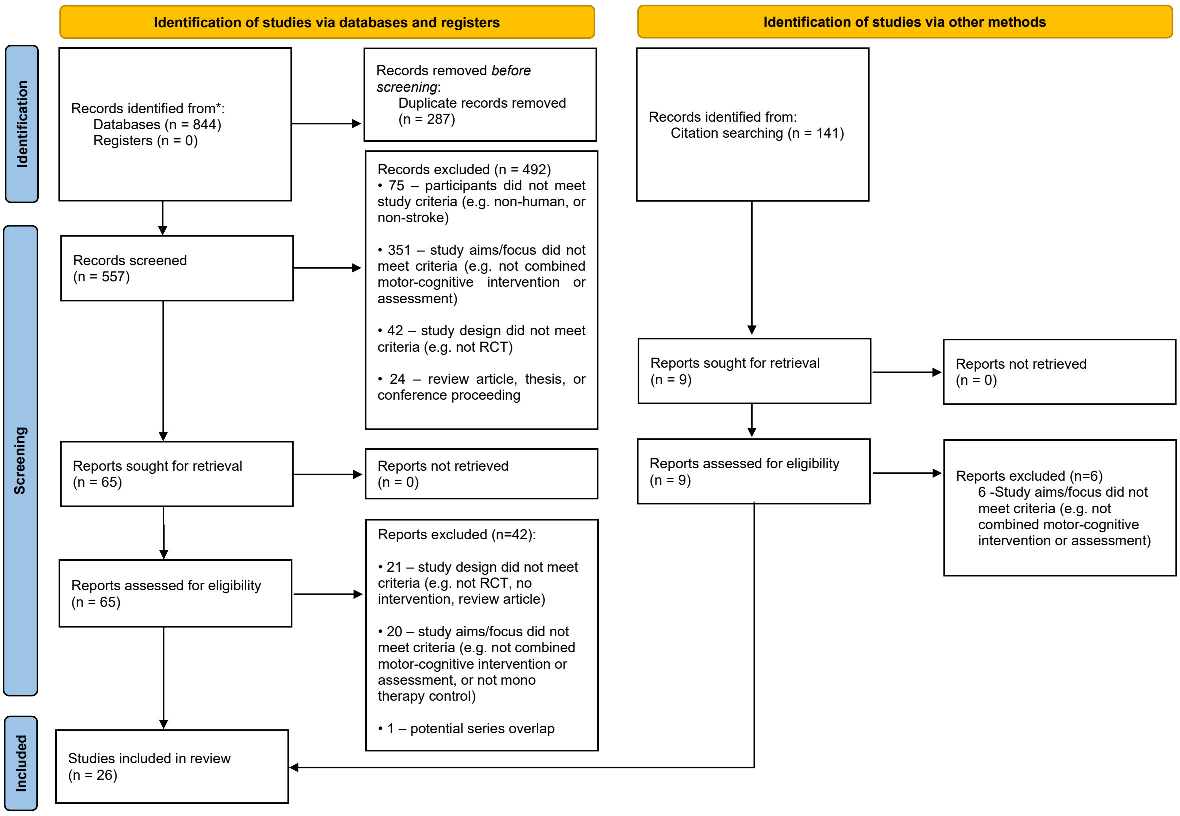

Figure 2.1. PRISMA flow diagram for identifying publications included in the systematic review

through a process of guided discovery and cognitive strategy use (globally (i.e., Goal-Plan-Do-Check strategy) and specifically (i.e., attention to doing, task modification, feeling the movement)) [74]. Additionally, a Wii Fit™ balance training using a non-immersive VR balance intervention with integrated cognitive components (e.g., soccer game with weight-shifting to hit a soccer ball, whilst avoiding hitting other objects), together with additional non-VR cognitive tasks such as naming animals [65] was categorized as CMT Integrated considering cannot be considered a classical ‘dual-task’ approach.Control groups were classified as no therapy, motor only therapy, or cognitive only therapy. The ‘no therapy group’ received no (additional) therapy. The motor only therapies were conventional physical [56, 63, 65, 71], occupational therapy [53, 55, 62] or both [64, 69], gait training with [51] or without VR (no cognitive components) [49, 50, 56-60], balance training [52, 65, 75], GRASP training (Graded Repetitive Arm Supplementary Protocol) [63, 72], horse riding therapy [61] or proprioceptive neuromuscular facilitation [54]. Cognitive only therapies were either conventional cognitive training [68] or computer-based cognitive training [66].

Quality assessment/risk of bias

PEDro ratings for all included papers are included in Appendix 3, as well as separately for those that included CMT Dual-task [9, 49-60] (Appendix 4), CMT Integrated [61-73] (Appendix 5), motor outcomes [9, 49-73] (Appendix 6), cognitive outcomes [9, 52, 53, 60, 62-64, 67-70, 72] (Appendix 7) or motor-cognitive outcomes [51, 55, 56, 58, 59] (Appendix 8). Overall, 13 studies were rated as *low* risk of bias [50, 51, 53, 55, 56, 61, 63, 64, 67, 70], 15 as *some concerns* [50, 52, 54, 57-60, 62, 65, 66, 68, 69, 71-73], and one as *high* risk of bias [49]. All studies addressed PEDro criteria 2 (random allocation), criteria 10 (reporting of between group comparison)), and criteria 11 (point measure and variability reporting). Criteria that were not well addressed included criteria 5 (blinding of subjects), criteria 6 (blinding of therapists), and criteria 7 (blinding of assessors) (Figure 2.2).

Meta-analysis

A total of 251 effects from 26 studies were included in the multi-level meta-analysis.

Pre-post effectiveness of combined vs mono therapies on motor, cognitive and cognitive-motor outcomes

CMT demonstrated a moderate positive effect compared to no therapy for motor outcomes (g [95% CI] = 0.49 [0.10, 0.98]) and cognitive-motor outcomes (g [95% CI] = 0.29 [0.03, 0.54], but no significant effect for cognitive outcomes (g [95% CI] = 0.34 [-0.46, 1.15]). There was high heterogeneity overall (I^2 = 60.90%), all coming from between study heterogeneity (Figure 3.1). When compared to motor only therapy, CMT showed a small positive effect overall (g [95% CI] = 0.18 [0.00, 0.35]. However, when evaluating outcome categories separately, no significant effect for motor outcomes (g [95% CI] = 0.12 [-0.01, 0.24]), cognitive outcomes (g [95% CI] = -0.02 [-0.16, 0.12]) and cognitive-motor outcomes (g [95% CI] = 0.63 [-0.31, 1.57]) was shown. There was moderate to high heterogeneity overall (I^2 = 63.10%), with 37.03% coming from effect size heterogeneity and 26.09% coming from between study heterogeneity (Figure 3.2). When compared to cognitive only therapy, CMT showed a small effect for cognitive outcomes (g [95% CI] = 0.18 [0.01, 0.36]). There was low heterogeneity (12.61%), all coming from effect size heterogeneity (Figure 2.3.1-2.3.3).

Table 2.1. Intervention and Comparison Group Characteristics and Outcome Measures

Author (year)	CMT approach and content	Comparison	Outcome Domains, ICF levels and Outcomes evaluated
An (2014), Korea [49]	CMT - Dual task: motor and cognitive dual-task gait training 30min 3x wkly for 8wks	MT: motor dual-task gait training 30min 3x weekly for 8wks	<u>Motor:</u> Body function: biomechanics (postural control); Activity: walking, balance
Bunketorp-Käll (2017), Sweden [57]	CMT - Integrated: rhythm and music therapy 2x wkly for 12 wks	NT: waitlist; MT: horse-riding therapy 2x wkly for 12 wks	<u>Motor:</u> Body function: strength (upper limb) Activity: walking, balance
Cho (2015), Korea [51]	CMT - Dual task: treadmill walking with virtual reality & cognitive load exercises 30min 5x wkly for 4 wks	MT: treadmill walking with virtual reality (no cognitive load) 30min 5x weekly for 4 wks	<u>Motor</u>: Body function: biomechanics (gait: spatiotemporal parameters) <u>Cognitive and motor:</u> degree of dual-task interference: biomechanics (gait: spatiotemporal parameters)
Choi, J (2015), Korea [9]	CMT - Dual task: balance and cognitive dual-task training 30min 5x wkly for 4wks + treatment as usual	MT: conventional physical therapy 60min 5x wkly for 4wks	<u>Cognitive:</u> body function: attention, cognitive screening, executive function, memory <u>Motor:</u> Body function: biomechanics (postural control), selectivity (lower limb)
Choi, W (2015), Korea [50]	CMT - Dual task: treadmill walking with cognitive load exercises 15min 3x wkly for 4wks + treatment as usual	MT: conventional physical and occupational therapy 5x wkly for 4 wks	<u>Motor:</u> Body function: biomechanics (postural control), gait (gait speed)
Faria (2018), Portugal [62]	CMT - Integrated: augmented reality rehabilitation with motor and cognitive components: 45min 3x wkly for 4 wks + conventional occupational therapy	MT: conventional occupational therapy 45-60min 2-3x wkly for 4 wks	<u>Cognitive:</u> body function: cognitive screening, attention <u>Motor:</u> Body function: selectivity, strength, spasticity (upper limb) Activity: upper limb activities
Fujioka (2018), USA [63]	CMT - Integrated: music supported therapy 3x wkly for 10 wks	MT: conventional physiotherapy for 10 wks	<u>Cognitive:</u> body function: executive function, memory <u>Motor:</u> activity: upper limb activities

Givon (2016), Israel [71]	CMT – Integrated: group video game intervention 60min 2x wkly for 12 wks	MT: traditional group therapy 60min 2x wkly for 12 wks	Motor: Body function: strength (upper limb), biomechanics (spatiotemporal) Activity: upper limb activities, walking
Grau-Sánchez (2018), Spain [64]	CMT - Integrated: music supported therapy 30min 5x wkly for 4 wks + treatment as usual	MT: conventional physical and occupational therapy for 4 wks	Cognitive: body function: executive function, memory Motor: Body function: selectivity, strength (upper limb) Activity: upper limb activities
Her (2011), Korea [52]	CMT - Dual task: motor and cognitive dual-task training 30min 3x wkly for 6wks	MT: motor dual-task training 30min 3x weekly for 6wks	Motor: Body function: biomechanics (postural control) Activity: balance
Jonsdottir (2021), Italy [73]	CMT – Integrated: motor-cognitive virtual reality training 45 min 5x wkly 12 wks	NT: usual activities	Motor: Body function: strength (upper and lower limb), biomechanics (spatiotemporal) Activity: balance, upper limb activities, walking Cognitive: Body function: cognitive screening Activity: memory (working, short-term, long-term)
Kannan (2019), USA [65]	CMT - Integrated: cognitive-motor exergame training 90 minutes, 11 times, for 6wks	MT: progressive balance training 90 minutes, 11 times, for 6wks	Motor: Body function: biomechanics (gait: gait speed) Activity: balance, walking
Kim (2011), Korea [66]	CMT - Integrated: cognitive rehabilitation and virtual reality training 30min 5x wkly for 4wks	CT: cognitive rehabilitation 30min 5x wkly for 4wks	Cognitive: body function: attention, cognitive screening, memory, executive function Motor: body function: strength (upper and lower limb)
Kim (2014), Korea [60]	CMT - Dual task: dual-task gait training 30min 3x wkly for 4wks + treatment as usual	MT: single-task gait training 30min 3x wkly for 4wks + treatment as usual	Motor: Body function: biomechanics (gait: gait speed) Activity: walking
Kim (2015), Korea [57]	CMT - Dual task: treadmill walking with virtual reality training and	MT: treadmill training 30min 3x wkly for 4 wks	Motor: Body function: biomechanics (spatiotemporal)

	cognitive load exercises 3x wkly for 4 wks		
Lee (2015), Korea [54]	CMT - Dual task: VR exercise program: simultaneous cognitive tasks in VR with weight shifting 45min 3x wkly for 6wks	MT: proprioceptive neuromuscular facilitation 45min 3x wkly for 6wks	Motor: activity: balance and walking
Liu (2017), Taiwan [56]	CMT - Dual task: dual-task gait training 30min 3x wkly for 4wks	MT1: motor dual-task training 30min 3x weekly for 4wks; MT2: conventional physical therapy	Motor: Body funsion: biomechanics (gait: gait speed, cadence, stride time, stride length) Cognitive and motor: degree of dual-task interference: Motor task (forward walking), with cognitive dual-task (serial-3-subtractions), biomechanics (gait: gait speed, cadence, stride time, stride length)
Liu-Ambrose (2015), Canada [67]	CMT - Integrated: exercise and recreation program 3x wkly for 6 months	NT: waitlist	Cognitive: body function: executive function
Maier (2020), Spain [68]	CMT - Integrated: VR adaptive cognitive training 30min 5x wkly for 6wks	CT: standard cognitive training 30min 5x wkly for 6wks	Cognitive: body function: attention, executive function, memory
Meester (2019), Jordan [58]	CMT - Dual task: treadmill walking with virtual reality training and cognitive load exercises 30min 2x wkly for 10 wks	MT: treadmill training 30min 2x wkly for 10 wks	Motor: activity: walking distance Cognitive and motor: degree of dual-task interference during 2 min walk test, correct cognitive responses, distance change under dual-task
Pang (2018), China [55]	CMT - Dual task: dual-task balance/mobility training 60min 3x wkly for 8wks	MT: conventional occupational therapy 60min 3x wkly for 8wks	Cognitive and motor: degree of dual-task interference: Motor task (forward walking and Timed Up and Go), with cognitive dual-task (verbal fluency test, serial-3-subtractions)
Park (2019), Korea [53]	CMT - Dual task: dual-task training 30min 3x wkly for 6wks	MT: conventional occupational therapy 30min 3x wkly for 6wks	Cognitive: body function: executive function, memory Motor: Body function: selectivity Activity: balance

Plummer (2021), USA [59]	CMT - Dual task: dual-task gait training 30min 3x wkly for 4 wks	MT: treadmill training 30 min 3x wkly for 4 wks	Motor: Body function: biomechanics (spatiotemporal) Activity: walking ability Cognitive and motor: degree of dual-task interference (reaction time and accuracy interference), gait speed preferred and fast
Rogers (2019), Australia [69]	CMT - Integrated: virtual rehabilitation 30min 3x wkly for 4 wks + conventional training	MT: conventional physical and occupational therapy 30 min 3x wkly for 4 wks	Cognitive: body function: cognitive screening, executive function, memory Motor: activity: upper limb activities
Wilson (2021), Australia [72]	CMT - Integrated: virtual rehabilitation 30min 3-4x wkly for 8 wks	MT: GRASP protocol (Graded Repetitive Arm Supplementary Protocol) 30min 3-4x wkly for 8 wks	Cognitive: body function: cognitive screening Motor: activity: upper limb activities
Wolf (2016), Canada [70]	CMT - Integrated: cognitive-strategy and task-specific training for 10 sessions	MT: conventional occupational therapy	Cognitive: body function: executive function Motor: activity: upper limb activities

CMT: cognitive-motor therapy, CT: cognitive therapy, ICF: International Classification of Functioning, Disability and Health, MT: motor therapy, NT: no therapy, wkly: weekly, wks: weeks.

Table 2.2. Demographic and Injury Characteristics of the Participants

Author (year)	Groups	Age (years)	Sample size	Gender (M/F)	Education (years)	Hand (R/L)	First Stroke	Time Since Stroke with post-stroke phase	Stroke Type (I/H/B/U)	NIHSS Score	Stroke Location (L/R)
An (2014), Korea [49]	CMTdt MT	NR	12 12	NR	NR	NR	NR	NR	NR	NR	NR
Bunketorp-Käll (2017), Sweden [57]	CMTi MT NT	62.7 (6.7) 62.6 (6.5) 63.7 (6.7)	41 41 41	23/18 24/17 22/19	14.2 (4.1) 12.5 (4.2) 13.5 (4.3)	NR	NR	969.8 (422.9) days 1101.9 (576.1) days 1096.3 (439) days Chronic phase	32/9 27/14 28/13	3.0 (2.9) 2.7 (3.1) 2.8 (3.6)	21/20 21/20 23/18
Cho (2015), Korea [51]	CMTdt MT	60.0 (9.38) 58.64 (11.86)	11 11	5/6 2/9	NR	NR	Yes	273.9 (191.74) days 263.9 (144.64) days Chronic phase	9/2 6/5	NR	4/7 7/4
Choi, J (2015), Korea [9]	CMTdt MT	64.8 (10.5) 54.6 (11.8)	12 12	6/4 6/4	NR	NR	Yes	22.90 (8.9) days 23.20 (9.7) days Early subacute phase	7/3 5/5	NR	5/5 6/4
Choi, W (2015), Korea [50]	CMTdt MT	49.11 (11.93) 49.33 (8.27)	19 18	17/2 14/4	NR	NR	NR	18.16 (6.83) months 18.28 (4.70) months Chronic phase	NR	NR	12/7 6/12
Faria (2018), Portugal [62]	CMTi MT	57.1 (11.0) 68.9 (9.8)	12 12	8/4 7/5	6.0 (2.8) 5.7 (4.2)	NR	NR	24.9 (20.3) months 41.1 (41.0) months Chronic phase	11/1 11/1	NR	8/4 7/5
Fujioka (2018), USA [63]	CMTi MT	64.2 (9.4) 54.3 (11.3)	14 14	9/5 11/3	15.2 (2.4) 16.2 (3.2)	14/0 13/1	Yes	6.1 (6.6) years 4.7 (6.7) years Chronic phase	NR	NR	8/6 12/2
Givon (2016), Israel [71]	CMTi MT	56.7 (9.3) 62.0 (9.3)	23 24	11/12 17/7	13.5 (2.2) 14.3 (3.6)	2/21 24/0	Yes	3.0 (1.8) years 2.6 (1.8) years Chronic phase	21/3 19/5	NR	9/14 8/16
Grau-Sánchez (2018), Spain [64]	CMTi MT	60.1 62.5	19 20	11/8 12/8	NR	NR	Yes	65.8 days 64.9 days Early subacute phase	18/1 14/6	5.8 5.3	NR

Her (2011), Korea [52]	CMTdt CMTdt MT	63.5 (6.4) 64.5 (4.8) 64.8 (5.2)	13 13 12	8/5 5/8 7/5	NR	NR	Yes	>1year Chronic phase	9/4 7/6 5/7	NR	7/6 6/7 6/6
Jonsdottir (2021), Italy [73]	CMTi NT	56.7 (17.4) 60.2 (9.6)	11 23	5/6 13/8	15.2 (3.7) 12.7 (3.2)	NR	NR	>6 months Chronic	NR	NR	6/5 8/13
Kannan (2019), USA [65]	CMTi MT	57.5 (8.04) 61 (4.6)	13 12	7/6 6/5	15 (3) 13 (1.6)	NR	NR	8.9 (5.39) years 9.09 (6.36) years Chronic phase	8/5 4/7	NR	6/7 5/6
Kim (2011), Korea [66]	CMTi CT	66.5 (11.0) 62.0 (15.8)	15 13	5/10 6/7	NR	NR	Yes	18.2 (11.3) days 24.0 (31.1) days Early subacute phase	12/3 9/4	NR	6/9 5/8
Kim (2014), Korea [60]	CMTdt MT	58.4 (7.58) 58.2 (8.07)	10 10	NR	NR	NR	NR	16.6 (11.88) months 19.3 (14.12) months Chronic phase	NR	NR	NR
Kim (2015), Korea [57]	CMTdt MT	51.0 (13.5) 48.1 (7.5)	20 24	12/8 11/13	NR	NR	NR	Chronic phase	13/7 12/8	NR	12/8 13/6
Lee (2015), Korea [54]	CMTdt MT	57.2 (9.2) 52.7 11.7)	10 10	6/4 5/5	NR	NR	NR	NR	NR	NR	4/7 3/7
Liu (2017), Taiwan [56]	CMTdt MT1 MT2	51.0 (7.1) 48.8 (11.7) 50.8 (13.5)	9 9 10	8/1 8/1 8/2	NR NR NR	NR	Yes	36.4 (14.6) months 36.2 (25.7) months 49.8 (59.8) months Chronic phase	4/5 5/4 7/3	NR	4/5 5/4 6/4
Liu-Ambrose (2015), Canada [67]	CMTdt NT	62.9 (12.1) 66.9 (9.0)	10 14	4/6 11/3	NR	NR	Yes	2.4 (1.0) years 2.9 (1.1) years Chronic phase	6/4 9/5	NR	6/4 3/7
Maier (2020), Spain [68]	CMTi CT	63.6 (6.7) 67.2 (6.5)	19 19	11/8 12/7	NR	NR	Yes	2.3 (2.2) years 3.5 (3.8) years Chronic phase	12/7 14/5	NR	11/8 14/5

Meester (2019), Jordan [58]	CMTdt MT	60.9 (14.9) 62.3 (15.5)	26 24	15/11 11/13	NR	NR	Yes	60.2 (25.7) months 62.2 (32.7) months Chronic phase	18/7/1 13/10/1	NR	13/11/2 13/6/5
Pang (2018), China [55]	CMTdt NT	59.9 (6.8) 62.4 (6.3)	28 28	22/6 18/10	NR	NR	NR	71.9 (63.6) months 87.5 (83.3) months Chronic phase	17/11 14/14	NR	13/15 13/15
Park (2019), Korea [53]	CMTdt NT	56.30 (7.14) 59.75 (7.75)	15 15	NR	NR	NR	NR	21.67 (5.64) months 21.45 (2.83) months Chronic phase	NR	NR	NR
Plummer (2021), USA [59]	CMTdt MT	54.4 (16.4) 59.6 (14.5)	17 19	10/7 9/10	14.2 (2.7) 14.6 (3.8)	NR	NR	8.8 (11.9) months 6.8 (9.5) months Chronic phase	14/0/0/3 14/5	NR	9/8 6/13
Rogers (2019), Australia [69]	CMTi NT	64.3 (17.4) 64.6 (12.0)	10 11	4/6 5/6	13.5 (2.1) 12.5 (1.9)	NR	Yes	22.8 (14.8) days 30.0 (15.9) days Early subacute phase	9/1 9/2	3.0 (1.8) 2.3 (1.6)	4/6 5/6
Wilson (2021), Australia [72]	CMTi MT	69.9 (13.8) 77.3 (8.9),	10 7	7/3 5/2	NR	NR	NR	137.5 (152.4) 107.4 (56.4) Late subacute phase	9/1 5/2	6.7 (3.0) 7.8 (5.0)	6/4 5/2
Wolf (2016), Canada [70]	CMTi NT	57.5 (14.0) 54.4 (14.0)	19 16	13/6 9/7	14.7 (4.2) 13.2 (2.0)	17/2 14/2	NR	40.1 (20.4) days 46.5 (21.3) days Early subacute phase	19/0 16/0	NR	8/11 3/13

Note. Values are *mean (standard deviation)*. B: bilateral, CMTdt: cognitive-motor therapy – Dual task, CMTi: cognitive-motor therapy – Integrated, CT: cognitive therapy, I/H: ischemic/haemorrhagic, L/R: left/right, M/F: male/female, MT: motor therapy, NR: not reported, NT: no therapy, R/L: right/left, U: uncertain.

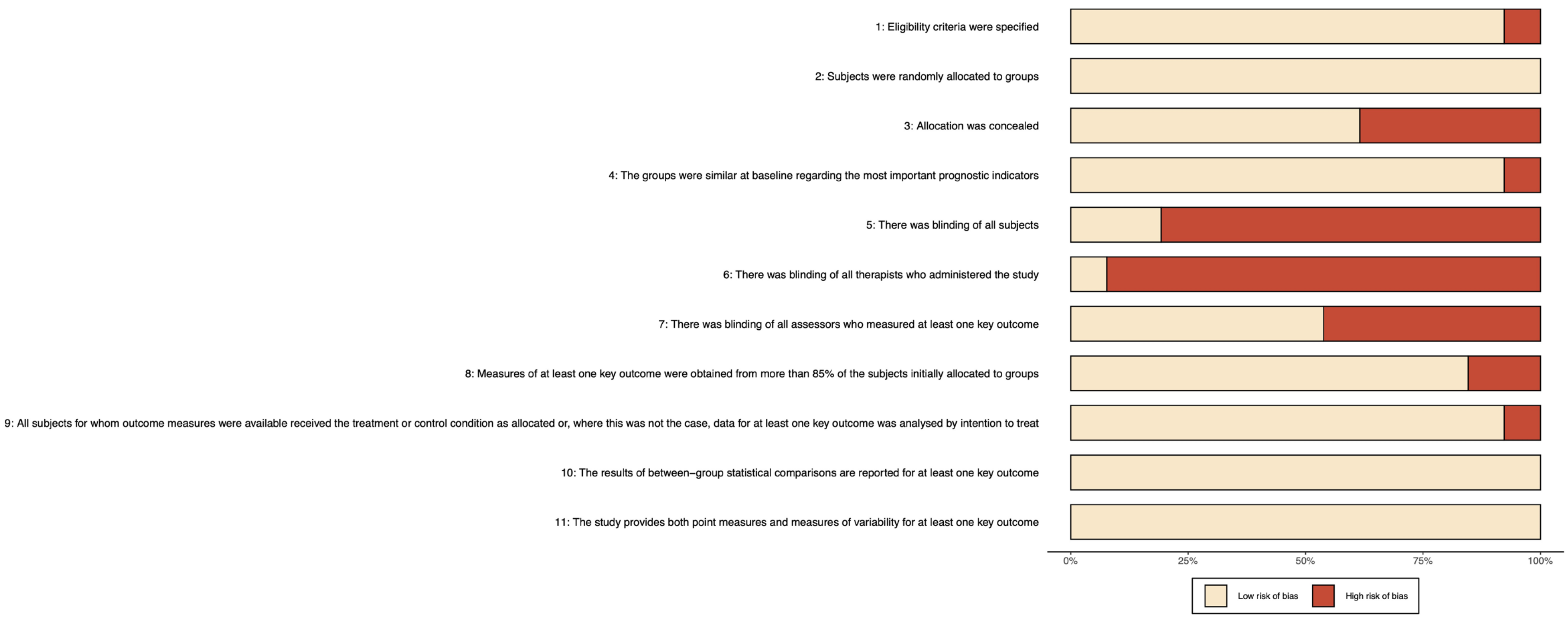

Figure 2.2. Summary of PEDro assessment for all papers.

Figure 2.3.1

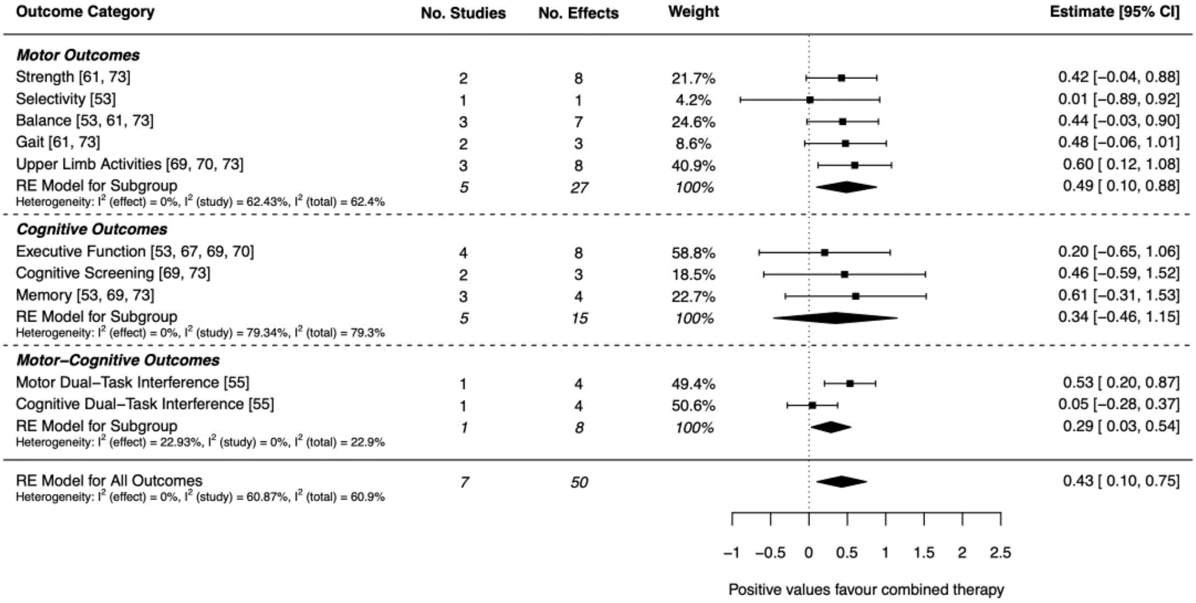

Figure 2.3.2

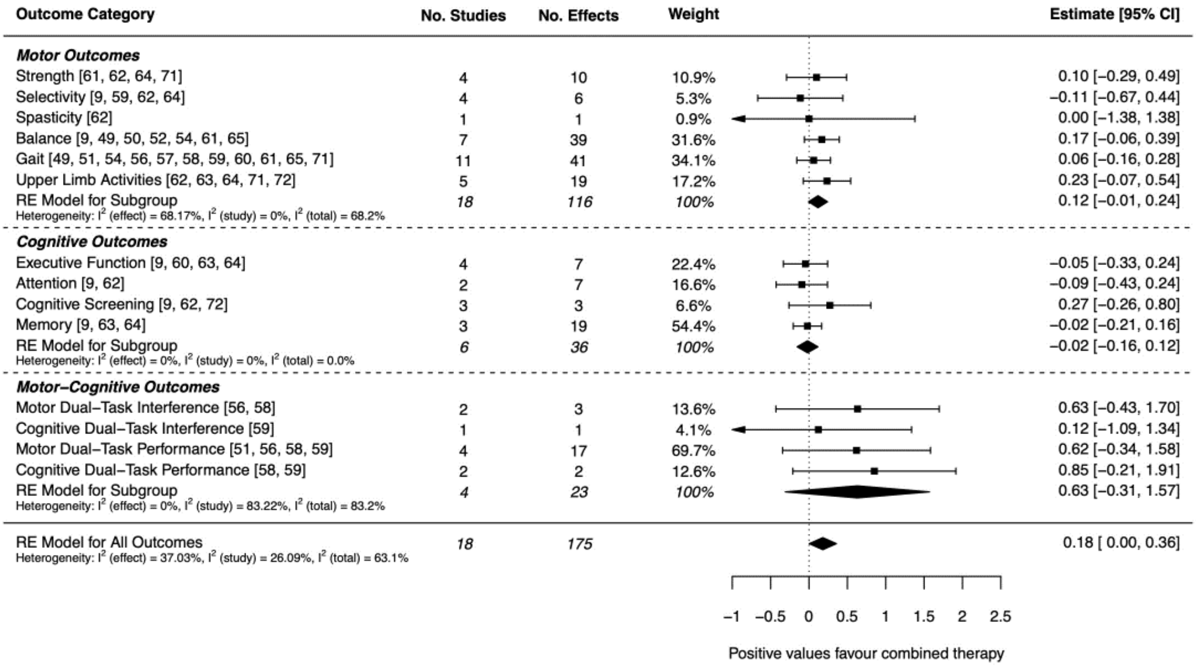

Figure 2.3.3

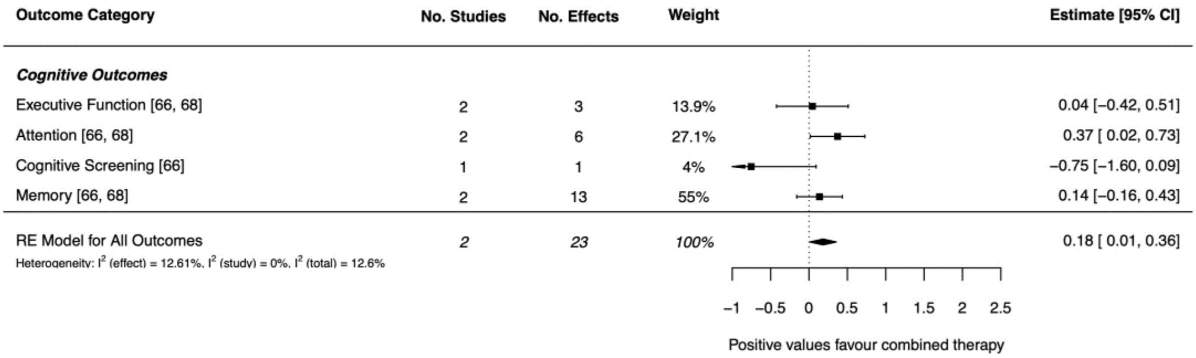

Figure 2.3.1 – 2.3.3. Pre-post effects of CMT vs monotherapies.

Post-follow-up effectiveness of combined vs mono therapies on motor, cognitive and cognitive-motor outcomes

Of the 26 studies, 12 evaluated follow-up effects [55, 58, 60, 62-64, 68-73]. CMT demonstrated no overall follow-up effect compared to no therapy or motor therapy (*g* [95% CI] = 0.07 [-0.04, 0.18]). Further, there was no significant effect for motor outcomes (*g* [95% CI] = 0.04 [-0.11, 0.19]), cognitive outcomes (*g* [95% CI] = 0.26 [-0.04, 0.55]) and cognitive-motor outcomes (*g* [95% CI] = -0.05 [-0.37, 0.26]). There was low heterogeneity overall (I^2 = 18.0%), with 10.05% coming from effect size heterogeneity and 7.96% coming from between study heterogeneity (Figure 2.4).

Figure 2.4

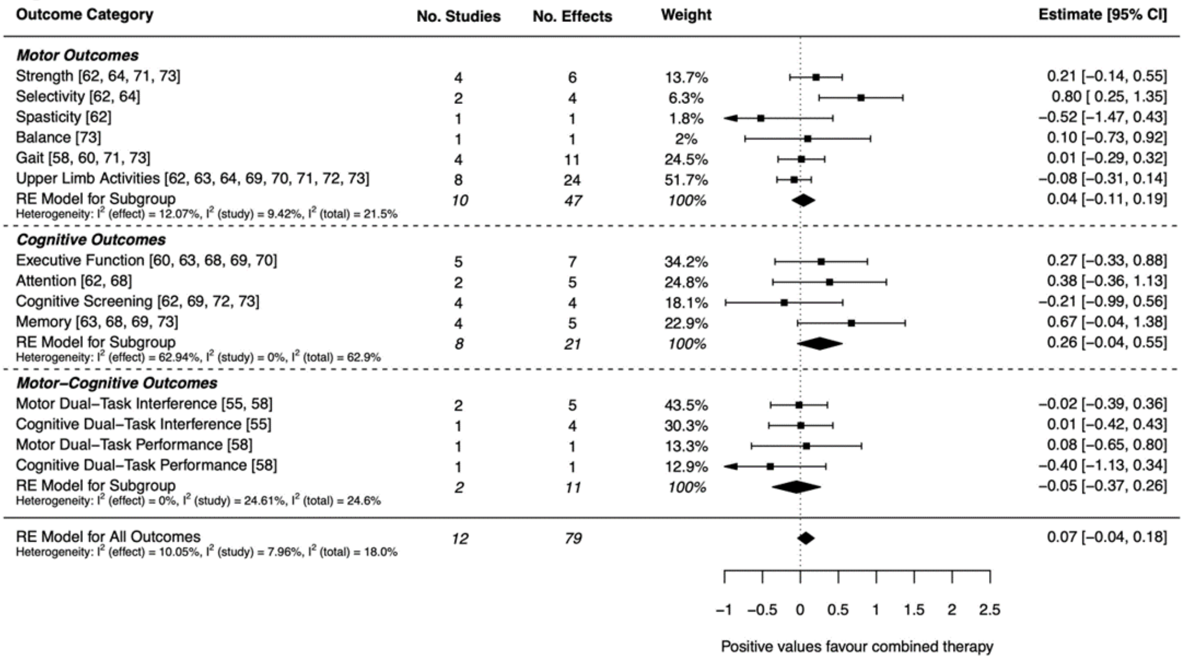

Figure 2.4. Post-follow-up effects of CMT vs monotherapies

Pre-post effectiveness of CMT Dual-task vs CMT Integrated on motor, cognitive and cognitive-motor outcomes

CMT Dual-task demonstrated an overall moderate effect for motor, cognitive and cognitive-motor outcomes (*g* [95% CI] = 0.27 [0.06, 0.50]). However, when evaluating the outcome categories separately, no significant effects were found for motor outcomes (*g* [95% CI] = 0.12 [-0.07, 0.31]), cognitive outcomes (*g* [95% CI] = -0.42 [-0.15, 0.99]) and cognitive-motor outcomes (*g* [95% CI] = 0.55 [-0.16, 1.27]). There was medium heterogeneity overall (I^2 =

86.6%), with 41.4% coming from effect size heterogeneity and 27.19% coming from between study heterogeneity (Figure 2.5.1).

CMT Integrated demonstrated an overall effect for motor and cognitive outcomes (*g* [95% CI] = 0.22 [0.01, 0.42]). A small effect for motor outcomes was found (*g* [95% CI] = 0.27 [0.05, 0.49]), but no effect was shown for cognitive outcomes (*g* [95% CI] = 0.14 [-0.24, 0.52]). There was medium heterogeneity overall (I^2 = 55.8%), with 11.67% coming from effect size heterogeneity and 44.15% coming from between study heterogeneity (Figure 5.2). The training effects of CMT Dual-task and CMT Integrated did not differ on motor ($F_{1, 139}$ = 0.10, *P*= .750) or cognitive outcomes ($F_{1, 77}$ = 2.64, *P* =.108) (Figure 2.5.2).

Additional moderator analysis

Supplementary Table 2.3 shows the moderator analysis. These indicate that ‘therapy comparison’ (i.e., no therapy, motor therapy, cognitive therapy) was the only significant outcome moderator (*p* = .041). Therapy type (*p* = .825), outcome type (*p* = .078), ICF level (*p* = .269), hours of therapy (*p* = .546), post-stroke phase (subacute, chronic) (*p* = .073) and risk of bias (*p* = .839) were not significant outcome moderators.

Discussion

This study evaluated (1) the efficacy of CMT compared with no therapy or mono-therapies (single cognitive or motor therapy) on motor and/or cognitive outcomes after stroke, (2) follow-up effects of CMT, (3) which approach (CMT Dual-task or Integrated) would be most effective for improving motor and/or cognitive outcomes after stroke, and (4) which factors would moderate effectiveness. CMT was shown to be superior to no therapy. It delivered no added benefits on motor, cognitive and cognitive-motor outcomes as compared to motor therapy, and only small added benefits for cognitive outcomes as compared to cognitive therapy. No significant follow-up effect of CMT was found compared to no therapy or motor therapy. Comparison of CMT Dual-task and Integrated approaches showed that both were equally effective; however, when evaluated separately, the CMT Integrated approach showed a small significant effect on motor outcomes, whereas the CMT Dual-task did not.

The findings of this meta-analysis differ from those of previous meta-analyses that tended to report more favourable effects of CMT, mainly considering motor outcomes such as gait and upper limb outcomes [22-25]. Our findings do not replicate these, and rather indicate that

Figure 2.5.1

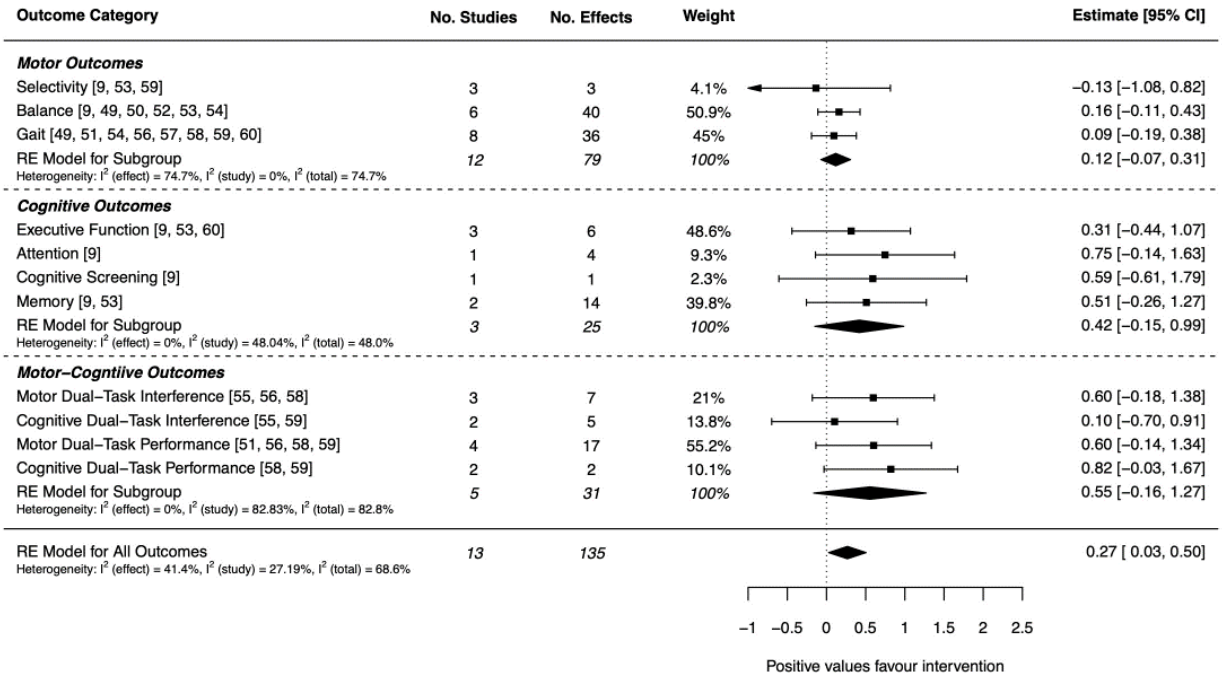

Figure 2.5.2

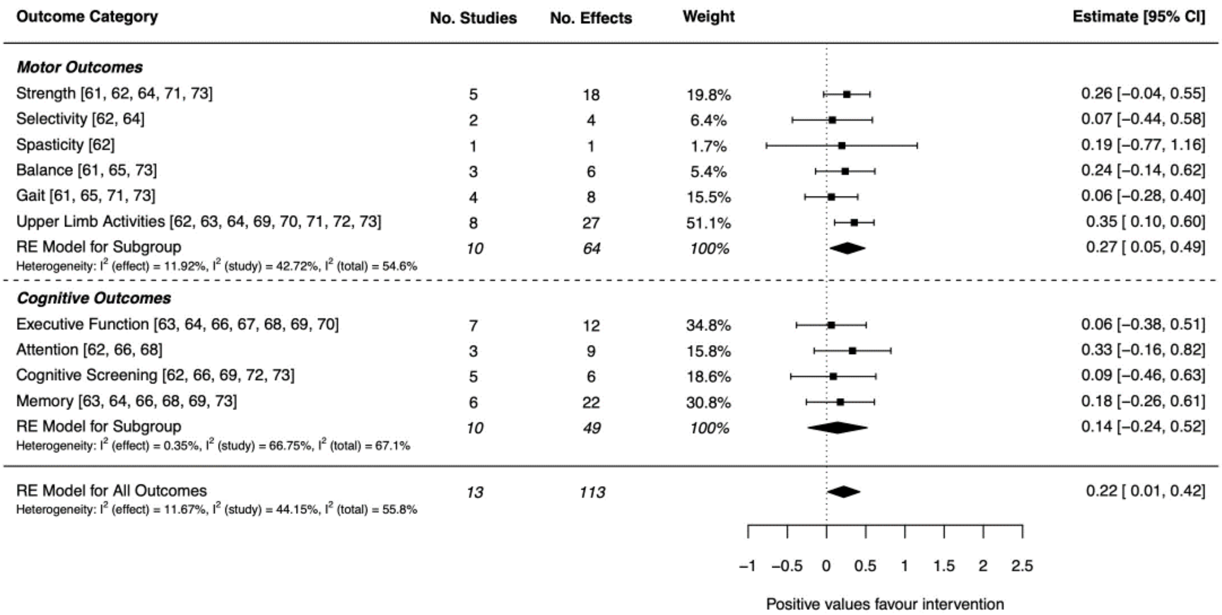

Figure 2.5.1-2.5.2. Pre-post effects of CMT dual-task vs integrated

CMT has no added value on motor outcomes compared to motor only therapies. As for cognitive outcomes, the current study is consistent with the results from Huber et al. [22] as only a small added benefit of CMT compared to cognitive only therapy was found. This was mainly situated within the attention domain. However, given the limited number of studies assessing the effects of CMT on cognition, these findings should be interpreted with caution. The current meta-analysis contributes to the existing literature by examining a broader range of outcomes, therapy types (not limited to CMT Dual-task), different stages of stroke recovery, and follow-up effects.

Although theoretically a CMT approach to rehabilitation would be considered more effective than mono-therapies, the current study showed that this is yet to translate to clinical research and practice. CMT research for stroke rehabilitation was shown to be in its infancy still, evidenced by the high proportion of pilot RCTs with small sample sizes (ranging from 19 to 123). How and when therapy is delivered varied greatly across studies. Although this is true, moderator analysis shows that only *therapy comparison* was a significant moderator, and that therapy type, outcome type, ICF level, hours of therapy, post-stroke phase, and risk of bias did not significantly moderate the effects.

Moving CMT research forward: fine-tuning content and timing of the intervention

With regards to *how* therapy is currently delivered, stratification and selection of participants based on their clinical profile (e.g., motor, cognitive, intellectual, visual, and/or motivational status) in CMT context seems key, together with choosing the right rehabilitation tool to deliver therapy. CMT involves the simultaneous performance of motor and cognitive tasks. This implicates that attention needs to be divided between two concurrent tasks, which loads upon the limited attentional capacity of an individual [76]. For example, during a *classical dual-task* such as walking while subtracting numbers, one has to divide their attention between walking (primary motor task) and the mathematical task (secondary cognitive task) [76]. In those for whom walking is performed autonomously, performance of this motor task requires only minimal attention and more attention can be directed toward the cognitive task (i.e., subtracting). However, in people with stroke, the primary motor task itself may already pose a significant challenge that enlists greater (if not full) attention, leaving minimal attentional reserve for cognitive task performance [76]. In this case, it would be necessary to adapt (i.e., to choose a different primary motor task feasible for the participant, or an easier secondary cognitive task) or even postpone CMT until the desired primary motor task can be performed. The same holds for the CMT Integrated approaches. New technologies, such as AR and VR, have the advantage to appropriately adjust task difficulty relative to the participants' level of function. Considering therapy intensity, only 4 studies provided intensive therapy in terms of hours of therapy delivered (>24 hours). In most of the studies, trainings were often performed with low-dose regimes with the majority (52%) delivering less than 12 hours of therapy.

With regards to *when* CMT is delivered, 19 out of 27 (70%) of the included RCT's were initiated in the chronic phase (i.e., >6 months post-stroke). This is in line with most rehabilitation research [77] and stands in stark contrast with how stroke rehabilitation is often organised in clinical practice, as rehabilitation is usually delivered within the first weeks (usually starting within 30 days) post-stroke [28]. In stroke survivors, greatest recovery occurs within the first 3 months post-stroke [28] and interventions outside this time window seem to have rather modest effects (15, 17, 18). Due to the lack of studies here, it is unknown how CMT would interact with these neurobiological recovery processes.

Should we assess CMT effectiveness differently?

Current theory on skill acquisition and learning provide principles that support effective training for relearning skills after stroke [78]. Most rehabilitation research suggests that the effects of intervention are context- and task-specific, and are mostly confined to the tasks that are directly practiced in therapy [79]. The ultimate goal of rehabilitation is that the learned skills (often practiced in safe environments), generalize or transfer to another task or context [78]. Because of the nature of the interventions, CMT trains skills that are mainly situated at the activity level of the ICF [7]. It is therefore relevant that assessment is in line with what is trained (i.e., assessment of cognitive-motor interactions), particularly given that most daily activities are indeed cognitive-motor behaviours. Only 5 studies [51, 55, 56, 58, 59] assessed CMT effectiveness by evaluating dual-task interferences as an outcome measure with all other studies using either a motor or cognitive only assessment method. Therefore, the trained motor-cognitive skills are not assessed directly, but rather inferred from motor and cognitive outcomes, separately. It could be that the small effects on these outcomes is a result of a partial (or no) transfer of skills to the mono-assessments [79]. Also, when only mono-outcomes are evaluated, and not motor-cognitive interactions or outcomes, it remains unknown whether the improvement seen on outcomes are a result of improved dual-task performance (e.g., a reduced dual-task cost), or rather a result of having prioritized tasks during CMT (priority to primary/secondary task) resulting in benefits for the prioritized task and not necessarily the dual-task [76].

Clinical implications

Although effect sizes are generally small, both CMT Dual-task and Integrated seem equally effective. The rehabilitation approach should be chosen in light of the desired rehabilitation goal and should be tailored to the participant's clinical profile (i.e., their motor, cognitive, intellectual, visual and motivational status). To improve rehabilitation effectiveness, clinicians should ensure that the primary 'mono' task per se (e.g., walking) is feasible for the participant before adding a secondary task (e.g., cognitive task) during training. Skill learning stages (from the cognitive stage to the associative and eventually autonomous stage) should be considered, and practice should support these stages accordingly within an optimal learning environment [80].

The evaluation of optimal skill learning environments that can be tailored for the individual participant is an important topic for future research. Practice is necessary for improved performance and most effective (at least in healthy subjects) when it is delivered distributed, rather than blocked, with frequent and longer rest periods between repetitions [80]. Variability of practice is key and would improve retention of skills [80]. In most of the recent studies evaluating CMT Dual-task approaches, training tasks are often delivered using a massed practice approach and low-dose regimes (ranging from 3 [50] to 72 [67] hours in total).

Study limitations

Variability in the use of motor and cognitive assessment tools across studies was high. To provide more clarity, outcomes were categorized in 'domains' according to the primary function or activity assessed by the measurement tool. For example, the 'attention' domain encompasses measures for sustained, selective, and (visuo)spatial attention. This allowed the description of CMT effects across the attention domain in general, but limited the evaluation of separable functions or activities. However, we also categorized outcomes according to the ICF level that is assessed, and evaluated in a moderator analysis whether this impacted upon the effects, which was not the case.

The focus of this systematic review and meta-analysis was on contemporary research published after 2010, which includes a new wave of therapies using AR and VR. As such, we feel that the current review (while not extended far back in time) is representative of the current state of work in the field. Although we have made a distinction between CMT Dual-task and Integrated, no differentiation was made between the efficacy of new technologies (AR/VR) and other approaches (e.g., music therapy). Therefore, there is a high heterogeneity of rehabilitation methods within the two CMT approaches.

The study only focused on stroke rehabilitation. However, the initial focus was also on dementia and traumatic brain injury. After reviewing the databases for these other conditions, insufficient numbers of publications in those domains were found to analyze those conditions on their own. It was then decided not to mix results from disparate etiologies, and to focus solely on stroke.

Finally, all included studies were conducted in developed countries (North America, Western Europe, Korea, China, or Australia, see Table 2.1 and 2.2). This prevents the generalizability of the results to low-resource countries.

Conclusions

The use of CMT is superior to no therapy whereas it delivered only a small but significant additional benefit for cognitive outcomes compared with single cognitive therapy. Effectiveness of CMT Dual-task and Integrated were comparable suggesting that training tasks that enlist a cognitive load per se, can benefit outcomes that are likely to be clinically significant to people with stroke. CMT research is still in its infancy considering the dominance of pilot studies on participants in the chronic phase post-stroke, small-sample designs, and relatively low-dose regimes. Future research should focus on addressing these limitations, and should stratify and select participants based on their clinical profile (e.g., motor, cognitive, intellectual, visual, and/or motivational status) to maximize therapy potential.

Contributions

The study was coordinated and designed by TM, JR, CD, BS, TCWN and PHW. The screening of articles was performed by EE, TM, JR, and the methodological quality assessment by TM, JR, CD, BS, TCWN and PHW. Data was extracted by TM, JR and EE. Meta-analyses were performed and analysed by TM. EE and TM interpreted the data. All authors interpreted the results of the meta-analysis and gave input to the writing of the manuscript. The manuscript was written by EE, and all authors have seen, reviewed and approved the final version.

Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest.

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Supplementary Table 2.3. Moderator Analysis

Moderator	*k*	*n*	Weight (%)	*Estimate [95% CI]*	SE	ICC	Study sigma^2	Effect sigma^2	*P-value*
Baseline	27	251	100	0.29 [0.10, 0.48]	0.09	0.563	0.194	0.151	-
Therapy Comparison	27	251	-	-	-	0.527	0.161	0.145	0.018
Cognitive Therapy	2	23	8	0.16 [-0.46, 0.77]	0.31	-	-	-	-
Motor Therapy	18	172	65	0.18 [-0.02, 0.38]	0.1	-	-	-	-
No Therapy	8	56	27	0.59 [0.32, 0.86]	0.14	-	-	-	-
Therapy Type	27	251	-	-	-	0.567	0.198	0.151	0.343
CMT Dual-Task	14	139	53	0.38 [0.12, 0.64]	0.13	-	-	-	-
CMT Integrated	13	112	47	0.2 [-0.08, 0.47]	0.14	-	-	-	-
Outcome Type	27	251	-	-	-	0.579	0.204	0.149	0.109
Cognitive	14	79	28	0.25 [0.01, 0.49]	0.12	-	-	-	-
Motor	23	141	59	0.25 [0.04, 0.45]	0.1	-	-	-	-
Cognitive-Motor	5	31	13	0.59 [0.25, 0.93]	0.17	-	-	-	-
ICF Level	27	251	-	-	-	0.562	0.195	0.152	0.449
Activity	20	75	36	0.33 [0.12, 0.55]	0.11	-	-	-	-
Body Function	25	176	64	0.27 [0.07, 0.47]	0.1	-	-	-	-
Hours of Therapy	24	228	-	-	-	0.575	0.245	0.181	0.806
< 12 hours	14	158	55	0.25 [-0.03, 0.53]	0.14	-	-	-	-
12-24 hours	6	43	21	0.34 [-0.11, 0.79]	0.23	-	-	-	-
> 24 hours	4	27	14	0.45 [-0.10, 1.00]	0.28	-	-	-	-
Stroke Phase	26	187	-	-	-	0.474	0.205	0.228	0.194
Chronic	20	164	75	0.22 [-0.00, 0.45]	0.11	-	-	-	-
Subacute	6	23	7	0.57 [0.10, 1.04]	0.24	-	-	-	-
Risk of Bias	27	251	-	-	-	0.572	0.203	0.152	0.585
High	1	17	4	0.12 [-0.82, 1.05]	0.47	-	-	-	-
Low	13	121	49	0.39 [0.12, 0.66]	0.14	-	-	-	-
Unclear	13	113	47	0.2 [-0.08, 0.48]	0.14	-	-	-	-

CI: confidence interval, ICC: intra-class coefficient, k: number of studies, n: number of effects, SE: standard error.

Appendices

Appendix 1. Sample search strategy

String	Search
1	attention/ or cognition/ or cognitive defect/ or problem solving/ or executive function/ or neuropsychology/ or thinking/ or memory/ or cognitive function.mp.
2	arm/ or gait/ or motor activity/ or motor dysfunction/ or motor performance/ or motor control/ or motor coordination/ or psychomotor performance/ or walking/ or hemiparesis/ or spasticity/ or physical activity.mp.
3	1 and 2
4	(cognitive-motor or cognitive motor or motoric cognitive or motor cognitive or grounded cognition or embodied cognition).mp.
5	3 or 4
6	intervention study/ or early intervention/ or rehabilitation/ or rehabilitation care/ or cognitive rehabilitation/ or stroke rehabilitation/ or rehabilitation research/ or occupational therapy/ or physiotherapy/ or training/ or exercise therapy.mp or physical therapy.mp or dual task.mp
7	5 and 6
8	brain hemorrhage/ or brain ischemia/ or cerebrovascular accident/ or stroke.mp
9	7 and 8
10	limit 9 to article
11	limit 10 to English
12	limit 11 to yr="2010 -Current"
13	remove duplicates from 12

Appendix 2.

See online supplementary material https://doi.org/10.1016/j.apmr.2023.05.010

Appendix 3

Risk of bias domains

Study	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	Overall
An 2014	X	+	X	X	X	X	X	+	+	+	+	X
Bunketorp–Käll 2017	+	+	+	+	X	X	+	+	+	+	+	+
Cho 2015	+	+	+	+	X	X	+	+	+	+	+	+
Choi JH 2015	+	+	X	+	+	X	X	+	+	+	+	−
Choi W 2015	+	+	+	+	X	+	+	+	+	+	+	+
Faria 2018	+	+	+	+	X	X	X	X	+	+	+	−
Fujioka 2018	+	+	+	X	+	X	+	+	+	+	+	+
Givon 2016	X	+	X	+	X	X	+	+	+	+	+	−
Grau–Sánchez 2018	+	+	+	+	X	X	+	+	+	+	+	+
Her 2011	+	+	X	+	X	X	X	+	+	+	+	−
Jonsdottir 2021	+	+	X	+	X	X	+	+	+	+	+	−
Kannan 2019	+	+	+	+	X	X	X	X	X	+	+	−
Kim 2011	+	+	X	+	X	X	X	+	+	+	+	−
Kim 2014	+	+	X	+	X	X	X	+	+	+	+	−
Kim 2015	+	+	X	+	X	X	X	+	+	+	+	−
Lee 2015	+	+	X	+	X	X	X	+	+	+	+	−
Liu 2017	+	+	+	+	+	X	X	+	+	+	+	+
Liu–Ambrose 2015	+	+	+	+	+	X	+	+	+	+	+	+
Maier 2020	+	+	+	+	X	X	X	X	+	+	+	−
Meester 2019	+	+	X	+	X	X	+	+	X	+	+	−
Pang 2018	+	+	+	+	+	X	+	+	+	+	+	+
Park 2019	+	+	+	+	X	X	+	+	+	+	+	+
Plummer 2021	+	+	+	+	X	X	+	+	+	+	+	+
Rogers 2019	+	+	+	+	X	X	X	+	+	+	+	−
Wilson 2021	+	+	+	+	X	X	+	+	+	+	+	+
Wolf 2016	+	+	+	+	X	+	+	X	+	+	+	+

D1: Eligibility criteria were specified
D2: Subjects were randomly allocated to groups
D3: Allocation was concealed
D4: The groups were similar at baseline regarding the most important prognostic indicators
D5: There was blinding of all subjects
D6: There was blinding of all therapists who administered the study
D7: There was blinding of all assessors who measured at least one key outcome
D8: Measures of at least one key outcome were obtained from more than of the subjects initially allocated to groups
D9: All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by intention to treat
D10: The results of between–group statistical comparisons are reported for at least one key outcome
D11: The study provides both point measures and measures of variability for at least one key outcome

Judgement
+ Low
− Unclear
X High

Appendix 4

Risk of bias domains

Study	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	Overall
An 2014	X	+	X	X	X	X	X	+	+	+	+	X
Cho 2015	+	+	+	+	X	X	+	+	+	+	+	+
Choi JH 2015	+	+	X	+	+	X	X	+	+	+	+	−
Choi W 2015	+	+	+	+	X	+	+	+	+	+	+	+
Her 2011	+	+	X	+	X	X	X	+	+	+	+	−
Kim 2014	+	+	X	+	X	X	X	+	+	+	+	−
Kim 2015	+	+	X	+	X	X	X	+	+	+	+	−
Lee 2015	+	+	X	+	X	X	X	+	+	+	+	−
Liu 2017	+	+	+	+	+	X	X	+	+	+	+	+
Meester 2019	+	+	X	+	X	X	+	+	X	+	+	−
Pang 2018	+	+	+	+	+	X	+	+	+	+	+	+
Park 2019	+	+	+	+	X	X	+	+	+	+	+	+
Plummer 2021	+	+	+	+	X	X	+	+	+	+	+	+

D1: Eligibility criteria were specified
D2: Subjects were randomly allocated to groups
D3: Allocation was concealed
D4: The groups were similar at baseline regarding the most important prognostic indicators
D5: There was blinding of all subjects
D6: There was blinding of all therapists who administered the study
D7: There was blinding of all assessors who measured at least one key outcome
D8: Measures of at least one key outcome were obtained from more than of the subjects initially allocated to groups
D9: All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by intention to treat
D10: The results of between−group statistical comparisons are reported for at least one key outcome
D11: The study provides both point measures and measures of variability for at least one key outcome

Judgement
+ Low
− Unclear
X High

Appendix 5

Risk of bias domains

Study	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	Overall
Bunketorp–Käll 2017	+	+	+	+	X	X	+	+	+	+	+	+
Faria 2018	+	+	+	+	X	X	X	X	+	+	+	−
Fujioka 2018	+	+	+	X	+	X	+	+	+	+	+	+
Givon 2016	X	+	X	+	X	X	+	+	+	+	+	−
Grau–Sánchez 2018	+	+	+	+	X	X	+	+	+	+	+	+
Jonsdottir 2021	+	+	X	+	X	X	+	+	+	+	+	−
Kannan 2019	+	+	+	+	X	X	X	X	X	+	+	−
Kim 2011	+	+	X	+	X	X	X	+	+	+	+	−
Liu–Ambrose 2015	+	+	+	+	+	X	+	+	+	+	+	+
Maier 2020	+	+	+	+	X	X	X	X	+	+	+	−
Rogers 2019	+	+	+	+	X	X	X	+	+	+	+	−
Wilson 2021	+	+	+	+	X	X	+	+	+	+	+	+
Wolf 2016	+	+	+	+	X	+	+	X	+	+	+	+

D1: Eligibility criteria were specified
D2: Subjects were randomly allocated to groups
D3: Allocation was concealed
D4: The groups were similar at baseline regarding the most important prognostic indicators
D5: There was blinding of all subjects
D6: There was blinding of all therapists who administered the study
D7: There was blinding of all assessors who measured at least one key outcome
D8: Measures of at least one key outcome were obtained from more than of the subjects initially allocated to groups
D9: All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by intention to treat
D10: The results of between–group statistical comparisons are reported for at least one key outcome
D11: The study provides both point measures and measures of variability for at least one key outcome

Judgement
+ Low
− Unclear
X High

Appendix 6

Risk of bias domains

Study	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	Overall
An 2014	X	+	X	X	X	X	X	+	+	+	+	X
Bunketorp–Käll 2017	+	+	+	+	X	X	+	+	+	+	+	+
Cho 2015	+	+	+	+	X	X	+	+	+	+	+	+
Choi JH 2015	+	+	X	+	+	X	X	+	+	+	+	−
Choi W 2015	+	+	+	+	X	+	+	+	+	+	+	+
Faria 2018	+	+	+	+	X	X	X	X	+	+	+	−
Fujioka 2018	+	+	+	X	+	X	+	+	+	+	+	+
Givon 2016	X	+	X	+	X	X	+	+	+	+	+	−
Grau–Sánchez 2018	+	+	+	+	X	X	+	+	+	+	+	+
Her 2011	+	+	X	+	X	X	X	+	+	+	+	−
Jonsdottir 2021	+	+	X	+	X	X	+	+	+	+	+	−
Kannan 2019	+	+	+	+	X	X	X	X	X	+	+	−
Kim 2014	+	+	X	+	X	X	X	+	+	+	+	−
Kim 2015	+	+	X	+	X	X	X	+	+	+	+	−
Lee 2015	+	+	X	+	X	X	X	+	+	+	+	−
Liu 2017	+	+	+	+	+	X	X	+	+	+	+	+
Meester 2019	+	+	X	+	X	X	+	+	X	+	+	−
Park 2019	+	+	+	+	X	X	+	+	+	+	+	+
Plummer 2021	+	+	+	+	X	X	+	+	+	+	+	+
Rogers 2019	+	+	+	+	X	X	X	+	+	+	+	−
Wilson 2021	+	+	+	+	X	X	+	+	+	+	+	+
Wolf 2016	+	+	+	+	X	+	+	X	+	+	+	+

D1: Eligibility criteria were specified
D2: Subjects were randomly allocated to groups
D3: Allocation was concealed
D4: The groups were similar at baseline regarding the most important prognostic indicators
D5: There was blinding of all subjects
D6: There was blinding of all therapists who administered the study
D7: There was blinding of all assessors who measured at least one key outcome
D8: Measures of at least one key outcome were obtained from more than of the subjects initially allocated to groups
D9: All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by intention to treat
D10: The results of between–group statistical comparisons are reported for at least one key outcome
D11: The study provides both point measures and measures of variability for at least one key outcome

Judgement
+ Low
− Unclear
X High

Appendix 7

Risk of bias domains

Study	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	Overall
Choi JH 2015	+	+	X	+	+	X	X	+	+	+	+	−
Faria 2018	+	+	+	+	X	X	X	X	+	+	+	−
Fujioka 2018	+	+	+	X	+	X	+	+	+	+	+	+
Grau–Sánchez 2018	+	+	+	+	X	X	+	+	+	+	+	+
Jonsdottir 2021	+	+	X	+	X	X	+	+	+	+	+	−
Kim 2011	+	+	X	+	X	X	X	+	+	+	+	−
Kim 2014	+	+	X	+	X	X	X	+	+	+	+	−
Liu–Ambrose 2015	+	+	+	+	+	X	+	+	+	+	+	+
Maier 2020	+	+	+	+	X	X	X	X	+	+	+	−
Park 2019	+	+	+	+	X	X	+	+	+	+	+	+
Rogers 2019	+	+	+	+	X	X	X	+	+	+	+	−
Wilson 2021	+	+	+	+	X	X	+	+	+	+	+	+
Wolf 2016	+	+	+	+	X	+	+	X	+	+	+	+

D1: Eligibility criteria were specified
D2: Subjects were randomly allocated to groups
D3: Allocation was concealed
D4: The groups were similar at baseline regarding the most important prognostic indicators
D5: There was blinding of all subjects
D6: There was blinding of all therapists who administered the study
D7: There was blinding of all assessors who measured at least one key outcome
D8: Measures of at least one key outcome were obtained from more than of the subjects initially allocated to groups
D9: All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by intention to treat
D10: The results of between–group statistical comparisons are reported for at least one key outcome
D11: The study provides both point measures and measures of variability for at least one key outcome

Judgement
+ Low
− Unclear
X High

Appendix 8

Risk of bias domains

Study	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	Overall
Cho 2015	+	+	+	+	X	X	+	+	+	+	+	+
Liu 2017	+	+	+	+	+	X	X	+	+	+	+	+
Meester 2019	+	+	X	+	X	X	+	+	X	+	+	−
Pang 2018	+	+	+	+	+	X	+	+	+	+	+	+
Plummer 2021	+	+	+	+	X	X	+	+	+	+	+	+

D1: Eligibility criteria were specified
D2: Subjects were randomly allocated to groups
D3: Allocation was concealed
D4: The groups were similar at baseline regarding the most important prognostic indicators
D5: There was blinding of all subjects
D6: There was blinding of all therapists who administered the study
D7: There was blinding of all assessors who measured at least one key outcome
D8: Measures of at least one key outcome were obtained from more than of the subjects initially allocated to groups
D9: All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by intention to treat
D10: The results of between–group statistical comparisons are reported for at least one key outcome
D11: The study provides both point measures and measures of variability for at least one key outcome

Judgement
+ Low
− Unclear
X High

Appendix 9

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			PAGE
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
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.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5,6, Appendix

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.	6
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.	6
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.	6
	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.	6
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.	7
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.	7,8
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)).	7,8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	7,8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7,8
	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.	7,8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	7,8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	7,8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	7,8
RESULTS			PAGE
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.	8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	8-9, tables 1-2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	10 + figure 2 + appendix
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.	8-10
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8
	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.	10-12

	20c	Present results of all investigations of possible causes of heterogeneity among study results.	10-12
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	10-12
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	10-12
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12-15
	23b	Discuss any limitations of the evidence included in the review.	12-16
	23c	Discuss any limitations of the review processes used.	15-16
	23d	Discuss implications of the results for practice, policy, and future research.	12-16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5, 15-16
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	16
Competing interests	26	Declare any competing interests of review authors.	13
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.	5

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/

CHAPTER 3

THE RELATIONSHIP BETWEEN SPATIAL NEGLECT AND POSTURAL CONTROL AFTER STROKE

CHAPTER 3.1

THE ASSOCIATION BETWEEN VISUOSPATIAL NEGLECT AND BALANCE AND MOBILITY POST-STROKE ONSET: A SYSTEMATIC REVIEW

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Published in Annals of Physical and Rehabilitation Medicine (2021): Embrechts E, Van Criekinge T, Schröder J, Nijboer T, Lafosse C, Truijen S, Saeys W. The association between visuospatial neglect and balance and mobility post-stroke onset: A systematic review. Ann Phys Rehabil Med. 2021 Jul;64(4):101449. DOI: 10.1016/j.rehab.2020.10.003.

Abstract

Background. Although previous narrative reviews have highlighted a potential association between visuospatial neglect (VSN) and balance disorders, to what extent different areas of balance and mobility could be affected is still unclear.

Objectives. This systematic review updates previous literature findings and systematically reviews sitting balance, standing balance and mobility outcomes.

Methods. PubMed, Web of Science, ScienceDirect, Naric-Rehabdata, PEDro and the Cochrane Trials Library were systematically searched. Methodological quality was assessed by the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. The association between VSN and sitting balance, standing balance and mobility (walking, stair climbing/descending and transfers) was investigated.

Results. In total, 48 studies were included (4595 stroke survivors): at least 1319 (29%) showed symptoms of VSN. VSN was associated with less independence during sitting, with an asymmetric posture toward the affected body side. For standing balance, we revealed a significant negative association between VSN and mediolateral stability and weight-shifting, whereas only activities of daily living-related VSN was associated with weight-bearing asymmetry during static stance. While walking, patients with VSN laterally deviated from their path. Results were inconclusive regarding other aspects of mobility,. The association between VSN and balance/mobility seemed to decrease over time.

Conclusions. Despite great heterogeneity in results, this study suggests that stroke survivors with VSN show specific deviations in posture and movement in the mediolateral direction. Although the association between VSN and balance/mobility has been extensively investigated, explanatory studies evaluating underlying mechanisms of the frequently present association are lacking. Future studies should address this by combining clinical and instrumented assessment of balance and gait performance, preferably longitudinally to investigate the associations over time.

Keywords. stroke, visuospatial neglect, balance, mobility, walking

Introduction

Spatial neglect is a post-stroke disorder characterised by impaired awareness for stimuli located on the contralesional side of space [1]. This neglect results in problems with reporting, responding or orienting toward contralesional stimuli, which cannot be explained by sensory or motor impairments [1]. Spatial neglect is a heterogeneous disorder because it can encompass different clinical subtypes, which might involve different frames of references (egocentric, allocentric), processing modalities (e.g., sensory, representational) or regions of space (personal, peri-personal, extra-personal) [2].

Visuospatial neglect (VSN) concerns neglect for visual stimuli and is the most frequently present and investigated type of spatial neglect [2]. VSN can be present after a right- or left-sided brain lesion but is more frequently present in right-sided brain lesions [3, 4]. Within the first 2 weeks post-stroke, VSN occurs in approximately 50% of patients [5]. Spontaneous neurological recovery of VSN follows a natural logistic pattern of improvement within the first 12 to 14 weeks post-stroke. Afterward, the curve flattens and the severity of VSN remains merely invariant, leaving 40% of patients with initial VSN still with symptoms at 1 year post-stroke [5].

The high frequency and persistence of VSN might have major consequences; indeed, various studies suggest a negative association between VSN and post-stroke recovery of motor function and abilities [6-8]. Apart from the seemingly suppressive influence of VSN on the recovery of upper-limb strength and synergy acquisition [8], balance and mobility might also be affected owing to an impaired postural control system [6]. This spatially oriented system has 2 major behavioural goals [9, 10]: on the one hand, it ensures a correct postural orientation proportionate to gravity, internal references and surroundings; on the other, it guarantees postural stability relative to the base of support to ensure the desired body orientation or the performance of controlled movement [9, 10]. Postural control is thought to be organized around internal models, closely related to the “postural body scheme,” which may represent a neural process incorporating sensory information from multiple modalities, resolving sensory ambiguity and integrating afferent and efferent information [9, 10]. A spatial (orientational) bias of attention is a key characteristic of VSN [11] and might thus reflect a disruption in spatial information processing, which could impair body representation. This could result in impaired postural control and therefore impaired balance and functional mobility.

Although previous narrative reviews have highlighted a potential association between VSN and balance disorders [6], to what extent different areas of balance and mobility could be affected is still unclear. To fill this gap in the literature, this systematic review thoroughly updates previous research and systematically reviewed sitting balance, standing balance and mobility outcomes.

Materials and methods

Protocol and registration

The protocol of this systematic review was registered on PROSPERO (registration no. CRD42020141817). This review adheres to the guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [12] (See Appendix A).

Search strategy and study selection

A systematic literature search was conducted on August 11, 2020 in PubMed, Web of Science, ScienceDirect, Naric-Rehabdata, PEDro and the Cochrane CENTRAL Library ('Trials' subsection). Search queries were built by using the following free-text terms as well as medical subject headings: "visuospatial neglect", "stroke", "balance", "gait" and their synonyms (see Appendix B). No restrictions or filters were added. We included articles that 1) investigated adult stroke survivors with no restrictions on lesion type or location; 2) evaluated an association between VSN and balance or mobility by comparing patients with and without VSN or by evaluating this association by correlation or regression analyses; 3) were original research (i.e., no clinical answers, reviews or meta-analyses) and 4) were written in English, German or Dutch. For intervention studies, only baseline characteristics were considered because we were not interested in effects of any intervention. We excluded studies that were 1) unavailable in full-text format even after contacting the authors; 2) were case studies, because this does not allow to compare patients with and without VSN; 3) evaluated balance/mobility in a virtual environment because of the inability to evaluate whether potential associations with balance/mobility are due to VSN or exposure to virtual environments; and 4) investigated a specific subgroup of patients with pusher syndrome: this complex multifactorial disorder results in a specific clinical behaviour in which patients actively push themselves away from the midline (straight) position [13]. Owing to the multifactorial nature of the disorder, evaluating the sole contribution of VSN to the outcome in this subgroup of stroke patients would be difficult.

Screening on the title, abstract and full text was performed by two independent reviewers (EE, TVC). During full-text screening, reference lists of included studies were screened for secondary literature. Disagreements between reviewers were resolved by discussion.

Definitions

Predefined definitions concerning the criteria related to VSN, balance and mobility were used to decrease the potential for ambiguity in article selection. VSN was defined as a cognitive disorder characterised by impaired awareness of visual stimuli located on the contralesional side of space [1]. We included studies that adhered to this definition, even if no specific diagnostic test for VSN was used. If specific diagnostic tests were used, we distinguished between isolated (paper-and-pencil) tests (e.g., Star Cancellation Test), test batteries (e.g., Behavioural Inattention Test) and tests evaluating VSN during activities of daily living (ADL) with observational scales (e.g., Catherine Bergego Scale [CBS]). When VSN is assessed during ADL using observational scales, such tests evaluate more than solely VSN (e.g., auditive, tactile, motor and body neglect) without providing a distinction between these forms. Because they also evaluate VSN and because of the widespread use of the test to measure VSN, studies using such scales were not excluded but were referred to as evaluating "ADL-related VSN" [14].

Considering balance and mobility, 3 main categories were defined, "sitting balance", "standing balance" and "mobility", based upon definitions of the International Classification of Functioning, Disability and Health [15]. "Sitting balance" is defined as 'the ability to maintain a sitting posture in static or dynamic situations' [15]. "Standing balance" is described as 'the dynamics of a standing body posture in order to prevent falling, whose assessment may be performed under both static or dynamic circumstances [15]. Concerning standing and sitting balance, static circumstances are situations in which the body is sitting or standing quietly, whereas within dynamic situations, the body is moving within the base of support (such as sit-to-stand [STS] ability or reaching) [9]. Finally, the definition of mobility is "moving by transferring from one place to another (e.g., by changing base of support) such as during walking, stair climbing and transfers (e.g., bed-to-chair) [15]. All variables of interest could be assessed with clinical or instrumented methods. “Clinical methods” refer to clinical assessment scales (such as the Berg Balance Scale) without using any instrumented device, whereas “instrumented methods” refer to biomechanical assessment using such devices (e.g., force plates or gait analysis instruments).

Quality assessment

Risk of bias of included studies was assessed with the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [16]. For intervention studies, the same tool was used because only the pre-intervention characteristics of participants were investigated. Therefore, they were considered cross-sectional studies. This quality assessment tool assesses internal validity, including sources of bias (e.g., patient selection and detection), confounding factors, study power, the strength of the association between factors and outcomes, and other factors. It scores risk of bias by rating “yes”, “no” or “cannot determine/not reported/not applicable” for each criterion. One point is rewarded for every “yes” given, indicating a low risk of bias. The criteria were adjusted to be more consistent with the research objectives (see Appendix C). Because no categories of methodological quality are predefined by the NIHLBI, quality was estimated by calculating percentiles to subcategorise studies as low, moderate and high methodological quality. Studies within percentiles 10-20 (score <7) were considered at “low” methodological quality, studies with percentiles 30-60 (score 7-8) at “moderate” methodological quality and studies within percentiles 70-100 (score ≥9) at “high” methodological quality.

Data extraction and analyses

The following data were extracted by 2 independent reviewers (EE, TVC) from the included studies: authors, year, study design, number of participants with and without VSN, age, time post-stroke at inclusion, time(point) post-stroke of final assessment for longitudinal studies, VSN assessment, the evaluated outcomes for balance (sitting vs standing) or mobility and their subcategories, and main findings of the studies. Tables 2-5 show further which assessment scales and methods were used to evaluate the different outcome categories.

Results

Study selection

In total, 1631 unique articles were retrieved. Considering screening on "title and abstract" and "full text", we found 74% and 85% agreement between the reviewers, respectively. All ambiguities were resolved during discussion, and ultimately, 48 articles were included (Figure 1).

Risk of bias (Table 3.1.1)

Agreement between the reviewers concerning risk of bias was 96%, and disagreements were successfully resolved during discussion. Scores ranged from 4 to 12 out of 14. All but 2 studies received a zero on item 5, which evaluates sample size justification and power description. In addition, item 13 scored positive for every study, because none of the studies experienced loss to follow-up of >20%. Percentiles were calculated to classify studies according to methodological quality. Nine studies were of poor methodological quality [17-25], 21 studies moderate methodological quality [26-46] and 18 studies good methodological quality [47-64].

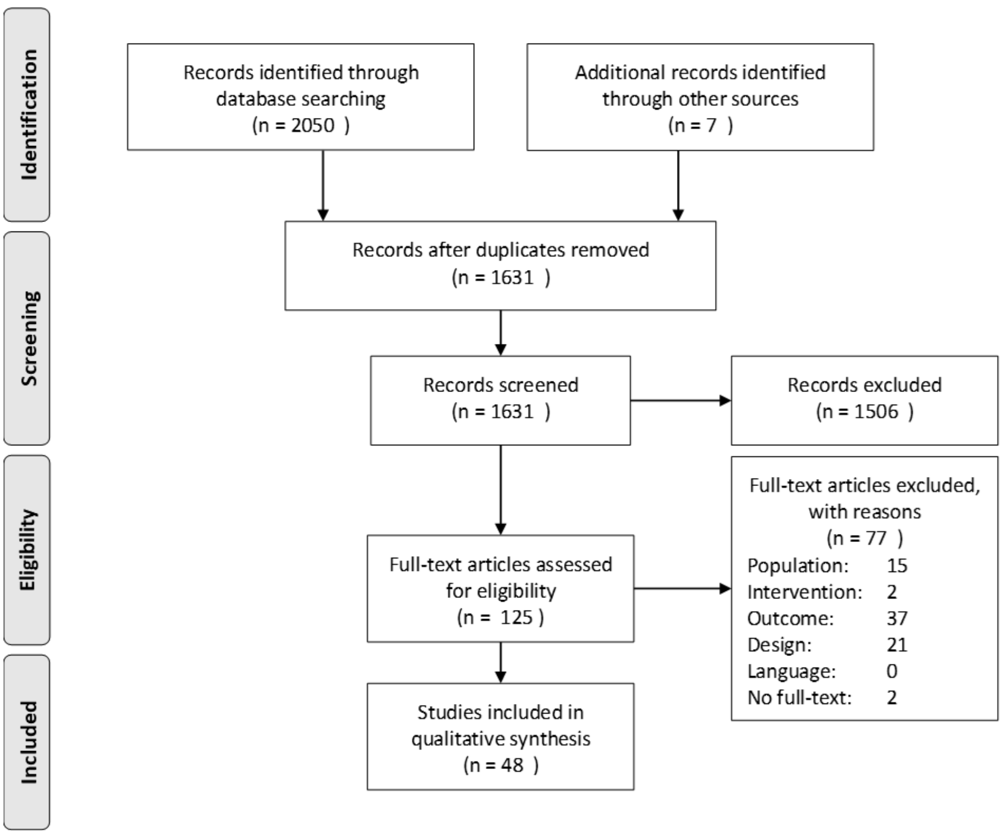

Figure 3.1.1. Flowchart of the selection of eligible studies [12].

Table 3.1.1. Methodological quality items per study

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total Y	Total N/NA/NM	MQ*
Alexander et al. 2009 [26]	Y	Y	N	Y	N	N	N	Y	Y	N	Y	Y	Y	NM	8	6	Moderate
Barra et al. 2009 [27]	Y	Y	N	Y	N	N	N	Y	Y	N	Y	N	Y	N	7	7	Moderate
Bonan et al. 2004 [28]	Y	Y	N	Y	N	N	N	N	Y	N	Y	N	Y	Y	7	7	Moderate
Bonan et al. 2006 [29]	Y	Y	N	Y	N	N	N	N	Y	N	Y	N	Y	Y	7	7	Moderate
Bonan et al. 2007 [30]	Y	Y	N	Y	N	N	Y	N	Y	N	Y	N	Y	N	7	7	Moderate
Colombo et al. 2019 [31]	Y	Y	Y	Y	N	N	N	N	Y	N	Y	N	Y	Y	8	6	Moderate
Dai et al. 2014 [32]	Y	Y	Y	Y	N	NM	N	N	Y	N	Y	N	Y	Y	8	6	Moderate
de Haart et al. 2004 [47]	Y	Y	N	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	11	3	Good
de Haart et al. 2005 [33]	Y	Y	N	Y	N	N	Y	N	Y	N	Y	N	Y	Y	8	6	Moderate
Ferreira et al. 2015 [17]	Y	N	N	Y	N	N	NM	N	N	N	N	N	Y	Y	4	10	Poor
Genthon et al. 2008 [48]	Y	Y	N	Y	N	Y	N	Y	Y	N	Y	N	Y	Y	9	5	Good
Goldie et al. 1999 [49]	Y	Y	N	Y	N	N	Y	N	Y	Y	Y	N	Y	Y	9	5	Good
Goto et al. 2009 [18]	N	Y	Y	Y	N	N	NM	N	N	N	Y	N	Y	Y	6	8	Poor
Huitema et al. 2006 [34]	Y	Y	N	Y	N	Y	N	N	Y	N	Y	N	Y	Y	8	6	Moderate
Ishii et al. 2010 [35]	Y	Y	N	Y	N	Y	N	N	Y	N	Y	N	Y	Y	8	6	Moderate
Jackson et al. 2000 [50]	Y	Y	Y	N	N	Y	N	N	Y	N	Y	Y	Y	Y	9	5	Good
Kalra et al. 1997 [19]	Y	N	N	Y	N	Y	N	N	Y	N	Y	N	Y	N	6	8	Poor

Katz et al. 1999 [36]	Y	Y	N	Y	N	Y	Y	N	Y	N	N	N	Y	N	7	7	Moderate
Kawanabe et al. 2018 [37]	Y	Y	N	Y	Y	N	N	N	N	N	Y	N	Y	Y	7	7	Moderate
Kimura et al. 2019 [51]	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y	11	3	Good
Kinsella et al. 1980 [38]	Y	Y	N	Y	N	N	Y	N	N	Y	Y	N	Y	Y	8	6	Moderate
Kinsella et al. 1985 [52]	Y	Y	N	Y	N	N	Y	N	Y	Y	Y	N	Y	Y	9	5	Good
Kollen et al. 2005 [53]	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	N	Y	N	9	5	Good
Maeshima et al. 1997 [39]	Y	N	N	N	N	N	Y	N	Y	Y	Y	N	Y	Y	7	7	Moderate
Mercer et al. 2014 [54]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	12	2	Good
Morone et al. 2015 [55]	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	N	Y	N	9	5	Good
Morone et al. 2018 [40]	Y	Y	Y	Y	N	Y	N	N	N	N	Y	N	Y	NM	7	7	Moderate
Nijboer et al. 2013 [56]	Y	Y	NM	Y	N	N	Y	N	Y	Y	Y	N	Y	Y	9	5	Good
Nijboer et al. 2014 [57]	Y	Y	N	Y	N	Y	N	Y	Y	N	Y	N	Y	Y	9	5	Good
Paolucci et al. 1998 [41]	Y	Y	Y	Y	N	Y	NM	N	N	N	Y	N	Y	Y	8	6	Moderate
Paolucci et al. 2001[A] [58]	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	Y	9	5	Good
Paolucci et al. 2001[B] [59]	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	N	Y	Y	10	4	Good
Paolucci et al. 2008 [60]	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	N	Y	Y	9	5	Good
Petrilli et al. 2002 [42]	Y	Y	Y	Y	N	N	N	N	N	N	Y	N	Y	N	6	8	Poor
Perry et al. 2006 [20]	Y	Y	Y	Y	N	Y	Y	N	N	N	N	N	Y	N	7	7	Moderate
Rousseaux et al. 2013 [21]	Y	Y	N	Y	N	N	N	N	Y	N	Y	N	Y	N	6	8	Poor

Stapleton et al. 2001 [61]	Y	Y	N	Y	N	N	Y	N	Y	Y	Y	N	Y	N	8	6	Moderate
Stein et al. 2009 [43]	Y	N	Y	Y	N	Y	Y	N	Y	N	Y	NM	Y	Y	9	5	Good
Sturt et al. 2013 [46]	Y	Y	NM	Y	N	NM	N	N	Y	N	Y	N	Y	Y	7	7	Moderate
Tarvonen-Schröder et al. 2020[A] [64]	Y	Y	Y	Y	N	NM	N	Y	Y	N	Y	Y	Y	Y	10	4	Good
Tarvonen-Schröder et al. 2020[B][63]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	12	2	Good
Taylor et al. 1994 [22]	Y	N	Y	Y	N	NM	N	N	Y	N	Y	N	Y	N	6	8	Poor
Tromp et al. 1995 [23]	Y	N	N	N	N	NM	N	N	Y	N	Y	N	Y	N	4	10	Poor
Tyson et al. 2006 [24]	Y	Y	N	Y	N	N	N	N	Y	N	Y	N	Y	N	6	8	Poor
van Nes et al. 2008 [44]	Y	N	Y	Y	N	Y	N	N	Y	N	Y	N	Y	N	7	7	Moderate
van Nes et al. 2009[A] [62]	Y	Y	N	Y	N	N	Y	N	Y	Y	Y	N	Y	Y	9	5	Good
van Nes et al. 2009[B] [45]	Y	Y	N	Y	N	N	N	N	Y	N	Y	N	Y	Y	7	7	Moderate
Yelnik et al. 2006 [25]	Y	Y	N	Y	N	N	N	N	Y	N	Y	N	Y	N	6	8	Poor

Maximum obtainable score: 14. **Abbreviations**: max, maximum possible; MQ*, level of methodological quality based on percentiles; N, no; NA, not applicable; NM, not mentioned; Y, yes

Participants and descriptive data (Table 3.1.2)

Of the 48 included studies, 21 were cross-sectional [18, 19, 21-29, 31, 32, 34, 35, 37, 44, 45, 48, 57, 64] and 26 were longitudinal [17, 20, 30, 33, 36, 38-43, 47, 49-56, 58-62, 64]. A total of 4595 stroke survivors were studied; at least 1319 (29%) showed symptoms of VSN, with mean or median age from 52 to 77 years. All except 3 studies [17, 20, 42] reported a standardized assessment to detect VSN, with great variability in tools used. Paper-and-pencil tests were used most frequently, by 39 studies [18, 19, 21-25, 27-35, 37-41, 43, 45-47, 49, 50, 52-62]. Ten studies used only a paper-and-pencil test to assess VSN [22, 28, 45, 46, 49, 53, 56, 57, 61, 62], 26 studies used a paper-and-pencil test combined with other VSN tests [18, 19, 21, 23-25, 27, 29-31, 33-35, 37-41, 47, 50, 52, 54, 55, 58-60], and 3 studies used paper-and-pencil tests within a complete test battery for VSN, namely the Behavioural Inattention test [32, 36, 43]. VSN was assessed 6 times by using observation, with a computerized visual reaction-time test [44], with the National Institute of Health Stroke Scale (NIHSS) neglect item [26], without reporting a scale [20], and by using the CBS (ADL-related VSN) [21, 27, 65]. Assessment with the NIHSS neglect item was not combined with other tests to detect VSN. The CBS was used in 3 studies in isolation [48, 63, 64] and in 2 combined with paper-and-pencil tests [21, 27]. In only 8 studies was VSN evaluated on different levels (e.g., measured as a continuous variable [severity] [26, 27, 48, 53, 54, 63, 64] or divided according to regions of space affected [57]).

Considering the time post-stroke of the initial or single VSN and balance/mobility assessment, one study evaluated stroke patients in the acute phase [45], 31 in the early subacute phase [18-22, 24, 25, 29-33, 35-37, 40, 41, 44, 46, 47, 51, 53-58, 60, 61, 63, 64], 4 in the late subacute phase [23, 27, 48, 50] and 4 in the chronic phase post-stroke [26, 28, 34, 62, 66] according to the phases proposed by Bernhardt et al. [67]. Eight studies did not mention the time post-stroke [17, 38, 39, 42, 43, 49, 52, 59].

Sitting balance (Table 3.1.3)

Clinical assessment

All studies demonstrated a significant negative relationship between VSN and sitting balance [22, 36, 37, 45]. Patients with VSN were significantly more dependent considering static sitting [37], and the prevalence of abnormal sitting equilibrium was significantly greater in patients with than without VSN [36]. Also, an asymmetric sitting posture with the trunk shifted towards the paretic side was more prevalent in patients with than without VSN [22]. Moreover, VSN

Table 3.1.2. Descriptive data

Author	D	N (lesion side)	VSN+/VSN-	Age (SD or range) in years	TPS initial/single assess (SD or range)	CTPi	TPS final assess	VSN assessment tools
Alexander et al. 2009 [26]	CS	37 (19 R, 18 L)	7/ 30	Sym: 60.5 (14.4) Asym: 50.6 (15.4)	Sym: 38.3 (32.4) m Asym: 57.7 (53.2) m	Chronic	NA	NIHSS neglect item
Barra et al. 2009 [27]	CS	22 (13 R, 9 L)	NM	57.14 (14.04)	13 (7.5) w	Late subac	NA	Bell's test, line bisection test, catherine bergego scale
Bonan et al. 2004 [28]	CS	40 (20 R, 20 L)	9/ 40	49.5 (16) (IQR 35-78)	19 (15) m (IQR 12-108)	Chronic	NA	Bell's test
Bonan et al. 2006 [29]	CS	30 (17 R, 13 L)	15/ 15	59 (IQR 21)	39,5 d (IQR 37)	Early subac	NA	Bell's test, line bisection test
Bonan et al. 2007 [30]	C	28 (14 R, 14 L)	8/20	57.5 (IQR 22)	22.5 d (IQR 33)	Early subac	6m	Bell's test, line bisection test, scene copy test
Colombo et al. 2019 [31]	CS	89 (46 R, 43 L)	22/ 67	VSN+: 72.13 (8.45) VSN-: 70.46 (9.98)	VSN+: 47d VSN-: 39 d	Early subac	NA	Bell's test, line bisection test
Dai et al. 2014 [32]	CS	60 (all R)	40/ 20	A+VSN+: 61.85 (13.68) A-VSN+: 62.00 (16.24) A-VSN-: 60.35 (9.60)	A+VSN+: 68.30 (41.35) d A-VSN+ 52.10 (28.98) d A-VSN-: 62.30 (55.70) d	Early subac	NA	Behavioural inattention test - conventional subtests
de Haart et al. 2004 [47]	C	37 (24 R, 13 L)	16/ 21	61.6 (12.9) (27-82)	10 (5.4) w (3.3-24.1)	Early subac	12w after recr	Dutch O-search test, line bisection test, First 6 items of the block design subtest of Wechsler Adult Intelligence Scale
de Haart et al. 2005 [33]	C	36 (23 R, 13 L)	15/ 21	61.8 (13.0) (27-82)	10.0 (5.5) w (3.3-24.1)	Early subac	12w after recr	Dutch O-search test, line bisection test, First 6 items of the block design subtest of the

								Wechsler Adult Intelligence Scale
Ferreira et al. 2015 [17]	C	201 (99 R/102 L)	19/ 182	56.9 (21-90)	NM	NM	6m after rehab	NM
Genthon et al. 2008 [48]	CS	41 (25 R, 16 L)	NM	58.8 (13.5)	93.0 (46.2) d	Late subac	NA	Catherine bergego scale
Goldie et al. 1999 [49]	C	42 (23 R, 19 L)	10/ 32	66 (IQR 50-76)	As soon as possible after adm	NM	8w after adm	Shape cancellation test
Goto et al. 2009 [18]	CS	247 (77 R*)	10/ 67*	65.5 (10.5) (37-83)	51.7 d	Early subac	NA	Line bisection test, cancellation test, replication of picture of house/cube, drawing clock/human/hand, observation
Huitema et al. 2006 [34]	CS	20 (12 R, 8 L)	6/14	L VSN-: 55.9 (35.6-73.2) R VSN- : 59.5 (37.3-73.6) R VSN+: 67.5 (63.5-69.8)	L VSN-: 447 (202-692) d R VSN-: 819 (485-1023) d R VSN+: 406 (93-1066) d	Chronic	NA	Bell's test, line bisection test, letter cancellation test, double simultaneous stimulation test
Ishii et al. 2010 [35]	CS	12 (all R)	7/5	68.6 (9.9)	15.8 (9.4) d	Early subac	NA	Line bisection test, line crossing test
Jackson et al. 2000 [50]	C	119 (45 R, 67 L, 7 NM)	29/ 71 (19 NT)	54 (IQR 47–60)	13.4 (IQR 9.1-17.5) w	Late subac	Disch	Line bisection test, star cancellation test, copying a diagram, drawing a clock
Kalra et al. 1997 [19]	CS	146 (75 R, 71 L)	47/ 99	77.0 (8.2)	8 d	Early subac	NA	Visual and sensory confrontation tests, line bisection test, observation during activities
Katz et al. 1999 [36]	C	40 (all R)	19/ 21	VSN+: 57.4 (10.1) VSN-: 58.36 (8.0)	VSN+: 34.5 (10.9) d VSN-: 25.4 (9.0) d	Early subac	Disch	Complete behavioural inattention test

Kawanabe et al. 2018 [37]	CS	107 (50 R, 50 L, 7 both)	21/ 86	71.1 (12.9)	20.7 (27.4) d	Early subac	NA	Line bisection test, line cancellation test, and double-dot detection task[1]
Kimura et al. 2019 [51]	C	94 (all R)	56/ 38	69.9 (9.3)	VSN+CI+: 36.5 (28.3-45.5) d VSN+CI-: 33.0 (24.8-48.0) d VSN-CI-: 30.0 (17.8-42.0) d	Early subac	Disch	Stroke impairment assessment set
Kinsella et al. 1980 [38]	C	31 (14 R, 17 L)	8/23	62 (33-74)	4-6 w after adm	NM	12w after adm	Albert's test, copy of complex figure of Rey, copy of drawings of a Maltese cross and flower, line bisection test, tri-modal double simultaneous stimulation
Kinsella et al. 1985 [52]	C	28 (13 R, 15 L)	8/20	62 (33-74)	4-6 w after adm	NM	18m PS	Albert's test, copy of complex figure of Rey, copy of drawings of a Maltese cross and flower, line bisection test, tri-modal double simultaneous stimulation
Kollen et al. 2005 [53]	C	101 (61 R, 41 L)	NM	65.4 (10.5)	7.3 (2.8) d	Early subac	52w PS	Letter cancellation test
Maeshima et al. 1997 [39]	C	22 (13 R, 9 L)	10/ 12	59.7 (8.8) (46-78)	Adm	NM	Disch	Line cancellation test, line bisection test, figure copying task
Mercer et al. 2014 [54]	C	32 (23 R, 10 L)	17/ 15	58.7 (17.3) (24-97)	1 m	Early subac	6m PS	Letter cancellation test, start cancellation test
Morone et al. 2015 [55]	C	435 (187 R, 248 L)	76/ 359	71 (Q1 59, Q3 78)	14 d (Q1 9, Q3 25)	Early subac	Disch	Letter cancellation test, line cancellation test, sentence reading test, Wundt-Jastrow Area Illusion test
Morone et al. 2018 [40]	C	257 (142 R, 115 L)	60/ 197	69.91 (13.75)	18.35 (16.11) d	Early subac	Disch	Letter cancellation test, line cancellation test, sentence reading

								test, Wundt-Jastrow Area Illusion test
Nijboer et al. 2013 [56]	C	184 (115 R, 69 L)	53/ 131	VSN+: 55.5 (10.29) VSN-: 58.1 (11.33)	VSN+: 56.1 (29.84) d VSN-: 47.6 (20.31) d	Early subac	36m PS	Letter cancellation test
Nijboer et al. 2014 [57]	CS	81 (32 R, 45 L, 4 bilateral)	16/ 65	VSN+ 59.0 (12.7) VSN- 55.84 (12.5)	VSN+: 41.0 (32.9) d VSN-: 36.5 (39.6) d	Early subac	NA	Shape cancellation test
Paolucci et al. 1998 [41]	C	440 (206 R/234 L)	83/ 357	63.55 (11.57)	54.14 (37.45) d	Early subac	Disch	Letter cancellation test, line cancellation test, sentence reading test, Wundt-Jastrow area illusion test
Paolucci et al. 2001[A] [58]	C	178 (all R)	89/ 178	VSN+: 69.10 (9.51) VSN-: 69.67 (9.60)	VSN+: 38.98 (15.40) d VSN-: 38.42 (17.06) d	Early subac	Disch	Letter cancellation test, line cancellation test, sentence reading test, Wundt-Jastrow area illusion test
Paolucci et al. 2001[B] [59]	C	141 (Non-PDT: R 60%, L 40% PDT: R/L 50%)	32/ 109	Non-PDT: 58.72 (15.26) PDT: 62.54 (10.69)	Disch	NM	1y post-Disch	Letter cancellation test, line cancellation test, sentence reading test, Wundt-Jastrow area illusion test
Paolucci et al. 2008 [60]	C	500 (R 49%, L 51%)	117/ 383	68.19 (13.22) (10-97)	21.18 (7) d	Early subac	Disch	Letter cancellation test, line cancellation test, sentence reading test, Wundt-Jastrow area illusion test
Petrilli et al. 2002 [42]	C	93 (36 R, 57 L)	25/ 68	64.8 (29-90)	NM	NM	Disch	Not mentioned
Perry et al. 2006 [20]	C	55 (NM)	17/ 55	63.7 (16.6)	9.2 (10.9) d	Early subac	Disch	Not mentioned: occupational therapy exam[1]

Rousseaux et al. 2013 [21]	CS	42 (NM)	21/21	VSN+: 61.0 (14.4) VSN-: 55.5 (11.1)	VSN+: 59.6 (33.7) d VSN-: 64.7 (37.3) d	Early subac	NA	Line bisection, scene copying, bell's test, Catherine Bergego Scale
Stapleton et al. 2001 [61]	C	14 (10 R, 4 L)	7/7	60 (21–80)	34 (12-129) d	Early subac	6 w after recr	Star cancellation test
Stein et al. 2009 [43]	C	25 (all R)	12/ 13	VSN+: 77.7 (8) (65-87) VSN-: 74.1 (11) (53-89)	Adm	NM	5 w after disch	Behavioural Inattention Test
Sturt et al. 2013 [46]	I	18 (12 R, 6 L)	6/ 12	R&VSN+: 75.0 (13.3) R&VSN-: 67.8 (6.1) L&VSN-: 73.0 (15.9)	R&VSN+: 19.2 (12.1) d R&VSN-: 52.7 (48.2) d L&VSN-: 47.2 (60.7) d	Early subac	NA	Star cancellation test
Tarvonen-Schröder et al. 2020[A] [64]	CS	173 (69 R, 104 L)	126/ 47	R&VSN+: 65.1 (IQR 56. 71.2) R&VSN-: 57.6 (IQR 51.1 67.2) L&VSN+: 66.5 (65.1-74. L&VSN-: 60 (56.1-71.4)	R&VSN+: 36.0 (IQR 23-62) d R&VSN-: 44.5 (IQR 16-83) d L&VSN+: 37.0 (IQR 17-72) d L&VSN-: 25.0 (IQR 18-43) d	Early subac	NA	Catherine Bergego Scale
Tarvonen-Schröder et al. 2020[B][63]	C	173 (69 R, 104 L)	126/ 47	R&VSN+: 65.1 (IQR 56. 71.2) R&VSN-: 57.6 (IQR 51.1 67.2) L&VSN+: 66.5 (IQR 65. 74.3) L&VSN-: 60 (IQR 56.1-71.4)	R&VSN+: 36.0 (IQR 23-62) d R&VSN-: 44.5 (IQR 16-83) d L&VSN+: 37.0 (IQR 17-72) d L&VSN-: 25.0 (IQR 18-43) d	Early subac	Disch	Catherine Bergego Scale
Taylor et al. 1994 [22]	CS	38 (21 R, 17L)	13/ 25	72 (49-86)	6w	Early subac	NA	Star cancellation test
Tromp et al. 1995 [23]	CS	9 (all R)	5/ 9	56 (27-72)	21 (14) w (5-45)	Late subac	NA	Drawing task, letter cancellation test, line bisection test

Tyson et al. 2006 [24]	CS	75 (46 R, 29 L)	21/ 53	71.5 (12.2) (34-92)	21 (5) d	Early subac	NA	Star cancellation test, line bisection test
van Nes et al. 2008 [44]	CS	16 (8 R, 8 L)	NM	62.7 (7.6)	5.6 (1.7) w	Early subac	NA	Computerized visual reaction-time task
van Nes et al. 2009[A] [62]	C	53 (28 R, 25 L)	13/ 40	61.1 (10.3)	366 (10.4) d	Chronic	12 w after adm	Letter and star cancellation test
van Nes et al. 2009[B] [45]	CS	78 (44 R, 34 L)	17/ 61	VSN+: 74.9 (9.5) VSN-: 70.6 (12.9)	VSN+: 6.2 (2.4) d VSN-: 5.3 (2.4) d	Acute	NA	Letter and star cancellation test
Yelnik et al. 2006 [25]	CS	25 (14 R, 11 L)	11/14	52 (13)	30.1 (12.6) d	Early subac	NA	Bell's test, bisection of single line

Data are mean or median. **Abbreviations:** D, design; C, cohort; CS, cross-sectional; I, interventional; CI, cognitive impairment; N, number of participants; R, right-sided stroke, L, left-sided stroke; CTPi, critical time period post-stroke of initial assessment; TPS, time post-stroke; d, days; w, weeks; m, months; y, years; SD, standard deviation; sym, symmetric; asym, asymmetric; VSN+, patients with VSN; VSN-, patients without VSN; NM, not mentioned; NA, not applicable; NT, Not tested; subac, subacute; assess, assessment; adm, admission; rehab, rehabilitation; disch, discharge; recr, recruitment; PS, post-stroke. * The authors performed a sub-analysis to evaluate the association of mobility and VSN on a sample of 77 patients with a right-hemispheric lesion only; [1]Authors were contacted and they either provided the VSN test carried out or confirmed upon the definition of VSN.

was a significant, negative predictor of outcome on both static and dynamic sitting balance [45].

Instrumented assessment: posturography

VSN was not significantly associated with centre of pressure (CoP) excursions [44, 57] or velocities [44] in the anteroposterior direction. Neither were patients with and without VSN significantly different considering combined anteroposterior and mediolateral CoP excursions [57]. With regard to the mediolateral direction, 2 studies of moderate methodological quality found no significant association between VSN and mediolateral CoP excursions [29, 44] or velocities [44], whereas one study of good methodological quality found a significant association for mediolateral CoP excursions [57]. Yelnik et al. [25] investigated sitting balance under optokinetic stimulation (OKS) and showed that VSN was unrelated to body tilt under OKS, but it was positively related to the stabilization reaction (i.e., ratio for total length of CoP displacement under OKS). In summary, although consensus was reached on an absent association in the anteroposterior direction, the association between CoP excursions in the mediolateral direction and VSN is still uncertain.

Standing balance (Table 3.1.4)

Clinical assessment

All studies demonstrated that the presence of VSN was significantly and negatively related to independence regarding sit to stand (STS) from a toilet [37]. However, no association was found for STS from a (wheel)chair in studies of poor and moderate quality, respectively [20, 37]. Concerning a combined assessment approach for static and dynamic standing balance, a significant independent and negative association with VSN was found in 2 studies [45, 62], and the opposite was found in one study [61].

Instrumented assessment: posturography

Only ADL-related VSN, measured with the CBS, was significantly related to weight-bearing asymmetry in favour of the non-paretic leg[27, 65], whereas VSN evaluated with paper-and-pencil tests did not [27, 35, 47]. Additionally, ADL-related VSN was the best negative predictor of mediolateral instability [65] but was unrelated to anteroposterior instability [65]. One study found no relationship between VSN and an equilibrium score based on postural sway during the Sensory Organisation test [28]. During weight-shifting, VSN was unrelated to weight-

Table 3.1.3. Sitting balance

Author	Sub-category	Assessment tool	Conclusion	Relationship VSN-Outc?	MQ
Clinical assessment					
Katz et al. 1999 [36]	Static	Observed abnormal sitting equilibrium	Prevalence of abnormal sitting equilibrium was >3 times higher in VSN+ patients as compared to VSN- patients at admission and discharge (VSN+: 84%, VSN-: 24%)	Yes	Mod
Kawanabe et al. 2018 [37]	Static	Observed sitting on toilet	VSN+ patients were significantly less independent considering sitting on the toilet as compared to VSN- patients (VSN+: β=-1.130 (SE=0.469, p=0.016))	Yes	Mod
Kawanabe et al. 2018 [37]	Static	Observed sitting in wheelchair	VSN+ patients were significantly less independent considering sitting in the wheelchair as compared to VSN- patients (VSN+: β=-0.932 (SE=0.434, p=0.032))	Yes	Mod
Taylor et al. 1994 [22]	Static	Observed sitting on firm horizontal surface	A significantly greater proportion of VSN+ patients (n=8) showed asymmetric sitting towards the affected side as compared to VSN-patients (n=1)	Yes	Poor
van Nes et al. 2009[B] [45]	Static & dynamic	Trunk Control Test	VSN was a significant, negative predictor for the Trunk Control Test (β=-14.065, CI: [-24.474; -3.656])	Yes	Mod
van Nes et al. 2009[B] [45]	Static & dynamic	Trunk Impairment Scale	VSN was a significant, negative predictor for the Trunk Impairment Scale (: β=-2.674, CI: [-5.002;-0.346])	Yes	Mod
Instrumented assessment: posturography					
Nijboer et al. 2014 [57]	Static: mediolateral direction	Average mediolateral CoP displacement (30s), in EO/EC conditions	Average mediolateral CoP was significantly displaced in patients with isolated peripersonal VSN as compared to VSN- patients (EO: U=108.0, Z=-2.62, p=0.009; EC: U=129.0, Z=-2.24, p=0.025)	Yes	Good
Bonan et al. 2006 [29]	Static: mediolateral direction	Course of each subject's CoP in the lateral plane for 25 seconds, mean CoP deviation, length of the course	No significant relation between balance and VSN	No	Mod

Van Nes et al. 2008 [44]	Static: mediolateral direction	RMS of the COP amplitudes (ML), in EO/EC and stable/unstable conditions (feet supported)	No significant association between VSN and CoP amplitude in anteroposterior and mediolateral directions	No	Mod
Van Nes et al. 2008 [44]	Static: mediolateral direction	RMS of the COP velocities (ML), in EO/EC and stable/unstable conditions (feet supported)	No significant association between VSN and CoP velocities in anteroposterior and mediolateral directions	No	Mod
Nijboer et al. 2014 [57]	Static: anteroposterior direction	Average anteroposterior CoP displacement (30s), in EO/EC conditions	The average anteroposterior CoP was not significantly different between patients with and without VSN (Z<-1.65, p>0.099)	No	Good
Van Nes et al. 2008 [44]	Static: anteroposterior direction	RMS of the COP amplitudes (AP) in EO/EC and stable/unstable conditions (feet supported)	No significant association between VSN and CoP amplitude in anteroposterior and mediolateral directions	No	Mod
Van Nes et al. 2008 [44]	Static: anteroposterior direction	RMS of the COP velocities (AP), in EO/EC and stable/unstable conditions (feet supported)	No significant association between VSN and CoP velocities in anteroposterior and mediolateral directions	No	Mod
Nijboer et al. 2014 [57]	Static: postural sway	Postural sway (shifts in CoP from the ideal weight distribution (i.e. 50–50%)) in EO/EC conditions	Postural sway was not significantly different between patients with and without VSN (Z<-1.67, p>0.095)	No	Good
Yelnik et al. 2006 [25]	Static: optokinetic stimulation	Body tilt (lateral deviation of CoP), stabilization reaction	No significant correlation between VSN and body tilt under OKS. Significant correlation between the stabilization reaction and VSN for rightward (p<0.05) and leftward rotation (p<0.019)	Yes*	Poor

Abbreviations: Outc, outcome; Yes*, a significant relationship was found but only in certain cases (e.g. specific time points or types of VSN); VSN+, patients with visuospatial neglect; VSN-, patients without VSN; MQ, methodological quality; CI, confidence interval; Mod, moderate; NM, not mentioned; CoP, centre of pressure; EO, eyes open, EC, eyes closed; RMS, root mean square error; OKS, optokinetic stimulation; stabilization reaction, (total length (Le) of CoP displacement), rLe = (OKS Le-basic Le)/basic Le.

bearing asymmetry [35]. However, initial VSN was related to lateral and sagittal stability limits during weight shifting at 6 months post-stroke [30]. In addition, although VSN was negatively related to weight-shifting speed over time [33], it did not affect the relative improvement of weight-shifting speed [33]. Furthermore, patients with VSN showed a relatively large weight-transfer time asymmetry (i.e., average time needed to transfer weight from the non-paretic to paretic leg divided by average time needed to shift weight from the paretic to non-paretic leg) [33]. STS was evaluated in only one study using posturography: patients with the most severe VSN had lower paretic leg weight-bearing recovery during STS [54].

Mobility (Table 3.1.5)

Walking

Clinical assessment

Regarding gait speed, results were contradictory. A study of high quality found no significant association between initial VSN and gait speed at 6 months post-stroke [54], but a moderate-quality study did [30]. In addition, 2 cross-sectional studies of moderate quality that evaluated walking independence showed contradictory results: Huitema et al. [34] showed no significant relation, whereas van Nes et al. [45] showed that VSN was a weak although significant negative predictor of independent walking.

Predictive modelling to evaluate whether initial VSN could predict walking independence at discharge revealed that the absence of VSN at admission was a positive predictor for independent walking inside without aid or supervision [60] but not for independent walking outside or independent walking with a cane or other aid at discharge [60]. Kimura et al. [51] showed that VSN at admission was only a significant, negative predictor for independent walking at discharge if other cognitive impairments were present. Regarding prevalence of VSN in independent walking groups, a study of good quality showed a significantly higher prevalence of VSN in the group who did not achieve independent walking versus the group who did [50]. These results are contradictory to the results of a poor- [17] and moderate- [42] quality study that found no such differences. Concerning the interaction between walking independence and VSN over time [53, 62], conflicting evidence was found: Kollen et al. [53] showed that VSN was a negative and independent predictor for independent walking recovery, whereas van Nes et al. [62] did not (both high-quality studies). Finally, patients with VSN regained independent walking significantly later than patients without VSN [50].

Table 3.1.4. Standing balance

Author	Sub-category	Assessment tool	Conclusion	Relationship VSN-Outc?	MQ
Clinical assessment					
Kawanabe et al. 2018 [37]	STS	Observed STS from toilet	VSN+ patients were less independent considering STS from the toilet bowl as compared to VSN- patients (VSN+: β=-1.015 (SE=0.421, p=0.016))	Yes	Mod
Kawanabe et al. 2018 [37]	STS	Observed STS from wheelchair	VSN+ patients were not significantly different regarding independence in STS from wheelchair as compared to VSN- patients (VSN+: β=-0.637 (SE=0.382, p=0.095))	No	Mod
Perry et al. 2006 [20]	STS	Functional independence measure: CAL	No significant difference in number of VSN+ and VSN- at admission between groups that improved STS CAL | VSN at admission was no significant predictor of STS CAL improvement over time (VSN+: OR = 2.16 (p=0.37), CI: [0.40;11.7])	No	Poor
van Nes et al. 2009[B] [45]	Static and dynamic	BBS	VSN was a significant, negative independent predictor for the BBS (VSN+β=-9.934, CI: [-16.843; -3.025])	Yes	Mod
Stapleton et al. 2001 [61]	Static and dynamic	BBS	Initial VSN presence was not significantly associated to initial BBS	No	Good
van Nes et al. 2009[A] [62]	Static and dynamic	BBS	VSN was significantly, negatively and independently longitudinally associated to the BBS	Yes	Good
Instrumented assessment: posturography					
Bonan et al. 2004 [28]	Static	Equilibrium score (based on postural sway during Sensory Organisation Test)	In right hemispheric lesions, there was no significant difference in results between VSN+ and VSN- patients	No	Mod
Genthon et al. 2008 [48]	Static	Mean amplitude of the resultant CoP trajectories along the mediolateral axes	ADL-related VSN was a significant predictor for mediolateral instability (VSN+: r=0.31 (p<0.05))	Yes	Good
Genthon et al. 2008 [48]	Static	Mean amplitude of the resultant CoP trajectories along the anteroposterior axes	ADL-related VSN was no significant predictor for anteroposterior instability (VSN+: r=0.15 (p>0.05))	No	Good
Genthon et al. 2008 [48]	Static	WBA	ADL-related VSN was a significant predictor for WBA (β=-0.29 (p<0.05))	Yes	Good

de Haart et al. 2004 [47]	Static	WBA	No significant main or interaction effect of VSN on WBA	No	Mod
Barra et al. 2009 [27]	Static	WBA	ADL-related VSN has a significant relationship with WBA (r=0.53 (p<0.01)). Non-ADL related VSN did not have a significant relationship with WBA (p>0.05)	Yes*	Mod
Ishii et al. 2010 [35]	Static	WBA	No significant relationship between VSN and the percentage of weight shifted onto the non-paretic leg in a static standing posture (r=0.27 (p=0.40)	No	Mod
Ishii et al. 2010 [35]	Weight shifting	WBA	No significant relationship between VSN and the percentage of weight shifted onto the non-paretic leg in a dynamic standing posture (r=-0.37 (p=0.24))	No	Mod
Bonan et al. 2007 [30]	Weight shifting	Lateral stability limits, sagittal stability limits (course CoP for 52 seconds)	Significant relationship between initial VSN and lateral and sagittal stability limits at 6m post-stroke (r not given, p ≤ 0.01)	Yes	Mod
de Haart et al. 2005 [33]	Weight shifting	Weight-shifting speed; weight-transfer time asymmetry	VSN at baseline had a significant negative influence on the speed of weight shifting ($F_{1.34}$=4.21; p<0.05). Patients with VSN showed a relatively large weight-transfer time asymmetry (A=1.4).	Yes	Mod
Mercer et al. 2014 [54]	STS	Peak vertical ground reaction force (PLEL)	Patients with the most severe VSN (lowest quartile on SCT) had lower rates of recovery for paretic leg weight bearing during STS. Moreover, an increase in baseline SCT score of 9, corresponded to an increase in PLEL at 6m post-stroke of 0.0067 (p = 0.013).	Yes	Good

Abbreviations: Outc, outcome; Yes*, a significant relationship was found but only in certain cases (e.g. specific time points or types of VSN); VSN+, patients with visuospatial neglect; VSN-, patients without VSN; MQ, methodological quality; CI, confidence interval; Mod, moderate; NM, not mentioned; STS, sit-to-stand; WBA, weight-bearing asymmetry; SCT, star cancellation test; CAL, caregiver-assistance level; PLEL, paretic leg extremity loading; BBS, Berg Balance Scale

Instrumented assessment: gait analysis

All studies evaluating gait speed instrumentally showed no significant relation between VSN and gait speed [23, 26, 30, 34]. VSN was not significantly related to temporal gait symmetry;however, all patients with VSN belonged to the asymmetric group [26]. Participants with VSN experienced significantly more collisions against door frames [23] and had significantly larger lateral deviations from their walking path [23, 34]. This deviation was not uniform across patients because patients with VSN and accurate walking ability seemed to deviate toward the contralesional side, whereas those with impaired walking ability deviated toward the ipsilesional side [34].

Stairs (Table 3.1.6)

Stair climbing and descending was evaluated only clinically. On admission, patients with and without VSN did not significantly differ in stair climbing independence [39]. Similarly, studies found no relation between VSN and stair-climbing independence at 4 or 12 weeks post-admission or 18 months post-stroke [38, 52]. However, at 8 weeks post-admission, one study found a significant negative relationship indicating more dependency in patients with than without VSN [38]. VSN at admission was significantly negatively related to complete recovery of independent stair climbing [40]. Moreover, it was a negative predictor of and a prognostic factor for a greater risk of failing to achieve independent stair climbing at discharge [52]. Contrary to this, VSN at admission was not a significant predictor for independent partial stair-climbing recovery [40]. Patients with VSN were more dependent in stair descending at 8 weeks but not 4 or 12 weeks post-admission or 18 months post-stroke [38, 52].

For managing stairs (i.e., climbing and descending), patients with than without VSN were more dependent on admission and discharge [63, 64]. Likewise, Nijboer et al. [56] evaluated the effect of VSN on the combination of independent stair climbing and walking, showing that patients with VSN were initially more impaired than those without, although the difference between groups decreased over time.

Transfers (Table 3.1.6)

Transfer ability was evaluated only clinically. Regarding bed-to-chair transfer ability, patients with than without VSN had a significantly lower independence on admission, but these differences diminished over time (i.e., discharge) [39]. At 4 or 7 weeks post-admission and 18 months post-stroke, patients with and without VSN did not differ in transfers, but the groups differed at 12 weeks post-admission [38]. Morone et al. [55] further showed that VSN at

Table 3.1.5. Mobility: walking

Author	Sub-category	Assessment tool	Conclusion	Relationship VSN-Outc?	MQ
Clinical assessment					
Bonan et al. 2007 [30]	Gait speed	10-m walk test	Significant relationship between initial VSN and comfortable walking speed at 6m post-stroke ($p \leq 0.01$)	Yes	Mod
Mercer et al. 2014 [54]	Gait speed	10-m walk test	Baseline VSN score was no significant predictor for gait speed at 6m post-stroke (β 0.0093 ($p<0.10$))	No	Good
Ferreira et al. 2015 [17]	Independent community ambulation	Hoffer classification	No significant difference in number of patients with and without VSN, between the group who achieved independent community ambulation and the group who did not ($p=0.09$)	No	Poor
Kimura et al. 2019 [51]	Walking independence	FIM walking score	Presence of VSN with other cogn imp at baseline is a significant negative predictor of independent gait at discharge (VSN+ with cogn imp: OR=5.5, CI:[1.19;23.04]). Presence of VSN without other cogn imp at baseline is no significant predictor of independent gait at discharge	Yes*	Good
Jackson et al. 2000 [50]	Walking independence	NM	There were significantly more VSN+ patients in the group who did not achieve walking (47%) as compared to the group who did (20%)	Yes	Good
Petrilli et al. 2002 [42]	Walking independence	10-m walk test	No significant difference in number of patients with and without VSN, between the group who was ambulatory and the group who was not ambulatory	No	Mod
Paolucci et al. 2008 [60]	Walking independence	Walking outside without aid or supervision	VSN at admission was no significant independent predictor for independent walking outside without aid or supervision at discharge ($p>0.05$)	No	Good
Paolucci et al. 2008 [60]	Walking independence	Walking inside without aid or supervision	The absence of VSN at admission was a significant positive predictor for walking inside without aid or supervision at discharge [VSN-: β= 1.58 (SE=0.54) ($p=0.004$)]	Yes	Good
Paolucci et al. 2008 [60]	Walking independence	Walking with a cane or other aid	VSN at admission was no significant independent predictor for independent walking with a cane or other aid at discharge ($p>0.05$)	No	Good
Huitema et al. 2006 [34]	Walking independence	FAC	No significant difference in FAC score between patients with and without VSN ($p>0.05$)	No	Mod

Kollen et al. 2005 [53]	Walking independence	FAC	VSN was weakly, but significantly and negatively associated to recovery of gait. More reductions in VSN is associated to more improvements in gait over time [β=-0.010 (SE=0.006) (p=0.00)]	Yes	Good
van Nes et al. 2009[A] [62]	Walking independence	FAC	After controlling for paresis, VSN did not remain significantly and longitudinally related to the FAC score (β=-0.037, SE=0.022, p=0.09)	No	Good
van Nes et al. 2009[B] [45]	Walking independence	FAC	VSN was a weak but significant negative predictor for the FAC (β=-0.964 [CI: -1.620; -0.309])	Yes	Mod
Jackson et al. 2000 [50]	Time to achieve walking	Time to achieve walking	VSN+ patients regain walking later (32w) as compared to VSN- patients (24w) (p=0.02)	Yes	Good
Gait analysis					
Alexander et al. 2009 [26]	Walking	Gait speed	No significant correlation between NIHSS VSN scores and gait speed 'R = -0.200 (p=0.264)	No	Mod
Goldie et al. 1999 [49]	Walking	Gait speed	No significant relation between VSN at baseline and gait speed 8w post-admission (p>0.05); and between VSN and change in gait speed (p>0.05)	No	Good
Huitema et al. 2006 [34]	Walking	Gait speed	No significant difference in comfortable gait speed between patients with and without VSN	No	Mod
Tromp et al. 1995 [23]	Walking	Gait speed	No significant difference between VSN+ and VSN- groups (p>0.05) concerning gait speed (p>0.05)	No	Poor
Alexander et al. 2009 [26]	Walking	Temporal symmetric or non-symmetric walking groups	Significantly higher NIHSS VSN scores in the temporal asymmetric group as compared to within temporal symmetric group (p=0.012). All patients with VSN belonged to the asymmetrical group.	Yes	Mod
Alexander et al. 2009 [26]	Walking	Temporal gait symmetry ratio	No significant correlation between NIHSS VSN scores and temporal gait symmetry ratio's [R=0.333 (p=0.059)]	No	Mod
Huitema et al. 2006 [34]	Walking	Walking trajectory ([absolute] maximum lateral deviation)	VSN+ have a larger lateral deviation within their walking trajectory as compared to VSN- patients (p=0.001). VSN+ patients with good walking ability deviated towards the contralesional side; VSN+ with impaired walking ability deviated ipsilesionally	Yes	Mod

Tromp et al. 1995 [23]	Walking	A) Presence of collision; B) Path followed and side of collision	VSN+ patients experienced significantly more collisions compared to VSN- patients ($F(2.24) = 45.31$, $p<0.001$)), with 4 of the 6 patients following a left path with left collisions and 2 of the 6 patients following a right path with right collisions	Yes	Poor

Abbreviations: Outc, outcome; Yes*, a significant relationship was found but only in certain cases (e.g. specific time points or types of VSN); VSN+, patients with VSN; VSN-, patients without VSN; CI, confidence interval; cog imp, cognitive impairments; m, months; w, weeks

Table 3.1.6. Mobility: clinical assessment only: stairs and transfers

Author	Sub-category	Assessment tool	Conclusion	Relationship VSN-Outc?	MQ
Stairs					
Nijboer et al. 2013 [56]	Walking independence and managing stairs	FIM	VSN+ patients scored approximately 2.16 points lower compared to VSN- patient at start (β=2.16 CI: [1.00;3.33], p<0.001). With each subsequent measurement (6m, 12m, 36m) the difference decreased with approximately 0.70 points VSN (VSNxTime: β=-0.70; CI: [-1.11;-0.30, p<0.001)	Yes	Good
Kinsella et al. 1980 [38]	Stair climbing independence	Northwick Park ADL Index	VSN+ patients are significantly more dependent considering stair climbing at 8w post-admission as compared to VSN- patients (p<0.01), but not at 4 and 12w post-admission	Yes*	Mod
Kinsella et al. 1985 [52]	Stair climbing independence	Northwick Park ADL Index	VSN+ patients are not significantly more dependent considering stair climbing at 18m post-stroke as compared to VSN- patients (p>0.05)	No	Good
Maeshima et al. 1997 [39]	Stair climbing independence	BI	VSN+ and VSN- groups did not differ significantly considering stair climbing independence on admission and discharge (p>0.05)	No	Mod
Morone et al. 2018 [40]	Stair climbing independence	BI: complete recovery of stair climbing	VSN+ at admission was a significant negative predictor for complete stair climbing recovery at discharge. VSN presence at admission reduced the possibility of complete stair climbing recovery by approximately 5.5 times (VSN: β=-1.703 (SE 0.853), p=0.046, OR=0.182)	Yes	Mod
Morone et al. 2018 [40]	Stair climbing independence	BI: partial recovery of stair climbing	VSN at admission was no significant independent predictor for partial stair climbing recovery at discharge	No	Mod
Morone et al. 2015 [55]	Stair climbing independence	BI	VSN at admission was a significant prognostic factor for a greater risk of failing to achieve independent stair climbing at discharge (β=1.701 (SE 0.453), p<0.001, CI: [2.252;13.318], OR 5.47)	Yes	Good
Kinsella et al. 1980 [38]	Stair descending independence	Northwick Park ADL Index	VSN+ patients are significantly more dependent considering stair descending 8w (p<0.01), but not at 4 or 12w (p>0.05) post-admission as compared to VSN-patients	Yes*	Mod

Kinsella et al. 1985 [52]	Stair descending independence	Northwick Park ADL Index	VSN+ patients are not significantly more dependent considering stair descending at 18m post-stroke as compared to VSN- patients (p>0.05)	Yes	Good
Tarvonen-Schröder et al. 2020[A] [64]	Managing stairs (climbing & descending)	FIM	R-sided stroke patients: Patients with VSN at admission (median 1 (IQR 1-4)) were significantly more dependent concerning managing stairs compared to those without VSN (median 6 (IQR 6-7)) (p=0.007) at admission. L-sided stroke patients: Patients with VSN at admission (median 1 (IQR 2-6) were significantly more dependent with managing stairs compared to those without VSN (median 6 (IQR 6-7)) (p<0.0003) at admission.	Yes	Good
Tarvonen-Schröder et al. 2020[B][63]	Managing stairs (climbing & descending)	FIM	R-sided stroke patients: Patients with VSN at admission (median 4 (IQR 1-5) were significantly more dependent with managing stairs at discharge compared to those without (median 6 (IQR 4-6)) (p=0.04)). L-sided stroke patients: Patients with VSN at admission (median 3 (IQR 1-5) were significantly more dependent with managing stairs at discharge compared to those without (median 6 (IQR 5-7)) (p<0.0003).	Yes	Good
Transfers					
Kinsella et al. 1980 [38]	Bed-to-chair transfer independence	Northwick ADL Index	VSN+ patients are significantly more dependent considering transfer from bed to chair at 12w (p<0.01), but not at 4w or 8w, post-admission as compared to VSN- patients (p>0.05)	Yes*	Mod
Kinsella et al. 1985 [52]	Bed-to-chair transfer independence	Northwick ADL Index	VSN+ patients are not significantly more dependent considering transfer from bed to chair at 18m post-stroke as compared to VSN- patients (p>0.05)	No	Good
Maeshima et al. 1997 [39]	Bed-to-chair transfer independence	BI (admission)	VSN+ patients had significantly lower transfer independence on admission as compared to VSN- patients (F=5.46, df=1, p<0.05)	Yes	Mod
Maeshima et al. 1997 [39]	Bed-to-chair transfer independence	BI (discharge)	VSN+ and VSN- groups did not differ significantly at discharge considering transfers (p>0.05)	No	Mod

Morone et al. 2015	Bed-to-chair transfer independence	BI	VSN at admission was a significant prognostic factor for a greater risk of failing to achieve independent transfer ability at discharge (β=1.856 (SE 0.375), p<0.001, CI [3.067;13.353], OR 6.4)	Yes	Good
Kinsella et al. 1980 [38]	Standing up from the floor	Northwick ADL Index	VSN+ patients are significantly more dependent considering standing up at 4 (p<0.05) and 12w (p<0.01), but not at 8w (p>0.05) post-admission as compared to VSN- patients	Yes*	Mod
Kinsella et al. 1985 [52]	Standing up from the floor	Northwick ADL Index	VSN+ patients are not significantly more dependent considering standing up from the floor at 18m post-stroke as compared to VSN- patients (p>0.05)	No	Good
Nijboer et al. 2013 [56]	Transfer independence (various transfers)	FIM	VSN+ patients scored approximately 3.11 points lower compared to VSN-patient at start (β=3.11, CI: [1.85-4.36], p<0.001). With each subsequent measurement (6m, 12m, 36m) this difference decreased with approximately 1.01 points (VSNxTime: β=-1.01; CI: [-1.46;-0.58, p<0.001)	Yes	Good
Tarvonen-Schröder et al. 2020[A] [64]	Transfer independence (various transfers)	FIM	R-sided stroke patients: Patients with VSN at admission (median 5 (IQR 3-6)) were significantly more dependent concerning transfers compared to those without VSN (median 6.7 (IQR 6-7)) (p=0.006) at admission. L-sided stroke patients: Patients with VSN at admission (median 4 (IQR 2-6)) were significantly more dependent concerning transfers compared to those without VSN (median 7 (IQR 6-7)) (p<0.0003) at admission.	Yes	Good
Tarvonen-Schröder et al. 2020[B][63]	Transfer independence (various transfers)	FIM	R-sided stroke patients: Patients with VSN at admission (median 6 (IQR 4.3-6)) were significantly more dependent concerning transfers at discharge compared to those without VSN (median 6.8 (IQR 6-7)) (p=0.01) at admission. L-sided stroke patients: Patients with VSN at admission (median 6 (IQR 4-7)) were significantly more dependent concerning transfers at discharge compared to those without VSN (median 7 (IQR 6.7-7)) (p<0.0003) at admission.	Yes	Good

Abbreviations: Outc, outcome; Yes*, a significant relationship was found but only in certain cases (e.g. specific time points or types of VSN); VSN+, patients with visuospatial neglect; VSN-, patients without VSN; MQ, methodological quality; CI, confidence interval; Mod, moderate; NM, not mentioned; w, weeks; m, months; L, left, R, right, FIM, functional independence measures; BI, barthel index; ADL, activities of daily living admission was a prognostic factor for greater risk of failing to achieve independent bed-to-chair transfer at discharge. Patients with than without VSN were more dependent in standing up from the floor at 4 and 12 weeks post-admission but not at 8 weeks post-admission and 18 months post-stroke. Three studies of good quality used an assessment approach that evaluated various transfers (e.g., bed-to-chair, toilet, shower/bath): patients with than without VSN were significantly more dependent in such transfers at admission and discharge [63, 64]. This difference between groups decreased over time [56].

Clinical assessment batteries that combine balance and mobility tasks (Table 3.1.7)

Patients with than without initial VSN showed worse Postural Assessment Scale for Stroke (PASS) scores at discharge but not at 5 weeks post-discharge. Three moderate-quality studies evaluated the association between initial VSN and PASS scores on admission and baseline: 2 showed no significant association [43, 46] and one did [30]. There was no association between scores on the PASS and performance on the line bisection test but a positive relation between scores on the PASS and performance on the Bell's test, scene copy test and CBS [21]. Dai et al. [32] showed that VSN had a negative relationship with PASS scores only if VSN was present in combination with anosognosia for hemiplegia.

Considering effectiveness on the Rivermead Mobility Index (RMI), reflecting improved mobility achieved during rehabilitation, patients with than without VSN were significantly less effective [58]. Moreover, VSN was an independent negative predictor of effectiveness on the RMI [58] and the risk that patients without VSN will have high effectiveness on the RMI was approximately 8 times higher than patients with VSN [41]. In contrast, presence of VSN was not associated with increased or decreased risk of low effectiveness on the RMI [41]. Regarding efficiency on the RMI, which is the amount of improvement in score divided by duration of rehabilitation, patients with than without VSN had a lower efficiency [58]. Additionally, VSN was an independent negative predictor of efficiency on the RMI [58]. VSN was unrelated to no response on the RMI [41]; however, there were significantly more patients with a low response on the RMI in the VSN than non-VSN group and fewer patients with a high response on the RMI in the VSN than non-VSN group [58].

Patients with than without VSN had significantly lower index scores on the Tinetti test, and VSN was negatively associated with this index score [31]. However, on all other scales, no.

Table 3.1.7. Clinical assessment scales: assessment batteries combining sitting & standing balance and mobility

Author	Sub-category	Assessment tool	Conclusion	Relationship VSN-Outc?	MQ
Postural Assessment Scale for Stroke					
Bonan et al. 2006 [29]	PASS	S, Std, Mob	No significantly relation between balance and VSN	No	Mod
Bonan et al. 2007 [30]	PASS	S, Std, Mob	Significant relationship between initial presence of VSN and PASS score at admission, and PASS score at 6 m post-stroke (p ≤ 0.01). Significantly lower PASS score for patients with initial VSN as compared to patients without initial VSN at 6 m [VSN-: 32 (SD 7); VSN+: 22 (SD 9) (p<0.05]	Yes	Mod
Dai et al. 2014 [32]	PASS	S, Std, Mob	Patients with VSN and anosognosia had a significantly lower PASS score as compared to patients with solely VSN or patients without VSN or anosognosia (p=0.009)	Yes*	Mod
Rousseaux et al. 2013 [21]	PASS	S, Std, Mob	Scores on the scene copy test, bell's test and CBS test were weakly but significantly negatively associated with PASS scores (p<0.05) (PASS vs 1. Scene Copy test R=-0.305; 2. Bell's test: R=-0.342 3. CBS: R=-0.406). The scores on the line bisection test were not [R= -0.240 (p>0.05)]	Yes	Poor
Stein et al. 2009 [43]	PASS	S, Std, Mob	Patients with VSN on admission had significantly lower PASS scores as compared to patients without VSN at discharge (p<0.002) but not at admission and 5 weeks post-stroke (p>0.002°)	Yes*	Mod
Sturt et al. 2013 [46]	PASS	S, Std, Mob	Baseline PASS scores prior to the intervention were not significantly different between the R&VSN+, R&VSN- and L&VSN- group [F(2, 15)=1.5 (p=0.25)]	No	Mod
Rivermead Mobility Index					
Bonan et al. 2007 [30]	RMI	S, Std, Mob	Significant relationship between initial VSN and RMI scores at 6m post-stroke (p ≤ 0.01)	Yes	Mod
Huitema et al. 2006 [34]	RMI	S, Std, Mob	No significant difference in RMI score between patients with and without VSN	No	Mod

Paolucci et al. 2001[A] [58]	RMI	S, Std, Mob	The VSN+ group had significantly lower admission and discharge scores on the RMI (z=-4.96 (p<0.001)	Yes	Good
Paolucci et al. 2001[B] [59]	RMI	S, Std, Mob	The odds that patients with VSN at admission will have a significant decline in RMI score at follow-up are 3.01 times higher as compared to VSN- patients [OR VSN = 3.01, CI: [1.21;7.50] (p<0.05)]	Yes	Good
Paolucci et al. 1998 [41]	No response	S, Std, Mob	VSN was not significantly and independently associated with 'no response on RMI'	No	Mod
Paolucci et al. 2001[A] [58]	Low response	S, Std, Mob	There were significantly more patients with a low response on the RMI in the VSN+ group (27%) as compared to the VSN- group (6%) [chi-square = 12.32 (p<0.001)]	Yes	Good
Paolucci et al. 2001[A] [58]	High response	S, Std, Mob	There were significantly less patients with a high response on the RMI in the VSN+ group (7%) as compared to the VSN- group (36%) [chi-square = 19.94 (p<0.001)]	Yes	Good
Paolucci et al. 1998 [41]	Low effectiveness	S, Std, Mob	VSN was not significantly independently associated with 'low effectiveness on RMI'	No	Mod
Paolucci et al. 1998 [41]	High effectiveness	S, Std, Mob	The risk that patients without VSN will have a high effectiveness on the RMI is approximately 8 times higher than that of patients with VSN (RR=7.95; CI: [2.45;25.84])	Yes	Mod
Paolucci et al. 2001[A] [58]	Effectiveness	S, Std, Mob	The VSN+ group had a significantly lower effectiveness on the RMI as compared to the VSN- group (F=34.45, p<0.001)	Yes	Good
Paolucci et al. 2001[A] [58]	Effectiveness	S, Std, Mob	VSN+ was a significant and independent and negative predictor of effectiveness on RMI [β=-0.23 (p<0.005)]	Yes	Good
Paolucci et al. 2001[A] [58]	Efficiency	S, Std, Mob	The VSN+ group had a significantly lower efficiency on the RMI as compared to the VSN- group F=40.21 (p<0.001)	Yes	Good
Paolucci et al. 2001[A] [58]	Efficiency	S, Std, Mob	VSN+ was a significant, independent and negative predictor of efficiency on RMI [β=-0.31 (p<0.001)]	Yes	Good

Other scales					
Colombo et al. 2019 [31]	Tinetti test	S, Std, Mob	VSN+ group had significantly lower Tinetti Index scores compared to the VSN- group; VSN was significantly and negatively associated with the Tinetti Index score [R=-0.347 (p<0.001)]	Yes	Mod
Goto et al. 2009 [18]	"Tomei"* Mobility Level	S, Std, Mob	No significant difference between VSN+ and VSN- patients considering Tomei mobility level (p=0.0879)	No	Poor
Kalra et al. 1997 [19]	Sitting – Standing – Walking classification	S, Std, Mob	VSN+ group (median 2.5) had a significantly better balance classification as compared to VSN- group (median 2) (p=0.01)	No	Poor
Tyson et al. 2006 [24]	Brunel Balance Assessment	S, Std, Mob	VSN was not a significant and independent predictor for balance disability (p=0.714)	No	Poor

Abbreviations: Outc, outcome; S, Std, Mob, sitting, standing, mobility; Yes*, a significant relationship was found but only in certain cases (e.g. specific time points or types of VSN); VSN+, patients with visuospatial neglect; VSN-, patients without VSN; sig, significant(ly); CI, confidence interval; NM, not mentioned; PASS, Postural Assessment Scale for Stroke; RMI, Rivermead Mobility Index. °Bonferonni corrected p-value.

association was found with VSN [18, 24]. Kalra et al. [19] found that patients with than without VSN had even better accomplishment of functional tasks.

Discussion

This study updates previous research and systematically identifies the specific areas of balance and mobility in which stroke survivors with VSN show difficulties. By looking into clinical assessment methods as well as instrumented analyses, both dependency levels and quality of movement could be evaluated. Patients with than without VSN were more dependent during sitting [37] [45] and they sat asymmetrically with their trunk deviated toward the paretic side [22]. However, posturographic studies evaluating mediolateral CoP displacements did not provide consensus on reduced sitting stability in patients with VSN [29, 44, 57]. The observed asymmetric sitting posture could be related to an impaired postural orientation, which could be associated with impaired verticality perception [6, 9, 10, 68]. Misperception of verticality is frequently present in patients with VSN [69, 70] and might induce a tilted internal reference frame. The observation that patients with VSN tend to sit asymmetrically could reflect the patients' aim to align themselves within this frame, a phenomenon sometimes referred to as "lateropulsion" [71]. Although this asymmetric position would be assumed to increase the effect of gravitational forces and heighten stability demands, the absence or inconclusiveness regarding increased CoP displacements indicates their ability to maintain stability by compensating for increasing mechanical demands [72].

Contrary to the observation in sitting, (ADL-related) VSN was associated with increased weight-bearing asymmetry favouring the non-paretic leg and increased mediolateral CoP excursions while standing. However, upright standing is an inherently more demanding posture owing to the height of the centre of mass relative to the base of support [9]. Hence, sitting stability as well as increased weight-bearing on the non-paretic leg might reflect the ability of patients with VSN to accurately compensate for their impairments. This was also seen when STS ability was evaluated. Patients with and without VSN were equally dependent when evaluated by clinical scales [20, 37], but a high-quality study using posturography indicated that patients with severe VSN showed less recovery of paretic leg loading during standing [54]. Although this finding shows a difference between groups, it also indicates that even with severe VSN, patients were still able to incorporate compensatory strategies to perform the dynamic standing task. However, performing such tasks within a stimuli-free laboratory setting may simply not have been not challenging for patients to overload the attentional resources used by the postural control system to control balance [72]. Increased attentional load is assumed to decrease the ability to compensate for visuospatial deficits [73]. Previous research suggested the importance to assess patients in a lifelike, stimuli-dense environment, which indicates that VSN assessment tools incorporating dynamic aspects and high cognitive and motor load leave patients with VSN with less compensational abilities [74]. Studies specifically evaluating such balance and mobility tasks within demanding environments are lacking but would provide crucial insights into the role of VSN-specific compensation strategies for balance control.

Results regarding mobility tasks such as stair climbing and transfers were variable among studies. These tasks are inherently more complex as compared with, for example, static standing and therefore considered more sensitive to discover differences between patient groups. A reason for such inconclusive results might be the complexity of VSN itself. VSN can manifest in various ways, so it is a disorder with pronounced heterogeneity concerning its clinical manifestation. Therefore, the type of assessment method to detect VSN is crucial. Most studies included in this review assessed the presence of VSN by using paper-and-pencil tests, which solely evaluate peripersonal VSN and are therefore unable to map the whole complexity of the disorder, such as extrapersonal regions of space. Given that few studies have investigated extrapersonal VSN, how visual information is integrated across regions of space in healthy controls and in patients with VSN remains unclear [75]. Additionally, studies suggest that patients with only mild or moderate VSN can easily compensate for their deficit on paper-and-pencil tests because they lack complexity, interaction with the environment and therefore ecological validity concerning the cognitive/attentional demand of daily life [74, 76-79]. Combining paper-and-pencil tests with tests that evaluate ADL-related VSN (such as the CBS, but also the Mobility Assessment Course [80] [74]) might increase the probability of finding an association between VSN and balance or mobility. Because such ADL-related assessment methods also include dynamic mobility tasks, they will increase attentional load for patients to a greater extent, so they are inherently more demanding than cancellation tasks [78].

Only a few prospective studies used fixed measurement time points post-stroke, rather than a relative moment in time such as “at admission” or “at discharge” [53, 54, 66, 81]. However, the use of fixed moments would reduce variation concerning time post-stroke and therefore increase comparability between studies. Of the studies using this, only 2 measured VSN repeatedly over time [53, 56]. Because both VSN and balance or mobility are time-dependent outcomes, longitudinal assessment of both is crucial to evaluate their longitudinal association, especially since the results of this review suggest that the association decreases over time. Moreover, no studies combined clinical measurements with instrumented analyses. Clinical measurements have the tendency to evaluate balance and mobility on an activity level (e.g., if the patient can perform a functional task), whereas instrumented analyses evaluate how the task is actually performed, which is by definition on the body-function International Classification of Functioning, Disability and Health level [82]. Therefore, combining both would provide insights into underlying mechanisms of how VSN potentially affects certain aspects of balance and mobility.

Clinical implications

This study highlights the importance of a systematic assessment of post-stroke patients on VSN as well as different categories of balance and mobility, preferably repetitively throughout the patient's recovery process. VSN assessment should be assessed thoroughly by using a combination of paper-and-pencil tests and observational ADL-related scales. Moreover, other cognitive domains beyond visuo-spatial abilities should be assessed as well. Considering balance and mobility, individuals with VSN should be assessed dynamically within a life-like stimulus-dense environment to increase cognitive load. Because this would reduce the patient's ability to compensate, it would allow for better clinical decision making (i.e., regarding rehabilitation strategies). In addition, balance and mobility tasks could be assessed by using a combined approach of clinical scales and instrumented analyses to gain further insight into the underlying mechanisms responsible for the individual's behaviour.

Limitations and strengths

A limitation was the restricted search strategy in that only articles written in English, German or Dutch were included. Therefore, potentially relevant studies might have been missed. In addition, the focus of this study was on VSN. The other sensory domains, apart from the vision, might also negatively affect balance and mobility. However, most research concerns visual neglect, and most conventional and innovative neglect tests are visual in nature. Neglect in other domains (e.g., auditory, tactile, motor) is less studied and rarely tested in clinical settings. Focus on different sensory domains, both in research and clinical practice, would improve our understanding of neglect in general. Nevertheless, the current review has given us important insights into the interactions between lateralised visual attention deficits and motor impairments as well as indications for future research and clinical practice. A strength of this study is its focus on both clinical measures and instrumented analyses, which enabled the evaluation of balance and mobility performance on the accomplishment as well as the underlying biomechanics.

Conclusion

Despite great heterogeneity in results of included studies, this review suggests that stroke survivors with VSN show specific deviations in posture and movement in the mediolateral direction. Indeed, VSN was associated with less independence during sitting, with an asymmetric posture toward the paretic side. During standing, studies showed a significant negative association between VSN and mediolateral stability and weight-shifting, whereas only ADL-related VSN was associated with weight-bearing asymmetry during static stance. These mediolateral aspects were also evident during walking because patients with VSN laterally deviated from their path. Regarding other facets of mobility, results were generally inconclusive. Explanatory studies assessing the underlying mechanisms for patients' behaviour are lacking. However, these mechanisms should be addressed in future research by combining clinical and instrumented assessment methods, preferably within a longitudinal study design with fixed time points to improve study comparability. In addition, balance and mobility should be assessed dynamically within a life-like stimulus-dense environment to increase cognitive load and decrease the patient's ability to compensate for VSN-related deficits. This assessment will allow for better clinical decision-making (e.g., regarding rehabilitation strategies).

Funding

This work was supported by the BOF University Research Fund under a STIMPRO Grant [39800] and DOCPRO Grant [40180].

Conflict of Interest

None declared.

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CHAPTER 3.2

THE ASSOCIATION OF PERSONAL NEGLECT WITH MOTOR, ACTIVITIES OF DAILY LIVING, AND PARTICIPATION OUTCOMES AFTER STROKE: A SYSTEMATIC REVIEW

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Published in Archives of Clinical Neuropsychology (2023):
Elissa Embrechts, Renata Loureiro-Chaves, Tanja C W Nijboer, Christophe Lafosse, Steven Truijen, Wim Saeys. The Association of Personal Neglect with Motor, Activities of Daily Living, and Participation Outcomes after Stroke: A Systematic Review. Arch Clin Neuropsychol. 2023 Aug 17;acad063. Doi: 10.1093/arclin/acad063.

Abstract

Objective. Despite its potential clinical impact, the association of personal neglect (PN) with motor, ADL and participation outcomes after stroke is not well-understood. This first-ever systematic review on the topic therefore evaluates this association, taking into account suggested subtypes of PN, including body representation neglect, somatosensory neglect, motor neglect and premotor neglect.

Methods. A systematic literature search was conducted on February 17th, 2023 in PubMed, Web of Science, Scopus, PubPsych and PsycArticles databases. The study adheres to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and its protocol was registered on PROSPERO (CRD42020187460).

Results. Eleven observational studies were included, gathering 1400 individuals after stroke (429 showed PN). Results show that individuals with body representation neglect after stroke have significantly decreased movement control and motor strength, lower functional mobility and ADL independency compared to those without body representation neglect after stroke. Individuals with motor neglect after stroke showed worse motor function and spasticity than to those without motor neglect after stroke. Non-specified PN (i.e., PN evaluated with an outcome measure that does not allow subcategorization) was related to worse lateropulsion with pushing, longer length of stay and greater odds of being discharged to somewhere other than home. No study evaluated somatosensory and premotor neglect.

Conclusion. This review highlights the limited research in this area and emphasizes the need for a more comprehensive PN assessment. However, currently available assessment tools show limited ability to accurately diagnose PN subtypes and future research should prioritize the development of comprehensive diagnostic test batteries.

Keywords: stroke, personal neglect, spatial neglect, motor, ADL, participation

Introduction

Spatial neglect is a common disorder after stroke that involves a lateralized spatial cognition, awareness and attention deficit with an impaired ability to report toward stimuli primarily within the contralesional hemispace, that cannot be attributed to sensorimotor, perceptual, or memory impairments [1, 2]. The clinical manifestation of the disorder is highly heterogeneous, such that neglect symptoms may manifest within three physical spaces: the self-body space (personal neglect - PN), within-reach (peri-personal neglect) and beyond-reach area (extra-personal neglect).

The association of peri-personal and extra-personal neglect subtypes (e.g., visuospatial neglect (VSN)) with motor, activities of daily living (ADL), and participation-related outcomes after stroke is well-documented [3-5]. VSN concerns neglect for visual stimuli [6], and is the most frequently present and investigated type of spatial neglect, with prevalence ranging from 23 to 48% in the acute phase post-stroke [7, 8]. It is typically assessed using traditional paper-and-pencil tests, such as cancellation tests, line bisection tests and representational drawing tests, or test batteries, such as the Behavioural Inattention Test [9-15]. Prior studies have demonstrated that more severe VSN is associated with worse motor function, balance, walking, ADL independency and participation outcomes [3-5]. In contrast to VSN, the association of PN with such outcomes is not well-understood. Despite the potential impact on daily life through the presentation of specific clinical observations, such as individuals only shaving the non-neglected facial side, forgetting to dress the neglected body side, or disregarding the neglected arm [6, 16], PN remains a highly understudied disorder, and its systematic consideration in scientific and clinical studies is limited [16]. Consequently the association of PN with motor, ADL and participation-related outcomes is unknown. The lack of a uniform definition of PN may contribute to this, although recent studies suggest that multiple subtypes exist under this term [17], including body representation neglect (i.e., reduced body exploration related to a disorder in the representation of one's own body [6, 16-18]), somatosensory neglect (i.e., errors tactile or proprioceptive stimuli perception applied on the neglected body side, without primary somatosensory deficits [6, 16, 17]), motor neglect (i.e., reduced spontaneous use of the contralesional body side [6, 16, 17, 19]) and premotor neglect (i.e., reduced tendency to move the non-neglected limbs toward the neglected body side [6]).

Given the limited understanding of PN and its association with motor, ADL and participation outcomes after stroke, a systematic review of the existing literature is warranted. This first-ever review will therefore evaluate the association between PN (and its subtypes) with motor, ADL and participation outcomes after stroke.

Methods

Protocol and registration

This review adheres to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20], and its protocol has been registered on PROSPERO (CRD42020187460).

Search strategy and study selection

A systematic literature search was conducted on February 17th, 2023 in PubMed, Web of Science, Scopus, PubPsych and PsycArticles databases. Search queries were built by using the following free-text terms and medical subject headings: “PN”, “stroke”, “upper limb”, “lower limb”, “activities of daily living”, “participation”, and their synonyms (Supplementary files). We included studies that 1) investigated adult individuals after stroke with PN adhering to the definitions (see introduction); 2) evaluated the association between PN and motor, ADL or participation outcomes, and 3) were written in English, Portuguese, Spanish, German or Dutch. No restrictions or filters were added. We excluded studies that 1) did not perform sub-analysis for PN when multiple types of neglect were present as this prohibits the ability to evaluate the single contribution of PN to the outcome; 2) were letters to the editors, meta-analyses, reviews or abstracts, and 3) were unavailable in full-text. After removing duplicates, the first author (EE) performed screening on title and abstract. In case of uncertainty, a consensus meeting with the second author (RL-C) was held. Afterwards, screening on full-text was independently performed by both reviewers (EE, RL-C) and disagreements were resolved by discussion.

Risk of bias

Risk of bias of the included studies was independently assessed by two independent reviewers (EE, RL-C) using the Newcastle-Ottawa Scale (NOS). It assesses risk of bias using a star rating system, judging three categories: selection, comparability and outcome. A star was given if a criterion was met, suggesting low risk of bias for that criterion. Items were adapted to fit the research questions. Nine stars can be obtained for longitudinal and ten for cross-sectional studies. No cut-off values are known for the NOS and different study designs, therefore the cut-off values as described by McPheeters, Kripalani and colleagues [21] were used. A score of ≥7 was considered good, of 5 or 6 moderate and of <5 poor. Disagreements were resolved by discussion. Depending on study design, the checklists for cohort or cross-sectional studies were used (Supplementary files).

Data extraction and definitions

Two reviewers (EE, RL-C) independently extracted authors, year, study design, number individuals, lesion information, age, sex, different participant groups, PN assessment tools, PN subtype evaluated, other spatial neglect assessment tools (when applicable), other cognitive functions assessed, time post-stroke of assessments from the studies. Also the evaluated outcomes (motor, ADL, participation outcomes) and study results were collected (Tables 4-7).

To define PN, we refer to the definitions stated within the introduction. When PN assessment tools used by the studies prohibited the differentiation of a specific PN subtype (for example, in the case of the Semistructured Functional Evaluation Scale [16]), we used the term non-specified PN. Definitions on outcome variables of interest can be found in Table 3.2.1.

Results

Study selection

A total of 2778 unique articles were retrieved. Considering screening on Title and Abstract, EE had to consult RL-C for three studies (i.e., in 0.10% of cases), after which consensus was reached to evaluate these studies further during the Full-text screening phase. Regarding screening on full-text, there was 84.6% agreement between reviewers. All ambiguities concerned PN definition and were successfully resolved. Ultimately 11 articles were included. The selection process is visualised in the flowchart (Figure 3.2.1).

Risk of Bias

Agreement between reviewers concerning risk of bias was 72.6%, and disagreements were successfully resolved. Scores ranged from 4-8 out of 9. Four studies had good methodological quality [24-27], 6 moderate [28-33] and 1 poor [34]. All 7 longitudinal cohort studies received

Table 3.2.1. Terms and definitions

Term	Definition
Motor outcomes	Clinical or instrumented assessment methods that evaluate motor function of the trunk and the upper and lower limbs (i.e., paresis, reaching, grasping, balance, lateropulsion (with/without pushing), body alignment, gait, …). In case of motor neglect, in which the definition implies the absence of spontaneous movements, measures of such spontaneous movements were not regarded as 'motor outcome', but as a measure of motor neglect. These spontaneous movements refer to the spontaneous use of the limbs, for example during talking or other activities. Movements carried out upon verbal prompts or involuntary movement (such as spasticity) are not considered spontaneous movements.
Lateropulsion with pushing (LwP)	Disorder of postural control, characterized by a typical lateropulsion to the paretic side which is accompanied by pushing with the non-paretic limbs and a tilted pelvis toward the paretic side [22].
Activities of daily living	The execution of tasks or actions of daily living. This includes routine activities people perform every day related to (mainly) self-care, such as eating, bathing, dressing. This could be evaluated using observational scales (such as the Barthel Index) or questionnaires completed by the patient/caregivers [23].
Participation	These outcomes encompass active involvement in a variety of contexts, such as domestic, community, social, educational, recreational, economic, cultural and civil life. This includes for example attending social events, engaging in hobbies or leisure activities, and participating in community activities (e.g., grocery shopping, attending medical appointments). Within this review, also discharge destination and length of stay are considered participation outcomes. These are not typically considered as direct outcomes of participation, but rather indirect as they are influenced by the extent of participation abilities of the individual [23].

a star on the item assessing the selection of a cohort of individuals without PN from the same source as those with PN after stroke. Additionally, they received a star on the item of ascertainment of exposure, representing that standardized PN assessment tools were employed for PN diagnosis. However, only 2 studies earned a star on the item regarding the demonstration of the outcome of interest at the beginning of the study, which required the diagnosis of PN before identifying outcome on any other measure, such as ADL [24, 28]. Similarly, also all 4 cross-sectional studies received one star on the item assessing the selection

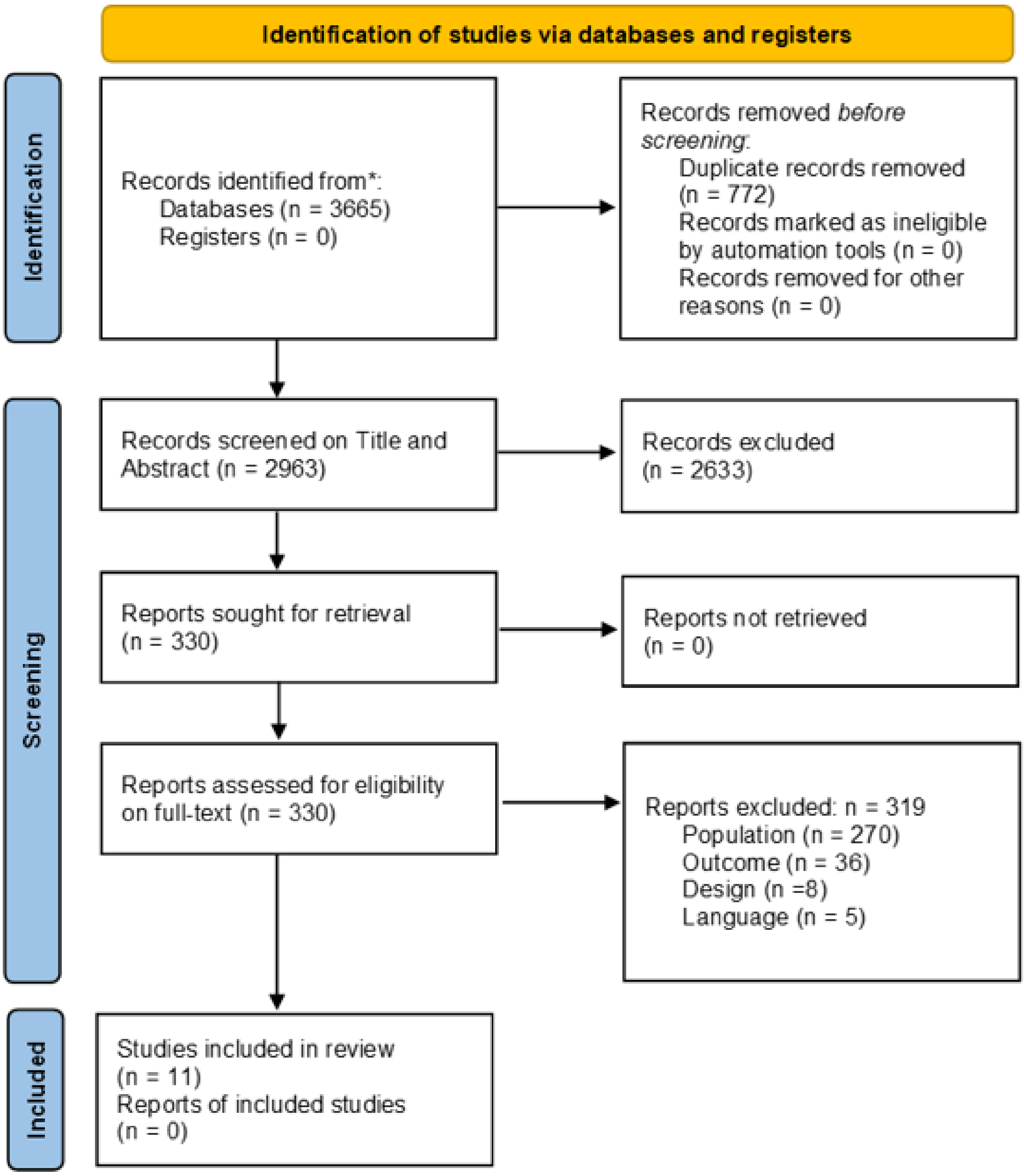

Figure 3.2.1. Flowchart showing the selection process of eligible studies [20].

of a cohort of individuals without PN from the same source as those with PN after stroke, and on the item of ascertainment of exposure. However, none of the studies received a star on outcome assessment that implicates independent blind assessment of the outcome of interest (Table 3.2.2 and 3).

Descriptive data

All studies were observational with four cross-sectional [30-33] and seven longitudinal [24-29, 34] studies. In total, 1400 individuals with stroke were analysed, at least 950 had a right-sided stroke and 406 a left-sided stroke. The lesion-side of the remaining 44 individuals was not

Table 3.2.2. Nottingham Ottawa Scale risk of bias assessment: longitudinal cohort studies

Author	Selection				Comparability	Outcome			Total	MQ
	1	2	3	4	1	1	2	3		
Appelros et al. (2004) [28]		*	*	*	**		*		6	Mod
Iosa et al. (2016) [24]		*	*	*	**	*	*	*	8	Good
Lafosse et al. (2005) [25]	*	*	*		**	*	*		7	Good
Siekierka-Kleiser et al. (2006) [26]	*	*	*		**	*		*	7	Good
Spaccavento et al. (2017) [27]		*	*		**	*	*	*	7	Good
Wee and Hopman (2005) [34]	*	*	*				*		4	Poor
Wee and Hopman (2008) [29]	*	*	*				*	*	5	Mod

Abbreviations: Mod: moderate; MQ: methodological quality category.

Table 3.2.3. Nottingham Ottawa Scale risk of bias assessment: cross-sectional studies

	Selection				Comparability	Outcome		Total	MQ
	1	2	3	4	1	1	2		
Chen-Sea (2000) [30]			*	**	**		*	6	Mod
Chen-Sea (2001) [35]			*	**	**		*	6	Mod
Jamal et al. (2018) [32]	*	*	*	**				5	Mod
Rousseaux et al. (2013) [33]			*	**		*	*	5	Mod

Abbreviations: Mod: moderate; MQ: methodological quality category.

specified. However, two studies did provide more detailed information about stroke location, demonstrating that only medial cerebral artery territory strokes were included in their analysis [25, 26]. Stroke severity was evaluated in only 3 studies, by using the National Institute of Health Stroke Scale (NIHSS) [28], Canadian Neurological Scale [24] or lesion volume metrics [33]. These studies evaluated whether stroke severity was associated with the (severity of) PN, of which only one found a significant association at 1 year post-stroke [28].

The Draw-A-Man test [30, 31] and the Subjective Straight Ahead test [32, 33] were indicated as measures for body representation neglect. Activity trackers were used to determine spontaneous movement activity as a measure for motor neglect [26]. The Semistructured Functional Evaluation Scale of Zoccolotti [24, 25, 27, 28] as well as observation [29, 34] were used to evaluate non-specified PN. Of the 1400 individuals, at least 429 individuals had confirmed symptoms of PN: 48 individuals had body representation neglect [30-33], 19 had motor neglect [26] and 368 individuals had non-specified PN [24, 25, 27-29, 34]. Considering the evaluated rehabilitation outcomes, motor function was assessed by 7 studies [24, 25, 30-33], ADL by 7 studies [24, 27-31, 34] and participation outcomes by two studies [29, 34]. Motor outcomes were divided into six subcategories: voluntary movement control of the contralesional limbs [30, 31], motor strength on the ipsilesional limbs [30, 31], functional mobility [24], standing balance [32], combined balance (sitting, standing, mobility) [33] and lateropulsion with pushing [25] (Table 3.2.4).

Body representation neglect

Motor outcomes. As shown by four moderate methodological quality studies [30-33], individuals with body representation neglect after stroke had significantly lower voluntary movement control of the contralesional limbs and motor strength of the ipsilesional limbs compared to individuals without body representation neglect after stroke (P<.004 and P<.001, respectively) [30]. Chen-Sea and colleagues [31] evaluated co-existing visuospatial neglect (VSN). Individuals with both body representation neglect and VSN after stroke had significantly lower voluntary movement control of the contralesional limbs and motor strength of the ipsilesional limbs, compared to individuals without co-existing body representation neglect and VSN after stroke (*P*<.05), but not compared to those with only VSN after stroke [31]. Additionally, body representation neglect after stroke was significantly associated with lower scores on the Postural Assessment Scale for Stroke, which evaluates balance and mobility (r=-0.34, *P*=.027) [33], while it was not significantly associated with weight-bearing asymmetry during quiet standing (*P*>.05) [32] (Table 3.2.5).

ADL. As shown by two moderate methodological quality studies [30, 31], individuals with body representation neglect after stroke showed significantly lower Klein Bell ADL scores (*P*<.001), as well as lower dressing (*P*<.001), elimination (*P* <.001), mobility (*P* <.0001), bathing (*P*<.001) and communication (*P*<.001) sub-scores on the Klein-Bell ADL compared to individuals

Table 3.2.4. Descriptive data: study design, assessment tools, individuals

Author	**Design**	**PN assessment tools *(PN type)***	**Other spatial neglect assessment tools****	**Other cognitive functions evaluated**
Appelros et al. (2004)	OBS: long (pr)	Semistructured Functional Evaluation Scale *(non-specified PN)*	Behavioral Inattention test	Cognitive impairment (MMSE), aphasia. MMSE was not significantly associated with PN at 2-4 weeks, 6 months and 1 year post-stroke (P>.05).
Chen-Sea (2000)	OBS: CS	Draw-A-Man test *(body representation neglect)*	NA	NA
Chen-Sea (2001)	OBS: CS	Draw-A-Man test *(body representation neglect)*	Random Chinese Word Cancellation	NA
Iosa et al. (2016)	OBS: long (re)	Semistructured Functional Evaluation Scale *(non-specified PN)*	Barrage test, letter cancellation test, sentence reading test, Wundt-Jastrow area illusion test	NA
Jamal et al. (2018)	OBS: CS	Subjective Straight Ahead *(body representation)*	Bell's Cancellation Test, 20 cm Line Bisection Test, Fluff test[1], OTA test[2]	NA
Lafosse et al. (2005)	OBS: long (pr)	Semistructured Functional Evaluation Scale *(non-specified PN)*	Albert's test, observation (searching for a comb, eating from a plate, remove blocks from a board, draw a daisy, match and sort figures)	NA
Rousseaux et al. (2013)	OBS: CS (re)	Subjective Straight Ahead *(body representation)*	Line Bisection Test, Scene Copy Test, Bell's Cancellation Test	NA
Siekierka-Kleiser et al. (2006)	OBS: long (pr)	Activity trackers to evaluate spontaneous motor behavior of the upper limbs (*Motor neglect)*	NA	NA
Spaccavento et al. (2017)	OBS: long (re)	Semistructured Functional Evaluation Scale *(non-specified PN)*	Barrage test, Letter Cancellation Test, sentence reading test, Wundt-Jastrow area illusion test	NA
Wee and Hopman (2005)	OBS: long (pr)	<u>Sensory testing:</u> one side of body ignored + <u>Observation:</u> lack of awareness of one body side (*non-specified PN)*	Describing of a complex picture (observation)	Cognitive impairment (MMSE), aphasia, apraxia (taken into account in further analyses)

Wee and Hopman (2008)	OBS: long (pr)	Sensory testing: one side of body ignored; Observation: lack of awareness of one side of the subject's own body *(non-specified PN)*	Line Bisection Test, Rivermead perceptual assessment battery testing, reading of sentences, reading of a menu, cancellation tests, light board examination, clock drawing	Aphasia (not taken into account in further analyses)

Abbreviations: CS: cross-sectional, long: longitudinal, MMSE: Mini-Mental State Examination, NA: not applicable, OBS: observational, PN: personal neglect, pr: prospective, re: retrospective

Table 3.2.4. Descriptive data: study design, assessment tools, individuals (continued)

Author	**Different groups**	**Mean age (SD/range) in years**	**Biological sex (M/F)**	**'PS of (initial) assessment mean and SD/range)**	**TPS of follow-up**	**Stroke severity and lesion location**
Appelros et al. (2004)	<u>Total:</u> n=37 <u>PN+:</u> n=23 <u>PN-</u>: n=14	74 (33-90)	15/22	-4 w	6 m, 1 y	<u>Severity:</u> National Institute of Health Stroke Scale (NIHSS): significantly correlated with PN at 1 year (r=0.42, P<.05), but not at 2-4 weeks and 6 months post-stroke (P>.05). <u>Location:</u> R, no further information provided
Chen-Sea (2000)	<u>Total:</u> n=51 <u>PN+</u>: n=13 <u>PN-</u>: n=38	PN+: 59.46 (7.59) (42-70) PN-: 59.39 (9.09) (37-75)	PN+: 8/5 PN-: 30/38	'N+: 106.85 (49.71)(60-234) d 'N-: 110.16 (66.50)(56-400) d	NA	<u>Severity:</u> NM <u>Location:</u> R, no further information provided
Chen-Sea (2001)	<u>Total:</u> n=44 <u>PN-, VSN-:</u> n=26 <u>PN-, VSN+</u>: n=7 <u>PN+, VSN+</u>: n=11	PN-, VSN-: 57.65 (0.96) PN-, VSN+: 65.57 (7.76) PN+, VSN+: 58.81 (8.08)	34/12	'N-, VSN-: 102.62 37.46)(56-185) d 'N-, VSN+: 99.43 51.71)(67-213) d 'N+, VSN+: 104.82 47.81)(60-234) d	NA	<u>Severity:</u> NM <u>Location:</u> NM
Iosa et al. (2016)	<u>Total:</u> n=49 <u>Mod PN+:</u> n=17 <u>Sev PN+:</u> n=18 <u>PN-:</u> n:14	PN-: 68.79 (14.45) Mod PN+: 63.59 (16.25) Sev PN+: 68.56 (13.44)	NM	'N-: 14.93 (7.36) d /lod PN+: 15.29 (8.19) d ev PN+: 17.06 (6.62) d	Discharge	<u>Severity:</u> Canadian Neurological Scale score: no difference between PN-, Mod PN+ and Sev PN+ groups at admission (P=.900) and discharge (P=.611). <u>Location:</u> NM
Jamal et al. (2018)	Total: n=30 Groups: NM	60.3 (10)	24/6	.78 (3) y	NA	<u>Severity:</u> NM <u>Location:</u> 15R, 15L, no further information provided

Lafosse et al. (2005)	Total: n=114 Groups: NM	67.7 (7.06)	57/57	2.29 (34.64) d	12 w post-admission	Severity: NM Location: 56R, 58L (all ACM territory)
Rousseaux et al. (2013)	Total: n=42 VSN+ group: n=21 VSN- group: n=21 *(no PN groups, only VSN groups)*	VSN+: 61.0 (14.4) VSN-: 55.5 (11.1)	VSN+: 8/13 VSN-: 10/11	'SN+: 59.6 (33.7) d 'SN-: 64.7 (37.3) d	NA	Severity: Lesion volume: did not significantly correlate with balance (PASS, r=-0.233, P>.05), and PN (SSA, r=0.256, P>.05) Location: R
Siekierka-Kleiser et al. (2006)	Total: n=52 PN+: n=19 PN-: n=33	PN+: 65 (15) PN-: 60 (14)	PN+: 11/8 PN-: 24/9	)ay 1 post-stroke	Day 7 post-stroke	Severity: NM Location: 30R, 22L (all ACM territory)
Spaccavento et al. (2017)	Total: n=359 PN+: n =60 PN-: n=299	71.92 (11.46)	199/160	2.38 (33.20) d	Discharge	Severity: NM Location: R, no further information provided
Wee and Hopman (2005)	Total: n=313 PN+: n=134 PN-: n=179	76 (8)	162/151	7 (22) d	Discharge	Severity: NM Location: "R/L equally divided" , no further information provided
Wee and Hopman (2008)	Total: n=309 PN+: n=134 PN-: n=179	75.5 (8.1)	161/148	7 (22) d	Discharge	Severity: NM Location: "R/L equally divided", no further information provided

Abbreviations: D: days, L: left, mod: moderate, n: number, NM: not mentioned, PN: personal neglect, PN+/-: individuals with/without personal neglect, R: right, SD: standard deviation, sev: severe, VSN: visuo-spatial neglect, VSN+/-: individuals with/without visuo-spatial neglect, w: weeks.

without body representation neglect after stroke. Eating scores (*P* >.05) were similar between these groups [30]. Chen-Sea and colleagues [31] measured body representation neglect and VSN, and showed that individuals with both types after stroke showed significantly lower scores compared to individuals with only VSN or without neglect after stroke, within the following categories: total Klein Bell ADL (*P*<.001 and *P*≤0.006, respectively), dressing (*P*<.001 and *P*≤0.006, respectively), elimination (*P*≤0.006 and *P*<0.05, respectively), mobility (*P* <0.001 and *P*≤0.006, respectively), bathing (*P*<0.001 and *P*≤0.006, respectively) and communication scores (*P*<.05 and *P*<.05, respectively). On eating scores, individuals with both body representation neglect and VSN after stroke did not significantly differ from individuals without neglect or with only VSN after stroke (*P*>.05) [31] (Table 3.2.5).

Motor neglect

Motor outcomes. One good methodological quality study demonstrated that at day 1 post-stroke, individuals with motor neglect showed worse motor scores, subjective self-assessment scores for motor function and spasticity scores compared to individuals without motor neglect after stroke (*P*<.01), with similar scores for grip strength reduction, apraxia, limb coordination and dexterity [26]. Within the motor neglect group, there were two distinct recovery groups with one group experiencing almost full recovery at day 7 post-stroke (*P*<.05) and the other showing only very limited recovery throughout the first 7 days after stroke. In those with a good recovery profile, bilateral spontaneous movement activity of the hands was inversely correlated to motor score recovery (r=-0.75, *P* not given) [26] (Table 3.2.6).

Non-specified PN

Motor outcomes. One good methodological quality study demonstrated that individuals with moderate or severe PN after stroke had similar functional mobility as individuals without PN after stroke, both at admission and discharge [24]. Moreover, PN did not significantly correlate with functional mobility scores at admission and discharge (*P*=.757 and *P*=.646, respectively), neither with improvement of functional mobility (*P*=.960) [24] (Table 3.2.7).

Another good methodological quality study [25] evaluated lateropulsion with pushing after stroke (defined according to Davies [36]). In individuals with a right-sided stroke, left PN was significantly associated with lateropulsion with pushing on admission (r=0.19, *P*<.037) and at 12 weeks post-admission (r=0.47, *P*<.001). When sex was considered in the analysis within

Table 3.2.5. Association of body representation neglect with outcomes

Author	Assessment tool and/or category	Score type	Results	PN related to outcome?	MQ
Motor outcomes					
Chen-Sea and colleagues [30]	Brunnstrom's assessment: voluntary movement control of UL/LL (CL)	Total (1-6)	Sig. difference between PN+ (8.00 ± 3.00) and PN- group (12.08 ± 4.52) (t=3.03, *P*<.0039*)	Yes	Mod
Chen-Sea and colleagues [31]	Brunnstrom's assessment: voluntary movement control of UL/LL (CL)	Total (1-6)	Sig. difference between 'PN-, VSN- group' (12.73±4.49), 'PN-, VSN+ group' (11.57±5.47) and 'PN+, VSN+ group' (8.09±2.59); (F=4.56, *P*=.016*). Post-hoc: sig. difference between the 'PN-, VSN- group' and the 'PN+, VSN+ groups' only (*P*<.05*)	Yes*	Mod
Chen-Sea and colleagues [30]	Muscle strength using MRC: UL/LL, dynamometer; grip (CL)	Total (0-5), N	Sig. difference between PN+ (47.75±12.43) and PN- group (64.67± 22.68) (t=3.17, *P*<.0001*)	Yes	Mod
Chen-Sea and colleagues [31]	Muscle strength using MRC: UL/LL, dynamometer; grip (CL)	Total (0-5), N	Sig. difference between 'PN-, VSN- group' (68.04±23.51), 'PN-, VSN+ group' (52.14±14.46) and 'PN+, VSN+ group' (47.36±12.96) (F=4.73, *P*<.016*). Post-hoc: sig. difference between the 'PN-, VSN- group' and the 'PN+, VSN+ groups' only (*P*<.05*)	Yes*	Mod
Jamal, Leplaideur and colleagues [32]	WBA quiet stance: standing balance	% toward most-affected leg (mean of 4 trials, 2 eyes open, 2 eyes closed)	No sig. correlation between WBA and SSA (r unknown, *P*=.580)	No	Mod
Rousseaux, Honore and colleagues [33]	PASS: Sitting, standing balance, mobility	Total (0-36)	The SSA correlated sig. with the PASS (r=-0.34, *P*=.027*)	Yes	Mod
ADL outcomes					
Chen-Sea and colleagues [30]	Klein-Bell ADL scale	Total (0-313)	Sig. difference between PN+ (178.46±59.95) and PN- group (271.21± 44.45) (t=5.93 (*P*<.0001*).	Yes	Mod
Chen-Sea and colleagues [31]	Klein-Bell ADL scale	Total (0-313)	Sig. difference between 'PN-, VSN- group' (276.77±43.01), 'PN-, VSN+ group' (260.14±55.73) and 'PN+, VSN+ group' (166.73±52.18) (F= 21.17, *P*≤.0001*). Post-hoc: sig. lower scores for the 'PN+, VSN+ group' compared to the 'PN-, VSN- group' (*P*≤.0001*) and 'PN-, VSN+ group' (*P*≤.006*).	Yes	Mod

Chen-Sea and colleagues [30]	Klein-Bell ADL scale	Dressing (0-103)	Sig. difference between PN+ (58.15±23.12) and PN- group (93.21± 12.45) (t=5.21, *P*≤.0001*).	Yes	Mod
Chen-Sea and colleagues [31]	Klein-Bell ADL scale	Dressing (0-103)	Sig. difference between 'PN-, VSN- group' (95.19±10.92), 'PN-, VSN+ group' (88.86±17.24) and 'PN+, VSN+ group' (53.36±20.22) (F= 31.82, *P*≤.001*). Post-hoc: sig. lower scores for the 'PN+, VSN+ group' compared to the 'PN-, VSN- group' (*P*≤.0001*) and 'PN-, VSN+ group' (*P*≤.006*).	Yes	Mod
Chen-Sea and colleagues [30]	Klein-Bell ADL scale	Elimination/ toilet (0-46)	Sig. difference between PN+ (25.38±13.13) and PN- group (40.03±9.45) (t=4.35, *P*≤.0001*).	Yes	Mod
Chen-Sea and colleagues [31]	Klein-Bell ADL scale	Elimination/ toilet (0-46)	Sig. difference between 'PN-, VSN- group' (41.73±7.35), 'PN-, VSN+ group' (36.86 ±11.99) and 'PN+, VSN+ group' (23.45±12.66) (F= 13.88, *P*≤.0001*). Post-hoc: sig. lower scores for the 'PN+, VSN+ group' compared to the 'PN-, VSN- group' (*P*≤.006*) and 'PN-, VSN+ group' (*P*≤.05*).	Yes	Mod
Chen-Sea and colleagues [30]	Klein-Bell ADL scale	Mobility (0-68)	Sig. difference between PN+ group (19.54±18.47) and PN- group (52.32±18.68); (t=5.48, *P*≤.0001*).	Yes	Mod
Chen-Sea and colleagues [31]	Klein-Bell ADL scale	Mobility (0-68)	Sig. difference between 'PN-, VSN- group' (54.38±19.10), 'PN-, VSN+ group' (47.71±22.95) and 'PN+, VSN+ group' (16.45±16.94) (F= 15.22, *P*≤.0001*). Post-hoc: sig. lower scores for the 'PN+, VSN+ group' compared to the 'PN-, VSN- group' (*P*≤.0001*) and 'PN-, VSN+ group' (*P*≤.006*).	Yes	Mod
Chen-Sea and colleagues [30]	Klein-Bell ADL scale	Bathing (0-56)	Sig. difference between PN+ (37.62±8.88) and PN- group (49.00±5.90) (t=5.25, *P*≤.0001*).	Yes	Mod
Chen-Sea and colleagues [31]	Klein-Bell ADL scale	Bathing (0-56)	Sig. difference between 'PN-, VSN- group' (50.23±5.95), 'PN-, VSN+ group' (46.71 ±5.59) and 'PN+, VSN- group' (36.09±7.62) (F= 19.20, *P*≤.0001*). Post-hoc: sig. lower scores for the 'PN+, VSN+ group' compared to the 'PN-, VSN- group' (*P*≤.001*) and 'PN-, VSN+ group' (*P*≤.006*).	Yes	Mod
Chen-Sea and colleagues [30]	Klein-Bell ADL scale	Eating (0-30)	No sig. difference between PN+ (28.77±2.52) and PN- group (29.34±2.31) (t=0.75, *P*>.05)	No	Mod

Chen-Sea and colleagues [31]	Klein-Bell ADL scale	Eating (0-30)	No sig. difference between 'PN-, VSN- group' (29.15±2.74), 'PN-, VSN+ group' (30.00±0.00) and 'PN+, VSN+ group' (28.55±2.70) (F= 0.71 (*P*>.05).	No	Mod
Chen-Sea and colleagues [30]	Klein-Bell ADL scale	Communication (0-10)	Sig. difference between PN+ (9.00±1.41) and PN- group (9.95±0.32) (t=2.39, *P*<.05*).	Yes	Mod
Chen-Sea and colleagues [31]	Klein-Bell ADL scale	Communication (0-10)	Sig. difference between 'PN-, VSN- group' (9.92±0.39), 'PN-, VSN+ group' (10.00±0.00) and 'PN+, VSN+ group' (8.82±1.47) (F= 8.37, *P*≤.0009*). Post-hoc: sig. lower scores for the 'PN+, VSN+ group' compared to the 'PN-, VSN- group' (*P*≤.05*) and 'PN-, VSN+ group' (*P*≤.05*).	Yes	Mod

Abbreviations: ADL: activities of daily-living, CL: contralesional, LL: lower limb, Mod: moderate, MQ: methodological quality, MRC: Medical Research Council scale, n: number, NM: not mentioned, PASS: Postural Assessment Scale for Stroke, PN: personal neglect, PN+/-: individuals with/without personal neglect, R: right, r: correlation coefficient, RMI: Rivermead Mobility Index, sig.: significant(ly), SSA: Subjective Straight Ahead test, UL: upper limb, VSN: peri -or extra-personal visuo-spatial neglect, VSN+/-: individuals with/without peri -or extra-personal visuo-spatial neglect, WBA: weight-bearing asymmetry, Yes*: in some cases; ±: SD.

Table 3.2.6. Association of motor neglect with outcomes

Author	Assessment tool and category	Score type	Results	PN related to outcome?	MQ
Siekierka-Kleiser, Kleiser and colleagues [26]	Motor score: maximal grip force reduction, subjective self-assessment, spasticity, apraxia, limb coordination, dexterity (at day 1 and evolution (day 1-7))	Sub-scores, total scores (0=normal; 32=complete loss)	Day 1 post-stroke: no sig. difference between PN+ and PN- for grip force reduction, apraxia, limb coordination and dexterity (*P* not given); sig. difference (*P*<.01*) for total motor score (PN+: 21±5; PN-: 13±5), subjective self-assessment (PN+: 3.7±0.8; PN-: 2.7±1.3) and spasticity (PN+: 3.5±0.9, PN-: 1.4±1.4) scores. Two distinct recovery profiles in the PN+ group: group who improved limitedly (n=13, change score of ±3) and group with almost complete recovery (n=5, change score of ±15) from day 1 to 7 (*P*<.05*)	Yes	Good
Siekierka-Kleiser, Kleiser and colleagues [26]	Motor score: maximal grip force reduction, subjective self-assessment, spasticity, apraxia, limb coordination, dexterity in different recovery groups	Sub-scores, total scores (0=normal; 32=complete loss)	In individuals with PN and a good recovery profile, recovery of the motor score was inversely correlated with the spontaneous movement activity of both hands (r=-0.75, *P* not given)	Yes	Good

Abbreviations: MQ: methodological quality, PN: personal neglect, PN+/-: individuals with/without personal neglect, r: correlation coefficient, sig.: significant(ly), Yes*: in some cases, ±: SD.

right-sided strokes, lateropulsion with pushing was only significantly associated with left PN in females, both on admission (r=0.47, *P*<.001) and 12 weeks post-admission (r=0.71, *P*<.001). In left-sided strokes, right PN was significantly associated with lateropulsion with pushing on admission (r=0.40, *P*<.001), but not at 12 weeks post-admission (r=0.08, *P*=.502). In left-sided strokes, right PN was associated with lateropulsion with pushing in males (r=0.38, *P*=.008) and females (r=0.45, *P*<.001) at admission. The correlation increased at 12 weeks post-admission for females (r=0.71, *P*<.001), but disappeared in males (r=0.18, *P*=.237) (Table 3.2.7) [25].

ADL. One good methodological quality study measured ADL independency using the Barthel Index (for instrument details, see Quinn, Langhorne and colleagues [37]), and showed that individuals with moderate or severe PN after stroke had similar scores as those without PN after stroke at admission (*P*=.654) and discharge (*P*=.896) [24]. Also the percentage of improvement from admission to discharge was similar in these groups (*P*=.574) [24]. PN did not significantly correlate with scores at admission (*P*=.984), scores at discharge (*P*=.880) and effectiveness (*P*=.986) [24]. This effectiveness score reflects the proportion of functional improvement achieved with respect to the maximum achievable improvement (Table 3.2.7).

ADL was also evaluated using the Functional Independence Measures (FIM) (for instrument details, see Linacre, Heinemann and colleagues [38]). As shown by two studies, PN correlated significantly with lower FIM scores (r not given, *P*<.001) [34] (poor methodological quality study), both at 2-4 weeks post-stroke (r=0.42, *P*<.01), 6 months post-stroke (r=0.41, *P*<.05) and 1 year post-stroke (r=0.45, *P*<.05) [28] (moderate methodological quality study). However, it was not a significant independent predictor for motor [27], cognitive [27] and total [27, 34] FIM scores (*P*>.05) on admission, based on one poor [34] and one good methodological quality study [27]. Additionally, one good methodological quality study showed that PN was not significantly associated with FIM effectiveness (p>0.05) [27] (Table 3.2.7).

Regarding co-existing VSN, one moderate methodological quality study showed that individuals with both PN and VSN after stroke had significantly lower total FIM scores on admission and discharge than individuals with only VSN after stroke (*P*-values not given). Individuals with right PN after stroke had significantly lower FIM scores at admission, but not at discharge, compared to individuals with right VSN after stroke (*P*-values not given) [29]. Individuals with right PN after stroke and individuals with both (left or right) PN and VSN after stroke had similar improvements on the FIM from admission to discharge (*P*-values not given). Individuals with only PN after stroke showed greater FIM gains (improvements from admission to discharge) compared to individuals with only VSN after stroke [29] (Table 3.2.77).

Participation. A poor methodological study showed that PN was a predictor of a longer length of stay (*P*<.05), however, the significance disappeared when corrected for balance [34]. With regards to PN side, those with right PN (either with or without co-existing VSN) after stroke had a significantly longer length of stay compared to those with left VSN after stroke (*P*=.044), even when the regression model was adjusted for balance, number of impairments, support at home, and aphasia, as shown by a moderate methodological quality study [29].

The same studies show that individuals with PN after stroke were 2.2 times more likely to be discharged to a destination other than home (*P*=.045), even when the regression model was adjusted for balance, cognitive impairment and support at home [34] and the amount of individuals discharged to a destination other than home was significantly higher in individuals with PN after stroke (31.1%) compared to those without PN after stroke (13%) (*P*<.001) [29] (Table 3.2.7).

Discussion

This first-ever systematic review on the association between PN subtypes and motor, ADL and participation outcomes post-stroke highlights the limited research in this area and warrants the need for further research. Despite limited literature on the topic, we were able to provide a first indication of an association between PN subtypes and post-stroke outcomes. Specifically, studies showed that individuals with body representation neglect experience significantly lower voluntary movement control and motor strength, as well as lower scores on the Postural Assessment Scale for Stroke and multiple ADL domains as compared to individuals without body representation neglect after stroke. Similarly, motor neglect was associated with worse total motor scores, subjective self-assessment scores for motor function, and spasticity scores. Non-specified PN was linked to lower total FIM scores and lateropulsion with pushing compared to individuals without PN after stroke, but did not correlate with functional mobility scores or the Barthel Index. The results of the present systematic review show a marked level of heterogeneity in results, which may have been

Table 3.2.7. Association of non-specified neglect with outcomes

Author	Assessment tool and category	Score type	Results	PN related to outcome?	MQ
Motor outcomes					
Iosa, Guariglia and colleagues [24]	RMI: functional mobility at adm	Total (0-15)	No sig. difference between PN- group (1±2), Mod PN+ group (0±1) and Sev PN+ group (0±2) (*P*=.889). No sig. correlation between PN score and RMI-score: r=-0.045 (*P*=.757).	No	Good
Iosa, Guariglia and colleagues [24]	RMI: functional mobility at disch	Total (0-15)	No sig. difference between PN- group (3±4), Mod PN+ group (5±4) and Sev PN+ group (3±4) (*P*=.960). No sig. correlation between PN score and RMI-score (r=0.067, *P*=.646).	No	Good
Iosa, Guariglia and colleagues [24]	RMI: effectiveness	Improvement (0-15)	No sig. correlation between PN score and effectiveness (improvement): r=-0.102, *P*=.539)	No	Good
Lafosse, Kerckhofs and colleagues [25]	Davies' LwP criteria: severity of LwP at adm (L-sided stroke)	Total (0 (no LwP)-3 (LwP while standing, sitting and lying)	R PN was sig. correlated with LwP (r=0.40, *P*<.001*)) while L PN was not (r=0.16, *P*=.099).	Yes*	Good
Lafosse, Kerckhofs and colleagues [25]	Davies' LwP criteria: severity of LwP at adm (L-sided stroke): sex-related differences	Total (0 (no LwP)-3 (LwP while standing, sitting and lying)	<u>Male:</u> R PN was sig. correlated with LwP (r=0.38, *P*=.008*), L PN was not (r=0.15, *P*=.122); <u>Female:</u> R PN was sig. correlated with LwP (r=0.45, *P*<.001*), no info on L PN.	Yes*	Good
Lafosse, Kerckhofs and colleagues [25]	Davies' LwP criteria: severity of LwP at adm (R-sided stroke)	Total (0 (no LwP)-3 (LwP while standing, sitting and lying)	L PN was sig. correlated with LwP (r=0.19, *P*<.037*), R PN was not (r=-0.04, *P*=.704).	Yes*	Good
Lafosse, Kerckhofs and colleagues [25]	Davies' LwP criteria: severity of LwP at adm (R-sided stroke) : sex-related differences	Total (0 (no LwP)-3 (LwP while standing,	<u>Male:</u> L PN (r=-0.08, *P*=.562) and R PN (r=0.14, *P*=.584)) were not sig. correlated with LwP; <u>Female</u>: L PN was sig. correlated with LwP (r=0.47, *P*<.001*), R PN was not (r=-0.15, *P*=.257).	Yes*	Good

		sitting and lying)			
Lafosse, Kerckhofs and colleagues [25]	Davies' LwP criteria: severity of LwP at 12w post-admission	Total (0 (no LwP)-3 (LwP while standing, sitting and lying)	<u>In participants with LBD:</u> R PN was not sig. correlated with LwP (r=0.21 , *P*=.071); no info on L PN. <u>In participants with RBD:</u> L PN was sig. correlated with LwP (r=0.47, *P*<.001*), R PN was not (r=0.08, *P*=.0.502))	Yes*	Good
Lafosse, Kerckhofs and colleagues [25]	Davies' LwP criteria: severity of LwP at 12w post-admission: sex-related differences	Total (0 (no LwP)-3 (LwP while standing, sitting and lying)	<u>In participants with LBD:</u> Male: R PN was not sig. correlated with LwP (r=-0.08, *P*=.652), no info on L PN; Female: R PN was sig. correlated with LwP (r=0.48, *P*=.004*), no info on L PN. <u>In participants with RBD:</u> Male: L PN (r= 0.18, *P*=.237) and R PN (r=0.18, , *P*=.236) were not sig. correlated with LwP; Female: L PN was sig. correlated with LwP (r=0.71, *P*<.001*), no information on R PN available.		
ADL outcomes					
Appelros, Nydevik and colleagues [28]	Functional Independence Measures	Total (1-7)	**2-4w:** sig. correlation between BIT-subtest scores for PN (higher = less PN) and FIM scores (r=0.42, *P*<.01*); **6m:** sig. correlation between PN+ and FIM score (r=0.41, *P*<.05*); **1y:** sig. correlation between PN+ and FIM score (r=0.45, *P*<.05*) (Although evaluated, the analyses were not corrected for MMSE scores).	Yes	Mod
Wee and Hopman and colleagues [34]	Functional Independence Measures	Total (1-7)	Correlation analysis: PN was sig. correlated to lower FIM scores (r not given, *P*<.001*). Regression model adjusted for balance (BBS), number of impairments and cognitive impairment (MMSE): PN was not sig. associated with lower FIM scores (no values given).	No	Poor
Wee and Hopman and colleagues [29]	Functional Independence Measures	Total (adm) (1-7)	Sig. difference between 'R PN+, R VSN+ group' (81.1±17.0) and 'L VSN+ only group' (97.2±16.0). Sig. difference between 'L PN+, L VSN+ group' (81.8±15.2) and 'L VSN+ only group' (97.2±16.0). Sig. difference between 'R PN+ only group' (77.7±14.9) and 'R VSN+ only group' (88.6±20.8). Sig. difference between 'VSN+, PN+ group' (81.5±15.9) and 'VSN+ only group' (93.7±18.5).	Yes*	Mod
Spaccavento, Cellamare and colleagues [27]	Functional Independence Measures	Adm: total, motor, cognitive (1-7)	PN was not a sig. predictor in the model for the prediction of the total, motor or cognitive FIM (β not given, *P*>.05).	No	Good

Wee and Hopman and colleagues [29]	Functional Measures	Independence	Total (disch) (1-7)	Sig. difference between 'R PN+, R VSN+ group (100.2±17.1))' and 'L VSN+ only group' (110.8±12.5); sig. difference between 'L PN+, L VSN+ group' (96.4±18.1) and 'L VSN only group' (110.8±12.5); sig. difference between 'VSN+, PN+ group' (97.9± 17.7)' and 'VSN+ only group' (107.3±16.0).	Yes*	Mod
Spaccavento, Cellamare and colleagues [27]	Functional Measures	Independence	Effectiveness (NM)	PN was not a sig. predictor in the model for the prediction of the effectiveness for total, motor or cognitive FIM scores (β not given, p>0.05).	No	Good
Spaccavento, Cellamare and colleagues [27]	Functional Measures	Independence	Effectiveness (NM)	PN was not sig. correlated with effectiveness for total (r=-0.09), motor (r=-0.11) or cognitive (r=-0.15) FIM scores (*P*>.05).	No	Good
Wee and Hopman and colleagues [29]	Functional Measures	Independence	Gains (improvement from adm-disch)	FIM scores improved sig. for 'R PN+, R VSN+ group', 'L PN+, L VSN+ group' and 'R PN+ only group' (*P*<.001*), but not for the 'L PN+ only group' (*P*=.005). Those with PN+ only showed larger gain than those with VSN+ only (no values given).	Yes	Mod
Iosa et al. 2016 [24]	Barthel Index		Total (0-20)	<u>Adm</u>: No sig. difference between PN- group (15±17); Mod PN+ group (16±16) and Sev PN+ group (12±14) (*P*=.654). <u>Disch</u>: No sig. difference between PN- group (52±20), Mod PN+ group (57±23) and Sev PN+ group (53±40) (*P*=.896).	No	Good
Iosa, Guariglia and colleagues [24]	Barthel Index		% of improvement (adm-disch)	No significant difference between PN- group (41.46±18.24), Mod PN+ group (47.43±21.44) and Sev PN+ group (51.76±28.44) (*P*=.574).	No	Good
Iosa, Guariglia and colleagues [24]	Barthel Index		Total and improvement (adm-disch) (0-20)	No sig. correlation between PN and BI at admission (r=-0.003, *P*=.984) and discharge (r=.022, *P*=.880). No sig. correlation between PN score and improvement (r=0.003, *P*=.986).	No	Good
Participation						
Wee and Hopman and colleagues [34]	Length of stay		Total days	PN was sig. related to longer length of stay (r not given, *P*=.001). Regression model adjusted for balance (BBS), number of impairment, support at home and aphasia: PN was no longer sig. associated with longer LOS.	No	Poor
Wee and Hopman and colleagues [29]	Length of stay		Total days	Sig. differences between 'R PN+, R VSN+ group' (64.0±25.3) and 'L VSN+ only group' (43.5±19.0); Sig. difference between 'R PN+ only group' (67.1±17.1) and 'L VSN+ only group' (43.5±19.0); Sig. difference between 'PN and VSN group' (59.7±24.0' and 'no PN and/or VSN group' (51.7±21.8) (*P*=.044).	Yes	Mod

Wee and Hopman and colleagues [34]	Discharge destination	Destination (home/other than home)	PN was sig. correlated to a discharge destination 'other than home' (r not given, *P*=.001). Regression model adjusted for balance (BBS), cognitive impairment (MMSE) and support at home: PN remained a sig. predictor for 'other than home' discharge destination (OR=2.20, *P*=.045, 95%CI [1.00;4.84]).	Yes	Poor
Wee and Hopman and colleagues [29]	Discharge destination	Destination (home/other than home)	Sig. difference between number of individuals with PN+ (31.1%) and without PN (13.0%) that are discharged to a destination other than home (*P*<.001).	Yes	Mod

Abbreviations: Adm: admission, BBS: Berg Balance Scale, CI: confidence interval, DD: discharge destination, disch: discharge, PN: personal neglect, PN+/-: individuals with/without personal neglect, CI: confidence interval, d: day(s), L: left, LOS: length of stay, LwP: lateropulsion with pushing, MMSE: Mini-Mental State Examination, MQ: methodological quality, NM: not mentioned, OR: odd's ratio, R: right, r: correlation coefficient, sig.: significant(ly), vs: versus, VSN+/-: individuals with/without visuo-spatial neglect, ±: SD.

influenced by the assessment tools used to evaluate PN. Specifically, most studies relied on a limited number of tests, typically only one or two, to detect PN, with,a primary focus on non-specified PN. Additionally, certain types of PN, such as somatosensory and premotor neglect, are yet to be addressed.

The difficulty of conducting a thorough and efficient assessment of PN and its subtypes may have contributed to the heterogeneity in study results. Currently available tests provide only a general indication of the disorder rather than a definitive diagnosis [6, 16], highlighting the pressing need for more comprehensive and standardized assessment tools to advance research on PN. Studies that have utilized assessment tools capable of detecting specific PN subtypes (e.g., motor neglect or body representation neglect) exhibited greater consistency in their results, particularly when assessing certain outcomes such as ADL independence [30, 31]. In addition, Chen-Sea and colleagues [31] demonstrated that mainly the combined presence of PN and VSN was negatively associated with motor outcomes and ADL independence. However, it is worth nothing that Chen-Sea and colleagues [31] employed the Draw-A-Man test, a representational drawing test, to assess PN. This test evaluates both body representation as well as visual representation. This is significant because representational drawing tests are also included in commonly used VSN test batteries, such as the Behavioral Inattention Test. Nonetheless, despite its overlap with VSN assessment, the Draw-A-Man test has also been demonstrated a reliable and valid instrument for assessing PN [30]. Therefore, a thorough assessment on various spatial neglect characteristics seems necessary to gain better understanding of potential associations. It is possible that PN becomes a significant factor to consider only when it is present in combination with other types of neglect. However, it is unclear whether the larger negative outcomes observed in individuals with both PN and VSN reflect the true impact of this co-existence or rather the presence of different lesion characteristics, such as a larger lesion volume, considering this was generally not taken into account by the studies during analyses.

Apart from neglect assessment tools, also the outcome measures employed by the studies were diverse, with limited attention given to motor and participation outcomes. Outcomes should be more thoroughly evaluated, preferably repeatedly over time, given the potential for divergent recovery patterns between individuals. For example, some individuals with PN (here, motor neglect) may experience rapid and complete motor recovery, while others may exhibit only limited recovery over time [26]. The distinction between these two recovery groups may already be found in the acute post-stroke phase. This underscores the importance of early evaluation of PN, particularly since the majority of behavioral recovery occurs in the first few weeks post-stroke onset [26]. Additionally, the relationship between the subtypes of PN and an individual's participation in life situations, their independence, and their need for caregiver assistance remains unclear due to the limited assessment of participation outcomes. This is a crucial area that needs to be addressed to assist individuals in their transition back to society, particularly since individuals with PN were found to have longer stays in care facilities and are frequently discharged to locations other than their homes [29, 34].

Another important aspect to consider when evaluating the association of PN with the investigated outcomes after stroke is the potential mediating role of other cognitive impairments. This is especially relevant considering that the prevalence of cognitive impairments has been reported to be higher in individuals with neglect compared to those without neglect after stroke [39, 40]. However, the mediating role of these cognitive impairments could not be thoroughly evaluated within the present systematic review as only three studies documented the presence of such impairments [28, 29, 34], with only one study specifically examining their mediating role [34]. Wee and Hopman and colleagues [34] show a significant correlation between the presence of PN and reduced independence in ADL, longer hospital stays, and higher odds of being discharged to a destination other than home [34]. However, when the presence of other cognitive impairments was considered within the analysis, the significant contribution of PN to ADL independence and length of stay disappeared, while it remained significant for discharge destination. These findings highlight the complex interplay between PN, cognitive impairments, and post-stroke outcomes, and emphasize the need for comprehensive assessments that consider multiple cognitive domains.

Suggestions for further research and clinical implications

This study highlights the lack of research on the association between PN and rehabilitation outcomes, underlining the need for more comprehensive and longitudinal assessments of PN, including its various subtypes. However, the assessment tools available only provide a general indication of the disorder rather than a definitive diagnosis, which makes it challenging to accurately identify specific PN subtypes. Therefore, future research should prioritize the development of comprehensive diagnostic test batteries that can efficiently and accurately identify subtypes. Co-existence of other types of spatial neglect, such as VSN, may be important to consider when evaluating rehabilitation outcomes. This calls for investigating the relationship between PN and other spatial neglect types further. Moreover, the current studies do not adequately evaluate the potential impact of lesion location, stroke severity and other cognitive impairments on the relationship between PN and rehabilitation outcomes. Therefore, future studies should more thoroughly investigate the influence of these factors on the association between PN and rehabilitation outcomes after stroke.

Strengths and limitations

A strength of this study is the subcategorization of PN into different subtypes, providing insight into the importance of doing so in clinical practice and future research. Another strength is the focus of outcomes on different levels of the International Classification of Functioning, Disability and Health [23, 41], which demonstrates a comprehensive approach. However, the limitations of the included studies, such as heterogeneity and limited sample sizes, may reduce the generalizability of the results and the ability to draw definitive conclusions regarding the association of PN with rehabilitation outcomes, which could also be considered a limitation of this review.

Conclusion

Although the association between PN and rehabilitation outcomes is largely understudied, this systematic review provides an initial indication of the association between PN subtypes and motor, ADL and participation outcomes post-stroke. Given that the majority of studies have focused on non-specified PN, future research should focus on the assessment of these subtypes, and should aim to develop a comprehensive test battery for PN that allows to evaluate them in a time-efficient way. The limited focus on motor and participation outcomes of the studies included in this review calls for further research in these areas.

Funding

This work was supported by the BOF University Research Fund under a STIMPRO Grant [39800] and DOCPRO Grant [40180].

Disclosure of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Appendix

Search strings according to databases used

Database	Keywords	Search string
PubMed	Stroke Body neglect Outcome (motor, activities of daily living, participation)	("stroke"[MeSH Terms] OR "stroke"[All Fields]) **AND** ((("personal"[All Fields]) AND ("neglect"[All Fields])) OR (("motor"[All Fields]) AND ("neglect"[All Fields])) OR (("Premotor"[All Fields]) AND ("neglect"[All Fields])) OR ((("body"[All Fields] AND "representation"[All Fields]) OR ("body representation"[All Fields])) AND ("neglect"[All Fields])) OR (("body"[All Fields]) AND ("neglect"[All Fields])) OR ((("somatosensorial"[All Fields] OR "somatosensory"[All Fields]) AND ("neglect"[All Fields]))) OR (("egocentric"[All Fields]) AND ("neglect"[All Fields])) OR "spatial neglect" OR "space perception" OR "perceptual disorders"[MeSH Terms] OR ("perceptual"[All Fields] AND "disorders"[All Fields]) OR heminegleclect OR ("perceptual disorders"[All Fields]) OR ("hemispatial"[All Fields] AND "neglect"[All Fields]) OR "hemi-inattention" OR "hemispatial neglect"[All Fields] OR (unilateral[All Fields] AND neglect[All Fields]) OR (("directional"[All Fields]) AND ("hypokinesia"[MeSH Terms] OR "hypokinesia"[All Fields])) OR (("motor-intentional"[All Fields]) AND ("neglect"[All Fields])) OR (("aiming"[All Fields]) AND ("neglect"[All Fields])) OR (tactile extinction) OR "Extinction, Psychological"[Mesh] OR "Touch/physiology"[Mesh] OR "Touch Perception"[Mesh]) **AND** ("balance"[All Fields] OR "gait"[MeSH Terms] OR "gait"[All Fields] OR "Gait analysis" OR "postural balance"[MeSH Terms] OR ("postural"[All Fields] AND "balance"[All Fields]) OR "postural balance"[All Fields] OR ("postural"[All Fields] AND "control"[All Fields]) OR "postural control"[All Fields] OR "balance control" OR "independency" OR "walking"[MeSH Terms] OR "walking"[All Fields] OR "locomotion"[MeSH Terms] OR "locomotion"[All Fields] OR "trunk"[All Fields] OR "Motor function" OR "Motor recovery" OR "ADL" OR "Activities of daily living" OR "Daily life" OR "daily living" OR "participation"[All Fields] OR "length of stay"[MeSH Terms] OR ("length"[All Fields] AND "stay"[All Fields]) OR "length of stay"[All Fields] OR "patient discharge"[MeSH Terms] OR ("patient"[All Fields] AND "discharge"[All Fields]) OR "patient discharge"[All Fields] OR "discharge"[All Fields] OR "Discharge destination" OR "independency"[All Fields] OR "Functional outcome" OR "Upper Extremity"[Mesh] OR "Upper Extremity"[All Fields] OR "Lower Extremity"[Mesh] OR "Lower Extremity"[All Fields] OR "Paresis"[Mesh] OR "Paresis"[All Fields] OR "Lower limb" OR "upper limb" OR "motor outcome" OR "return to work"[All Fields] OR "return to work"[MeSH Terms] OR "Social Participation"[Mesh] OR "social participation" OR "Leisure Activities"[Mesh] OR "Leisure Activities" OR "Community Participation"[Mesh] OR "community participation" OR "social behavior" OR "life style" OR "Social Behavior"[Mesh] OR "Life Style"[Mesh])
Web of Science	Stroke Body neglect Outcome (motor, activities of	(Stroke) **AND** ("Personal neglect" OR "Motor neglect" OR "Premotor neglect" OR "body neglect" OR "body representation neglect" OR "somatosensory neglect" OR "tactile neglect" OR "egocentric spatial neglect" OR spatial neglect OR space perception OR perceptual disorder OR hemispatial neglect OR hemineglect OR inattention OR unilateral neglect OR "directional hypokinesia" OR "motor-intentional neglect" OR "aiming neglect" OR "tactile extinction" OR "touch extinction") **AND** (Balance OR gait OR walking OR postural control OR locomotion OR "balance control" OR trunk OR "motor function" OR "motor recovery" OR "motor outcome" OR length of stay OR participation OR "daily life" OR "ADL" OR "activities of daily living" OR "daily living" OR "discharge" OR "Discharge destination" OR

	daily living, participation)	independency OR “upper limb” OR “upper extremity” OR “lower limb” OR “lower extremity” OR discharge OR “social life” OR “leisure activities” OR “social behaviour” OR “life style”)
Scopus	Stroke Body neglect Outcome (motor, activities of daily living, participation)	(Stroke) **AND** (“Personal neglect” OR “Motor neglect” OR “Premotor neglect” OR “body neglect” OR “body representation neglect” OR “somatosensory neglect” OR “tactile neglect” OR “egocentric spatial neglect” OR spatial neglect OR space perception OR perceptual disorder OR hemispatial neglect OR hemineglect OR inattention OR unilateral neglect OR "tactile extinction" OR “touch extinction”) **AND** (Balance OR gait OR walking OR postural control OR locomotion OR “balance control” OR trunk OR “motor function” OR “motor recovery” OR “motor outcome” OR length of stay OR participation OR “daily life” OR “ADL” OR “activities of daily living” OR “daily living” OR “discharge” OR “Discharge destination” OR independency OR “upper limb” OR “upper extremity” OR “lower limb” OR “lower extremity” OR discharge OR "social life" OR "leisure activities" OR "social behaviour" OR "life style")
PubPsych	Stroke Body neglect Outcome (motor, activities of daily living, participation)	(Stroke) **AND** (“Personal neglect” OR “Motor neglect” OR “Premotor neglect” OR “body neglect” OR “body representation neglect” OR “somatosensory neglect” OR “tactile neglect” OR “egocentric spatial neglect” OR spatial neglect OR space perception OR perceptual disorder OR hemispatial neglect OR hemineglect OR inattention OR unilateral neglect OR directional hypokinesia OR motor-intentional neglect OR aiming neglect OR tactile extinction OR touch extinction) **AND** (Balance OR gait OR walking OR postural control OR locomotion OR “balance control” OR trunk OR “motor function” OR “motor recovery” OR “motor outcome” OR length of stay OR participation OR “daily life” OR “ADL” OR “activities of daily living” OR “daily living” OR “discharge” OR “Discharge destination” OR independency OR “upper limb” OR “upper extremity” OR “lower limb” OR “lower extremity” OR discharge extremity OR social life OR leisure activities OR social behaviour OR life style)
PsycArticles	Stroke Body neglect Outcome (motor, activities of daily living, participation	Noft (Stroke) **AND** (Personal neglect OR Motor neglect OR Premotor neglect OR body neglect OR body representation neglect OR somatosensory neglect OR tactile neglect OR egocentric spatial neglect OR spatial neglect OR space perception OR perceptual disorder OR hemispatial neglect OR hemineglect OR inattention OR unilateral neglect OR directional hypokinesia OR motor-intentional neglect OR aiming neglect OR tactile extinction OR touch extinction) **AND** (Balance OR gait OR walking OR postural control OR locomotion OR balance control OR trunk OR motor function OR motor recovery OR motor outcome OR length of stay OR participation OR daily life OR ADL OR activities of daily living OR daily living OR discharge OR Discharge destination OR independency OR upper limb OR upper extremity OR lower limb OR lower extremity OR discharge extremity OR social life OR leisure activities OR social behaviour OR life style)

The Newcastle-Ottawa Quality Assessment Form for Cohort Studies and Cross-sectional Studies

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Selection

1) Representativeness of the exposed cohort (exposed cohort: PN present)

a) Truly representative ***(one star)*** PN present in **right AND left sided** strokes (all participants included within the same centers(s))

b) Somewhat representative ***(one star)*** PN present in **right AND left sided** strokes but only in combination with another type of neglect such as VSN) (all participants included within the same center(s))

c) Selected group (healthy, **only R OR L sided** stroke)

d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) Drawn from the same community as the exposed cohort ***(one star)*** (individuals with stroke without PN from the same center/population)

b) Drawn from a different source

c) No description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) Secure record (e.g., surgical record) ***(one star)*** Typical PN tests carried out throughout the whole cohort, with or without subleveling (e.g. low – moderate – severe PN)

b) Structured interview ***(one star)*** Clear description of the participants' behavior related to PN or observation of behavior to detect PN

c) Written self-report Just mentioning 'PN present' without a description of the tests used/observation carried out

d) No description

e) Other

4) Demonstration that outcome of interest was not present at start of study

a) Yes ***(one star)*** PN had to be detected/diagnosed BEFORE any other outcome measure had been identified (ADL – MF - …)

b) No or Not mentioned

Comparability

1) Comparability of cohorts based on the design or analysis controlled for confounders

Demographics are similar (no difference between demographic info between PN participants and controls (PN-/VSN participants); or analysis that controls for these factors (e.g. regression)

a) The study controls the most important factor: time post-stroke ***(one star)***

b) Study controls for other factors (list) at least two others: age, other types of neglect, hemiparesis, sensory level, lesion side/site, handedness, education level, … ***(one star)***

c) Cohorts are not comparable based on the design or analysis controlled for confounders (<2 other factors or no proper analysis that controls for these factors)

Outcome
1) Assessment of outcome

a) Independent blind assessment ***(one star)***

b) Record linkage ***(one star)*** (patient files -> retrospective analysis e.g.)

c) Self report

d) No description

e) Other

2) Was follow-up long enough for outcomes to occur

a) Yes ***(one star)*** longitudinal: at least 4 weeks of time-interval between first and last measurement to see a "recovery" or "worsening" process over time

b) No <4w

3) Adequacy of follow-up of cohorts

a) Complete follow up- all subject accounted for ***(one star)***

b) Participants lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. ***(one star)***

c) Follow up rate less than 80% and no description of those lost

d) No statement

Newcastle-Ottawa Scale adapted for cross-sectional studies

Selection: (Maximum 5 stars)

1) Representativeness of the sample:

a) Truly representative of the average in the target population. * PN present in **right AND left sided** strokes (all participants included within the same centers(s))
b) Somewhat representative of the average in the target population. * (non-random sampling) PN present in **right AND left sided** strokes but only in combination with another type of neglect such as VSN) (all participants included within the same center(s))
c) Selected group of users. (healthy, **only R OR L sided** stroke)
d) No description of the sampling strategy.

2) Sample size:

a) Justified and satisfactory. * Sample size calculation performed: always yes; if not: at least 15 individuals in each group.

b) Not justified OR If no groups described: no star rewarded

3) Selection of the non-exposed cohort:

a) Comparability between exposed and non-exposed characteristics is established, and the response rate is satisfactory. * (individuals with stroke without PN from the same center/population)

b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.

c) No description of the response rate or the characteristics of the responders and the non-responders.

4) Ascertainment of the exposure (risk factor):

a) Validated measurement tool. ** Typical PN tests carried out throughout the whole cohort, with or without subleveling (e.g. low – moderate – severe PN)

b) Non-validated measurement tool, but the tool is available or described.* Clear description of the participants' behavior related to PN or observation of behavior to detect PN

c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The participants in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled. Demographics are similar (no difference between demographic info between PN participants and controls (PN-/VSN participants); or analysis that controls for these factors (e.g. regression)

a) The study controls for the most important factor: time post-stroke *

b) The study control for at least two others: age, other types of neglect, hemiparesis, sensory level, lesion side/site, handedness, education level, …. *

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:

a) Independent blind assessment. **

b) Record linkage. ** (patient files -> retrospective analysis e.g.)

c) Self report.

d) No description.

2) Statistical test:

a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *

b) The statistical test is not appropriate, not described or incompletely given.

CHAPTER 3.3

ASSOCIATION BETWEEN SPATIAL NEGLECT AND IMPAIRED VERTICALITY PERCEPTION AFTER STROKE : A SYSTEMATIC REVIEW

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Published in Annals of Physical and Rehabilitation Medicine (2023):
Elissa Embrechts, Charlotte van der Waal, Dorine Anseeuw, Jessica van Buijnderen, Améline Leroij, Christophe Lafosse, Tanja CW Nijboer, Steven Truijen, Wim Saeys. Association between spatial neglect and impaired verticality perception after stroke: A systematic review. Annals of Physical and Rehabilitation Medicine. Volume 66, Issue 3, 2023. DOI: https://doi.org/10.1016/j.rehab.2022.101700.

Abstract

Objective: Although most research on spatial neglect (SN) has focused on spatial perception deficits with regards to the lateral (left-right) axis, deficits of spatial perception with regards to the vertical (up-down) axis, such as disturbances in the perception of verticality (e.g., judgement of vertical orientations), have also been suggested. We aim to systematically analyze reported associations between SN and characteristics of verticality perception whilst considering the time post-stroke.

Methodology: Databases were searched on May 24, 2022. Included were studies written in English that evaluated the association between SN and verticality perception (i.e. the Subjective Visual Vertical (SVV), Subjective Postural Vertical (SPV) and Subjective Haptic Vertical (SHV)) in adult participants with stroke. Left and right SN were considered and had to be assessed using standardized methods. Data were manually extracted, and risk of bias was assessed using the Newcastle-Ottawa Scale. The tilt of the line/chair relative to the gravitational vector and its direction, together with uncertainty (i.e., variability across measurements) were evaluated.

Results: Thirteen studies were included, gathering 431 stroke participants of which at least 191 showed SN. Mainly the first three-to-six months post-stroke were evaluated. SN was associated with SVV misperception, resulting in larger SVV tilts (mostly seen in contralesional direction) and uncertainty in those with SN compared to those without. SVV tilt magnitudes ranged from -8.9° to -2.3° in SN participants and from -1.6° to 0.6° in non-SN participants, the latter falling within normative ranges. Regarding SPV and SHV measurements, the magnitude of tilt and the uncertainty were insufficiently assessed or results were inconclusive.

Conclusions: SN is associated with larger SVV tilts and uncertainty, suggesting that SVV misperception is a key feature of SN. This highlights the importance of regular SVV assessment in those with SN in clinical practice (PROSPERO: CRD42019127616).

Key Words: Stroke, perception of verticality, spatial neglect

Introduction

Spatial neglect (SN) is a post-stroke disorder of lateralized spatial cognition, awareness and attention [1]. It is a cognitive disorder that cannot be attributed to sensorimotor or memory impairments [2]. The estimated prevalence of SN after a unilateral stroke is 30%, and SN is more common after a right- than a left-sided stroke [3]. Classically, SN is regarded a disorder of spatial perception with regards to lateral (left-right) axis. This is clinically evident, with SN participants demonstrating a decreased ability to report upon contralesional (and in some cases with moderate to severe SN also ipsilesional) stimuli and failing to explore the contralesional hemispace with their eyes and limbs [4, 5]. Although most research on SN has focused on spatial perception deficits with regards to this lateral axis, deficits of spatial perception with regards to the vertical (up-down) axis, such as disturbances in the perception of verticality (e.g., judgement of vertical orientations), have also been suggested [4-6].

Verticality perception is built up around internal models of verticality, established by the convergence of multisensory graviceptive information (i.e., somatosensory, visual, vestibular) [7]. The more precise and congruent this information is across sources, the more accurate the internal model of verticality will be [7]. Clinically, this internal model of verticality can be estimated by evaluating the perception of verticality, based on visual information (Subjective Visual Vertical), postural information (Subjective Postural Vertical, SPV) or haptic information (Subjective Haptic Vertical, SHV). An accurate perception of verticality is regarded essential for postural control and is therefore crucial for the performance of various functional activities such as standing and walking [8-10].

After a stroke, afferent information congruency or its processing can be impaired, hampering the spatial representation of the gravitational vector. Previous literature has already proposed the link between SN and verticality misperception [4, 6, 11, 12], and brought forward three interpretations [4]. The first one states that a stroke may impact two distinct but neighboring neural networks, one coding spatial information for the lateral axis, and the other for the vertical axis [13]. In the second interpretation, a stroke would impact certain networks that process three-dimensional spatial information, inducing SN and verticality misperception simultaneously [5]. The last one implies a form of SN bearing on graviception [6]. It involves verticality construction from vestibular and somesthetic input and suggests the existence of a ‘graviceptive neglect’. In this case, gravitational information would be non-symmetrically processed, resulting in a biased perception of verticality [4, 6, 11, 12].

Although the association of SN with verticality misperception seems plausible, it remains unclear how this association is represented [4, 14]. Therefore, this first-ever systematic review aims to systematically analyze the literature on reported associations between SN and the characteristics of the SVV, SPV and SHV. Since verticality misperception may differ according to the time post-stroke [15], the time post-stroke will be considered when analyzing the results.

Methodology

Protocol and registration

The protocol of this systematic review was registered on PROSPERO (CRD42019127616), and adheres to the guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [16] and Synthesis Without Meta-Analysis (SWiM) [17] guidelines (See Supplementary E-files).

Definitions

Definitions concerning the criteria related to SN, verticality perception, time post-stroke, and potential comorbidities were used to decrease the potential for ambiguity in article selection. SN was defined as a disorder of lateralized spatial cognition, awareness and attention [1], causing decreased ability to report upon contralesional (and sometimes ipsilesional) stimuli not attributable to sensorimotor or memory impairments [18]. The association of SN with verticality perception is evaluated across the post-stroke time phases. There are 4 phases described: acute phase (1-7 days), early subacute phase (1 week – 3 months), late subacute phase (3-6 months), and chronic phase (>6 months) [19].

Clinically, the internal model of verticality can be estimated by evaluating the perception of verticality, measured through 4 modalities: the SVV, SPV and SHV. The SVV, SPV and SHV concern the subjective perception of the visual, postural and haptic vertical, compared to the true vertical (i.e., gravitational vector), respectively. The SVV relies on visuo-vestibular information, the SPV on proprioceptive, tactile and visceral-graviceptive information and the SHV on tactile information [20].

The magnitude of tilt of the line/object/tilt chair (V) relative to the true vertical is described in relative (i.e., constant errors) and absolute values (i.e., unsigned errors). The constant errors represent the magnitude of tilt of the object/tilt chair, with respect to the true vertical, while considering the direction of tilt. Negative values indicate a counterclockwise, and positive values indicate a clockwise tilt of the subjective vertical. However, within this systematic review, the direction of tilt is described in relation to the stroke side and can therefore be contralesional (in a right-sided lesion, this implies a leftward or counterclockwise tilt) or ipsilesional (in a right-sided lesion, this implies a rightward or clockwise tilt). Reported normative values for the SVV (-2.5° to 2.5°) [14, 21], SPV (0.12° +/- 1.49°) [14, 21] and SHV (-4.5° to 4.5°) [14] were used to compare reported tilts with. A tilt was considered "biased" if it falls outside of these reported normative values. Unsigned errors represent the magnitude of tilt with respect to the true vertical, irrespective of the direction of tilt.

Uncertainty (U) of the measurements relates to the intra-individual variability of the tilts across the measurements. This reflects the robustness of the internal reference of verticality [21]. The higher the uncertainty, the more the magnitude and/or direction of tilt of the subjective vertical differs between trials, indicating that the subject is uncertain about the vertical position between trials.

The co-existing influence of lateropulsion with SN to the verticality perception measurements, when investigated by the included studies, was also considered. Lateropulsion refers to a lateral push at the origin of a lateral body tilt. This push can be performed by the non-hemiplegic side generating a body tilt toward the opposite side [22].

Search strategy and study selection

A systematic literature search was conducted on May 24, 2022 in PubMed, Web of Science, Scopus, PubPsych and PsycArticles databases. Search queries consisted of the following free-text terms and medical subject headings: "SN", "stroke" and "perception of verticality", and their synonyms. No restrictions or filters were added. Studies were included if they (1) investigated adult stroke survivors with no restrictions on lesion characteristics; (2) evaluated an association between SN and perception of verticality by comparing participants with and without SN, or by evaluating this association using correlation or regression analyses (the contribution of SN to the outcome had to be evaluated); (3) evaluated SN using standardized assessment methods; (4) evaluated the SVV, SPV and/or SHV; and (5) were written in English. For intervention studies, only baseline characteristics were considered. Studies were excluded if: (1) no full-text article was available; (2) being case reports, meta-analyses, reviews or abstracts; (3) they solely and specifically included participants with lateropulsion, even if they also evaluated the perception of verticality between those with and without SN. This was chosen due to the complexity of the disorder and because an association of lateropulsion with verticality misperception in all modalities has been shown by a recent systematic review [23]; and (4) they evaluated combined modalities (e.g., visual and postural/haptic) such as the SPV-eyes open and SHV-eyes open.

Potential series overlaps between studies was evaluated based on geographical setting and recruitment period to avoid multiple publication bias. Corresponding authors of relevant studies were contacted if it was unclear whether there was a potential overlap between studies. If overlap in series existed between studies evaluating the same outcome (i.e., SVV), the most relevant study was chosen based on a predefined list of priorities consisting of 1. evaluated outcome (both SVV and uncertainty, instead of only tilt or uncertainty), 2. sample size, 3. risk of bias and 4. choice of SN tests (the more validated tests used, the better).

Screening on title, abstract and full-text was independently performed by four reviewers (EE, DA, AL, JVB) using a double-blinded approach. During full-text screening, reference lists of included studies were screened for secondary literature. Disagreements between reviewers were resolved by discussion.

Quality assessment

Risk of bias of the included studies was independently assessed by three reviewers (DA, AL, JVB) using the Newcastle-Ottawa Scale. Disagreements were resolved by discussion. According to the study design, the checklist for longitudinal cohort or cross-sectional studies were used. The items were adapted to fit the research questions (See Supplementary E-files). This scale assesses the risk of bias using a star rating system, judging three categories: selection, comparability and outcome. A star was given if a predefined criterion was met, suggesting low risk of bias for that criterion. In total, nine stars could be obtained for longitudinal and ten for cross-sectional studies. Cut-off values as described by McPheeters et al. [24] were used for interpretation (score of ≥7 was considered good, 5 or 6 moderate and

<5 poor). For intervention studies, the checklist for cross-sectional studies was used because only the pre-intervention characteristics of subjects were investigated.

Data extraction and analyses

The association between SN and verticality misperception was evaluated by analyzing reported (mean/median) differences between groups (SN and non-SN participants) and/or by evaluating reported associations (e.g., correlations, regressions, …). Two researchers (EE, CvdW) independently extracted the following data from each included study: authors, year, study design, subject groups, age, time post-stroke of initial and final assessment (if applicable), and SN assessment tools used. Moreover, measurement methods and study results regarding the association of SN with verticality perception were collected. Disagreements were resolved by discussion.

Results

Study selection

In total, 1420 unique articles were retrieved. After screening on 'title and abstract', 34 studies were considered of which 13 were included after full-text screening (Figure 3.3.1).

Participants and descriptive data

Of the 13 included studies, 11 were cross-sectional [11, 25-34] and two were longitudinal prospective studies [8, 15]. In total, 431 stroke participants were studied (327 right-sided, 82 left-sided, 22 unknown). Of them, at least 191 showed SN and at least 205 did not. Of the 35 leftover participants, it was not reported whether they did or did not show SN. The reported mean/median age of the participants ranged from 52 to 71.8 years. Eleven studies assessed visuo-spatial neglect [8, 11, 25, 27-34]: 9 with conventional paper-and-pencil tests only [8, 11, 25, 27, 29, 30, 32-34] and two with the Behavioral Inattention Test Battery [28, 31]. The 2 remaining studies assessed multiple types of SN using the Catherine Bergego Scale (an ecological assessment tool for SN [35]) or a behavioral scale, combined with paper-and-pencil tests [26]. Considering time post-stroke, the early subacute phase (1 week - 3 months post-stroke) was most frequently evaluated (Table 3.3.1).

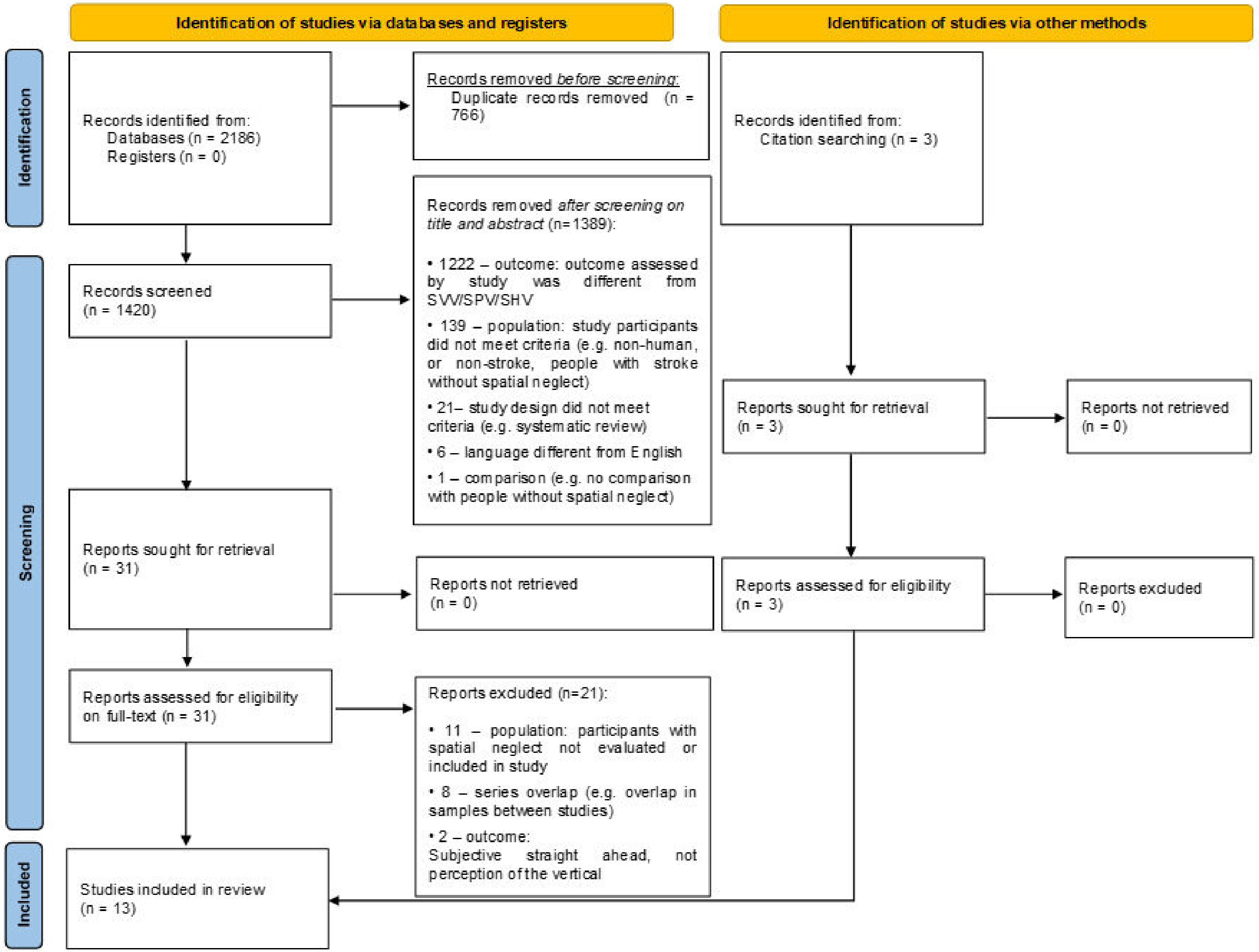

Figure 3.3.1. Flowchart of study selection process

Table 3.3.1. Sample characteristics

Author	Design	Subject groups according to lesion side (N)	Age in years (SD/IQD/range)	Time phase post-stroke of verticality measurements	Spatial neglect test	Spatial neglect diagnosis criteria
Baier et al. (2012) [25]	CS	**RBD (n=32):** SN+ (n=12), SN- (n=20); **LBD (n=22)**: SN+ (n=2), SN- (n=20)	**RBD+LBD:** 61.0 (SD 18)	*Early subacute* ***RBD:*** *4.5 (SD 2.1) days* ***LBD:*** *4.9 (SD 5.2) days*	Bell's test (Center of Cancellation)	NM
Barra et al. (2009) [26]	CS	**RBD (n=13), LBD (n=9)**	*57.14 (SD 13.7)*	Early to late subacute phase ***RBD:*** *12.3 (SD 6.9) weeks* ***LBD:*** *14.4 (SD 8.0) weeks*	Bell's test, LBT, behavioral scale	NM
Bonan et al. (2006) [15]	C: pro	**RBD (n=13)**: SN+ (n=11), SN- (n=2); **LBD (n=17)**: SN+ (n=2), SN- (n=15)	<u>**RBD**: 55 (IQD 18), **LBD**: 52 (IQD 17)</u>	Early subacute to chronic <u>Initial: RBD: 31 (IQD 15), LBD: 21 (IQD 9) days; also at 3 and 6 months</u>	Bell's test, LBT, CBS, baking tray task, animals test (Combined Index of Neglect Severity)	Combined Index of Neglect Severity was computed. Index ranged from 0 to 5, with 0 indicating no evidence of SN in any of the tests and 5 indicating SN in all tests. Score >2 indicated SN
Bonan et al. (2007) [8]	C: pro	**RBD (n=14)**: SN+ (n=8), SN- (n=6); **LBD (n=14)**: SN+ (n=0), SN- (n=14)	<u>**RBD+LBD:** 57.5 (IQD 22)</u>	Early subacute and chronic <u>22.5 (IQD 33) days, at 6 months</u>	Bell's test, LBT, scene copy test	SN when difference between the bells omitted on the left and right sides in the Bell's Test was >3, when bias in LBT was >0.6 cm and when at least one element was omitted in the scene copy test
Braem et al. (2014) [27]	CS	**RBD (n=16)**: SN+ (n=10), SN- (n=6)	SN+: 63.8 (SD 11.4), SN-: 57.3 (SD 15.8)	Early and late subacute *SN+: 7.4 (SD 2.0), SN-: 12 (SD 5.3) weeks*	Bell's test, LBT, scene copy test	SN when ≥ 2/3 tests indicated SN
Fukata et al. (2020) [28]	CS	**RBD (n=43)**: SN+LP- (n=10), SN+LP+ (n=11), SN-LP- (n=12), SN-LP+ (n=10)	SN+LP-: 63.9 (SD 12.9), SN+LP+: 70.1 (SD 10.4), SN-LP-: 65.4 (SD 10.8), SN-LP+: 66.3 (SD 12.4)	Early subacute SN+LP-: 14.0 (SD 6.6), SN+LP+: 14.0 (SD 8.3), SN-LP-: 15.2 (SD 5.0), SN-LP+: 12.1 (SD 4.7) days	Behavioral inattention test - conventional subtest	Score ranges from 0 to 146 points, with a score ≤131 indicative of SN

Funk et al. (2010) [29]	CS	**RBD (n=20):** SN+ (n=20), SN- (n=0)	SN+: 57 (*SD 12*)	Early subacute SN+: 2.5 (*SD 1.6*) months	LBT, star cancellation, letter cancellation, neglect-sensitive reading test	Cutoffs: deviations >5 mm from midpoint of 20 cm line in LBT, >4 omissions in star cancellation and letter cancellation tests, and >2 omissions/substitutions of letters/ words and/or prolonged reading time (>40 s).
Kerkhoff et al. (1998) [30]	CS	**RBD (n=27)**: SN+ (n=13), SN- (n=14); **LBD (n=14)**: SN+ (n=3), SN- (n=11)	**RBD:** SN+: 52.8, SN-: 45.8; **LBD:** SN+: 52.7 *(SD 9.7)*, SN-: 50.7 (other SD's NM or calculable)	Late subacute to chronic **RBD:** SN+: 6.2, SN-: 4.5; **LBD:** SN+: 8.0 *(SD 4.3)*, SN-: 5.0 months (other SD's NM or calculable)	Representational drawing, LBT, number cancellation task, copying task (daisy, face, house)	NM
Lafosse et al. (2004) [31]	CS	**RBD (n=43):** SN+ (n=31), SN- (n=12)	Mild SN+: 71.8 (SD 7.3), moderate SN+: 61 (SD 10.1), severe SN+: 66 (SD 8.3), SN-: 58 (SD 7.8)	Chronic Mild SN+:20.4 (SD 9.7), moderate SN+: 21.3 (SD 11.4), severe SN+: 15 (SD 11.2), SN-: 15.3 (SD 8.4) months	Behavioral inattention test - conventional subtest (SN severity: mild 89-129, moderate 70-90, severe <70)	SN if aggregate score < 129. Further classified in four groups, according to severity of SN: mild 89-129, moderate 70-90, severe <70
Mori et al. (2021) [32]	CS	**RBD (n=28):** SN+ (n=17), SN- (n=11); **LBD (n=15)**: SN+ (n=0), SN- (n=15)	**RBD+LBD:** SN+: 67.1 (SD 8.0), SN-: 63.8 (SD 10.4)	Early subacute SN+: 14.9 (SD 7.7), SN-: 9.8 (SD 4.7) days	LBT, star cancellation task, flower copying task	SN when at least 1 test exceeding the cut-off. Cut-off scores: LBT: ≤7 points, star cancellation: ≤ 51 points and ≥3 asymmetry points star cancellation task, copying task: 0 points
Pérennou et al. (1998) [11]	CS	**Stroke (n=22)** (number of SN+/- NM)	58.3 (SD 2.5)	Early subacute 83.2 (SD 10.7) days	Cancellation task	NM
Rousseaux et al. (2015) [33]	CS	**RBD (n=46):** SN+ (n=25), SN- (n=21)	RBD: 60.9 (SD 13.2)	Early subacute 43.3 (SD 30.2) days	LBT, scene copying test, bell's test	SN when performance was pathological in >2/3 tests. Cut-off scores: LBT rightward deviation>11%, scene copying score >1 out of 4 and bell cancellation left omissions >2 out of 15

Utz et al. CS (2011) [34]	**RBD (n=32):** SN+ (n=16), SN- (n=16)	**RBD:** SN+: 71 (range 52-86), SN: 70 (range 47-84)	Early subacute SN+: 78 (SD 53.02), SN-: 61 (SD 79.91) days	LBT, letter cancellation test, star cancellation test, figure copying, paragraph reading, number cancellation test	SN when at least 3 tests exceeding the cut-off

Abbreviations: C: cohort, CBS: Catherine Bergego Scale, CS: cross-sectional, IQD: inter-quartile distance, LBD: left brain damage, LBT: Line bisection test, long: longitudinal, n: number, prosp: prospective, RBD: right brain damage, SD: standard deviation, SN+: patients with spatial neglect, SN-: patients without spatial neglect. Underlined: indicates median values, italic: indicates self-calculated mean values and standard deviations.

Risk of bias

In total, 3 studies were of good [8, 15, 33], 5 of moderate [27, 30-32, 34] and 5 of poor [11, 25, 26, 28, 29] methodological quality. Each study received at least one star on the item that assesses ascertainment of exposure that evaluates whether a validated SN tool was used, with or without the description of a cut-off value. In contrast, none of the studies received a star on the 'assessment of outcome' item which evaluates whether outcome was assessed in a double-blinded fashion (Table 3.3.2).

Table 3.2.2. Risk of bias of cross-sectional and longitudinal studies

Risk of bias of cross-sectional studies

	Selection				**Comparability**	**Outcome**		**Total score**	**MQ**
	1	2	3	4	1	1	2		
Baier et al. (2012) [25]	*		*	*			*	4/10	Poor
Barra et al. (2009) [26]	*		*	*			*	4/10	Poor
Braem et al. (2014) [27]			*	**	**			5/10	Mod
Fukata et al. (2020) [28]				**	**			4/10	Poor
Funk et al (2010) [29]			*	**			*	4/10	Poor
Kerkhoff et al. (1998)[30]	*			*	**		*	5/10	Mod
Lafosse et al. (2004) [31]			*	**	*		*	5/10	Mod
Mori et al. (2021) [32]			*	**	**		*	6/10	Mod
Pérennou et al. (1998) [11]				*	**			3/10	Poor
Rousseaux et al. (2015) [33]		*		**	**	**		7/10	Good
Utz et al. (2011) [34]		*		**	**		*	6/10	Mod

Risk of bias of longitudinal cohort studies

	Selection				**Comparability**	**Outcome**			**Total score**	**MQ**
	1	2	3	4	1	1	2	3		
Bonan et al. (2006) [15]	*	*	*	*	*		*	*	7/8	Good
Bonan et al. (2007) [8]	*	*	*	*	*		*	*	7/8	Good

Abbreviations: Mod: moderate.

Measurement methods of verticality perception

Details regarding measurement methods (e.g., position, fixation during measurement, number of trials, …) can be found in Table 3.3.3.

SVV

For constant errors, four studies (two good, two moderate quality) showed significantly larger magnitudes of tilt in SN participants than non-SN participants [15, 30, 33, 34], whereas two (one poor, one moderate quality) did not find a difference between groups [28, 32]. The more severe SN was on the Catherine Bergego Scale (ADL-related scale), the more tilted the SVV

Table 3.3.3. Measurement information

Author	Measurement method and outcomes	Patient setting	Task	N of trials with starting positions
SVV				
Baier et al. (2012) [25]	Special goggles (ATHERMAL® GSF 166 DIN) that only show luminous rod of 29.5 cm, 1 cm width. V evaluated.	Seated in chair, 1.5 m distance to line, non-fixed head (patients were instructed to keep head upright), head position water level controlled.	Examiner oriented line until subject indicated it as vertical.	12 (random): 2 with line oriented at 20°, 30° or 40° to CW and CCW.
Barra et al. (2009) [26]	Dark room, luminous rod of 15 cm, 0.2 cm width, masked surround on a computer screen. V evaluated.	1.5 m distance to line, patient position and fixation NM.	Examiner oriented line until subject indicated it as vertical.	10 (pseudo-random): balanced between CCW and CW.
Bonan et al. (2006) [15]	Dark room, luminous rod of 30cm. V and U (range) evaluated.	Seated in (wheel)chair, 2m distance to line, non-fixed head.	Subject adjusted line to vertical by manipulating a box held in non-paretic hand. No time limit.	6 (3 series): in each series: 1 with rod oriented 60° CCW, 1 with rod oriented 60° CW.
Bonan et al. (2007) [8]	Dark room, white line on dark background. V and U (SD) evaluated.	Seated in (wheel)chair, 2 m distance to line, fixed head (chin rest).	Examiner oriented line until subject indicated it as vertical. No time limit.	8 (random): 4 with line oriented 40° to CCW, 4 with line oriented 40° to CW.
Braem et al. (2014) [27]	Dark room, rod of 25 cm with red LEDs. V evaluated.	Seated in bed, 0.4 m distance to line, fixed head (strap).	Examiner oriented line until subject indicated it as vertical. No time limit.	4 (random): 2 with line oriented 45° CCW, 2 with line oriented 45° CW.
Fukata et al. (2020) [28]	Subject viewed computer display through a cylindrical tube to obscure frame and remove visual cues. V and U (SD) evaluated.	Seated on chair, 0.5 m distance to line, feet flat on floor, fixed trunk (belts), non-fixed head (maintained freely upright).	Visual indicator oriented line at 5°/s by computer until subject indicated it as vertical (stopped by examiner).	8 (ABBABAAB sequence): during A, the line was oriented CCW; during B, the line was oriented CW (degrees not provided).
Kerkhoff et al. (1998) [30]	Dark background, white line of 18 cm, screen borders were hidden behind an oval-shaped mask. V and U (DT) evaluated.	0.5 m distance to line, fixed head and trunk (head-and-chin rest).	Examiner oriented line until subject indicated it as vertical, and then further until subject indicated that it is no longer vertical. No time limit.	Initial deviation 15° from vertical (CCW and CW).

Mori et al. (2021) [32]	Dark room, luminous line of 30 cm on screen, projected with hidden borders. V and U (SD) evaluated.	Seated, 1 m distance to line, fixed head and trunk (belts and cushions).	Examiner oriented line until subject indicated it as vertical. No time limit.	10 (random): 5 deviated 30° CCW, 5 deviated 30° CW. Beforehand 1 practice trial in a light room.
Rousseaux et al. (2015) [33]	Dark room, rod of 25 cm with 10 red light-emitting diodes. V evaluated.	Seated semi-recumbent on treatment table, 0.5 m distance from rod, fixed head and trunk (straps).	Examiner oriented line until subject indicated it as vertical. No time limit.	18 (2 per rod starting positions (n=3) and starting angles (n=3)): rod fixed on midsagittal plane of subject, or 15 cm left or right from subject. Starting angles: -45°, 0°, +45°.
Utz et al. (2011) [34]	Dark room with darkened box in which measurement took place, rod of 21.5 cm illuminated in red. V evaluated.	Seated, 0.4 m distance to line, fixed head (head-and-chinrest).	Subject received visual input only subject oriented line by rotating disc beneath rod (no haptic cues on verticality) with non-paretic hand until perceived as vertical. No time limit.	72 (3 times 6 trials for every starting angle (n=2) and plane (n=2)).
SPV				
Fukata et al. (2021) [28]	Vertical board in bright room. V and U (SD) evaluated.	Seated on board, arms folded across chest, feet off ground, fixed trunk (belts), non-fixed head and legs.	Examiners deviated subject at +/- 1.5°/s until subject indicated position as vertical. 2 sessions.	8 (ABBABAAB or BAABABBA sequence): during A, the line was oriented CCW; during B, the line was oriented CW. Starting position: 15° or 20°.
Lafosse et al. (2004) [31]	Rotating chair. V evaluated.	Seated, hands crossed on thighs, lateral stabilization of subject, legs freely hanging, head fixation NM.	Examiner deviated subject until subject indicated position as vertical. 2 sessions.	6 (random): starting position at least 35° CCW or CCW.
Pérennou et al. (1998) [11]	Rocking platform (unstable in 0ML direction), rigid support mounted on seesaw with horizontal rotation axis. V evaluated.	Seated centrally, no fixation, hands on thighs, legs freely hanging.	Examiners deviated subject until subject indicated position as vertical. 2 sessions.	NM
SHV				
Braem et al. (2014) [27]	Subject blindfolded, non-paretic hand on rod of 25cm. V evaluated.	Seated in hospital bed, 0.4m distance to line, fixed head (strap).	Subject oriented rod until perceived as vertical. No time limit.	4 (random across subjects): 2 with rod oriented 45° CCW, 2 with line oriented 45° CW.

Funk et al. (2010) [29]	Subject blindfolded, non-paretic hand on rod of 15cm. V and U (range) evaluated.	Seated on chair, fixed head (head-and-chinrest) + lying on medical stretcher.	Subject oriented rod until perceived as vertical. No time limit.	Seated and lying (each): 10 (random): 5 with rod oriented 40° CCW, 5 with line oriented 40° CW.
Rousseaux et al. (2015) [33]	Subject blindfolded, non-paretic hand on rod of 25cm. V evaluated.	Seated semi recumbent on treatment table, 0.5 m distance to rod, fixed head and trunk (straps).	Subject oriented rod until perceived as vertical. No time limit.	18 (2 per rod starting positions (n=3) and starting angles (n=3)): rod fixed on midsagittal plane of subject, or 15 cm left or right from subject. Starting angles: -45°, 0°, +45°.
Utz et al. (2011) [34]	Subject blindfolded, non-paretic hand on rod. V evaluated.	Seated, 0.4m distance to rod, fixed head (head-and-chinrest).	Subject oriented rod until perceived as vertical. No time limit.	18 (2 per rod starting positions (n=3) and starting angles (n=3)): rod fixed on midsagittal plane of subject, or 15 cm left or right from subject. Starting angles: -45°, 0°, +45°.

Abbreviations: CCW: counterclockwise, cm: centimeter, CW: clockwise, DT: difference threshold, m: meter, ML: mediolateral, SD: standard deviation, N: number, NM: not mentioned, SHV: subjective haptic vertical, SPV: subjective postural vertical, SVV: subjective visual vertical, U: uncertainty, V: tilt.

was (r=-0.623, p=0.002, [-0.827; -0.272]) [26]. In contrast, results are inconclusive regarding the correlation of the SVV with SN severity on a cancellation task [25, 26], and there was no significant correlation with SN severity on a line bisection task [26]. Tilts were mainly evaluated in the subacute post-stroke phase (i.e., first week to 6 months). Only one study (good quality) evaluated the chronic phase, showing that the association between SN and SVV misperception disappeared [15]. However, only 3 participants still showed SN at this time-point [15]. Two studies evaluated unsigned errors, and reported higher tilts in SN participants than in non-SN participants, in both the early subacute phase [8, 34] and chronic phase post-stroke [8].

Six studies reported magnitudes of tilts [8, 27, 28, 30, 32, 34], and found that magnitudes were larger in those with SN. They ranged from -8.9° [32] to -2.3° [28] in SN participants, and from -1.6° [32] to 0.6° [34] in non-SN participants. The presence of lateropulsion did not increase magnitude of tilts [28]. The reported mean/median magnitudes of tilt were beyond the normative range in those with SN in four studies, and therefore considered biased tilts [8, 27, 30, 34]. For non-SN participants, they were always within this range [8, 27, 28, 30, 32, 34] and are therefore not considered biased. In most studies, the direction of tilt was reported to be contralesional in SN participants (i.e., leftward tilt in right-sides strokes) [27, 30, 33, 34]. Two studies also reported upon ipsilesional tilts in some SN participants [28, 32]. In non-SN participants, the tilt was either not larger than 0° [27, 34], contralesional [28, 30] or ipsilesional [28, 30, 32].

Considering uncertainty, this was higher in SN participants (ranging from 2.0° [30] to 8.8° [32]) than in non-SN participants (ranging from 0.3° [30] to 1.6° [8]) [8, 15, 28, 32]. Uncertainty increased if SN and lateropulsion were simultaneously present (U=7.6°) [28] (Table 3.3.4).

SPV

Of the three studies evaluating the SPV, two (poor quality) found no association between SN and SPV misperception [11, 28] in the early subacute phase post-stroke, while one (moderate quality) did find an association in the chronic phase [31]. When an association was present, tilts were larger in SN participants than non-SN participants (V=0.2-0.4°), but only in case of moderate (V=-3.7°) to severe (V=0.7°) SN [31], or when lateropulsion was present in addition to SN (V=2.1°) [28]. Whereas it could not be evaluated whether the magnitudes of tilt were within or without normative limits for SN participants due to conflicting evidence, the

Table 3.3.4. SVV (results)

Author	MQ	Statistics	Values (V and U in ° (SD)), direction of deviation	Results for magnitude of deviation (V)	Results for uncertainty (U)
Baier et al. (2012) [25]	Poor	Pearson correlation	*NM*	*More severe neglect score (Bell's test CoC) is correlated with higher magnitude of deviation (r=0.487, p<0.001, CI NM)*	*NA*
Barra et al. (2009) [26]	Poor	NM	Direction: 6 out of 22: ipsilesional; 16 out of 22: contralesional. Unknown who show SN, as there are no cut-off values for SN reported.	Sig correlation of SVV and CBS score (r=-0.623, p=0.002, [-0.827; -0.272]). No sig correlation with the LBT (r=-0.209,p=0.350, [-0.580; 0,233]) and Bell's test (r=-0.15, p=0.491, [-0.541; 0.285])[A]	NA
Bonan et al. (2006) [15]	Good	Mann-Whitney U, spearman correlation	*RBD and LBD: CL (2 RBD: IL, unknown whether these showed SN)*	*Baseline: sig larger deviations in SN+ than SN- group (p=0.01, CI NM);* *3 months: sig larger deviations in SN+ than SN- group (p=0.04, CI NM);* *6 months: no sig difference between SN+ and SN- (p=0.1, CI NM), but only 3 patients showed SN))*	*Baseline: sig higher uncertainty in SN+ than SN- group (p=0.002, CI NM)* *3 months: sig higher uncertainty in SN+ than SN- group (p=0.004, CI NM)* *6 months: no sig difference between SN+ and SN- (p=0.07, CI NM), but only 3 patients showed SN)*
Bonan et al. (2007) [8]	Good	Mann-Whitney U, Kendall coefficient correlation	*Baseline: SN+: V=5.4° (IQD 5.0°), U=6.5° (IQD 4.9°); SN-: V=1.9° (IQD 3.5°), U= 1.6° (IQD 1.8°)* *6 months: SN+: V=3.2° (IQD 1.7°), U=3.2° (IQD 2.0°); SN-: V=1.7°(IQD 2.0°), U=1.5° (IQD 1.0°)* *Direction: NA (unsigned errors)*	*Unsigned errors* *Baseline: sig higher magnitude in SN+ than SN- group (p=0.02). SN and V: Sig correlation (r NM, p=0.02, CI NM)* *6 months: sig larger deviation in SN+ than SN- group (p=0.04, CI NM)*	*Unsigned errors:* *Baseline: sig difference between SN+ and SN- groups (p=0.005). Sig correlation between SN and uncertainty (r NM, p≤0.01, CI NM)* *6 months: sig larger uncertainty in SN+ than SN- group (p=0.01, CI NM)*

Braem et al. (2014) [27]	Mod	ANOVA with Newman-Keuls post-hoc	SN+: V=-3.9° (SD 4.14°), CL direction; SN-: V=0.5° (SD 3.7°), direction NS	SN+: p-value and CI NM SN-: p-value and CI NM	NA
Fukata et al. (2020) [28]	Poor	ANOVA with Bonferroni post-hoc, pearson correlation	SN+LP-: V=-2.3° (SD 3.7°), CL direction in 6 participants, IL direction in 2 participants, U=6.9° (SD 5.9°); SN+LP+ (V=-1.4° (SD 5.1°)), CL direction in 7 participants, IL in 4 participants, U=7.6° (SD 6.3°); SN-LP-: V=-0.6° (SD 2.2°), CL direction in 7 participants, IL direction in 5 participants, U=1.4° (SD 0.6°); SN-LP+ : V=1.5° (SD 5.7°), IL direction in 4 participants, CL direction in 5 participants, U=1.9° (SD 0.5°)	No sig difference between groups (p-value and CI NM)s	Sig higher uncertainty in SN+LP+ and SN+LP- than in SN-LP+ and SN-LP- groups (p<0.05). Uncertainty was *sig* correlated with the BIT score (r=0.752, p<0.001, CI NM)
Kerkhoff et al. (1998) [30]	Mod	ANOVA with Scheffé post-hoc	*RBD SN+: V= -4.9° (SD 3.8°), U=2.0° (SD 3.87°);* *RBD SN-: V=-0.2° (SD 0.5°), U=0.3° (SD 0.5°);* *LBD SN-: V=-0.4° (SD 0.8°), U=0.6° (SD 1.0°)*; SN+: CL direction, SN-: IL direction (LBD SN+ group not included in statistics)	RBD SN+ group had sig larger deviations than RBD SN- and LBD SN- groups (p<0.05, CI NM). No main effect of 'Rotation direction'	Sig group effect (F=23.11, p<0.0001, CI NM), post-hoc test not performed (CI NM)
Mori et al. (2021) [32]	Mod	One-sample T-tests, ANOVA with Tukey HSD post-hoc	SN+: V=-2.1° (SD 3.7°), U=8.8° (SD 5.2°); SN-: V NM; U=1.9° (SD 1.1°) <u>Group x direction interaction effect</u>: **SN+** : CL direction: V=-8.9° (SD 5.9°), U= 4.4° (SD 3.7°), IL direction: V=-4.7° (SD 6.1°)), 4.6° (SD 3.5°); **SN-** : CL direction: V=-1.6° (SD 3.0°), 0.8° (SD 0.5°), SN- IL: V=-0.8° (SD 3.7°), 1.0° (SD 0.6°). SN+: CL direction; SN-: direction NS <u>Direction:</u> generally CL, however, individual data shows IL tilt in 7 out of 17 SN+ participants, and 10 out of 26 SN- participants	Sig difference between groups (F=3.2, p=0.046, CI NM), but post-hoc tests showed no sig differences between SN+ and SN- groups <u>Sig group x direction interaction effect</u> (F=3.4, p=0.035, CI NM): sig larger magnitude of deviation in relation to initial starting position in SN+ than SN-group. Starting direction influenced the results: SVV was more deviated if started from CL side compared to IL side (p=0.015, CI NM)	Uncertainty was sig higher in SN+ than in SN- group (p<0.001, CI NM) <u>Sig group effect</u> (F=58.6, p<0.001, CI NM), no direction effect (F=0.3, p=0.61, CI NM) or interaction between these factors (F=0.0, p=0.99, CI NM). SN+ group had sig higher uncertainty when starting position was considered compared to SN- group (p<0.001, CI NM)

Rousseaux et al. (2015) [33]	Good	Chi-square test, Spearman correlation test	*CL direction*	*Sig larger deviation in SN+ than in SN- group (values NM, p=0.047, CI NM). A total of 21 participants (of whom 16 with SN) exceeded the cut-off (-2.6°) for a "true"deviation.*	NA
Utz et al. (2011) [34]	Mod	ANOVA with post-hoc Bonferroni test, one-sample T tests	Constant errors: SN+: V=-3.0° (SE 2.0°), CL direction; SN-: V=0.6° (SE 1.0°), direction NS; Unsigned error: SN+: V=5.0° (SE 1.4°); SN-: V=1.3° (SE 1.3°)	Constant errors: sig larger deviations in SN+ than SN- groups (p<0.04, CI NM). Unsigned errors: sig larger deviations in SN+ than SN- group (p=0.003, CI NM).	NA

CBS: Catherine Bergego Scale, CI: confidence interval, CL: contralesional, IL: ipsilesional, IQD: inter-quartile distance, LBD: left brain damage, MQ: methodological quality, NA: not applicable, NM: not mentioned, RBD: right brain damage, SD: standard deviation, SE: standard error, sig: significant, SN+: spatial neglect, SN-: no spatial neglect, SVV: subjective visual vertical, U: uncertainty, V: (magnitude of) dviation. *Italic text implies median values and non-parametric statistics.* ^{A} implies self-calculated values and/or statistics.

magnitudes of tilt fell within the normative range for non-SN participants, and are therefore not considered biased tilts [28, 31].

In both SN and non-SN participants, no conclusion on direction of tilt could be drawn considering both ipsi- and contralesional tilts were reported [11, 28, 31]. Uncertainty was evaluated by Fukata et al. [28], showing no difference between SN (U= 4.0°) and non-SN participants unless lateropulsion was present in addition to SN (U=6.6°) (Table 3.3.5).

SHV

Four studies (one poor [29], two moderate [27, 34], one good [33] quality) evaluated the association between SN and SHV misperception. When the SN (V=-5.9°) and non-SN groups (V=-4.9°) were compared regarding magnitudes of tilt, no significant difference was found between both [33, 34]. For both SN and non-SN groups, mean tilts were considered biased as they were outside reported normative values [27, 34]. The direction of tilt was always contralesional in SN participants, and in non-SN participants either not significantly larger than 0° [34] or also contralesionally deviated [27, 33]. In contrast to constant errors, unsigned errors were significantly higher in SN participants (V=7.1°) than in non-SN participants (V=4.1°) [34].

Only Funk et al. (poor quality) evaluated the correlation between SN severity and SHV misperception and shows that more cancellation errors and line bisection errors related to significantly higher SHV misperception [29]. The study was also the only one to investigate uncertainty, showing that more errors on the star cancellation test were significantly correlated with higher uncertainty [29]. Only the early and late subacute phases were evaluated (Table 3.3.6).

Discussion

The aim of this study was to systematically analyze the reported associations between SN and the perception of verticality, while considering the time post-stroke. If methodological quality is considered, evidence points towards larger SVV tilts and uncertainty in SN compared to non-SN participants in the first three-to-six months post-stroke. Contrary to this, no conclusions on the SPV and SHV modalities could be drawn due to a low number of studies investigating these modalities, which were often also of a low methodological quality.

Table 3.3.5. SPV (results)

Author	MQ	Statistics	Values (V and U in ° (SD)), direction of deviation	Results for magnitude of deviation (V)	Results for uncertainty (U)
Fukata et al. (2021) [28]	Poor	ANOVA with Bonferroni post-hoc	**SN+LP+:** V=-2.1° (SD 2.0°), CL direction in 9 participants, IL direction in 2 participants, U=6.6° (SD 2.0°); **SN-LP+:** V=-2.2° (SD 1.1°), CL direction, U=6.3° (SD 1.4°); **SN+LP-:** V=-0.2° (SD 1.4°), CL direction in 5 participant, IL direction in 4 participants, U=4.0° (SD 1.8°); **SN-LP-:** V=-0.4° (SD 1.0°), CL direction in 7 participants, IL direction in 5 participants, U=3.5° (SD 1.0°);	Sig larger deviations in SN+LP+ and SN-LP+ than in SN+LP and SN-LP- groups (p<0.05, CI NM)	Sig higher uncertainty in SN+LP+ and SN-LP+ than SN+LP- and SN-LP- groups (p<0.05) (CI NM)
Lafosse et al. (2004) [31]	Mod	ANOVA	**SN-:** V=0.3°, direction NS; **Mild SN+:** V=2.0°, IL direction; **Mod SN+:** V=3.7°, IL direction; **Severe SN+:** V=-0.7°, CL direction	Mod SN+ sig larger deviations compared with SN- group (p< 0.001, CI NM); Severe SN+ sig larger deviations than mod SN+ (p<0.001, CI NM)	NA
Pérennou et al. (1998) [11]	Poor	Correlation analysis (type NM)	CL direction	No sig correlation with magnitude of deviation and SN severity (p>0.05, CI NM)	NA

Abbreviations: CI: confidence interval, CL: contralesional, Mod: moderate, MQ: methodological quality, NA: not applicable, NM: not mentioned, NS: not significant, LP: lateropulsion, sig: significant, SN+: spatial neglect, SN-: no spatial neglect, SPV: subjective postural vertical, SD: standard deviation, U: uncertainty, V: mean deviation; negative values indicate a counterclockwise deviation.

Table 3.3.6. SHV (results)

Author	MQ	Statistics	Values (V and U in ° (SD)), direction of tilt	Results for magnitude of tilt (V)	Results for uncertainty (U)
Braem et al. (2014) [27]	Mod	ANOVA with Newman-Keuls post-hoc	SN+: V=-5.9° (SD 4.3°); SN-: V=-4.9° (SD 4.6°); SN+ and SN-: CL direction	P-value of between-group comparison NM.	NA
Funk et al. (2010) [29]	Poor	Spearman and Pearson correlations	CL direction	No sig correlation between SN severity (sum of tests with values above cut-off) and constant errors (r=0.21, p>0.15) or unsigned errors (r=0.21, p>0.15) (CI NM) Constant errors were sig correlated with star cancellation (r=0.57, p<0.01), E&R cancellation (r=0.53, p<0.05) and LBT (r=0.54, p<0.05); not with reading errors (r=-0.07, p>0.05) (CI NM) Unsigned errors were sig correlated with star cancellation (r=0.61, p<0.01) and E&R cancellation tests (r=0.59, p<0.01); not with LBT (r=0.42, p<0.05) and reading errors (r=0.21, p>0.05) (CI NM)	Sig correlation between SN severity (sum of tests with values above cut-off) and uncertainty (r=0.33, p<0.09, CI NM) Uncertainty was sig correlated with star cancellation (r=0.67, p<0.01); not with E&R cancellation, LBT and reading errors (r=0.63, r=0.19 and r=0.42, p<0.05 respectively) (CI NM)
Rousseaux et al. (2015) [33]	Good	Chi-square test, Spearman correlation test	SN+ and SN-: CL direction	No sig difference between SN+ and SN- groups for magnitude of tilt (p=0.178, CI NM). Nine patients of whom 7 with SN exceeded the cut-off (CCW -9.8°) for a SHV tilt.	NA
Utz et al. (2011) [34]	Mod	ANOVA with post-hoc Bonferonni test, one sample T-test	Constant errors: SN+: V=3.0° (SEM 3.2°), CL direction; SN-: V=1.1° (SEM 1.8°), direction NS; Unsigned errors: SN+: V=7.1° (SEM 1.7°), SN-: V=4.13° (SEM 1.5°)	Constant errors: no sig difference in magnitude of tilts between SN+ and SN- group (p=0.25, CI NM) Unsigned errors: SN+ group had sig larger tilts compared to SN- group (p=0.02, CI NM)	NA

Abbreviations: CI: confidence interval, CL: contralesional, LBT: Line Bisection Test, MQ: methodological quality, Mod: moderate, NA: not applicable, NM: not mentioned, NS: not significant, SD: standard deviation, sig: significant, SN+: spatial neglect, SN-: no spatial neglect, SHV: subjective haptic vertical, V: mean deviation; negative values indicate a counterclockwise deviation.

The direction of tilt differs across studies, modalities assessed and measurement methods used. For the SVV, most studies report upon a contralesional deviation in SN participants, however, ipsilesional deviations were also reported. For the SHV, there was agreement on a contralesional deviation in SN participants, whereas no conclusions could be drawn for the SPV. In non-SN participants, the direction was either also contralesional (with smaller magnitudes), ipsilesional, or not significantly larger than 0°. Interestingly, for the SVV, mean magnitudes of tilt were almost always outside the normative range for SN participants, whereas the mean tilts of non-SN participants were always within this range (-2.5° to 2.5° [14, 21]). This may indicate that a misperception of SVV is a key feature of SN, at least within the first six months post-stroke. Due to inconclusive evidence for the SPV and SHV conditions, no conclusions about whether the constant errors of these modalities were within normal ranges could be drawn. In addition, a lack of normative values for uncertainty measures, also prohibits conclusions on these measures.

Predominantly, the subacute phase post-stroke (1 week - 6 months) was evaluated. Consequently, associations between SN and SVV misperception were strongest in this time phase as well. Since repetitive measurements of verticality perception from the early subacute to chronic post-stroke phase are lacking, it is difficult to investigate the recovery patterns of verticality misperception However, the scant evidence points toward recovery from the subacute to chronic phases, both in SN and non-SN participants [8, 15]. SN follows a natural logistic pattern of improvement within the first 12-14 weeks post-stroke, after which the recovery curve plateaus [36]. Due to a lack of longitudinal studies, whether the recovery of verticality misperception shows a similar pattern cannot be evaluated.

There are methodological differences between studies that may account for some inconclusive evidence, such as SN assessment methods and verticality testing procedures. In all but two studies, SN was evaluated solely by paper-and-pencil tests. These tests are not sensitive enough to evaluate the complexity of SN, as they are easily compensated for in case of mild or even moderate SN [37]. In addition, they mainly assess visuospatial neglect, and do not sufficiently address other SN types (e.g., personal, motor, tactile neglect). The fact that mainly visuo-spatial neglect is evaluated, may also contribute to the observation that primarily the SVV is affected in SN participants. Indeed, visuo-spatial neglect implies neglect for visual stimuli, and the perception of the visual vertical relies primarily on visual input. In case of the SPV and SHV, visual input is eliminated and does not contribute to the outcome.

With regards to the verticality testing procedures, a crucial factor to consider is head fixation. Without fixation, head tilts can occur and could induce the 'E-effect' [38, 39], which implies a tilt of the subjective vertical toward the opposite side of the starting head-on-body position. The E-effect is already proven to exist for the SVV and SPV modalities [38, 39]. A lack of fixation can decrease the accuracy of the measurements as compensatory head movements can be performed by the subject [21, 38, 40], possibly ameliorating their result [11, 28, 31]. Head (and trunk) fixation is especially necessary in participants who are unable to sit independently, which is often the case in participants with SN in the early subacute phase [41].

Limitations

There are some methodological limitations within the included studies. Sample sizes were small, limiting not only statistical analyses but also the interpretation and generalization of results. Because of this, only associations between SN and misperception of verticality, and not causality, could be evaluated. Consequently, the suggested interpretation of the existence of a "graviceptive neglect" (see Introduction) cannot be answered nor refuted by this systematic review [4, 6, 11, 12].

Variability in the characteristics of included participants, use of SN assessment tools, SN cut-offs, time points of assessment, measurement methods used and sample sizes across studies was high and questions the robustness of the results that have been found by this review. However, most studies focused on one subtype of SN, namely visuospatial neglect. Even though heterogeneity was present, results were relatively consistent within the SVV modality, pointing towards SVV misperception being a potential key feature of SN.

Additionally, the generalizability of this review may be affected by the absence of geographical diversity considering most included studies were performed in high-income countries and by members of the same research groups. We have, however, tried to reduce the impact of this bias by excluding studies with an overlap in sample series. An overview of the studies with series overlap can be found in the Supplementary E-files.

Since lesion information was not considered, this review was unable to agree with or refute the first and second interpretation that was proposed to explain a potential association of SN with verticality misperception, described in the introduction. Including such information would have provided valuable insight into verticality misperception mechanisms, which should be encouraged in further research. Another limitation is the consideration of articles solely written in English.

Clinical implications and suggestions for further research

Evidence suggests that SN is associated with SVV misperception, and that SVV misperception could even be considered a key feature of SN. Considering the importance of accurate verticality perception for postural control [8, 9], this calls for a systematic and regular assessment of SVV perception in clinical practice, as an addition to standard SN assessment.

Most studies have a cross-sectional study design and do not allow to evaluate the recovery of verticality misperception in SN participants. In the longitudinal studies included, time-intervals were broad (≥ 3 months) [8, 15]. Future studies should evaluate the association of recovery of SN with recovery of verticality misperception over time, by systematically evaluating participants with SN at regular time-points from the acute to chronic phases post-stroke.

A more comprehensive assessment of SN, using more than solely paper-and-pencil tests that mainly evaluate visuo-spatial neglect, is warranted. Currently, it is unclear whether verticality misperception is expressed similarly across the different SN types (i.e., motor neglect, auditory neglect, personal neglect, …). Also the assessment of additional deficits, such as lateropulsion, should be encouraged.

Conclusion

In the first three-to-six months post-stroke, SN is associated with larger SVV tilts falling outside of normative ranges, together with higher SVV uncertainty than in non-SN participants. This suggests that SVV misperception is a key feature of SN. For the SPV and SHV, there was insufficient or inconclusive evidence, which may also be a result of them being highly under-investigated compared to the SVV. Currently, the recovery of verticality misperception cannot be evaluated due to a lack of longitudinal studies which should be addressed by future studies.

Funding

This work was supported by the BOF University Research Fund under a STIMPRO Grant

[39800]; and a DOCPRO Grant [40180].

Disclosure of interest

The authors declare that they have no competing interest.

Figure legend

Fig 3.1.1. PRISMA Diagram for new systematic reviews which included searches of databases and other sources

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CHAPTER 3.4

DOES VISUOSPATIAL NEGLECT CONTRIBUTE TO STANDING BALANCE WITHIN THE FIRST 12 WEEKS POST-STROKE? A PROSPECTIVE LONGITUDINAL COHORT STUDY

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Manuscript accepted at BMC Neurology (November 2023)
Elissa Embrechts, Jonas Schröder, Tanja C.W. Nijboer, Charlotte van der Waal, Christophe Lafosse, Steven Truijen, Wim Saeys. Does visuospatial neglect contribute to standing balance within the first 12 weeks post-stroke? A prospective longitudinal cohort study. DOI : 10.1186/s12883-023-03475-1.

Abstract

Background. Visuospatial neglect (VSN) has been suggested to limit standing balance improvement post-stroke. However, studies investigating this association longitudinally by means of repeated within-subject measurements early post-stroke are lacking. This prospective longitudinal cohort study evaluates the longitudinal association of egocentric and allocentric VSN severity with 1) standing balance independence and 2) postural control and weight-bearing asymmetry (WBA) during quiet standing, in the first 12 weeks post-stroke.

Methods. Thirty-six hemiplegic individuals after a first-ever unilateral stroke were evaluated at weeks 3, 5, 8 and 12 post-stroke. Egocentric and allocentric VSN severity were evaluated using the Broken Hearts Test. The standing unperturbed item of the Berg Balance Scale (BBS-s) was used to clinically evaluate standing independence. Posturographic measures included measures of postural control (mediolateral (ML)/anteroposterior (AP) net center-of-pressure velocities (COPvel)) and WBA during quiet standing. A linear mixed model was used to examine longitudinal associations between egocentric and allocentric VSN, and BBS-s, $COP_{vel\text{-}ML}$, $COP_{vel\text{-}AP}$ and WBA within the first 12 weeks post-stroke.

Results. Egocentric (β= -0.08, 95%CI[-0.15;-0.01], P=.029) and allocentric VSN severity (β= -0.09, 95%CI[-0.15; -0.04], P=.002) were significant independent factors for BBS-s scores in the first 12 weeks post-stroke. Egocentric and allocentric VSN were no significant independent factors for $COP_{vel\text{-}ML}$, $COP_{vel\text{-}AP}$ and WBA in the first 12 weeks post-stroke.

Conclusions. Allocentric and egocentric VSN severity were significantly associated with decreased standing independence, but not impaired postural control or greater asymmetric weight-bearing, in the early subacute post-stroke phase. This may involve traditional VSN measures being not sensitive enough to detect fine-grained VSN deficits due to a ceiling effect between 5 and 8 weeks post-stroke, once the individual regains standing ability. Future studies may require more sensitive VSN measurements to detect such deficits.

Clinical Trial Registration. Clinicaltrials.gov. unique identifier NCT05060458.

Keywords. Stroke, Visuospatial neglect, Longitudinal study, Posturography, Standing balance, Postural Control

Introduction

Independent standing after stroke is an essential precursor to reacquiring walking ability [1, 2]. Post-stroke standing balance is characterized by underlying impairments in postural control such as increased postural sway of the center-of-pressure (COP) as compared to healthy controls, together with greater weight-bearing on the less-affected leg [3-7]. Apart from more severe impairments in lower-limb muscle strength [3], somatosensation [8], and age [3], cognitive deficits have been associated with deficient standing balance after stroke [9, 10]. Among these cognitive deficits, visuospatial neglect (VSN) stands out as a particularly striking condition.

VSN is characterized by a lateralized deficit in visuospatial cognition, awareness and attention, not attributable to sensorimotor or memory impairments [11]. VSN is common after stroke, with a reported prevalence ranging from 23% to 48% within the acute phase [12, 13]. Individuals with VSN typically exhibit reduced accuracy and larger latency to visual stimuli on one side of space, usually contralesional, as compared to the other [14]. The clinical presentation of the disorder is highly heterogeneous, such that VSN symptoms may manifest within different frames of references (egocentric/viewer-centered, allocentric/object-centered) and regions of space (personal/body, peripersonal/within-reach, extrapersonal/beyond-reach) [15]. Individuals with VSN after stroke tend to experience a slower recovery in activities of daily living and may have a reduced participation as compared to those without [16-18].

A recent systematic review highlighted that VSN has been associated to impaired sitting balance, as reflected by more dependency during sitting and a more asymmetric weight-bearing (weight-bearing asymmetry, WBA) when compared with individuals without VSN [9]. However, the association between VSN and standing balance using clinical and posturographic measures remains unclear. Some studies have shown that VSN was linked to impaired standing balance [19-25], whereas others did not [9, 20, 21, 26-28]. Additionally, only two studies have evaluated the association between VSN and standing balance longitudinally throughout the initial weeks post-stroke [29-31], despite this being the period in which significant improvements in both VSN and balance are observed [10, 32]. Both studies merely evaluated the individual's ability to perform the standing balance task on clinical scales (such as the Berg Balance Scale (BBS) [30] or a sit-to-stand task [29]), without providing insight into underlying postural control deficits or WBA. Consequently, the extent to which VSN contributes to underlying postural control and WBA during the early weeks post-stroke remains unknown.

The overarching aim of this study was to evaluate the longitudinal association of VSN with standing balance within the first 12 weeks post-stroke, by using a repeated measurement design with fixed assessment points relative to stroke onset. For this purpose, we applied posturographic measures of quiet standing by recording ground reaction forces (GRFs) and COP sway. To investigate the mechanisms underlying the possible association between VSN and standing balance, this study proposes the following research questions:

1. How is VSN severity associated with independence in terms of standing balance within the first 12 weeks post-stroke?
2. How is VSN severity associated with underlying postural control and WBA within the first 12 weeks post-stroke?

Regarding our first question, we hypothesized that VSN would be longitudinally associated with decreased standing balance, such that individuals with more severe VSN would also exhibit decreased independence in standing. Regarding our second question, we expected that VSN severity would also be associated with greater deficits in underlying postural control, as reflected by increased COP sway and greater weight-bearing on the less-affected leg. Additionally, we hypothesized that for questions 1 and 2, the proposed longitudinal associations would be independent, such that VSN would remain a significant contributor to standing balance independence, postural control, and WBA after controlling for several covariates, including lower limb strength [3], presence of sensory loss [8], and age [3].

Methods

Study design

This longitudinal prospective cohort study is part of a larger research project, entitled TARGET (Temporal Analyses of hemiplegic Gait and standing balance Early post sTroke; for protocol see) [33]. The protocol is registered online (ClinicalTrials.gov identified: NCT05060458), and the study was conducted in conformity with the STROBE statement.

Subjects

Between October 2019 and December 2021, individuals admitted to one of the cooperating hospitals and rehabilitation facilities (Algemeen Ziekenhuis Geel, GZA Sint-Augustinus, GZA Sint-Vincentius, Universitair Ziekenhuis Antwerpen, RevArte) in the larger Antwerp region, Belgium, for acute or rehabilitation care after an ischemic or hemorrhagic stroke were screened for participation. Potential candidates were included when adhering to the following criteria: 1) CT/MRI-confirmed first-ever unilateral hemispheric stroke with onset less than 3 weeks ago, 2) Reduced muscle strength in the most affected lower limb, defined as a Motricity Index lower extremity score (MI-LE) of <91 (i.e., at least "movement against resistance but weaker" in one item) at inclusion, 3) Pre-morbid independence in basic activities of daily life (i.e., modified Rankin Scale </= 1), 4) Aged between 18 and 90 years old, 5) No severe orthopedic condition of the lower limbs and trunk or other neurological illness, 6) No severe cognitive or communication deficit that interferes with understanding of instructions, and 7) (Corrected to) normal visual acuity. These criteria are similar to those of the TARGET project for maintaining sample consistency and comparability [33, 34]. Screening and recruitment were performed by EE and JS together with the (para)medical staff employed at the stroke units and rehabilitation facilities.

Procedures

All procedures were conducted in accordance with the Declaration of Helsinki and were approved by the Medical Ethics Committee of the University Hospital Antwerp (No. 18/25/305; Belgium trial registration no. B300201837010). Additional approval was obtained from the medical ethics committee of other involved sites. After receiving information, all subjects provided written informed consent for participation.

Measurement procedures

Serial measurements were scheduled for each subject at week 3, 5, 8 and 12 post-stroke. At inclusion, subjects' sex, age, stroke side (left/right) and type (ischemic/hemorrhagic) were recorded. At each time-point, VSN measurements, clinical measurements and, once independent standing was achieved, posturographic evaluations were performed. Also the clinical covariates (lower limb strength and sensory loss) were evaluated at each timepoint. Two trained assessors (EE and JS) administered clinical measures (including clinical covariates), and all serial measurements of an individual subject were conducted by the initial assessor. VSN measurements were performed by EE and posturographic measurements by JS.

VSN measurements

We evaluated both egocentric and allocentric VSN. Egocentric VSN is defined as the impaired ability to report visual stimuli on the neglected, usually contralesional, side of space. Allocentric VSN is defined as the difficulty in perceiving object features on the neglected side regardless of the object's spatial position [13]. We used the Broken Hearts Test or its variation (Apple's test) for VSN assessment, which is part of the Oxford Cognitive Screen [35]. Three parallel versions were used and varied randomly across time points to avoid learning effects. This test is recommended for VSN screening and screens for both subtypes [35-37]. It is a paper-and-pencil task in which the individual must cancel complete hearts/apples (n=50) among distractors shaped as broken hearts/apples with either gaps on the right (n=50) or left (n=50) of the contour. It is presented on an A4 landscape paper, whose position is standardized within and across subjects. The paper was attached on a table, centrally and in front of the seated subject. The task was always performed with the less-affected hand, [35, 37] and subjects had a maximum of 3 minutes to complete the task.

Clinical measurement of standing balance

The activity scale for balance evaluation included the "standing unsupported" item of the Berg Balance Scale (BBS-s; score 0-4) [38]. The BBS-s evaluates standing independence, by asking the individual to stand without use of an aid or physical support for 2 minutes, without falling or requiring stepping responses due to instability. Higher scores indicate better performance [38].

Posturographic measurements

Postural control and WBA were assessed by instructing subjects to stand as still as possible for 40 seconds while keeping the arms alongside the trunk and eyes fixed at a non-moving visual target placed centrally in front of the subject. The bare feet were always positioned with 8.4 cm heel-to-heel distance and 9 degrees toe-out angle. No further instruction was given regarding weight-bearing symmetry. The first 10 seconds were removed from each trial to avoid starting effects and, if tolerated, at least three trials were performed with resting breaks in-between. To record ground reaction forces and COP excursions, we either used two floor-mounted force plates (Type OR6-7 Biomechanics Force Platform, AMTI, MA, US) at the *M²OCEAN* movement analyses laboratory (University of Antwerp, BE), or a portable plantar pressure plate (0.5m Footscan pressure plate 3D, RS Scan, Materialize, BE). The latter allowed data collection in clinical environments when access to our laboratory was restricted. Prior to the current study, we performed a comparability study of the two measurement instruments in healthy controls during vision-deprived stance. This yielded strong consistency by Pearson correlation, yet systematic differences, in line with previous studies [39, 40]. Therefore, repeated measurements *within* a specific subject were always performed using the same instrument type, and statistical analyses of pooled data *between* subjects were corrected using INSTRUMENT as a covariate (see statistical analyses). COP excursions were computed using custom-written Matlab scripts (force plate data) or the system's own software (pressure plate data). COP signals were subsequently low-pass filtered with a 10Hz second-order Butterworth filter [41].

Outcome variables

Dependent variables

The dependent variable to evaluate research question 1 was the BBS-s (score 0-4), a measure of standing independence. For research question 2, dependent variables were measures of postural control and WBA. To quantify postural control, we calculated the root mean square COP velocity in mediolateral and anteroposterior sway directions ($COP_{vel\text{-}ML}$, $COP_{vel\text{-}AP}$; in mm/s) [42]. This measure was shown to be reliable and valid, by being sensitive to higher-frequent changes in the COP signal reflecting the process of posture stabilization [43]. In addition, WBA (%) was calculated by dividing the average vertical GRF below the more-affected leg by half of the total GRF under both feet combined. A percentage score of 0 indicates perfect symmetry and a positive or negative score reflect, respectively, a greater load on the less- or most-affected leg. All outcomes were averaged to improve reliability [41].

Independent variables

VSN outcome variables. The difference between cancelled full outlines on the ipsilesional vs. contralesional side of the paper was used as a measure of egocentric VSN severity and hereafter referred to as *egocentric asymmetry*. Egocentric VSN was considered present when egocentric asymmetry was > 2 or < -2. Allocentric VSN severity was calculated by subtracting the number of contralesional and ipsilesional gap false positives, which is referred to as *allocentric asymmetry*. Allocentric VSN was considered present when allocentric asymmetry was > 1 or < -1. Positive values indicate contralesional VSN and negative values indicate ipsilesional VSN [13, 35].

Clinical covariates. Lower limb strength was evaluated using the Motricity Index of the Lower-Extremity (MI-LE) [44]. The MI-LE (0-100) was measured by asking subjects to produce a maximum voluntary torque in the direction of hip flexion, knee extension, and ankle dorsiflexion. It is a valid and reliable scale [44]. Sensory impairment at the contralesional foot was assessed by applying light pressure touch at 6 points of the contralesional foot, using the Erasmus MC revised Nottingham Sensory Assessment protocol [45]. Sensory impairment was considered present when at least 2 points on the contralesional foot were missed.

Statistical analyses

Statistical analyses were performed for subjects for whom data from at least two measurement points were available. We descriptively presented mean values with standard deviation of demographic information and each investigated outcome measure (i.e., egocentric asymmetry, allocentric asymmetry, BBS-s, MI-LE, sensory loss, $COP_{vel\text{-}ML}$, $COP_{vel\text{-}AP}$, WBA) at week 3, 5, 8, and 12 post-stroke.

Longitudinal association of VSN severity with clinical or posturographic measures

To investigate longitudinal associations between VSN severity and either clinical (BBS-s) or posturographic measures (i.e., $COP_{vel\text{-}ML}$, $COP_{vel\text{-}AP}$, and WBA), we fitted linear mixed models with the same model architecture for each dependent variable. The covariate TIME (categorical, four levels: weeks 3, 5, 8, and 12) was added as a fixed effect. A subject-specific random intercept was included to account for the dependency between the repeated within-subject measurements. Egocentric asymmetry or allocentric asymmetry were entered as independent variables in separate models. Before adding egocentric asymmetry or allocentric asymmetry as independent variables, we calculated the Spearman correlation coefficients between both factors to account for multicollinearity. This showed that both VSN subtypes were independent subtypes (r=.09, *P*=.297), justifying separate models. For posturographic measures, we accounted for systematic differences in COP between measurement instruments by adding an additional covariate, INSTRUMENT. The obtained regression coefficients (β) show the change in, respectively, BBS-s, $COP_{vel\text{-}ML}$, $COP_{vel\text{-}AP}$ or WBA by a one-unit increase in either egocentric asymmetry or allocentric asymmetry, respectively. The analysis technique of the linear mixed model allows the inclusion of patients with partial data missing at random [46].

Hierarchical model analyses

We further assessed whether the contribution of egocentric or allocentric asymmetry to the outcome variables remained significant after incorporating other relevant covariates, including MI-LE, SENSORY LOSS (yes/no), and AGE, by using a hierarchical linear mixed model. This was carried out solely for outcome measures that exhibited significant longitudinal associations with egocentric and/or allocentric asymmetry in the prior analysis. The proportional change in the β-estimates of egocentric asymmetry and allocentric asymmetry to the outcome after adding subsequent covariates (order: MI-LE, SENSORY LOSS (yes/no), AGE) was evaluated. To evaluate whether this would result in a better model fit, we evaluated change in model statistics using the sample size adjusted Akaike Information Criterion (AICc), with lower values indicating better fit.

Assessing potential ascertainment bias and its impact on standing independence

To control for potential ascertainment bias, which refers to the possibility that some subjects are more likely to be included in posturographic analysis than others because of their clinical status, we plotted the time courses of egocentric asymmetry and allocentric asymmetry for subjects who were and were not able to perform posturographic measurements (i.e., obtained a score of 4 on the BBS-s). To minimize the potential for bias in analysis, we re-ran the model for the BBS-s in subjects with available posturographic measures. For those without available posturographic measures, the statistical power was too low to yield meaningful results, and these were consequently excluded from further analyses.

All analyses were performed using JMP Pro® version 16. Histograms and Q-Q plots of residuals were inspected to confirm model assumptions.

Results

Subjects

Figure 1 shows the flow of subject recruitment. Approximately 180 first-ever stroke survivors were identified as potential candidates, of whom 45 adhered to the inclusion criteria and were successfully included. Of these, 36 successfully participated in at least two subsequent measurements and were included in the statistical analyses. Table 3.4.1 shows their baseline characteristics and Table 3.4.2 shows the mean values of each outcome variable at weeks 3, 5, 8, and 12 post-stroke. In addition, supplementary table 3.4.1 shows the baseline characteristics per subject. The mean age of the 36 included subjects was 59.78 (SD 15.96); 17 were female, 22 had a left-sided stroke, and 28 had an ischemic stroke. As shown, 14 individuals showed egocentric VSN at week 3, 7 at week 5, 9 at week 7 and 3 at week 12. Four individuals showed allocentric VSN at week 3, 6 at week 5, 3 at week 8, 4 at week 12.

Figure 3.4.1. Flowchart of screening, inclusion and follow-up

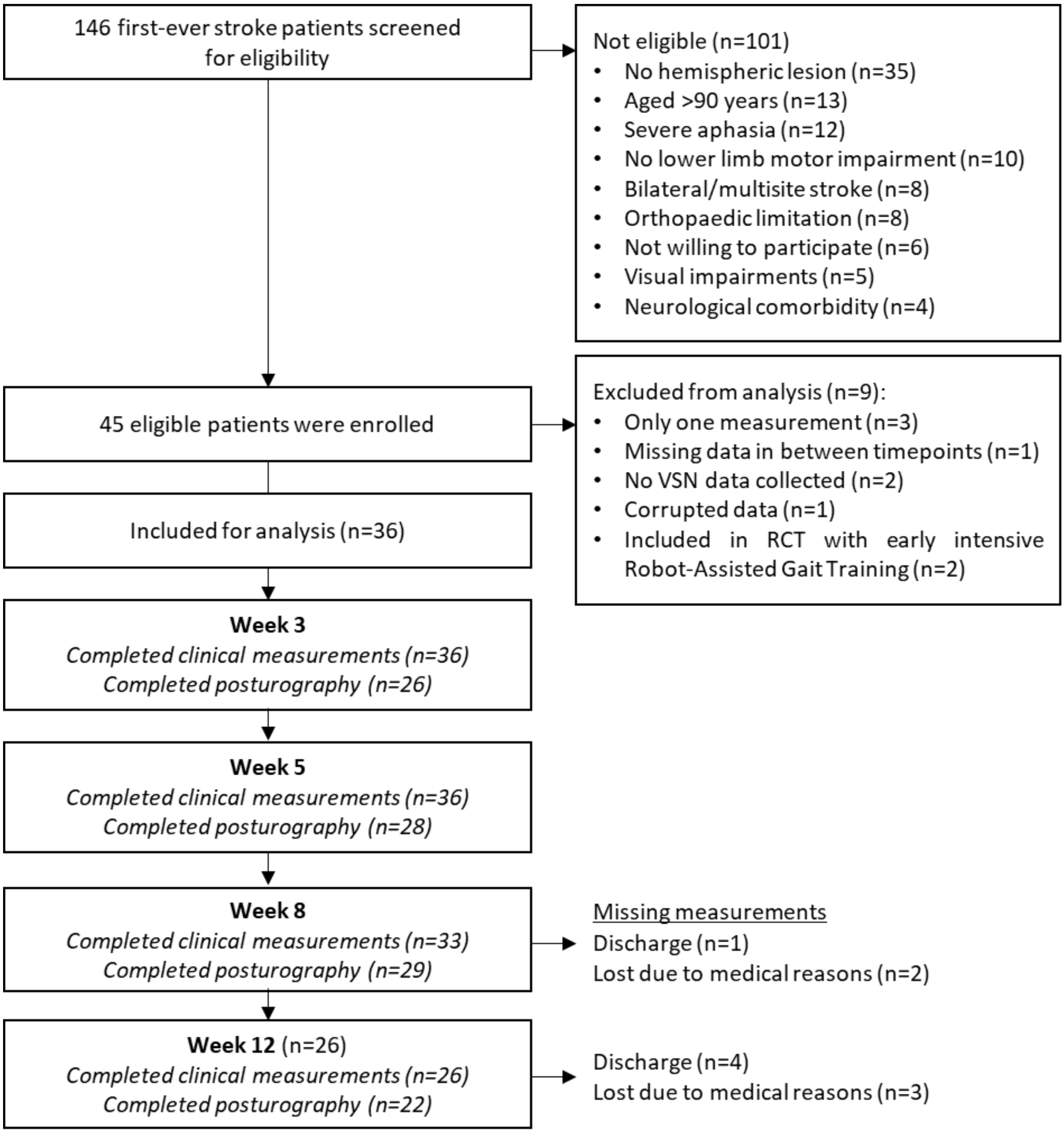


Table 3.4.1. Subject characteristics at 3 weeks post-stroke

	Total
Age (years)	59.78 (15.96)
Sex (female/male)	17/19
Body weight, kg	75.39 (14.06)
Lesion side (left/right)	14/22
Stroke type (isch/hem)	28/8
Time post-stroke (days)	24.56 (1.93)

Hem: hemorrhagic, isch: ischemic. Values are mean (standard deviation).

Table 3.4.2. Characteristics of subjects at 3, 5, 8 and 12 weeks

	Week 3	**Week 5**	**Week 8**	**Week 12**
Time post-stroke (days)	24.56 (1.93)	38.74 (2.12)	59.06 (2.31)	88.0 (4.42)
Egocentric asymmetry (0-20)°	2.97 (3.92)	2.03 (4.04)	1.85 (2.51)	1.08 (1.06)
Number of subjects with/without egocentric VSN	14/12	7/29	9/24	3/23
Allocentric asymmetry (0-20)°	1.83 (5.02)	0.56 (1.13)	0.42 (1.03)	0.73 (1.12)
Number of subjects with/without allocentric VSN	4/32	6/30	3/30	4/22
BBS-s score (0-4)	2.44 (1.75)	2.89 (1.51)	3.39 (1.06)	3.73 (0.53)
MI-LE (0-100)	57.42 (22.39)	65.00 (21.14)	71.09 (21.91)	72.31 (19.52)
Sensory loss (yes/no/NM)	9/18/9	8/19/9	6/20/7	4/16/6
N	26	28	29	10
Measurement instrument (FP/PP)	6/20	6/22	5/24	4/18
$COP_{vel\text{-}ML}$ (mm/s)	7.62 (7.51)	6.31 (6.00)	5.72 (5.58)	5.01 (4.48)
$COP_{vel\text{-}AP}$ (mm/s)	8.92 (7.45)	8.48 (8.00)	7.59 (6.76)	7.24 (6.36)
WBA (%)	43.65 (7.31)	44.40 (8.05)	43.04 (7.89)	43.75 (6.59)

BBS-s: Berg Balance Scale – standing item, $COP_{vel\text{-}AP}$: COP velocities in anteroposterior direction, $COP_{vel\text{-}ML}$: COP velocities in mediolateral direction, FP: force plate, MI-LE: lower extremity part of the motricity index, N: number, NM: not mentioned, PP: pressure plate, SD: standard deviation, VSN: visuospatial neglect, WBA: weight-bearing asymmetry. °Absolute values i.e., values irrespective of contra or ipsilesional side, otherwise these would cancel each other out. Values are mean (standard deviation).

Longitudinal association of VSN with clinical measures of standing balance independence

As shown in Table 3.4.3, egocentric asymmetry (β=-0.11; [-0.17;0.06], P<.001) and allocentric asymmetry (β=-0.10; 95%CI[-0.16; 0.03]; P=.002) were significant factors for BBS-s within the first 12 weeks post-stroke.

Longitudinal association of VSN with posturographic outcomes of standing balance

Table 3.4.3 shows that egocentric asymmetry was a significant factor for $COP_{vel\text{-}AP}$ (β=-0.41, 95%CI[-0.75; 0.07], *P*=.018), but not for $COP_{vel\text{-}ML}$ (β=-0.29, [-0.65; 0.08], *P*=.119) and WBA (β=-0.14, [-0.66; 0.38], *P*=.585). Allocentric asymmetry was not a significant factor for $COP_{vel\text{-}ML}$ (β=0.24, [-0.34;0.83], *P*=.413), $COP_{vel\text{-}AP}$ (β=0.30, 95%CI [-0.26; 0.86], *P*=.290) and WBA (β=-0.29, [-1.11; 0.54], *P*=.487)

Hierarchical model to evaluate influence of covariates on longitudinal associations and prediction errors

Table 3.4.4 shows that egocentric asymmetry (β= -0.08, 95%CI[-0.15;-0.01], *P*=.029) and allocentric asymmetry (β=-0.09, 95% CI[-0.15; -0.04], *P*=.002) maintained significant after adding MI-LE, SENSORY LOSS, and AGE to the BBS-s scores throughout the first 12 weeks post-stroke. The addition of these covariates resulted in a proportional change of -27.27% in the β-estimate of egocentric asymmetry and -10.00% in the β-estimate of allocentric asymmetry and decreased the estimated prediction error by 28.13% and 30.83%, respectively, for the prediction of BBS-s. In contrast, egocentric asymmetry did not remain a significant factor for $COP_{vel\text{-}AP}$ after adding the MI-LE.

Assessing potential ascertainment bias and its impact on standing independence

Figure 3.4.2 shows that three subjects in the egocentric asymmetry and four subjects in the allocentric asymmetry graph were unable to undergo posturographic measurements. It is essential to consider the potential influence of ascertainment bias on our evaluation of standing independence.

To minimize the potential for bias in analysis, we re-ran the model for the BBS-s in subjects with available posturographic measures. This analysis demonstrated that for those subjects, neither egocentric asymmetry (β = 0.00, 95% CI [-0.089; 0.08], P = 0.916) nor allocentric asymmetry (β = -0.06, 95% CI [-0.19; 0.07], P = 0.375) emerged as significant predictors of the BBS-s.

Table 3.4.3. Linear mixed models for activity measures and postural control parameters

Model with egocentric asymmetry as independent variable

Dependent variables	Egocentric asymmetry (β -value (SE, 95%CI, p-value))	Time (β-value (SE, 95%CI, p-value)) 3w	5w	8w	Instrument (β-value (SE, 95%CI, p-value))	**AICc**
BBS-s	**-0.11 (0.03, [-0.17;-0.06], *P*<.001)***	**-1.11 (0.23, [-1.57;-0.67], *P*<.001)***	**-0.78 (0.21, [-1.21;-0.35], *P*<.001)***	-0.24 (0.22, [-0.67;0.20], *P*=.280)		385.85
COP_{vel-ML}	-0.29 (0.18, [-0.65;0.08], *P*=.119)	**3.37 (0.78, [1.81;4.92], *P*<.001)***	1.42 (0.75, [-0.06;2.91], *P*=.061)	0.84 (0.73, [-0.62;2.30], *P*=.255)	**9.29 (2.06, [5.07;13.51], *P*<.001)***	576.16
COP_{vel-AP}	**-0.41 (0.17, [-0.75;-0.07], *P*=.018)***	**2.37 (0.72, [0.93;3.81], *P*=.002)***	1.17 (0.69, [-0.21;2.55], *P*=.095)	0.44 (0.68, [-0.92;1.79], *P*=.523)	**12.32 (2.33, [7.57;17.08], *P*<.001)***	572.34
WBA	-0.14 (0.26, [-0.66;0.38], *P*=.585)	-0.68 (1.12, [-2.91;1.55], *P*=.545)	1.02 (1.07, [-1.11;3.15], *P*= .344)	0.06 (1.05, [-2.03;2.15], *P*=.953)	-3.79 (3.22, [-10.37;2.80], *P*=.249)	656.96

Model with allocentric asymmetry as independent variable

Dependent variables	**Allocentric asymmetry** β -value (SE, 95%CI, p-value)	**Time** (β-value (SE, 95%CI, p-value)) 3w	5w	8w	**Instrument** (β-value (SE, 95%CI, p-value))	**AICc**
BBS-s	**-0.11 (0.03, [-0.17;-0.06], *P*<.001)***	**-1.11 (0.23, [-1.57;-0.67], *P*<.001)***	**-0.78 (0.21, [-1.21;-0.35], *P*<.001)***	-0.24 (0.22, [-0.67;0.20], *P*=.280)		385.85
COP_{vel-ML}	0.24 (0.30, [-0.34;0.83], *P*=.413)	**3.08 (0.77, [1.55;4.61], *P*<.001)***	1.33 (0.76, [-0.19;2.85], *P*=.085)	0.54 (0.72, [-0.89;1.97], *P*=.456)*	**9.64 (2.04, [5.48;13.80], *P*<.001)***	578.00
COP_{vel-AP}	0.30 (0.28, [-0.26;0.86], *P*=.290)	**1.95 (0.73, [0.50;3.40], *P*=.009)***	1.01 (0.72, [-0.42;2.45], *P*=.163)	-0.00 (0.68, [-1.35;1.35], *P*=.998)	**12.80 (2.28, [8.13;17.46], *P*<.001)***	577.04
WBA	-0.29 (0.41, [-1.11;0.54], *P*=.487)	-0.94 (1.07, [-3.08;1.20], *P*=.382)	0.78 (1.06, [-1.34;2.90], *P*=.464)	-0.12 (1.00, [-2.12;1.87], *P*=.902)	3.83 (3.25, [-10.47;2.81], *P*=.248)	656.76

Each row represents the respective model for a certain dependent variable. AICc: sample size adjusted Akaike Information Criterion, BBS-s: Berg Balance Scale – standing unsupported item, CI: confidence interval, COP_{vel-AP}: anteroposterior center-of-pressure velocities, COP_{vel-ML}: mediolateral center-of-pressure velocities, , SE: standard error, w: weeks; WBA: weight-bearing asymmetry, β: estimate, **P*<.05.

Table 3.4.4. Hierarchical model with addition of Motricity Index, sensory loss and age

Dependent variable	Model	β Egocentric asymmetry (SE, 95%CI, p-value)	β Egocentric asymmetry change	β MI-LE (SE, 95%CI, p-value)	β Sensory loss (SE, 95%CI, p-value)	β Age (SE, 95%CI, p-value)	AICc (change%)
Hierarchical models with egocentric asymmetry included as an independent variable							
		Independent variable		**Covariates**			
BBS-s	Standard	**-0.11 (0.03, [-0.17;-0.06], *P*<.001)***					385.85
	Model 1	**-0.11 (0.02, [-0.16;-0.07], *P*<.001)***	0%	**0.04 (0.01, [0.03;0.05], *P*<.001)***			352.38 (-8.67%)
	Model 2	**-0.08 (0.04, [-0.15;-0.01], *P*=.027)***	-27.27%	**0.03 (0.01, [0.02;0.05], *P*<.001)***	**0.57 (0.32, [-0.07;1.20], *P*=.079)***		275.00 (-28.73%)
	Model 3	**-0.08 (0.04, [-0.15;-0.01], *P*=.029)***	-27.27%	**0.03 (0.01, [0.02;0.04], *P*<.001)***	**0.58 (0.32, [-0.07;1.22], *P*=.078)***	-0.01 (0.00, [-0.03; 0.02], *P*=.617)	277.30 (-28.13%)
COP_{vel-AP}	Standard	**-0.41 (0.17, [-0.75;0.07], *P*=.018)***					572.34
	Model 1	-0.29 (0.17, [-0.63;0.06], *P*=.106)	-29.27%	**-0.12 (0.03,[-0.18;-0.05], *P*<.001)***			563.02 (-1.63%)
	Model 2	0.04 (0.15, [-0.26;0.34, *P*=.815)	-109.76%	**-0.07 (0.03; [-0.12;-0.01], *P*=.021]***	**-3.34 (1.00, [-5.33;-1.34], *P*=.001)***		409.72 (-28.41%)
	Model 3	0.04 (0.15, [-0.26;0.34, *P*=.793)	-109.76%	**-0.07 (0.03; [-0.13;-0.01], *P*=.017)***	**-3.37 (1.01, [-5.37;-1.37], *P*=.001)***	-0.05 (0.06, [-0.16;0.07], *P*=.396)	411.57 (-28.09%)
Hierarchical models with allocentric asymmetry included as an independent variable							
		Independent variable		**Covariates**			
Dependent variable	**Model**	**β Allocentric asymmetry** (SE, 95%CI, p-value)	β Allocentric asymmetry change	**β MI-LE** (SE, 95%CI, p-value)	**β Sensory loss** (SE, 95%CI, p-value)	**β Age** (SE, 95%CI, p-value)	**AICc (change%)**
BBS-s	Standard	**-0.10 (0.03; [-0.16;-0.03]; *P*=.002)***					392.58
	Model 1	**-0.07 (0.03, [-0.13;-0.02], *P*=.008)***	-30.00%	**0.04 (0.01, [0.02;0.05], *P*<.001)***			365.03 (-7.02%)
	Model 2	**-0.09 (0.03, [-0.15;-0.04], *P*=.001)***	-10.00%	**0.03 (0.01, [0.01;0.04], *P*<.001)***	**0.79 (0.31, [0.17;1.41], *P*=.013)***		269.10 (-31.45%)
	Model 3	**-0.09 (0.03, [-0.15;-0.04], *P*=.002)***	-10.00%	**0.03 (0.01, [0.01;0.04], *P*<.001)***	**0.79 (0.31, [0.17;1.41], *P*=.013)***	-0.00 (0.01, [-0.02;0.02], *P*=.724)	271.54 (-30.83%)

For each dependent variable, hierarchical models are presented, starting with the standard model (no covariates and only VSN severity as independent variable) and ending with Model 3 (also including MI-LE, sensory loss and age as covariates). Abbreviations: AICc: sample size adjusted Akaike Information Criterion, , BBS-s: Berg Balance Scale – standing item, COPvel-AP: anteroposterior center-of-pressure velocities, , Model 1: model with VSN and motricity index scores, Model 2: model with VSN, motricity index and sensory loss, Model 3: model with VSN, motricity index, sensory loss and age, SE: standard error, β: estimate.

Discussion

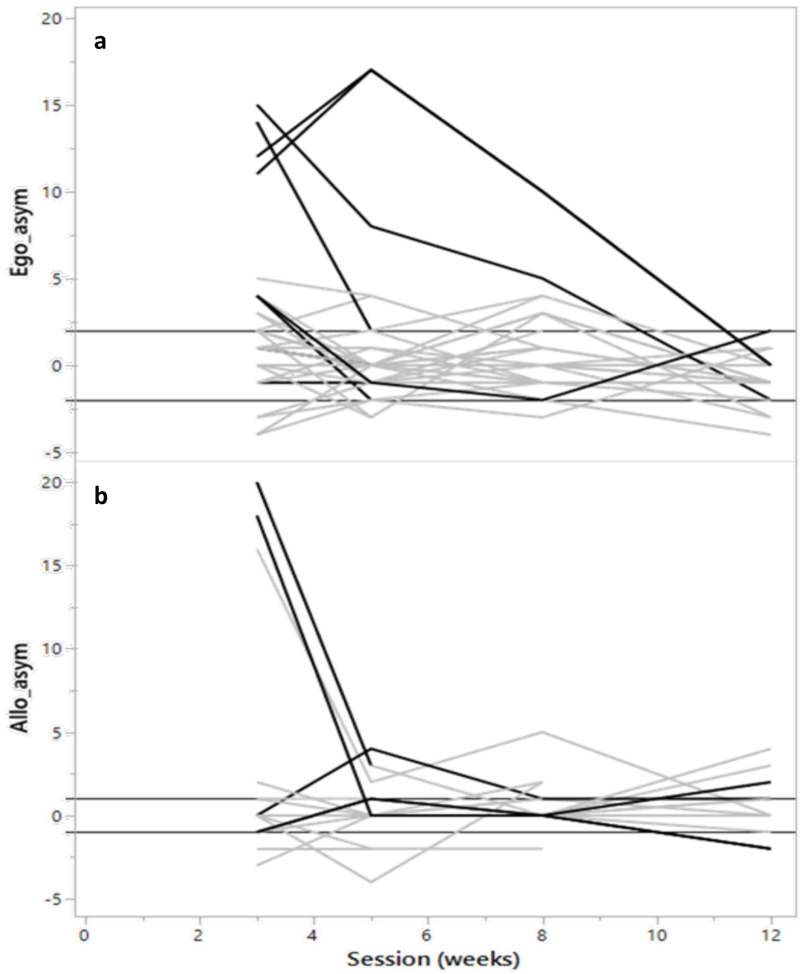
The present prospective cohort study evaluated the association of egocentric and allocentric VSN with 1) standing balance independence and 2) postural control and WBA during quiet standing, within the first 12 weeks post-stroke. Our main findings were that:

- Both egocentric and allocentric asymmetry were significant independent factors longitudinally associated with decreased standing independence in the first 12 weeks post-stroke.
- Egocentric and allocentric asymmetry severity did not significantly contribute to impaired postural control or WBA in the first 12 weeks post-stroke.
- When correcting for potential ascertainment bias, egocentric and allocentric asymmetry were no longer significantly associated with standing independence.

VSN remained a significant and independent predictor of decreased standing independence, even after controlling for various covariates, which confirms our first hypothesis. The finding is congruent with those from a prior prospective cohort study conducted by Van Nes and colleagues [30], which also demonstrated that egocentric VSN severity was accompanied with reduced standing and walking independence in the first 3-6 months post-stroke. However, our study extends this one by controlling for important covariates including the strength of the most-affected leg, sensory loss, and age in a multivariate way. Moreover, to the best of our knowledge, this is the first study to examine the relative contribution of both egocentric and allocentric VSN on standing balance recovery post-stroke, as previous studies have only focused on the association between egocentric VSN and standing balance after stroke [9]. Our findings suggest that both aspects contribute to poor standing balance independence.

Despite this finding, a lack of an independent longitudinal association with underlying impaired postural control and WBA was found. This is opposing our second hypothesis, and suggests that once a subject resumed independent standing, VSN did not independently contribute to deficits in postural control, as reflected by exaggerated COP sway. This may further indicate that delayed achievement of independent standing in individuals exhibiting VSN would result from factors other than impaired postural control. Furthermore, VSN did not independently contribute to WBA within the first 12 weeks post-stroke. This indicates that an

Figure 3.4.2a-b. Time course of egocentric asymmetry and allocentric asymmetry in subjects that were or were not able to perform posturographic measures.



Abbreviations: Allo_asym: allocentric asymmetry, Ego_asym: egocentric asymmetry.

Light grey lines show the time courses of egocentric asymmetry and allocentric asymmetry in those who were able to perform posturographic measures. Dark grey lines show the time courses for those who were unable to perform posturographic measures.

asymmetric stance with greater loading of the less-affected leg is not an expression of reduced attention to the most-affected side and a consequent shift in the representation of the mid-sagittal plane toward the less-affected side, as suggested previously [21]. Instead, it may merely reflect a compensatory strategy that favors the stronger, less-affected leg for balance control, due to reduced muscle strength in the most-affected leg [34].

Alternatively, the absence of a longitudinal association of VSN with postural control deficits and WBA may result from the observation that subjects with more severe (initial) VSN were unable to participate in posturographic measures, especially at the 3-week timepoint, as subjects must have the ability to stand independently to conduct such analyses**.** Potentially, once subjects with initial moderate-to-severe VSN (here measured using the Broken Hearts Test) reach standing ability, VSN may no longer be detectable on such tests. We observed that the VSN severity scores reached a ceiling effect between 5 and 8 weeks. Residual finer-grained impairments in lateralized visuospatial attention beyond this time window could not be demonstrated [47-49], making it difficult to establish significant associations between VSN recovery and underlying postural control deficits and WBA. This highlights that investigating how fine-grained changes in VSN beyond this time window contribute to postural control deficits and WBA over time poses a significant challenge for this field of research.

Limitations

Several limitations of this study should be acknowledged. One limitation is the small sample size together with the dropout rate from 8 weeks onwards (27.8%), which was due to medical reasons and difficulties in scheduling measurements in the clinical setting after early discharge. In addition, COVID-19 measures prohibited the subjects' outpatient access to the clinical sites. The limited sample size may have led to an underpowered analysis, potentially affecting our ability to establish statistical significance. Furthermore, only few subjects showed large deviations in VSN which may have further limited our results. Despite these limitations, our study's significant findings remain robust, and the p-values of the non-significant results consistently remained well above the significance threshold (α = .05). Nevertheless, our study underscores the need for future research with more substantial sample sizes. A second limitation is that the assessments of subjects were not initiated until 3 weeks post-stroke which may have resulted in missing early changes in the association of VSN with standing balance. Furthermore, posturographic measurements started even beyond this time-point in the more severely-affected subjects, which may have limited our findings. Third, posturographic data were collected using two different instruments. We believe that this did not affect our findings, considering we used the same instrument within subjects and added an extra covariate INSTRUMENT within the final analyses. Fourth, our study was constrained by the unavailability of more comprehensive lesion information, including details on etiology, severity, and topography. This limitation restricted our capacity to thoroughly assess the impact of lesion characteristics on the observed associations. Fifth, the linear mixed model approach used in the present study is that it combines within-subject and between-subject associations, which may limit the ability to fully understand the mechanisms driving the observed longitudinal associations between VSN severity and standing balance independence. Lastly, the BBS-s is a widely used tool, but it is a categorical measure rather than a continuous one, which may limit its sensitivity.

Clinical implications and suggestions for further research

The results of this study show that both egocentric and allocentric VSN contribute to standing balance independence within the first 12 weeks post-stroke. Given that independent standing is a prerequisite for walking, it emphasizes the clinical importance of conducting a comprehensive assessment of both subtypes of VSN. Notably, VSN is more severe in the early weeks after a stroke, highlighting the critical need for early and targeted detection [32]. Beyond the first 5 weeks post-stroke, it becomes crucial to incorporate more sensitive measures for VSN detection, which may involve tasks demanding heightened attention, as demonstrated by Bonato and colleagues [50]. These tasks could load more intensively on individuals' attentional resources, complicating the deployment of compensatory strategies [51].

The present study could not explain *how* visuospatial neglect was longitudinally associated with standing balance independence within the first 12 weeks post-stroke. Being able to stand independently is a multifactorial skill, and our study shows that by multiple factors contribute to it throughout the first weeks post-stroke, including lateralized visuospatial attention, lower limb muscle strength and sensory function at the most-affected side. However, it is important to note that additional factors could have contributed to the observed longitudinal association between visuospatial neglect and standing balance independence. This could include factors such as multisensory integration [52], visual dependency [53], or an impaired perception of verticality [22, 54, 55]. While previous studies have suggested links between VSN, balance, and verticality misperception [22, 54, 55], no comprehensive investigation has assessed this relationship using standardized posturographic assessments over time. Future studies should evaluate whether these factors would explain the significant association between VSN and standing independence over time.

Secondly, our study was only able to evaluate associations, and was unable to determine causality. Therefore, future studies should investigate whether targeted interventions designed to improved VSN symptoms would lead to improved standing balance independence over time. These studies should also consider exploring the impact of lesion characteristics on this association, which would provide valuable insights into the benefits of interventions aimed at addressing VSN within rehabilitation. Barrett and colleagues [56] have already suggested to evaluate the effectiveness of this approach, especially given the suggested suppressive impact of VSN on upper limb motor recovery [57].

Conclusion

Severity of egocentric and allocentric VSN was longitudinally associated with decreased standing independence in the first 12 weeks post-stroke. However, no significant longitudinal associations with postural control and WBA during quiet standing were observed. This suggests that the mechanisms underlying poor standing independence in individuals with VSN should involve other factors. However, this finding may have been influenced by the observation that the subjects with initially more severe VSN were unable to perform posturographic measurements. Consequently, evaluating postural control and WBA in those with initial moderate-to-severe VSN poses a significant challenge. Given that VSN may not be detectable anymore on classical paper-and-pen tests once these individuals regain standing ability, future research on standing balance recovery should implement more sensitive VSN measures that can detect residual impairments beyond this time window.

Acknowledgement

The authors thank the cooperating hospitals/rehabilitation facilities (Algemeen Ziekenhuis Geel, GZA Sint-Augustinus, GZA Sint-Vincentius, Universitair Ziekenhuis Antwerpen and RevArte). They also express their gratitude to Erik Fransen (StatUA, University of Antwerp) for statistical assistance.

Funding

The present study was partially funded by the Special Research Fund of the University of Antwerp (DOCPRO no. 40180, research fellow EE) and Research Foundation Flanders (FWO application no. 1S64819N, fellow JS).

Declaration of interest

The authors declare that there is no conflict of interest.

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Supplementary Table 3.4.1. Demographic, clinical and posturographic data per subject

ID	Age	Biological sex	Lesion side	Type	Ego asym	Allo asym	MI total	MI hip	MI knee	MI ankle	Sensory loss	BBS-s	TCT-s	FAC	RMI	Posturography avail?	COPvel-ML (mm/s)	COPvel-AP (mm/s)	WBA perc
1	61	M	L	i	-4	0	64	25	25	14	NT	4	2	3	8	1	16.03	26.51	46.21
2	76	F	L	i	0	0	75	25	25	25	NT	4	2	5	10	1	5.14	11.35	42.63
3	78	F	R	i	12	-1	58	25	19	14	NT	0	2	0	3	0			
4	73	F	R	i	2	-2	42	14	14	14	NT	3	2	0	3	1	19.39	18.44	33.24
5	49	M	R	i	0	0	83	25	33	25	NT	4	2	5	14	1	8.95	16.05	43.78
6	82	F	R	i	4	0	42	14	14	14	NT	1	2	1	4	1	22.38	20.20	16.42
7	40	F	L	h	-1	0	32	9	14	9	NT	0	2	0	2	0			
8	78	M	R	i	-4	0	47	14	19	14	NT	2	2	2	6	1	28.47	28.58	40.90
9	68	M	R	i	3	0	99	33	33	33	No	4	2	5	14	1	1.51	4.13	48.60
10	77	F	R	i	2	16	53	14	14	25	No	0	2	1	3	0			
11	42	F	L	i	-1	-1	61	14	33	14	No	4	2	3	9	1	2.22	3.86	43.35
12	74	M	L	h	3	-3	75	25	25	25	Yes	3	2	2	5	1	4.43	11.37	51.35
13	46	F	R	i	15	0	42	14	14	14	Yes	0	2	0	1	0			
14	56	M	L	i	2	0	52	19	19	14	No	4	2	4	9	1	5.42	5.22	43.41
15	46	M	L	h	2	0	52	14	19	19	No	3	2	2	6	1	10.33	9.38	36.39
16	20	F	R	i	0	1	91	25	33	33	No	4	2	5	14	1	1.60	1.91	48.20
17	69	M	L	i	-1	2	63	19	25	19	No	3	2	3	6	1	3.63	3.84	51.30
18	60	M	R	i	1	0	47	14	14	19	Yes	2	2	1	6	1	11.91	7.27	42.26
19	65	M	R	i	14	0	18	9	9	0	Yes	0	2	0	2	0			
20	59	M	R	i	0	0	47	14	14	19	Yes	4	2	4	8	1	5.41	6.60	38.98
21	67	F	R	i	4	20	0	0	0	0	Yes	0	2	0	1	0			
22	40	M	L	h	0	1	9	0	9	0	Yes	0	2	0	3	0			

23	69	F	R	i	5	0	83	33	25	25	No	4	2	3	6	1	2.87	5.75	49.02
24	36	F	L	h	2	0	75	25	25	25	No	4	2	5	13	1	1,63	2,81	46.63
25	51	M	R	i	0	0	59	25	25	9	No	4	2	4	7	1	5,79	6,72	46,39
26	82	F	R	i	0	0	83	33	25	25	No	4	2	4	9	1	1,57	3,47	49,70
27	24	F	R	h	0	0	83	25	33	25	No	4	2	4	11	1	3,34	3,09	45,63
28	66	M	L	h	1	0	52	19	19	14	Yes	0	2	0	2	0			
29	75	F	R	h	1	0	63	19	19	25	No	1	2	1	5	1	3,98	4,48	39,23
30	46	M	R	i	-3	0	58	14	25	19	Yes	2	2	1	5	1	19,97	14,01	52,73
31	60	M	L	i	-3	0	69	25	25	19	No	4	2	4	13	1	2,03	2,95	40,45
32	65	M	L	i	0	0	83	25	33	25	No	4	2	4	7	1	5,54	7,33	49,13
33	52	M	L	i	1	0	63	19	25	19	No	4	2	2	6	1	2,55	3,60	43,62
34	57	F	R	i	1	0	63	19	19	25	No	4	2	4	8	1	2,14	2,92	45,31
35	66	M	R	i	4	18	23	9	14	0	No	0	2	0	1	0			
36	77	F	R	i	11	-1	58	25	19	14	NT	0	2	0	2	0			

Abbreviations: ego asym: egocentric asymmetry, allo asym: allocentric asymmetry, MI total: total score on Motricity Index (lower limbs), MI hip/knee/ankle: Motricity Index – hip/knee/ankle subscore, BBS-s: Berg Balance Scale – Standing item, TCT-s: Trunk Control Test-static, FAC: Functional Ambulation Categories, RMI: Rivermead Mobility Index, COPvel-ML/AP: Net center-of-pressure velocities in mediolateral/anteroposterior direction, WBA perc: percentage of weight-bearing asymmetry

CHAPTER 4

TIME COURSE OF RECOVERY OF SPATIAL NEGLECT IN THE SUBACUTE PHASE POST-STROKE

CHAPTER 4.1

TIME COURSE OF RECOVERY OF VISUOSPATIAL AND PERSONAL NEGLECT IN THE FIRST 12 WEEKS AFTER STROKE: AN EXPLORATORY LONGITUDINAL COHORT STUDY

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Submitted at Neuropsychological Rehabilitation (2023)

Abstract

This prospective longitudinal cohort study explored recovery time courses of visuospatial and personal neglect during the first 12 weeks post-stroke onset. Twenty-nine individuals with a first-ever unilateral supratentorial stroke were included and followed-up at weeks 3, 5, 8, and 12 post-stroke onset. At each time point, three visuospatial (Broken Hearts Test (BHT), Line Bisection Test (LBT), Visuospatial Search Time Test (VSTT)) and two personal neglect tests (Fluff test, Lower Limb Tactile Extinction Test (LL-TE)) were performed. Variations in recovery patterns and associations between neglect subtypes over time were examined. Significant improvements in egocentric visuospatial neglect scores (BHT, VSTT) within the first 5 weeks post-stroke onset were observed, followed by a plateau. Allocentric visuospatial neglect did not improve (BHT, LBT). For personal neglect, body representation neglect (Fluff test) improved significantly from week 3 to 12, while no improvement in tactile neglect (LL-TE) was demonstrated. Meaningful associations (defined as a spearman correlation coefficient above .25) were observed between visuospatial neglect measures, particularly at 3 weeks post-stroke onset. Some neglect subtypes showed overlapping recovery patterns with divergent timing of plateaus. Other neglect subtypes did not show decreased severity over time, either due to the absence of recovery or limited test responsiveness.

Keywords

Visuospatial neglect, personal neglect, recovery, time course, stroke

Introduction

Neglect is a post-stroke cognitive disorder characterized by a lateralized attention deficit, with reduced attention towards the contralesional hemispace and increased capture of information in the ipsilesional hemispace [1-3]. Neglect in general is not considered a unitary phenomenon, but rather a syndrome consisting of multiple spatial and non-spatial (e.g., temporal) components [4]. Consequently, neglect can manifest in different ways depending on the reference frames (egocentric/viewer-centered, allocentric/object-centered), processing stages (sensory/representational/motor), and physical spaces (personal/body, peri-personal/within-reaching space, extra-personal/far space) affected [5].

To assess different aspects of the disorder, a diverse array of assessment tests and outcome measures have been developed. The majority of these assessments assess visual attention in peri-personal space (i.e., visuospatial neglect). Some examples are traditional paper-and-pen tests, such as cancellation tests and line bisection tests (LBT), as well as the Behavioral Inattention Test [5]. However, other types of neglect have received little attention in the literature.

The variability in the choice of assessment tests, aspects of neglect being evaluated, and timing of assessments have resulted in a wide range of reported prevalence rates of neglect, ranging from 18% to 80% [5, 6]. Only a few longitudinal studies have examined the time course of neglect recovery, revealing a period of significant improvement during the first 12-14 weeks post-stroke onset, followed by a plateau [7-13]. These studies have primarily focused on visuospatial neglect, particularly on its spatial characteristics (such as omissions and deviations), while its temporal aspects (such as search times in contra- versus ipsilesional hemispace) have not been evaluated [5, 14]. Additionally, the time course of recovery of other neglect subtypes, such as neglect of the personal space (i.e., personal neglect), remains unknown.

Recognizing this gap in literature, the overarching aim of this exploratory study was to prospectively investigate the time course of recovery of neglect during the initial 12 weeks following stroke. To achieve this, we employed a battery of assessment tests to capture potential variations in the recovery patterns over time. The first objective was to investigate the time course of recovery of visuospatial neglect during the first 12 weeks post-stroke onset.

Both traditional (Broken Hearts Test (BHT), LBT) and novel (Visuospatial Search Time Test (VSTT)) assessment tests were used to evaluate the spatial and temporal aspects. The second objective was to evaluate the time course of recovery of personal neglect. For this, the Fluff test [5, 15] and lower limb tactile extinction test (LL-TE) were used, indicative for body representation and tactile neglect, respectively [5]. The third objective was to investigate the relationships between neglect subtypes over time, by associating the severity of symptoms on the various tests. This knowledge would reveal potential overlaps or dissociations in recovery patterns of visuospatial and personal neglect, provide a deeper understanding of the commonalities and differences between these subtypes, and offer a more comprehensive understanding of the neglect syndrome.

Material and Methods

Study Design and Setting

This longitudinal cohort study used serial measurements at weeks 3, 5, 8 and 12 post-stroke onset. It is part of a larger research project (TARGEt: Temporal Analyses and Robustness of hemiplegic Gait and standing balance Early poststroke) that prospectively evaluates the pattern of cognitive and motor recovery relevant to standing balance and gait early after stroke [16].

This study was approved by the Medical Ethics Committee of the University Hospital Antwerp (No. 18/25/305; Belgium Trial Registration No. B300201837010). Additional approval was obtained from the medical ethics committee of the other involved clinical sites. All procedures were conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was designed in accordance with the STROBE guidelines [17] and was registered online (ClinicalTrials.gov identified: NCT05060458).

Participants

Individuals admitted to one of the six cooperating hospitals (Universitair Ziekenhuis Antwerpen, GZA Sint-Vincentius, GZA Sint-Augustinus, Algemeen Ziekenhuis Geel, RevArte, AZ Monica, all situated in the larger Antwerp region, Belgium) after an acute stroke were screened for participation between August 2020 and May 2022. For eligibility, they had to meet the following criteria: (1) CT and/or MRI confirmed first-ever unilateral ischemic or hemorrhagic supratentorial stroke; (2) aged between 18 and 90 years; (3) (corrected to) normal visual acuity; (4) premorbid independence in daily life activities (i.e., modified Rankin Scale score of 0-1), (5) no prior diagnosis of pre-stroke neurological disease; (6) no severe cognitive or communication deficits that interfere with understanding instructions and procedures; and (7) ability to provide written informed consent. All participants received usual care including physical therapy, occupational therapy, speech therapy, and neuropsychological rehabilitation, depending upon their individual needs.

Protocol, Data Collection and Outcome Measures

Recruitment and screening were performed by EE and JS together with the (para)medical staff employed at the stroke units and rehabilitation facilities. During intake, the participants' sex, age, and information about their stroke pathology (type: ischemic/hemorrhagic; most-affected side left/right) as well as clinical severity were collected. Clinical severity information encompassed lower limb motor function (Lower Limb Motricity Index) [18] and functional mobility (Rivermead Mobility Index) [19]. A trained assessor (EE) administered all the serial follow-up assessments.

Visuospatial Neglect Tests and Outcome Variables

A distinction between egocentric and allocentric visuospatial neglect was made throughout this study. Egocentric visuospatial neglect refers to the impaired ability to attend to visual objects on one side of space relative to their body (viewer-centered reference frame). Allocentric visuospatial neglect refers to the difficulty to attend to one side of a visual object (object-centered reference frame), irrespective of its spatial position.

BHT (Egocentric and Allocentric Visuospatial Neglect). We used the BHT or its variation (Apple's test), which is part of the Oxford Cognitive Screen [20]. It evaluates both ego- and allocentric visuospatial neglect [5]. Three parallel versions were used and varied randomly across time points to avoid learning effects. The participants had to cancel the complete hearts/apples (n=50) among distractors shaped as broken hearts/apples, with either gaps on the right (n=50) or left (n=50) of the contour. The test was presented on an A4 landscape paper, whose position was standardized within and across participants [20, 21]. Participants had a maximum of 3 minutes to complete the test.

Asymmetry was evaluated as a measure of neglect severity. The difference between the cancelled full outlines of the contralesional and ipsilesional sides of the paper was used as a measure of egocentric visuospatial neglect severity (BHT Ego_asym). Egocentric visuospatial neglect was considered present when BHT Ego_asym >2 or <-2. Allocentric visuospatial neglect severity was calculated by subtracting the number of contralesional and ipsilesional gap false positives, which is referred to as allocentric asymmetry (BHT Allo_asym). Allocentric visuospatial neglect was considered present when BHT Allo_asym >1 or <-1. Positive values indicate contralesional visuospatial neglect and negative values indicate ipsilesional visuospatial neglect.

Computerized Schenkenberg LBT (Allocentric Visuospatial Neglect). The participants had to bisect 20 horizontal lines with their less-affected hand. The lines were placed central to the midline or either more left or right, with peripheral starting points at equal distances from the midline [14]. Considering that performance on the test is dependent upon a correct perception of the length of the line, it primarily depends on an object-based, allocentric space representation [22]. Therefore, this test mainly evaluates allocentric visuospatial neglect. The LBT was performed using the Metrisquare DiaDiag software (www.metrisquare.com) on a Wacom® tablet (40 × 65 cm) (14). As a measure of severity, the mean percentage of the total deviation from the centers of the ipsilesional, contralesional, and centrally placed lines was used (LBT_dev). Normative performance in healthy individuals is a deviation of 0.4 ± 3.89 [14]. Positive and negative values indicate contralesional and ipsilesional deviation from the midline, respectively.

Computerized VSTT (Egocentric Visuospatial Neglect). The VSTT consists of 16 consecutive grids containing 20 different stimuli centered around one stimulus in the middle, presented in a green square [14]. The participant had to cross out a stimulus identical to the central stimulus as quickly as possible. Directly afterwards, the next grid was shown with a different central stimulus, and in this way, the task continued. This test was also performed with the Metrisquare DiaDiag software (www.metrisquare.com) using a Wacom® tablet (40 cm × 65 cm) [14]. The VSTT registers contra -and ipsilesional hemispace search times. The contralesional versus ipsilesional search time index was calculated as a measure of egocentric visuospatial neglect severity (VSTT_index). The normal range is 1.1 ± 0.39, based on data in healthy controls [14].

Personal Neglect Tests and Outcome Variables

A distinction between tactile and body representation neglect was made. Tactile neglect refers to the impaired ability to attend to tactile stimuli when applied simultaneously on the contra- and ipsilesional body side, without the presence of primary somatosensory deficits [23]. Body representation neglect refers to the reduced body exploration related to a disorder in the representation of one's own body [23].

LL-TE test (Tactile Neglect). The examiner gave light pressure touch with their index finger in a random order on predetermined spots on the participant's lower limbs, based on the Erasmus-modified Nottingham Sensory Assessment [24]. This was performed in a homologous way (ie, both on the same anatomical location on the left vs right side of the body. We focused on the lower limbs, as this protocol is part of a larger study evaluating the recovery of standing balance post-stroke (TARGEt [16]). The test was first demonstrated to the participants with their eyes open. Subsequently, the participant was blindfolded, and the examiner provided either a unilateral or bilateral touch stimulus. Participants reported whether the stimulus was delivered to the left, right, or both sides of the body (either verbally or by pointing, in case of aphasia). The total number of bilateral omissions was used as a measure of severity of tactile neglect (TE_number). The total number of unilateral omissions (i.e., in cases in which a unilateral stimulus was not reported) was also considered to evaluate unilateral sensory deficits.

Fluff test (Body Representation Neglect). Fifteen targets were applied on the contralesional side of the participant's body (6 on the arm, 6 on the leg, and 3 on the trunk) and nine targets on the ipsilesional side (6 on the leg and 3 on the trunk). Participants were blindfolded and unaware of the total number of targets attached, considering they were attached during the LL-TE test. Subsequently, they had to remove all targets using their less-affected hand. When participants had difficulty removing the targets owing to motor deficits (e.g., limited trunk control), the examiner assisted the participant with the movement (e.g., assisting the participant in a seated position) with as little sensory feedback as possible on their limbs or frontal trunk.

The performance on the ipsilesional side (number of targets found in relation to the total possible ipsilesional targets, in % (9)) was compared with the performance on the contralesional side (number of targets found in relation to the total possible contralesional targets, in % (15)). The difference in performance between contralesional and ipsilesional hits (Fluff_asym%) was used as a measure of severity of body representation neglect [15]. A negative or positive sign represents contralesional or ipsilesional neglect, respectively, with a difference of >±13.3% representing relevant asymmetry [15].

Statistical Analyses

Data analysis was performed on participants for whom data from at least two consecutive follow-up measurements were available. Drop-out prior to endpoint measurement at week 12 post-stroke was allowed, whereas individuals with missing data between serial measurements were excluded.

We descriptively presented the mean values with standard deviation of demographic information and each investigated outcome measure at weeks 3, 5, 8, and 12 post-stroke onset. To model the changes over time (Objective 1 and 2), linear mixed models (LMM) were fitted for all outcomes. The time course of TE_number was evaluated only in participants without an initial unilateral sensory loss. Across all LMMs, the fixed effect TIME (categorical: weeks 3, 5, 8, and 12) was included as a predictor, as well as a random subject-specific intercept, to account for the dependency of repeated measurements within participants. Unsigned (i.e., absolute) values were entered for each dependent variable. This was necessary considering that some individuals demonstrated changes from ipsilesional to contralesional neglect and vice versa. Relative values could have led to an incorrect interpretation of changes in the direction of asymmetry as worsening or improvement in neglect. For the same reason, it was crucial to adopt neglect-side neutral values for the VSTT index because an individual exhibited ipsilesional neglect (i.e., a VSTT index lower than 1). In contrast, individuals with contralesional neglect demonstrated a VSTT index of > 1. Diagnostic plots to assess model assumptions included histograms and Q-Q plots to evaluate the normality of residuals, and a plot of conditional residuals versus predicted values to evaluate homoscedasticity. Since these model assumptions were not met in four of the outcome variables (BHT Allo_asym and BHT Ego_asym, VSTT index, and LBT_dev), log-transformed values of these variables were entered as dependent variable. For BHT Allo_asym and BHT Ego_asym, for which some participants had an asymmetry score of 0, a value of 1 was added prior to log-transformation.

Post-hoc analysis was conducted using Tukey's HSD multiple comparison method, yielding estimates (through the regression coefficients β) for time-dependent changes over the entire period (from weeks 3 to 12) and for each epoch separately (weeks 3-5, 5-8, and 8-12). After fitting the LMMs, log-transformed β estimates were back transformed to the original scale using the exponential function (Exp(β)). For BHT Allo_asym and BHT Ego_asym, a value of 1 was subtracted from the back-transformed β estimates to obtain estimates on the original scale (Exp(β)-1).

To visualize the change in outcome over time, individual time courses (with relative values and signs denoting contra/ipsilesional deviations), together with mean values (absolute/side neutral) per time point, were plotted for all outcome measures. The range of unimpaired/normative values is indicated in the graphs as light-grey areas.

To evaluate the associations between the different subtypes (Objective 3), Spearman correlation analyses were conducted on data from the entire period and at each time point separately. The non-normal distribution of the outcome variable values necessitated the use of non-parametric methods. Correlation matrix heatmaps were generated, and Spearman's correlation coefficients were interpreted as follows: ≤.25, no meaningful relationship; .25–.50, low to fair; .50–.75, moderate to good; ≥.75, strong relationship. The significance level was set at $P<.05$. All analyses were performed using JMP Pro® version 16.

Results

Participants

Figure 4.4.1 shows the flow of participant recruitment. A total of 140 first-ever individuals with stroke were screened during the recruitment period, of which 30 were enrolled. Of these, 29 successfully participated in at least two serial measurements and were included in the analysis.

Descriptive data

The mean age of the 29 participants was 65.72 ± 15.28 years. Twelve (41.4%) were female, 11 (37.9%) had a left-sided stroke, and 22 (75.8%) had an ischemic stroke. Mean time post-stroke at first measurement was 25.17 ± 1.79 days, at week 5 38.41 ± 2.61 days, at week 8 58.61 ± 2.53 days and at week 12 85.42 ± 2.80 days.

Table 3.3.1 provides an overview of the mean unsigned or side-neutral values of neglect test scores over time. It also indicates the number of participants whose scores fall outside the normative or unimpaired ranges for each test. Additionally, the table includes clinical severity scores, such as the Lower Limb Motricity Index and the Rivermead Mobility Index, which serve as indicators of stroke severity.

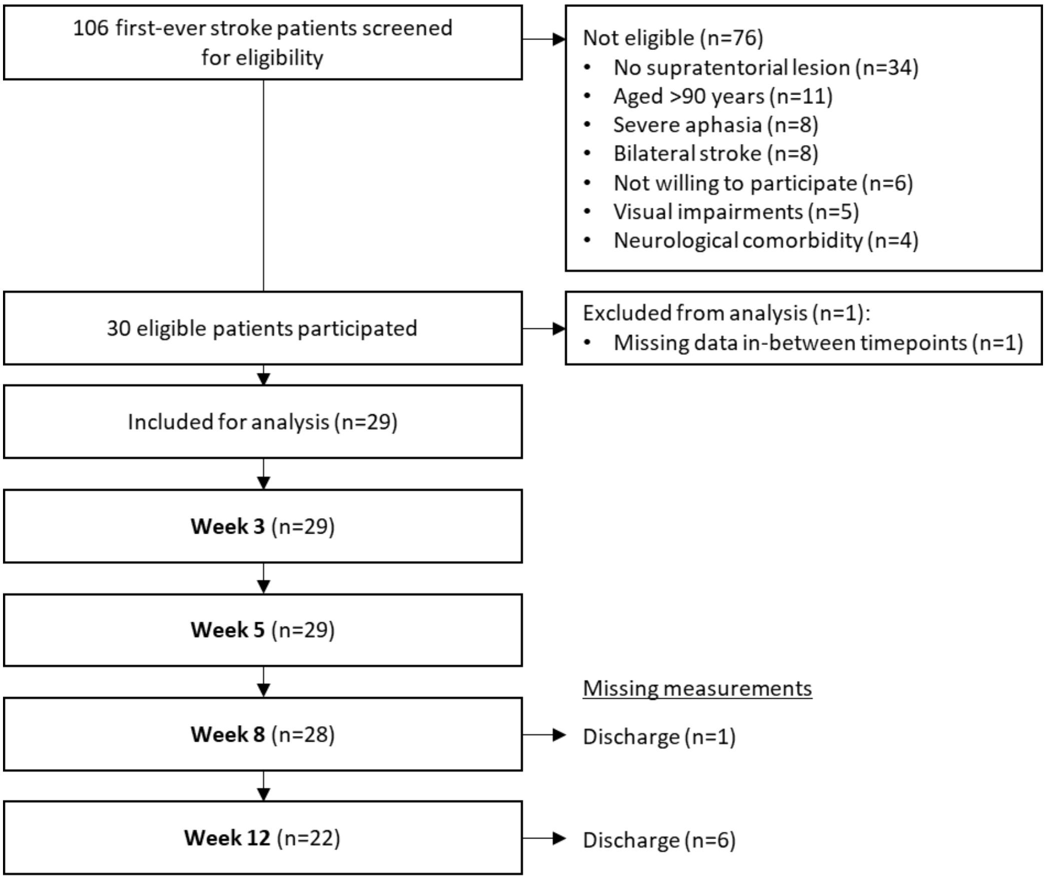

Figure 4.1.1. Flowchart of recruitment and inclusion of participants

At baseline assessment (3 weeks post-stroke onset), egocentric visuospatial neglect was observed in 13 participants according to the BHT Ego_asym and in 15 participants based on the VSTT_index measurement. Allocentric visuospatial neglect was identified in five participants using the BHT Allo_asym measurement and in 13 participants using the LBT_dev measurement. Furthermore, nine participants exhibited body representation neglect, while six participants showed tactile neglect.

Time Course of Visuospatial Neglect Recovery

There was a significant Time effect for BHT Ego_asym (Exp(β)-1 = -0.56, 95% CI [-0.06; -1.28], P = .016) and VSTT index (Exp(β) = -1.42, 95% CI [-1.04; -1.92], P = .019) from weeks 3 to 12

Table 4.1.1. Neglect test scores and clinical severity scores over time

	Week 3	Week 5	Week 8	Week 12
Number of participants	29	29	27	21
Time post-stroke (days)	25.17 (1.79)	38.41 (2.61)	58.61 (2.53)	85.42 (2.80)
Egocentric visuospatial neglect				
BHT Ego_asym (0-20, absolute values)°	3.66 (5.03)	1.52 (2.50)	1.42 (1.50)	1.57 (2.73)
Number of participants with/without egocentric visuospatial neglect on BHT Ego_asym	13/16	5/24	8/19	2/19
VSTT_index (side neutral values)	2.19 (1.73)	1.39 (0.84)	1.39 (0.77)	1.41 (0.50)
Number of participants with/without egocentric visuospatial neglect on VSTT	16/13	12/17	11/16	8/13
Allocentric visuospatial neglect				
BHT Allo_asym (0-20, absolute values)	2.14 (5.55)	0.48 (1.18)	0.42 (1.10)	0.52 (1.03)
Number of participants with/without allocentric visuospatial neglect on BHT Allo_asym	5/24	4/25	3/24	3/18
LBT_dev (%, absolute values)	6.67 (6.95)	5.39 (6.94)	4.64 (3.41)	5.09 (4.06)
Number of participants with/without allocentric visuospatial neglect on LBT	14/15	12/17	13/14	9/12
Personal neglect				
Fluff_asym% (absolute values)	11.65 (16.14)	5.67 (13.38)	4.44 (12.81)	1.22 (3.34)
Number of participants with/without body representation neglect on Fluff test	9/20	4/25	3/24	0/21
TE_number[A]	2.10 (3.91)	1.70 (3.44)	1.16 (2.36)	0.86 (3.21)
Number of participants with/without unilateral sensory loss	9/20	9/20	8/19	7/14
Number of participants without unilateral sensory loss and at least 1 tactile extinction point (tactile neglect)	6/14	8/12	8/11	6/8
Clinical severity				
Lower limb motricity index score (on 100)	58.00 (23.81)	66.21 (22.49)	70.82 (22.59)	72.19 (20.68)
Rivermead Mobility Index (on 24)	6.50 (3.97)	8.46 (4.50)	9.41 (4.39)	10.24 (4.07)

Abbreviations: BHT Allo_asym: allocentric asymmetry on the Broken Hearts Test, BHT Ego_asym: egocentric asymmetry on the Broken Hearts Test, Fluff_asym%: asymmetry on the Fluff test, LBT_dev: Line Bisection Test total deviation, TE_number: Tactile Extinction number of bilateral omissions, VSTT_index: Visuospatial Search Time Test index, [A] Only those without unilateral sensory loss at 3 weeks included. Unsigned values were used for the parameters presented. *Values are mean (standard deviation).*

post-stroke onset. Post-hoc tests demonstrated a significant decrease in scores between weeks 3 and 5 (BHT Ego_asym: exp(β)-1 = -0.64, 95% CI [-0.17; 1.31], P = .002; VSTT_index:

exp(β) = -1.41, 95% CI [-1.08; -1.83], P = .007). No significant changes were observed from week 5 onwards. The effect of Time was not significant for BHT Allo_asym or LBT_dev (Table 4.1.2 and Figure 4.1.2).

Time Course of Personal Neglect Recovery

During the first 12 weeks post-stroke onset, the effect of Time was significant for Fluff_asym% ($F(3,3)=4.16$, $P=.009$), with a significant improvement in scores from weeks 3 to 12 ($\beta=-8.37$, 95%CI [1.25; 15.50], $P=.015$). Post-hoc tests revealed no significant changes in each epoch separately. The effect of Time on TE_number was not significant (Table 4.1.2 and Figure 4.1.2).

Relationship between Neglect Subtypes over Time

Overall, across all timepoints, a statistically significant low correlation was found between the VSTT_index and BHT Allo_asym ($\rho=.35$, $P<.001$). The remaining correlations were either not significant ($P>.05$) or not meaningful ($\rho \leq .25$) (Figure 4.1.3). As shown in the Supplementary Files, at 3 weeks post-stroke, a significantly moderate correlation was found between the VSTT index and BHT Ego_asym ($\rho=.62$, $P<.001$) and a significantly fair correlation between the VSTT index and BHT Allo_asym ($\rho=.42$, $P=.031$). At 5 weeks, no significant correlations were observed. At 8 weeks, BHT Ego_asym and BHT Allo_asym were fairly correlated ($\rho=.42$, $P=.033$) and at 12 weeks, BHT Allo_asym and VSTT_index were moderately to strongly correlated ($\rho=.67$, $P=.033$).

Discussion

The present exploratory study prospectively investigated the time course of recovery of visuospatial and personal neglect during the first 12 weeks post-stroke, and evaluated the association between these subtypes over time. Significant improvements in egocentric visuospatial and body representation neglect were observed within the initial 12 weeks after stroke. For egocentric visuospatial neglect, these improvements were mainly situated within the first 5 weeks, with a plateau afterwards. Outcomes indicative of allocentric visuospatial and tactile neglect did not significantly improve over time. Within subject relationships between neglect subtypes, as represented by the severity of neglect on the different tests, were generally not meaningful or even absent.

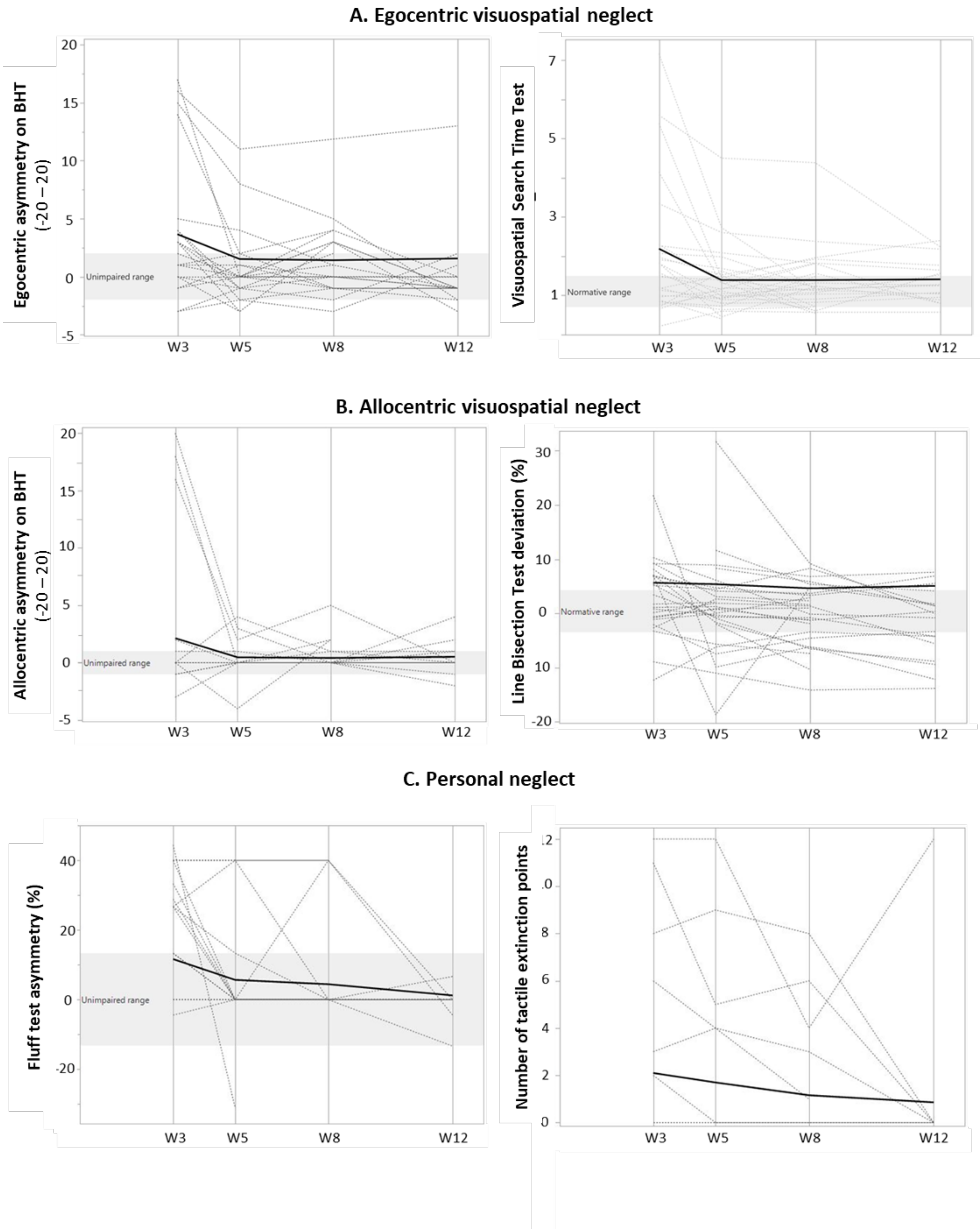

Figure 4.1.2. A-C. Recovery time course of egocentric visual neglect, allocentric visual neglect, and personal neglect measures. X-axis represents the time post-stroke in weeks, Y-axis represents the scores on the tests. Dotted lines show the individual time courses, and thick lines represent the mean of absolute/side-neutral values. Highlighted area in grey shows the normative/unimpaired ranges.

Table 4.1.2. Time course of visuospatial and personal neglect

		Week 3-12	Week 3-5	Week 5-8	Week 8-12
Egocentric visuospatial neglect variables (log-transformed)					
Δ BHT Ego_asym (0-20)	((exp)β)-1	-0.56	-0.64	+0.10	-0.06
	((exp)SE)-1	0.16	0.14	0.14	0.16
	(exp)95% CI	[-0.64;-1.28]	[-0.17;-1.31]	[-0.37;0.28]	[-0.28;0.56]
	P-value	.016*	.002*	.854	.982
Δ VSTT_index	((exp)β)	-1.42	-1.41	0.00	1.00
	((exp)SE)	1.12	1.11	1.11	1.12
	(exp)95% CI	[1.04;1.92]	[1.08;1.83]	[0.77;1.31]	[-0.74;1.36]
	P-value	.019*	.006*	1.000	1.000
Allocentric visuospatial neglect variables (log-transformed)					
Δ BHT Allo_asym (0-20)	((exp)β)-1	-0.22	-0.27	-0.03	+0.07
	((exp)SE)-1	0.17	0.15	0.16	0.17
	(exp)95% CI	[-0.19;0.84]	[-0.12;0.85]	[-0.30;0.52]	[-0.39;0.41]
	P-value	.598	.330	.996	.963
Δ LBT_dev	((exp)β)	-1.45	-1.57	+0.75	-1.16
	((exp)SE)	1.45	1.39	1.38	1.23
	(exp)95% CI	[0.54; 3.85]	[0.66;3.76]	[0.32;1.75]	[0.48;3.19]
	P-value	.754	.525	.802	.938
Personal neglect variables (non-transformed)					
Δ Fluff_asym%	β	-8.37	-5.98	-0.70	-1.70
	SE	2.71	2.39	2.45	2.74
	95% CI	[-1.25;-15.50]	[-0.30;12.25]	[-5.73;7.13]	[-5.49;8.89]
	P-value	.015*	.068	.992	.925
Δ TE_number[A]	β	-1.63	-0.40	-0.62	-0.61
	SE	0.64	0.57	0.58	0.64
	95% CI	[-0.07;3.33]	[-1.10;1.90]	[-0.91;2.15]	[-1.10;2.32]
	P-value	.064	.894	.701	.782

Abbreviations: BHT Allo_asym: allocentric asymmetry on the Broken Hearts Test, BHT Ego_asym: egocentric asymmetry on the Broken Hearts Test, CI: confidence interval, Fluff_asym%: asymmetry on the Fluff test, LBT_dev: Line Bisection Test total deviation, SE: standard error, TE_number: Tactile Extinction number of bilateral omissions, VSTT_index: Visuospatial Search Time Test index, Δ: difference, β: estimate, (exp)β: back-transformed value, [A] Only those without unilateral sensory loss at 3 weeks included, *P<.05.

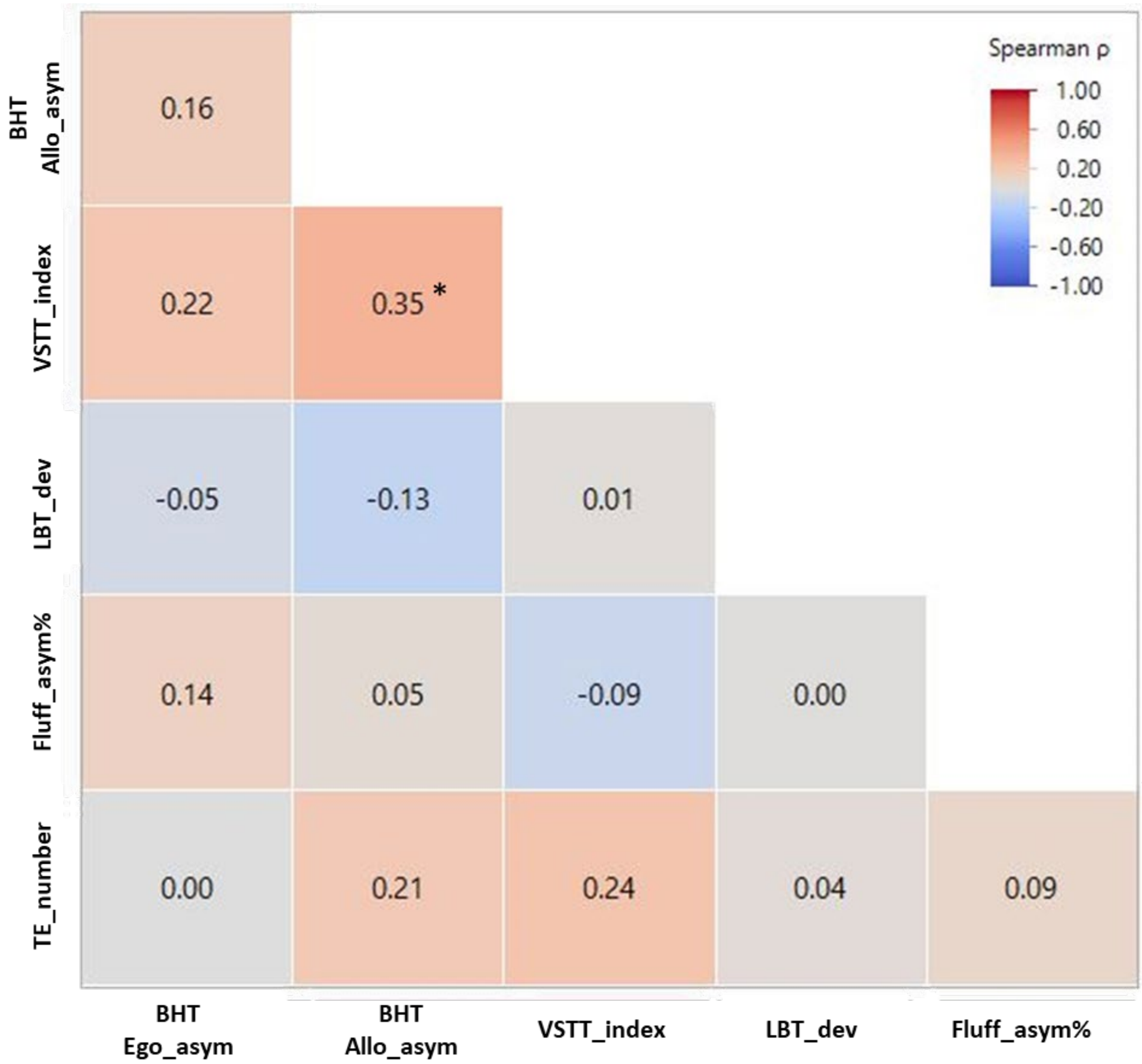

Figure 4.1.3. Correlation heatmap of within subject correlations over time. Asterix (*) shows significant (P.25) correlations. **Abbreviations:** BHT Ego_asym: egocentric asymmetry evaluated using the Broken Hearts Test, VSTT_index: Visual Search Time Index, BHT Allo_asym: allocentric asymmetry evaluated using the Broken Hearts Test, LBT_dev: mean deviation on Line Bisection Test, Fluff_asym%: asymmetry in hits on the Fluff test, TE_number: number of lower limb tactile extinction points.

The present study revealed that the majority of improvement in egocentric visuospatial neglect occurred within the initial 3 to 5 weeks post-stroke onset. This improvement rapidly levelled off afterwards. This finding aligns with previous studies that examined the time course of recovery of lower and upper limb motor impairments [25-27]. Collectively, these findings suggest the existence of an early, time-limited phase in which post-stroke recovery is most pronounced. It is noteworthy, however, that the current study observed an earlier plateau of improvement of egocentric visuospatial neglect compared to the findings reported by Nijboer et al. [7], who documented a plateau of improvement only at 12 weeks after stroke onset. Our sample size was considerably smaller (n=29) than that of Nijboer et al. (n=101), which may have resulted in the inclusion of fewer individuals with severe neglect impairments. Within our study, the proportion of participants exhibiting severe visuospatial neglect at baseline (i.e., those who displayed substantial deviation from normative or unimpaired ranges) was considerably lower, approximately 50%, in comparison to those presenting with mild-to-moderate symptoms (i.e., those who were closer to normative or unimpaired ranges). This may have contributed to a ceiling effect, wherein participants with milder neglect symptoms reached their maximum recovery potential earlier, thus leading to a faster attainment of the plateau.

In contrast to egocentric visuospatial neglect, the recovery of allocentric visuospatial neglect did not show significant improvements over time. A prior study by Moore et al. [28] also demonstrated that, in a subset of their sample, allocentric visuospatial neglect remained unchanged or became even worse throughout time. One possible explanation for the discrepancy between egocentric and allocentric visuospatial neglect is that the tests and outcome measures used to assess egocentric visuospatial neglect may be more sensitive to changes over time [28, 29]. It is also possible that egocentric visuospatial neglect is more responsive to therapeutic interventions or to learning compensatory strategies, leading to a seemingly faster improvement on these tests compared to allocentric visuospatial neglect [30-32]. Traditional interventions for addressing symptoms of visuospatial neglect, such as visual scan training, are primarily focused on (compensating for) neglect in the egocentric frame of reference [33]. However, the subjective experience of neglecting half of an object, regardless of its spatial position, differs from a more generalized neglect of one side of space. It seems thus possible that many of these therapies would be ineffective for allocentric visuospatial neglect. Learning how to compensate for or treating allocentric visuospatial neglect may therefore require a different approach.

With regard to the time course of recovery of personal neglect, the severity of body representation neglect decreased significantly over time, whereas that of tactile neglect did not. This suggests that the underlying mechanisms driving improvements in the mental representation of personal space are not directly associated with the attentional processes involved in detecting simultaneous tactile stimuli, also evidenced by the lack of significant relationships between both subtypes. The lack of improvement in tactile neglect contrasts with the findings of Kamtchum-Tatuene et al. [34], who observed a gradual decrease in the occurrence of tactile neglect over time, with no cases reported beyond 15 days post-stroke. These differences may be attributed to variations in sample characteristics. Within their study, individuals were included and assessed for tactile neglect in the acute phase after stroke, within one week of onset, whereas our assessment began at 3 weeks post-stroke onset. Additionally, they excluded individuals with unilateral sensory loss at inclusion, whereas we did not employ this exclusion criteria. Consequently, it is possible that some participants in our study may have experienced initial unilateral sensory loss during the acute post-stroke phase, which may have resolved and potentially resulted in tactile extinction, by the time they were included at 3 weeks post-stroke [34].

Overall, the relationships between neglect subtypes over time were absent or weak. They varied according to the time point of assessment, with stronger relationships situated at 3 weeks post-stroke. Clinically meaningful relationships were observed only between visuospatial neglect measures. The association observed between egocentric visuospatial neglect asymmetry (BHT Ego_Asym) and visuospatial processing speed (VSTT_index) over time suggests a parallel pattern of improvement in the spatial and temporal aspects of egocentric visuospatial neglect, also evidenced by similar time courses of recovery of these parameters. This indicates that a reduction in spatial attentional bias may contribute to faster visuospatial information processing within the neglected hemispace. Overall, the early observed post-stroke relationships may reflect manifestations of a common underlying deficit (e.g., lateralized inattention). However, the overall lack of strong and consistent relationships over time emphasizes the multifaceted nature of neglect and supports the notion that neglect subtypes can be considered separate entities.

Strengths and Limitations

Our study has several strengths. First, we used a longitudinal design with fixed time points post-stroke onset to allow for an accurate comparison between tests and to control for differences in post-stroke timing. Second, we evaluated the time courses of recovery of different neglect subtypes. For this, we used a multitude of clinically applicable tests with different task demands and performance components.

Despite these strengths, several limitations should be considered. A first limitation is the small sample size (n=29) together with the substantial dropout rate from 8 weeks onwards (24.1%). The dropout rate was attributed to difficulties in rescheduling measurements in the clinical setting after early discharge. Moreover, COVID-19 measures had prohibited outpatient access to clinical sites for follow-up measurements after discharge. This may have resulted in under-powered analysis to show significant improvements over time. Second, the limited sample size hindered the examination of neglect subtypes in combination. It is possible that individuals experiencing multiple subtypes of neglect may exhibit different patterns of recovery, with potentially reduced capacities to recover over time. Third, although participants were repeatedly assessed at time points relative to stroke onset, assessments were only started at 3 weeks post-stroke. As a result, the very early, potentially greater improvement in neglect symptoms was missed. Finally, not documenting lesion characteristics and other cognitive functions restricts our ability to assess their contribution to the observed outcomes.

Implications for Clinical Practice and Future Research

When evaluating the recovery of neglect, careful consideration of the choice of neglect tests is crucial. The selection should consider the subtypes and characteristics of neglect being targeted as well as the time elapsed since stroke onset. Individuals evaluated beyond five weeks post-stroke onset may exhibit apparent recovery from neglect or may not demonstrate any further improvement over time. However, it is important to note that this lack of improvement may be attributed to the robustness of the tests and potential ceiling effects, rather than the absence of residual neglect symptoms [35]. Therefore, future research should consider evaluating the recovery time course of neglect using more attention-demanding neglect tests to evaluate the presence of residual symptoms and their recovery. In this regard, tests that more closely resemble daily life situations, such as the Catherine Bergego Scale, could play a significant role [36]. Additionally, virtual and augmented reality assessments hold promise, as they can simulate or enhance daily life scenarios. These technologies offer the ability to gradually increase the complexity of tasks across multiple performance aspects (spatial and temporal), processing stages, physical spaces, and reference frames [37]. By investigating the time course of neglect recovery using such tasks, the presence of residual deficits and their recovery may be better determined. Second, future studies should evaluate how the combined presence of multiple subtypes of neglect would recover over time, as prior studies have demonstrated that neglect subtypes frequently co-occur after stroke [38, 39]. Lastly, our findings suggest that neglect subtypes can be considered separate entities and may involve unique neural mechanisms that lead to differential time courses of recovery. To further explore and confirm this hypothesis, future studies should incorporate neuroimaging techniques when studying time courses of recovery.

Conclusion

Visuospatial and personal neglect subtypes may represent distinct entities characterized by separate underlying mechanisms and patterns of recovery. Consequently, when assessing neglect, it is crucial to consider both the time since stroke onset and the specific subtypes of neglect being targeted. Future research should investigate the time course of neglect recovery using more attention-demanding neglect tests, such as virtual and augmented reality assessments. These findings may provide valuable insights into residual deficits and their recovery. Additionally, further investigation is needed to explore the neural mechanisms involved in the recovery of neglect subtypes as well as the factors that may influence this process, such as other cognitive deficits or lesion characteristics.

Acknowledgements

The authors wish to thank Prof. Dr. Erik Fransen (StatUA, UAntwerpen) for the statistical guidance. They also express their gratitude to the cooperating hospitals and their staff for assisting with recruitment and follow-up during the study period. Finally, they thank the participants for their effort in taking part in this research.

Declaration of Interest

The authors declare that they have no conflict of interest.

Data Availability

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

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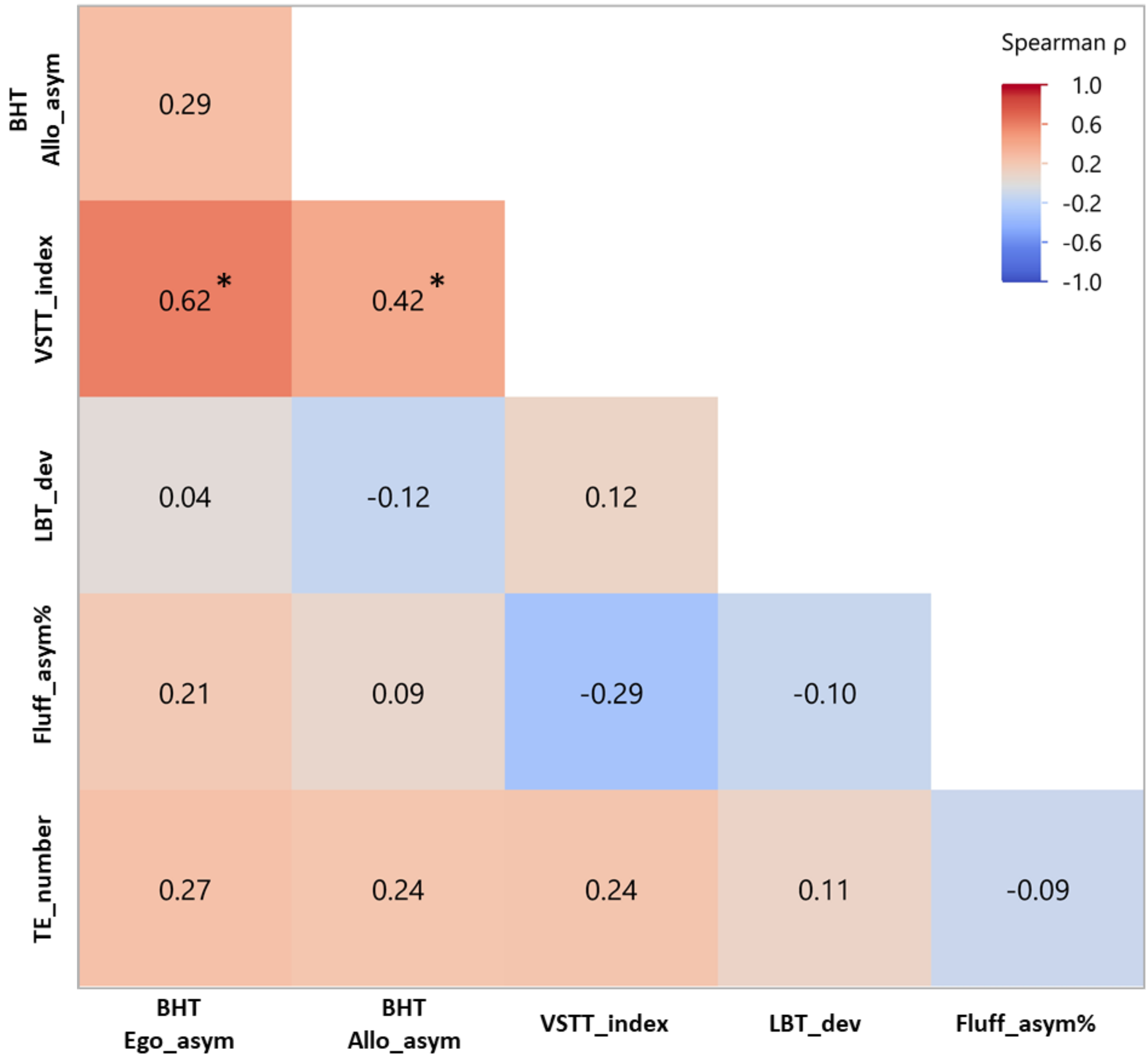
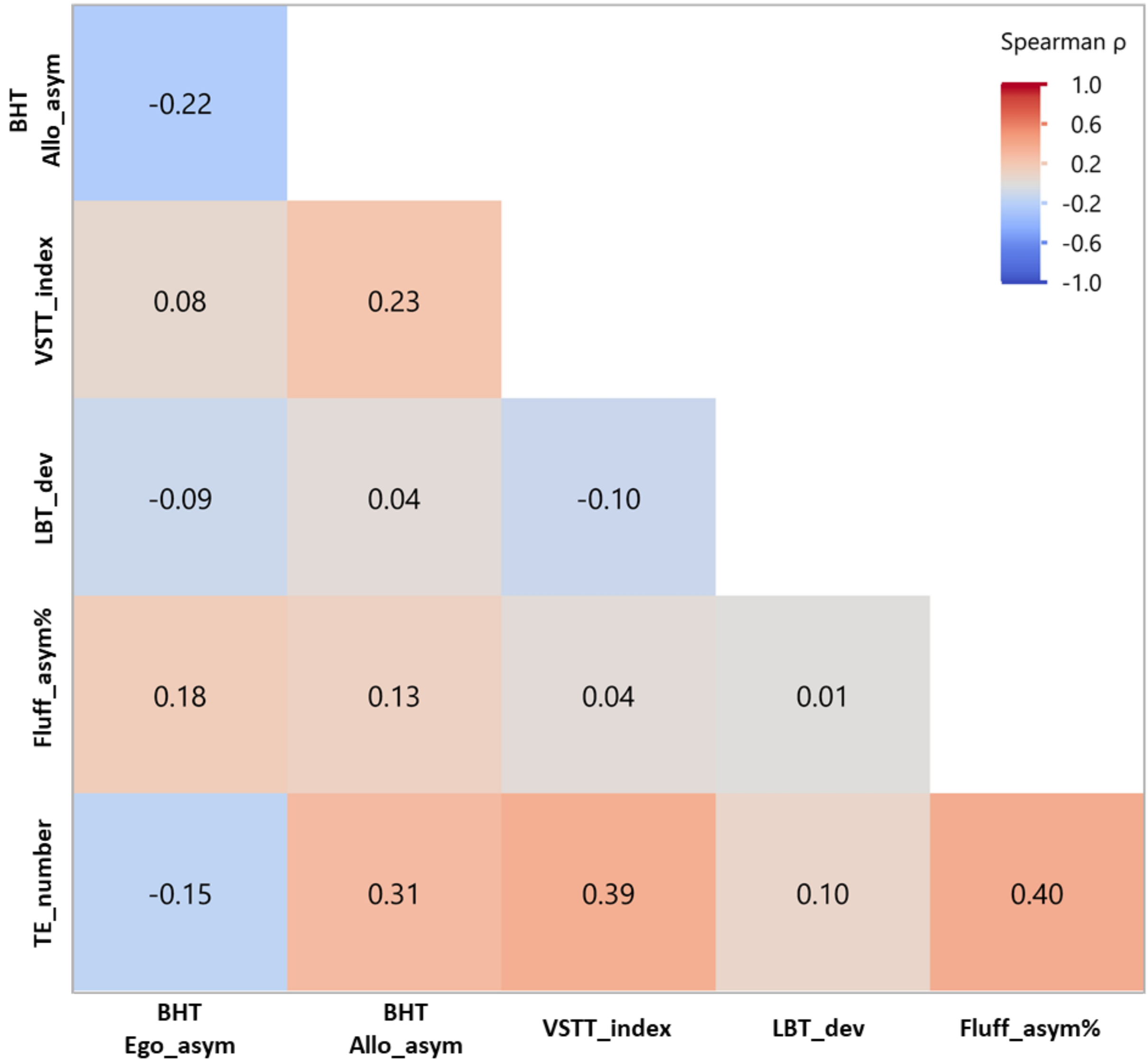
Supplementary files

Supplementary figure 1



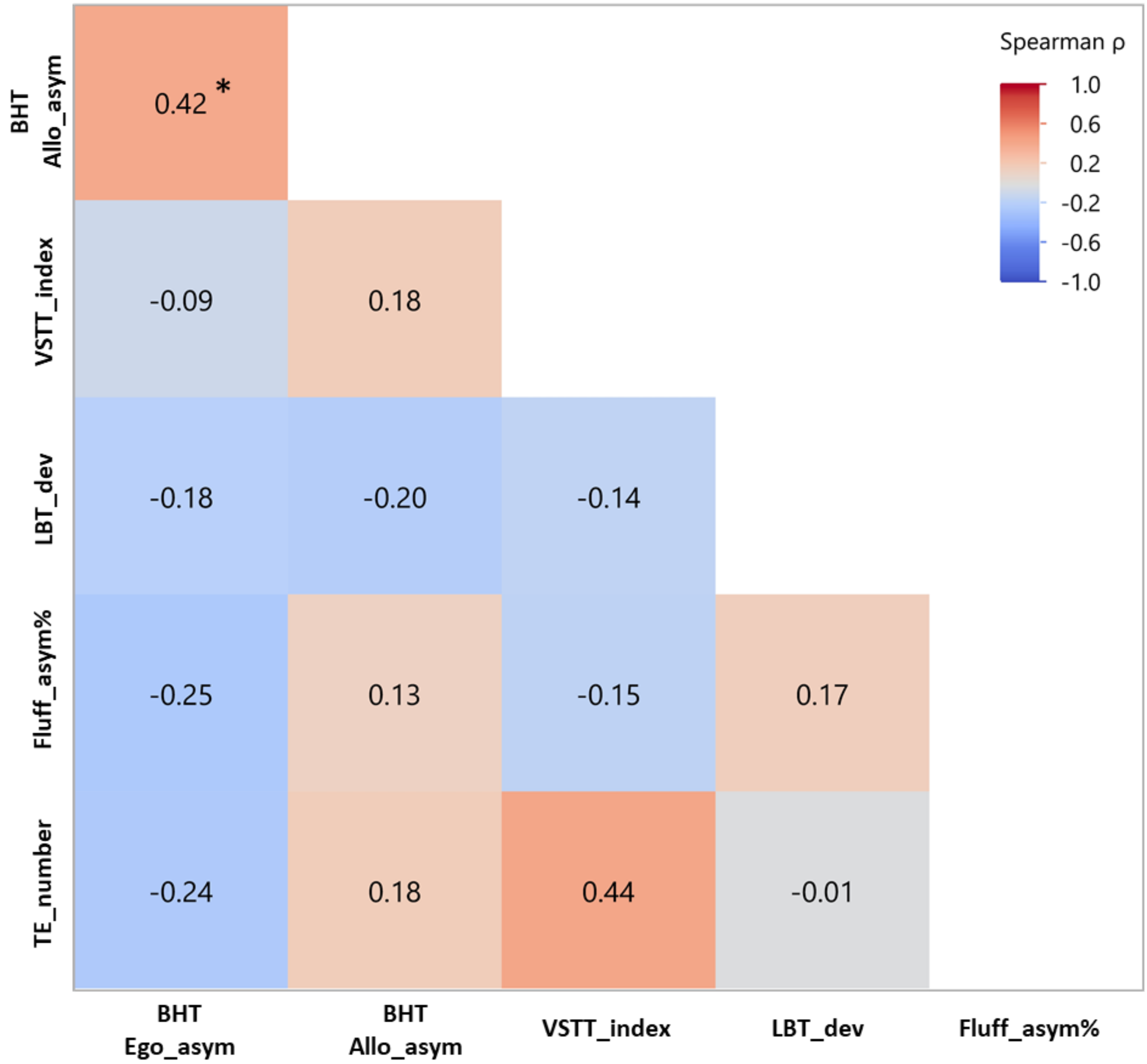
Supplementary Figure 1. Correlation heatmap of *within subject* correlations at three weeks post-stroke. Asterix (*) shows significant ($P<.05$), meaningful ($\rho>.25$) correlations. **Abbreviations:** BHT Ego_asym: egocentric asymmetry evaluated using the Broken Hearts Test, VSTT_index: Visual Search Time Index, BHT Allo_asym: allocentric asymmetry evaluated using the Broken Hearts Test, LBT_dev: mean deviation on Line Bisection Test, Fluff_asym%: asymmetry in hits on the Fluff test, TE_number: number of lower limb tactile extinction points.

Supplementary figure 2



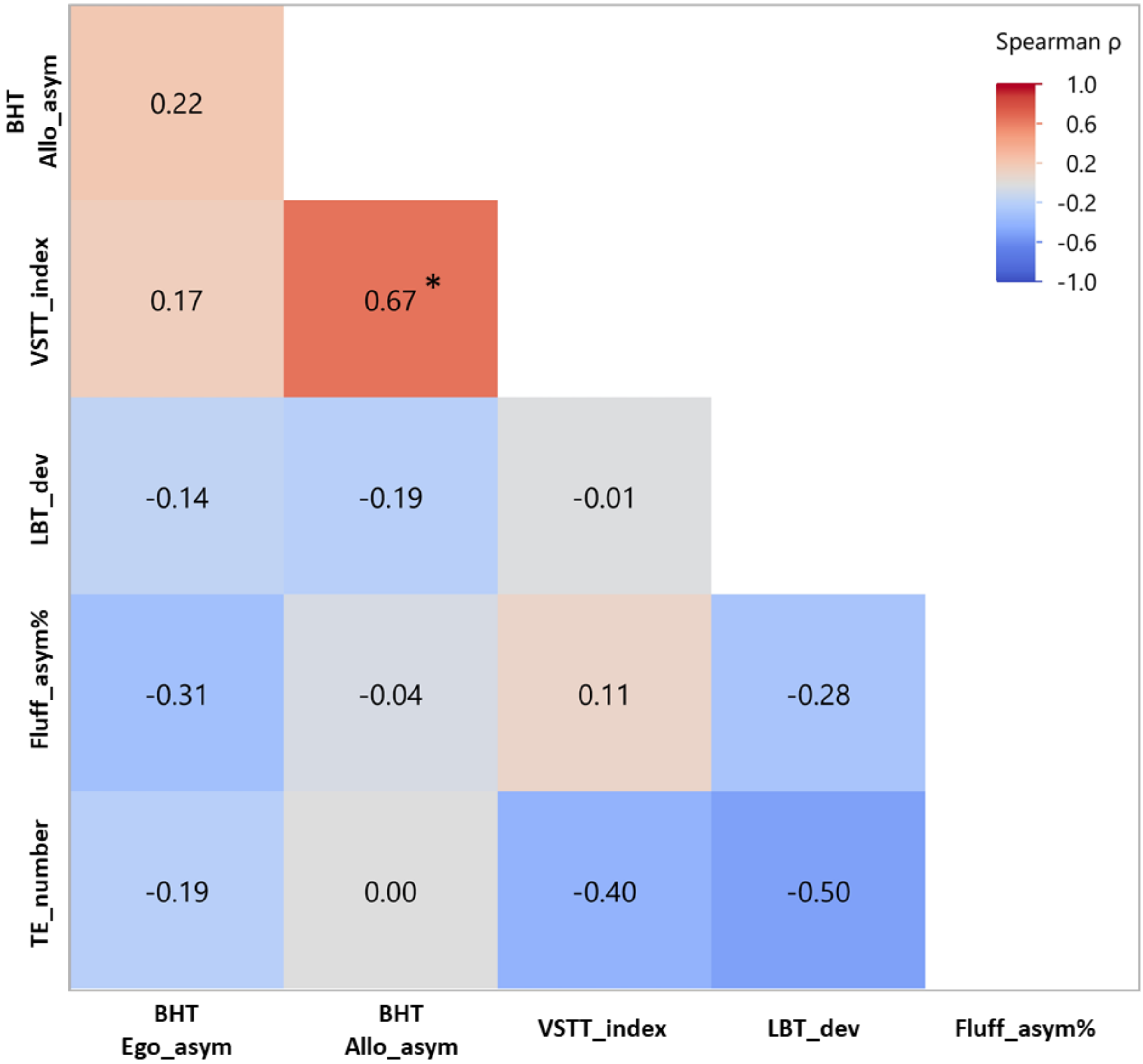
Supplementary Figure 2. Correlation heatmap of within subject correlations at five weeks post-stroke. Asterix (*) shows significant (P<.05), meaningful (ρ>.25) correlations. **Abbreviations**: BHT Ego_asym: egocentric asymmetry evaluated using the Broken Hearts Test, VSTT_index: Visual Search Time Index, BHT Allo_asym: allocentric asymmetry evaluated using the Broken Hearts Test, LBT_dev: mean on Line Bisection Test, Fluff_asym%: asymmetry in hits on the Fluff test, TE_number: number of lower limb tactile extinction points.

Supplementary figure 3



Supplementary Figure 3. Correlation heatmap of *within subject* correlations at eight weeks post-stroke. Asterix (*) shows significant ($P<.05$), meaningful ($\rho>.25$) correlations. **Abbreviations**: BHT Ego_asym: egocentric asymmetry evaluated using the Broken Hearts Test, VSTT_index: Visual Search Time Index, BHT Allo_asym: allocentric asymmetry evaluated using the Broken Hearts Test, LBT_dev: mean deviation on Line Bisection Test, Fluff_asym%: asymmetry in hits on the Fluff test, TE_number: number of lower limb tactile extinction points.

Supplementary figure 4



Supplementary Figure 4. Correlation heatmap of *within subject* correlations at 12 weeks post-stroke. Asterix (*) shows significant (*P*<.05), meaningful (ρ>.25) correlations. **Abbreviations**: BHT Ego_asym: egocentric asymmetry evaluated using the Broken Hearts Test, VSTT_index: Visual Search Time Index, BHT Allo_asym: allocentric asymmetry evaluated using the Broken Hearts Test, LBT_dev: mean deviation on Line Bisection Test, Fluff_asym%: asymmetry in hits on the Fluff test, TE_number: number of lower limb tactile extinction points.

CHAPTER 5

GENERAL DISCUSSION

Motor and cognitive deficits after stroke are frequent and enduring, and are central to the activity limitations and participation restrictions that make stroke a leading cause of disability worldwide [1]. Therefore, rehabilitation has the prominent goal of improving the post-stroke outcomes. The growing recognition of the relationship between cognitive and motor functions has sparked the development of cognitive-and-motor therapy (CMT) for stroke rehabilitation. Such a multimodal approach could produce a synergistic effect that would induce greater therapeutic gains than standalone monotherapy. While research into CMT's efficacy is expanding, its effects seem to be limited and have mainly been evaluated for gait and balance outcomes in the chronic post-stroke phase. Subsequently, questions persist regarding CMT's impact on a broad range of motor, cognitive, and cognitive-motor outcomes, especially within the subacute phase of stroke recovery (within six months) – the period that is the most intensive for rehabilitation [2].

A potential reason for the limited magnitude of CMT effects observed in prior studies could be the incomplete understanding of the relationship between cognitive and motor functions post-stroke. Therefore, the central focus of this dissertation was on deepening our understanding of the relationship between cognitive and motor functions after stroke. To gain more profound insight into this relationship, we focused on exploring the relationship between spatial neglect and postural control. This is particularly relevant as spatial neglect is a common cognitive disorder following stroke, characterized by a lateralized attention deficit [3]. This dissertation focused on visuospatial and personal neglect. Furthermore, among the various sensorimotor consequences of stroke, impaired postural control exerts a significant impact on daily activities [4, 5]. This complex motor skill aims to control the body’s position in space, for the dual purpose of stability and orientation.

To achieve this objective, we formulated three aims: 1) to assess CMT efficacy for improving cognitive, motor, and cognitive-motor outcomes after stroke, all time phases post-stroke considered, 2) to investigate the motor and cognitive relationship after stroke by examining the association between spatial neglect and postural control, and 3) to evaluate the recovery time course of spatial neglect, as this seems to be a crucial factor to consider when studying the association of spatial neglect with postural control.

This final Chapter consolidates and discusses the key findings of the thesis.

1. Main findings

- CMT delivered only a small but significant additional benefit for improving cognitive outcomes compared with standalone cognitive therapy. The approaches to delivering CMT (i.e., dual-task or integrated) were comparable in efficacy, suggesting that motor training that enlists a cognitive load per se can benefit outcomes that are likely to be clinically significant in people with stroke **(Chapter 2)**.
- Evidence was found for visuospatial neglect to be associated with an increased need for assistance while *sitting*, with an asymmetric posture toward the affected body side. For *standing balance*, visuospatial neglect was associated with larger mediolateral instability during weight-shifting, and in some cases, also larger weight-bearing asymmetry during static stance. For *goal-directed walking*, people with visuospatial neglect deviated laterally from their path **(Chapter 3.1)**.
- Although personal neglect is generally understudied, there is preliminary evidence of an association of personal neglect with decreased motor function, lower functional mobility and more dependency during activities of daily-living (ADL). People with personal neglect after stroke demonstrated a longer length of hospital stay and had greater odds of being discharged to somewhere other than home **(Chapter 3.2)**.
- Evidence was found for visuospatial neglect to be associated with Subjective Visual Verticality misperception in terms of line tilts and uncertainty measures. This may suggest that such misperception would be a key feature of visuospatial neglect **(Chapter 3.3)**.
- More severe allocentric and egocentric visuospatial neglect was significantly associated with decreased standing independence, but not with larger postural instability or greater asymmetric weight-bearing, throughout the first 12 weeks post-stroke (**Chapter 3.4)**.
- The time course of spatial neglect shows distinct recovery trajectories for different subtypes of spatial neglect. Significant improvements in egocentric visuospatial neglect scores within the first 5 weeks post-stroke were identified, followed by a plateau. Body representation neglect improved significantly from week 3 to 12 post-stroke. No significant improvements over time were found for allocentric visuospatial neglect and tactile neglect **(Chapter 4)**.

2. Discussion of the main findings

2.1. To assess cognitive-and-motor therapy efficacy for improving cognitive, motor and cognitive-motor outcomes after stroke

CMT has a small added benefit in improving cognition, mainly within the attention domain. Apart from this, no added benefits for cognitive outcomes, neither for motor and cognitive-motor outcomes were observed.

2.1.1. Current state of CMT research

It is worth noting that research on CMT is still in its infancy, with a considerable number of pilot randomized controlled trials characterized by small sample sizes. Our study has brought to light several methodological issues that may contribute to the limited effects observed, particularly concerning the included samples, assessment of CMT effects, and heterogeneity between studies on intervention characteristics.

The sample sizes in the included studies were notably small, with the majority of studies having 7–28 participants per group. Furthermore, they primarily involved relatively young participants, with ages ranging from 49 to 77 years, and an overrepresentation of males. Regarding stroke information, very few studies have considered clinical stroke severity, such as the use of the National Institutes of Health Stroke Scale (NIHSS) [6].

These observations raise concerns about the generalizability of our findings, as they limit our ability to provide suggestions for effective treatments for various groups, including those differing in age and stroke severity. In addition, the small sample sizes may have increased the chance of obtaining false-negative results. This underscores the need to address these concerns in future research to provide a more comprehensive understanding of the effects of CMT.

Regarding intervention delivery, there was large heterogeneity between studies in the methods and timing of therapy. Notably, the overall intensity of therapy was relatively low. In the majority of cases (52%), the training sessions lasted less than 12 hours. This low therapy intensity, coupled with the small sample sizes described above, likely played a role in limiting the magnitude of the observed effects. With regards to *when* CMT is delivered, a significant portion of the included studies (74%) initiated therapy after 6-month post-stroke (i.e., the chronic phase). This is in stark contrast to how stroke rehabilitation is often organized in clinical practice, as rehabilitation is usually delivered within the first week post-stroke (usually starting within 30 days). It is well known that the most significant recovery occurs within the initial 3 months after a stroke, and interventions administered outside this window tend to have modest effects. Due to the limited number of studies conducted within this crucial time window, we lack insights into how CMT might interact with neurobiological recovery processes present during this period.

The final methodological concern pertains to how the efficacy of CMT has been evaluated in prior studies. Presently, the predominant approach involves conducting assessments that exclusively target either cognitive or motor outcomes, with only a limited number of studies considering integrated cognitive-motor outcomes, including dual-task interference. Consequently, it is unknown whether the observed effects stem from an actual enhancement in dual-task performance (e.g., a reduction in dual-task costs) or from prioritizing the motor or cognitive tasks during CMT (favoring either the motor or cognitive subtask). A potential improvement in assessment methodology could involve an evaluation of the trained subcomponents of cognitive-motor tasks, encompassing metrics such as task completion time, precision, and the extent of motor-cognitive interference (see next section).

2.1.2. Suggestions for future CMT research

Future research on the efficacy of CMT in individuals with stroke should address these methodological limitations. To enhance the robustness of the findings and improve insights into CMT efficacy, I suggest the following.

1) **Document stroke information in a more detailed manner**

   Thoroughly document stroke-related details, including information on lesion sites and (neuropathological and clinical) stroke severity. This will provide insight into the (non-)suitability of CMT across various individuals and would facilitate the development of personalized CMT strategies. Such research requires a larger and more diverse sample.

2) **Explore optimal timing, dosage and duration of therapy:**

   Future research should explore more intensive CMT protocols with higher therapy intensities, especially within the first 3 months post-stroke. This will help determine whether there are critical windows for maximizing the benefits of CMT.

3) **Assess CMT efficacy by evaluating cognitive-motor outcomes**

This evaluation is essential to determine whether CMT genuinely enhances dual-task performance or primarily favors one aspect (motor or cognitive) during the intervention. This may include outcome measures that evaluate cognitive-motor interference, in which a single task (e.g., walking) would be compared to a dual-task condition (e.g., walking while performing an arithmetic task). One may then evaluate the pattern of interference (none, cognitive-related motor interference, motor-related cognitive interference, motor facilitation, cognitive facilitation, cognitive-priority trade-off, motor-priority trade- off, mutual interference, or mutual facilitation) (see Table 5.1).

	Cognitive performance		
	No change	Improved	Worsened
Motor performance			
No change	No dual-task interference	Cognitive facilitation	Motor-related cognitive interference
Improved	Motor facilitation	Mutual facilitation	Motor-priority trade-off
Worsened	Cognitive-related motor interference	Cognitive-priority trade-off	Mutual interference

Table 5.1. Nine possible patterns of cognitive-motor interference, as proposed by Plummer et al. Table derived from Plummer et al. [7].

2.1.3. Clinical implications

Although CMT research is still in its early stages, some recommendations for clinical practice can be made based on the findings in **Chapter 2**. The method of delivering CMT did not matter in terms of its efficacy. Thus, providing motor training that enlists a cognitive load per se, may benefit outcomes. However, in line with general rehabilitation protocols, CMT should be delivered through personalized rehabilitation that considers the specific cognitive and motor profiles of the individual. CMT involves performing both motor and cognitive tasks simultaneously. This approach challenges individuals on various levels. First, it necessitates the division of attention between motor and cognitive tasks, which demands divided attention capabilities. Second, individuals must maintain the motor task while temporarily storing and manipulating the information required for cognitive tasks, showcasing the importance of working memory functioning, a critical component of executive functions. Furthermore, other executive functions are involved in CMT, including action initiation, response inhibition, purposive action abilities, and planning [8].

For individuals who can walk autonomously, the motor task may demand only minimal cognitive resources, enabling them to allocate more resources to the cognitive task. In such cases, only a limited dual-task cost, such as cognitive-motor interference, may be present [8]. However, individuals who have experienced a stroke may already find the primary motor task to be challenging. Consequently, the motor task may already deplete most or all of their cognitive resources, leaving little room for cognitive task performance. In such cases, it is of interest to adapt CMT by selecting a more manageable primary motor task or simpler cognitive task. Alternatively, delaying CMT until the primary motor task can be effectively performed may be necessary.

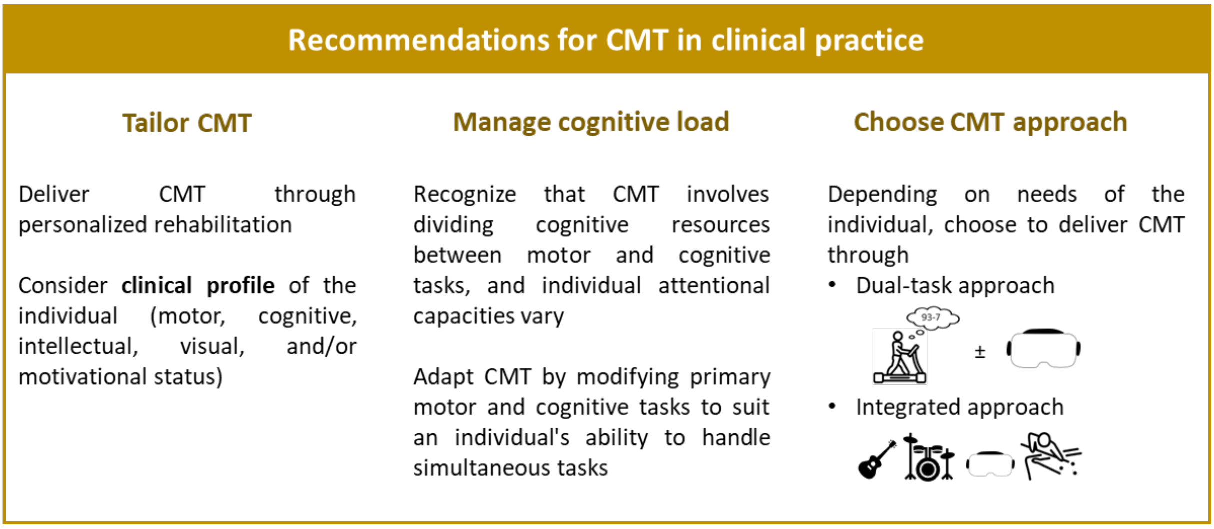


Figure 5.1. Recommendations for clinical practice regarding the implementation of cognitive-and-motor therapy. Abbreviations: CMT – cognitive-and-motor therapy.

New technologies, such as Augmented Reality (AR) and Virtual Reality (VR), have the advantage of appropriately adjusting the task difficulty relative to the participants' level of function. With recent technological advancements and growing accessibility of these technologies, their affordability has improved. This has resulted in an upsurge in their utilization in both clinical and research settings [9-11]. These technologies have some advantages, as they allow the simultaneous practice of cognitive and motor tasks in a safe and controlled setting while still ensuring ecological validity through their ability to simulate real-world activities [10, 11]. Such systems can collect extensive data on a participant's performance, including reaction times, eye and head movement patterns, and decision-making processes [12]. Such data may be invaluable for clinicians and researchers for tracking progression, identifying areas of improvement, and fine-tuning training programs. An additional benefit is the ability to provide personalized training programs in which the difficulty level of the tasks can be adapted based on the individual's performance, ensuring tailored and challenging training [10, 11]. Prior studies specifically on the user experience and feasibility of AR/VR have shown that individuals with stroke found such systems usable, engaging, motivating, and valuable for their rehabilitation [13-15]. Approximately 46% of the studies included in our meta-analysis incorporated either AR or VR. While it would have been interesting to explore whether these technological additions enhanced efficacy to a greater extent than interventions without such technologies, our study did not explore this aspect. Moreover, particularly relevant to our forthcoming discussion on spatial neglect, it is necessary to assess the implications of cognitive and non-cognitive impairments on the usability, feasibility, and efficacy of AR/VR in the context of CMT.

2.2. To investigate the association of spatial neglect with postural control after stroke

2.2.1. Visuospatial neglect and personal neglect associate to balance and functional mobility after stroke

Figure 5.2 consolidates the findings from **Chapters 3.1, 3.2, and 3.4**, and shows that visuospatial neglect was associated with decreased sitting and standing balance, as well as decreased functional mobility. Furthermore, specific subtypes of personal neglect, such as body representation neglect, were also associated with decreased functional mobility. These activities rely heavily on postural control. The significant associations highlight that individuals with spatial neglect after stroke may require a different rehabilitation approach as compared to those without.

Impaired sitting balance is recognized as a critical predictor for poor functional outcomes and longer hospitalization duration following stroke [16, 17]. Furthermore, the ability to stand independently is a fundamental prerequisite for regaining walking ability. Therefore, especially in the context of physical therapy, addressing the heightened need for assistance during siting and standing seems important, especially in those with visuospatial neglect after stroke (Figure 5.2). Prior research has demonstrated strong evidence that trunk training can effectively enhance trunk control, sitting and standing balance, and mobility [18]. An advantage of this training is its adaptability, making it suitable for individuals who cannot sit or stand. However, it is crucial to emphasize collaboration among healthcare professionals from various disciplines to provide comprehensive patient-centered care.

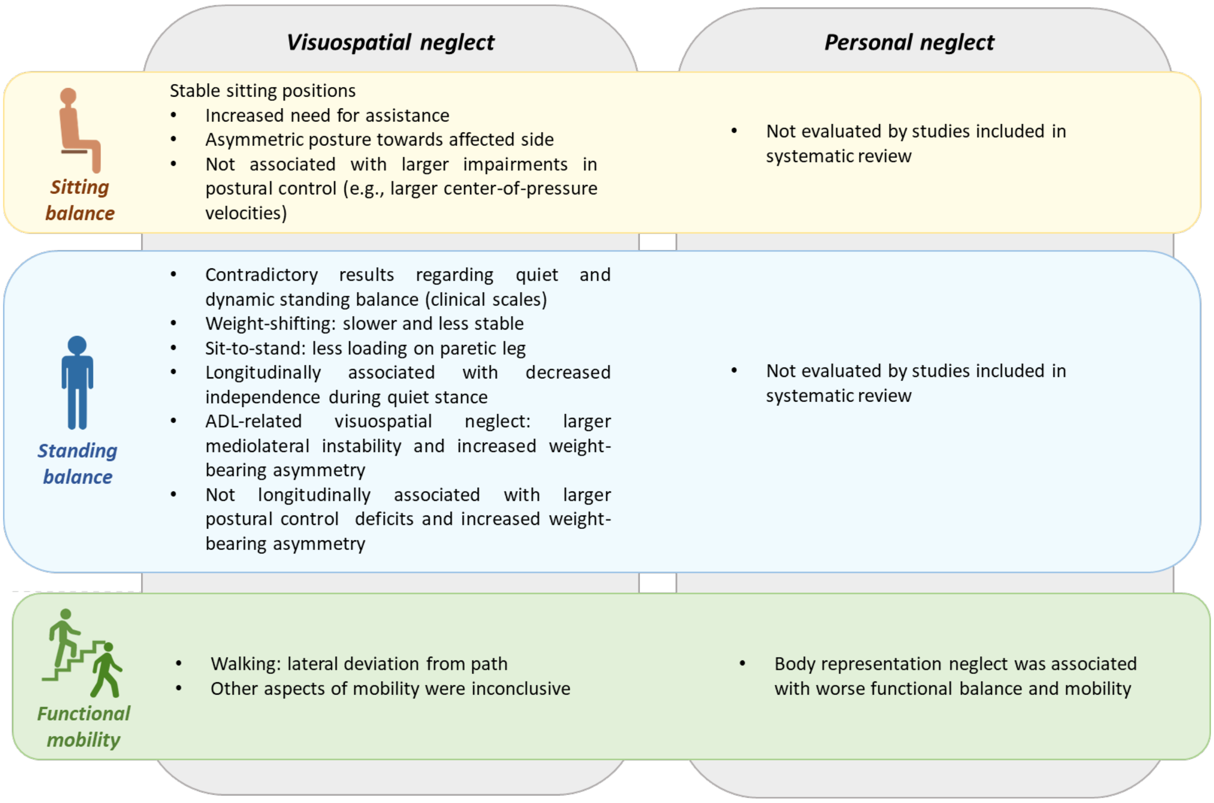


Figure 5.2. Summary of the association of visuospatial and personal neglect with sitting balance, standing balance, and functional mobility after stroke. Abbreviations: ADL – activities of daily-living

One notable observation from Figure 5.2 is that the association of personal neglect with balance and mobility outcomes after stroke has been widely understudied as compared to visuospatial neglect. The difference in research focus between personal and visuospatial neglect can be attributed to the nature of both the subtypes. Visuospatial neglect's difficulty in attending to one side of the visual space lends itself to (objective) measurement through easily administrable visual tasks. This aspect has naturally attracted more attention from both clinicians and researchers. In contrast, personal neglect presents challenges in measurement owing to its more *internal* nature, as it pertains to how a person perceives their own body, making it inherently more complex to assess [19].

2.2.2. Longitudinal association of visuospatial neglect with standing balance after stroke

One of the main gaps identified in **Chapter 3.1** was the lack of longitudinal cohort studies on visuospatial neglect and postural control. While systematic reviews have established an association between visuospatial neglect and postural control, there is limited understanding of how this association evolves over time. Our longitudinal cohort study has shed light on this, revealing a significant, independent association of egocentric and allocentric visuospatial neglect with the ability to stand independently but not with larger deficits in postural control and weight-bearing asymmetry. These analyses were corrected for lower-limb muscle strength on the most-affected side, sensory loss at the foot on the most-affected side, and age.

These findings suggest that visuospatial neglect is not directly associated with larger underlying postural control deficits or weight-bearing asymmetry. Instead, there could be other factors, such as a misperception of verticality, contributing to delayed independent standing post-stroke. Previous studies have linked such misperception to compromised balance after stroke [20, 21], and has even been proposed as a causal factor for reduced postural control [22]. **Chapter 3.3** highlighted that individuals with visuospatial neglect tend to have a more significant visual verticality misperception, as indicated by larger line tilts and greater uncertainty, compared to those without. Although largely understudied, we recently showed that individuals with visuospatial neglect had larger variability in subjective postural verticality [23]. A misperception of verticality may lead individuals to align their body with an internal vertical reference that deviates from the true vertical (i.e., gravitational vector), resulting in a phenomenon known as lateropulsion [22]. Lateropulsion is considered a postural reaction aimed at maintaining balance [22]. **Chapter 3.1** demonstrated the presence of lateropulsion while seated among individuals with visuospatial neglect after a stroke. This finding raises the possibility that lateropulsion could complicate the process of learning to stand upright. Surprisingly, we did not find pronounced weight-bearing asymmetry during standing (Chapter 3.4), which might be expected if lateropulsion was a significant factor. Thus, future studies are required to investigate the role of verticality misperception in the longitudinal association between spatial neglect and postural control.

Addressing this knowledge gap would require a longitudinal study that evaluates the recovery of individuals after stroke, preferably during the first 3–6 months after onset. Future studies should collect detailed stroke lesion information and evaluate these individuals at multiple levels, including spatial neglect (including multiple subtypes), postural control (using clinical scales and posturography), and verticality perception. It is essential to assess verticality perception in all three modalities, comprising the subjective visual vertical, subjective haptic vertical, and subjective postural vertical. Lastly, these studies should focus on recruiting subjects with both left and right hemispheric lesions, as currently most research on spatial neglect and verticality perception has been performed on individuals with a right hemispheric stroke.

The absence of a significant association between visuospatial neglect and deficits in postural control and weight-bearing asymmetry during standing might be attributed to the practical challenges involved in conducting posturographic assessments in individuals with visuospatial neglect, especially so early after stroke onset. In our longitudinal study, many of these individuals were unable to stand independently at three weeks post-stroke, making the assessment of standing balance posturography impossible. By five weeks post-stroke, they often no longer exhibited noticeable neglect symptoms on the Broken Hearts Test, making it difficult to establish significant associations between visuospatial neglect recovery and underlying postural control deficits and weight-bearing asymmetry.

To gain a more comprehensive understanding of the association between visuospatial neglect and underlying postural control mechanisms, it may be valuable to focus on seated positions. Previous studies have explored posturographic measures of sitting balance in individuals with visuospatial neglect, but their focus has mainly been on assessing sitting on stable surfaces [24-26]. However, these investigations generally did not reveal any significant association between visuospatial neglect and more pronounced deficits in postural control, such as increased center-of-pressure velocities [24-26]. Introducing an unstable surface during sitting posturography might more effectively challenge the postural control system, potentially revealing stroke and visuospatial neglect-related effects [27].

When opting for standing balance posturography as the preferred assessment method, once individuals are able to stand independently, it is crucial to incorporate highly sensitive measures for detecting visuospatial neglect. These should be capable of detecting neglect symptoms and improvements later in the recovery process (in this case, after 5 weeks post-stroke onset). This will be further discussed in the upcoming part.

2.3. To evaluate the time course of recovery of spatial neglect

The process of selecting neglect assessment tests, whether for clinical or research purposes, is complex. This requires careful consideration of the specific subtypes and features of spatial neglect being studied, as well as the time elapsed since stroke onset. While there is consensus that neglect assessment should encompass the disorder's diverse aspects concerning the affected reference frames, physical spaces, and modalities [28, 29], no study has yet provided guidelines for selecting the optimal neglect assessments in relation to the time post-stroke.

However, time is a crucial factor to consider, particularly when tracking recovery. As observed in **Chapter 3.4 and 4.1**, individuals assessed with a cancellation task (here, the Broken Hearts Test) or a relatively simple digitized test (here, the Visuospatial Search Time Test) more than five weeks post-stroke may show no (residual) improvements in egocentric visuospatial neglect. Indeed, the severity of egocentric visuospatial neglect in these tests notably decreased within the initial three–five weeks after stroke onset, after which recovery quickly levelled off. This finding aligns with previous studies that examined the time course of recovery of lower and upper limb motor impairments [30-32], and is thus suggestive of the existence of an early, time-limited phase in which post-stroke recovery is most pronounced.

However, it is important to note that this plateau in the recovery of egocentric visuospatial neglect could be attributed to the robustness of the tests and their potential ceiling effects, rather than the absence of residual improvements. In our study, the proportion of individuals exhibiting severe visuospatial neglect at baseline (i.e., those who displayed substantial deviation from normative or unimpaired ranges) was considerably lower (approximately 50 %) than that of those presenting with mild-to-moderate symptoms (i.e., those who were closer to normative or unimpaired ranges). This may have contributed to a ceiling effect, wherein participants with milder neglect symptoms reached their maximum recovery potential earlier, thus leading to a rapid attainment of a plateau.

However, this observation leaves clinical practice and research with significant challenges, especially when tracking recovery or evaluating intervention effects over time. For example, a multitude of randomized controlled trials investigating visuospatial neglect treatment have been published, many yielding neutral or only small effects [33]. A potential reason could be that additional benefits from an intervention could not be found, as the assessment tests used to evaluate these effects may be unable to identify residual, subtle symptoms of, or improvements in neglect over time.

Assessments that evaluate neglect symptoms during ADL (such as the Catherine Bergego Scale), make use of complex multitasks, or pertain VR and AR tasks may be valuable. These assessments place a heavier demand on an individual's attentional resources, potentially inducing overload and reducing their ability to compensate for (visuo)spatial deficits [34, 35]. Subsequently, otherwise undetected residual neglect symptoms may arise. This phenomenon was demonstrated by Knoppe et al. [34], who evaluated individuals who appeared to have recovered from visuospatial neglect on cancellation tests, but exhibited symptoms of neglect on more complex tasks. However, the feasibility of conducting more complex tasks with a higher attentional load shortly after stroke, as well as the time course of recovery in these tests, remains unexplored. Such tasks may be too difficult for individuals with spatial neglect to complete during the early post-stroke stages. Therefore, future research should prioritize assessing the feasibility of using more complex tests very early after a stroke and monitoring the recovery of symptoms on these tests over time.

Although a plateau around 5 weeks post-stroke was observed for egocentric visuospatial neglect, improvements in body representation neglect, a form of personal neglect, were seen up until 12 weeks post-stroke on the Fluff test. In contrast, no improvement was noted in allocentric visuospatial neglect or tactile neglect during these weeks. These differences in time courses make it necessary to select sensitive neglect assessment tools specific to certain subtypes, that are able to identify and track the recovery of subtle neglect symptoms over time.

Based on these findings, it is evident that recommending a comprehensive screening for spatial neglect, covering various aspects of physical space, reference frames, and modalities, is essential. However, an important concern to the clinical implementation of this advice, are the known constraints in time and resources of current clinical practice. These often restrict spatial neglect assessment to the visuospatial variant [19, 36].

A recent consensus statement on rapid preliminary neglect screening suggests giving priority to a visuospatial cancellation test, such as the Broken Hearts Test, as the primary method for neglect screening, especially when time allows for only one test [36]. When additional time is available, supplementary visuospatial neglect assessments like line bisection, figure copying, and the baking tray tasks are encouraged. More extensive functional evaluations, such as the Catherine Bergego Scale, should be considered only when logistically feasible [36]. It is worth noting that among these recommendations, the Catherine Bergego Scale stands out as the sole assessment tool that partially addresses aspects related to personal neglect [37]. However, as pointed out by Buxbaum et al. [38], visuospatial neglect often co-exists with personal neglect (as measured with the Fluff test), and its especially this co-existence that appears to be associated with decreased performance of ADL, as demonstrated in **Chapter 3.2**.

The recommendation to use cancellation tests as the primary screening tool is justified, especially in acute settings, where they can provide a quick screening of visuospatial neglect in newly admitted patients [36]. However, it is important for clinicians to recognize that these tests are specific to evaluating visuospatial neglect in peri-personal space and should not be relied upon as the sole means of assessing spatial neglect comprehensively. Additionally, findings from our study on the time course of spatial neglect indicate that improvement of symptoms on such a cancellation test plateaus around 5 weeks post-stroke onset, potentially due to a ceiling effect. Therefore, based on the results of Chapter 4, the following approach highlighted in Figure 5.3 is proposed.

Recommendations for spatial neglect screening	
Phase 1: **Within the first 5 weeks after stroke**	**Phase 2:** **> 5 weeks after stroke**
• **Paper-and-pencil tests** (e.g., a cancellation task), or **simple digitized assessments** (e.g., the VSTT) may be sensitive enough as a primary screener • Choose a paper-and-pencil tests that evaluates multiple subtypes of spatial neglect, such as the Broken Hearts Test	• Employ **more complex spatial neglect tests** as primary screening, such that a greater demand is placed upon the attentional system. These may include assessments conducted within the context of activities of daily-living, such as the Catherine Bergego Scale

When possible, include personal neglect tests during primary screening

When time allows:

- The Fluff test and tactile extinction tests are characterized by minimal material requirements, by efficiency as they can almost be performed simultaneously, and they can be completed within a total timeframe of 5-10 minutes

When time does not allow:

- Simple observations of ADL, such as monitoring the patient while they comb their hair or dress themselves, may unveil signs of personal neglect

Recommendations for tracking the recovery of spatial neglect

- Track recovery on multiple, though fixed, timepoints throughout time; especially throughout the first 12 weeks post-stroke
- Keep in mind potential ceiling effects of simple paper-and-pencil and digitized assessments
- Quickly introduce more complex spatial neglect tests, when feasible
- Be mindful of potential learning effects

Figure 5.3. Recommendations for spatial neglect screening and for tracking its recovery based on the results of Chapter 4. Abbreviations: VSTT – Visuospatial Search Time Test.

3. Limitations

3.1. Need for evaluating the motor-cognitive relationship beyond spatial neglect

In the current thesis, we opted to investigate the relationship between motor and cognitive functions after stroke by focusing on the time-dependent relationship between spatial neglect and postural control. While spatial neglect is undeniably a prevalent cognitive deficit after stroke [39], it should be recognized that an array of other post-stroke impairments also influence movement and behavior after stroke [40, 41]. Additionally, stroke survivors often struggle with a combined presence of cognitive and non-cognitive deficits [40, 42].

One limitation is that by narrowing our focus solely to spatial neglect, we had to constrain our interpretations exclusively within the context of this particular cognitive deficit. This may have led to an incomplete understanding of the broader cognitive deficits that post-stroke individuals might encounter [40]. Some examples are impairments in executive functioning, which governs higher-order cognitive processes such as decision-making and planning; limb apraxia, which relates to difficulties in performing purposeful movements; memory disorders, which can hinder the retention of motor sequences; aphasia, which affects language expression and comprehension; and attentional disorders, which influence the ability to sustain focus and concentration [40, 41].

A second limitation is that we did not evaluate mood disorder such as anxiety and depression. However, it is well-known that they are common after stroke [43, 44], and that they may have a negative impact on long-term recovery in daily-life activities [45]. In addition, a prior study by Williams et al. [44] showed that post-stroke depression was significantly associated with more severe visuospatial neglect symptoms, as measured with the Broken Hearts Test. Anxiety, too, displayed a similar association, although its significance disappeared after adjusting for depression scores.

A third limitation is that we did not evaluate the impact of homonymous hemianopia, which is a post-stroke visual field deficit, in which individuals have a loss of visual field to one side due to damage to the primary visual pathway [46]. While this is a distinct impairment from visuospatial neglect, both deficits are frequently confused because of the overlap in their clinical presentation, and the fact that they may both affect an individual's visual perception.

Whereas homonymous hemianopia primarily affects the 'input' level, impairing visual sensory input, spatial neglect is situated at the 'processing' level, compromising the processing of sensory information related to the visual hemispace (see Figure 1.3 in Chapter 1 – part 4.1) [46]. Nonetheless, prior studies have shown that these deficits may co-occur [47]. In our study, we did screen the medical records and excluded individuals with post-stroke homonymous hemianopia. However, we did not conduct homonymous hemianopia tests ourselves to confirm the absence of this deficit. Furthermore, it would have been valuable to investigate how the presence of homonymous hemianopia may impact the association between visuospatial neglect and post-stroke balance and mobility.

To more holistically evaluate the relationship of cognition and motor function post-stroke, future research should focus on evaluating a broader spectrum of cognitive and non-cognitive functions that extend beyond spatial neglect. This holistic perspective would enable researchers and clinicians to tailor interventions that address the interplay between cognitive impairments and motor recovery, facilitating more effective rehabilitation strategies.

3.2. Need for evaluating the impact of stroke lesion information on the observed results

One limitation of our longitudinal studies is our inability to assess the mediating role of stroke severity in the relationship between visuospatial neglect and standing balance, as well as in the recovery time courses of visuospatial and personal neglect (as discussed in Chapter 3.4 and Chapter 4.1). The primary reason for this limitation is the unavailability of comprehensive lesion information, encompassing both neuropathological and clinical details, such as etiology, severity, and topography. This lack of information has constrained our ability to thoroughly investigate the influence of lesion characteristics on the observed outcomes. Nevertheless, it is worth noting that a study by Nijboer et al. [48], conducted on a sample of 90 individuals with a first-ever ischemic stroke, did not find significant overall associations between clinical stroke severity (assessed using the Bamford Classification within the first 2 weeks post-stroke) and the severity of visuospatial neglect (assessed with a cancellation task). Furthermore, their study indicated that the recovery of visuospatial neglect was predominantly dependent upon the factor of 'time'. Further research should evaluate whether the other lesion characteristics would have an impact on this.

Another limitation is that we focused only on ischemic and cerebral hemorrhagic strokes, and that we did not evaluate the impact of this lesion type upon our results. However, due to their etiology, they may exhibit different clinical profiles and, potentially, different recovery time courses as well. Although this may be the case, a recent study has shown that the two stroke types showed an overlapped time course of functional recovery (modified Rankin Scale at discharge), with age and initial stroke severity being the main prognostic factors [49].

4. To conclude

This thesis clearly demonstrates the complexity of studying cognitive-motor relationships after stroke, and sheds light on several key findings that have significant implications for stroke rehabilitation and research. It has revealed that CMT currently offers a small but significant benefit for cognitive outcomes after stroke, with technology-enhanced approaches showing promising avenues for further research. The thesis also emphasizes the association of visuospatial with decreased sitting and standing balance, as well as decreased functional mobility, which highlights the need for a tailored rehabilitation approach for individuals with visuospatial neglect after stroke. It also brings to light the limited amount of research onto the topic of personal neglect. The study reflects the importance and complexity of assessing spatial neglect. Its distinct time courses of recovery call for a tailored approach to spatial neglect screening in clinical practice, keeping in mind the different subtypes of spatial neglect. Finally, this thesis underlines the necessity of broadening the scope of research beyond spatial neglect to encompass a wider range of cognitive impairments post-stroke.

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NEDERLANDSTALIGE SAMENVATTING

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Het centrale focuspunt van deze thesis lag op het verder uitdiepen van de relatie tussen cognitieve en motorische functies na een beroerte. Om dit te bereiken, hebben we drie doelen geformuleerd. Het *eerste doel* was het beoordelen van de effectiviteit van gecombineerde cognitief-en-motorische therapie (CMT) voor het verbeteren van cognitieve, motorische en cognitief-motorische uitkomsten na een beroerte. CMT betreft het simultaan uitvoeren van motorische en cognitieve taken. Er wordt gesuggereerd dat er hierdoor grotere therapeutische effecten kunnen worden behaald in vergelijking met geïsoleerde motorische of cognitieve interventies.

De tweede doelstelling was om dieper in te gaan op deze relatie door de associatie te onderzoeken tussen specifieke cognitieve en motorische tekortkomingen na een beroerte. Hoewel een beroerte kan leiden tot een breed spectrum van neurocognitieve en motorische tekortkomingen, richtte ons onderzoek zich specifiek op de associatie tussen spatieel neglect en posturale controle. Dit is bijzonder relevant gezien het feit dat spatieel neglect een veelvoorkomende cognitieve stoornis is na een beroerte. Het evalueren van deze relatie is bijzonder relevant gezien spatieel neglect een veelvoorkomende cognitieve aandoening is na een beroerte. Het wordt gekenmerkt door een gelateraliseerd aandachtstekort dat zich voornamelijk één kant van de ruimte of het lichaam uit. Ons onderzoek omvatte twee subtypen van spatieel neglect: visuospatieel neglect en persoonlijk neglect. Naast deze cognitieve aspecten hebben we ervoor gekozen om posturale controle te beoordelen als een cruciaal aspect van motorische functie. Posturale controle verwijst naar de controle van de positie van het lichaam in de ruimte, met het dubbele doel van stabiliteit (het controleren van het zwaartepunt in relatie tot de steunbasis) en oriëntatie (het controleren van de lichaamssegmenten ten opzichte van elkaar, de taak en de omgeving). Dit is een complexe motorische vaardigheid, voortkomend uit de interactie tussen meerdere sensorimotorische en cognitieve processen. Zoals de definitie impliceert, is posturale controle van groot belang voor de uitvoering van diverse dagelijkse activiteiten, zoals zitten, staan en functionele mobiliteit. Daarom is het belangrijk om een diepgaander begrip te krijgen van de factoren die bijdragen aan het herstel van posturale controle na een beroerte.

Hoofdstuk 1 van dit proefschrift omvat een algemene inleiding over beroertes, de gevolgen ervan en het herstelproces. Het introduceert de relatie tussen cognitie en motoriek, en het geeft achtergrondinformatie bij de vraag waarom het combineren van de behandeling van zowel cognitieve als motorische functies (CMT) tijdens revalidatie gunstiger zou zijn, vergeleken met afzonderlijke behandelingen. Het hoofdstuk stelt ook een hypothese op voor de observatie van de schijnbaar (huidige) beperkte doeltreffendheid van CMT. Daarnaast schuift het hoofdstuk het idee naar voren om de relatie tussen cognitie en motoriek na een beroerte verder uit te diepen, door in te zoomen op de relatie tussen spatieel neglect, een veelvoorkomend cognitief deficit na een beroerte, en posturale controle.

Hoofdstuk 2 onderzocht de effecten van CMT op motorische, cognitieve en cognitief-motorische uitkomsten na een beroerte via een meta-analyse van de huidige literatuur. Het laat zien dat CMT slechts kleine, doch significante, voordelen biedt voor het verbeteren van cognitie na een beroerte. Deze bevindingen suggereren dat de combinatie van een motorische training met de betrokkenheid van cognitieve aspecten, kan zorgen voor klinisch relevante verbeteringen voor patiënten na een beroerte. Hoewel huidige studies over CMT waardevolle inzichten bieden in de mogelijke voordelen en valkuilen van het integreren van cognitief en motorisch gedrag, blijft een alomvattend begrip van de onderliggende mechanismen die de waargenomen resultaten kunnen verklaren, ongekend.

Hoofdstuk 3 onderzocht de associatie tussen spatieel neglect en motorische functie na een beroerte. **Hoofdstuk 3.1** besprak de huidige literatuur over de associatie tussen visuospatieel neglect enerzijds, en balans en mobiliteit na een beroerte, anderzijds. De resultaten gaven aan dat er een verband bestaat tussen beiden, waarbij visuospatieel neglect gerelateerd is aan een verhoogde hulpbehoevendheid tijdens *zitten*, met een asymmetrische zithouding naar de aangetaste lichaamszijde toe. Voor staand evenwicht werd visuospatieel neglect geassocieerd met een grotere medio-laterale instabiliteit tijdens gewichttransfers, en in sommige gevallen ook een grotere asymmetrie in gewichtname tussen het linker en rechter been in een statische houding. Bij *doelgericht wandelen* weken mensen met visuospatieel neglect af van hun pad. Ondanks deze resultaten, is onderzoek naar de relatie tussen het herstel van visuospatieel neglect en verbeteringen in staand evenwicht en mobiliteit doorheen de tijd schaars. **Hoofdstuk 3.2** besprak de huidige literatuur over de relatie tussen persoonlijk neglect en de motorische functie, dagelijkse activiteiten en participatie-uitkomsten na een beroerte.

Huidige studies suggereren dat persoonlijk neglect geassocieerd is met een gedaalde motorische functie, verminderde functionele mobiliteit en verhoogde afhankelijkheid tijdens dagelijkse activiteiten. Mensen met persoonlijk neglect na een beroerte hebben een significant grotere kans op langere ziekenhuisopnames en een grotere kans op ontslag naar een niet-thuisomgeving. Deze resultaten gaven een eerste indicatie van een associatie. Er is echter een aanzienlijk gebrek aan onderzoeken die evalueren hoe het herstel van persoonlijk neglect verband houdt met dergelijke revalidatie-uitkomsten doorheen de tijd. **Hoofdstuk 3.3** zocht een verklaring voor de bevindingen in Hoofdstuk 3.1 en Hoofdstuk 3.2 en bekeek hoe spatieel neglect geassocieerd is aan misperceptie van verticaliteit na een beroerte. Spatieel neglect wordt geassocieerd met subjectieve visuele verticaliteits-misperceptie in termen van lijnhellingen en onzekerheidsmaten. Dit suggereert dat dergelijke misperceptie een belangrijk kenmerk is van spatieel neglect. Andere modaliteiten dan de visuele werden slechts beperkt onderzocht of leverden inconsistente resultaten op. Er is ook hier een tekort aan longitudinale studies die het herstel van misperceptie van verticaliteit na een beroerte evalueren. In **Hoofdstuk 3.4** trachtten we aan het tekort van longitudinale studies te tegemoet te komen. Een longitudinale observationele cohortstudie werd uitgevoerd, met als doel de associatie van egocentrisch en allocentrisch visuospatieel neglect met het herstel van het staand evenwicht in de eerste 12 weken na een beroerte te onderzoeken. Uit deze studie blijkt dat zowel egocentrisch als allocentrisch visuospatieel neglect significant gerelateerd zijn aan een hogere afhankelijkheid bij het staan. Echter zijn beiden niet gerelateerd aan een grotere posturale instabiliteit of grotere asymmetrie in gewichtname. Dit suggereert dat andere factoren moeten bijdragen aan het vertraagd onafhankelijk staan bij mensen met visuospatieel neglect.

In **Hoofdstuk 4** werd het tijdsverloop van visuospatieel en persoonlijk neglect geëvalueerd. Dit hoofdstuk toont significante verbeteringen in egocentrisch visuospatieel neglect binnen de eerste 5 weken na een beroerte, gevolgd door een plateau. Lichaamsrepresentatie-neglect verbeterde significant van week 3 tot 12 na een beroerte. Er werden geen significante verbeteringen doorheen de tijd gevonden voor allocentrisch visuospatieel neglect en tactiel neglect.

Samenvattend draagt dit proefschrift bij aan ons begrip over de relatie tussen cognitieve en motorische functies na een beroerte. De bevindingen benadrukten de mogelijke voordelen van CMT voor beroerterevalidatie en wierpen licht op de verbanden tussen spatieel neglect en motorisch functioneren. Het proefschrift benadrukte belangrijke klinische implicaties, waaronder de noodzaak voor een holistische benadering tot de revalidatie die rekening houdt met de relatie tussen cognitieve en motorische beperkingen. De potentiële voordelen van CMT werden benadrukt, vooral wanneer ze op maat zijn gemaakt voor het individu. Daarnaast werd de noodzaak van een holistische aanpak om spatieel neglect te beoordelen, met name rekening houdend met de tijd na een beroerte, benadrukt. Er werden aanbevelingen voor toekomstig onderzoek gegeven. Zo zou men CMT-methodologieën moeten verfijnen, dieper moeten ingaan op specifieke subtypen van neglect en hun verloop in de tijd, en diepgaander onderzoeken wat de invloed is van persoonlijk neglect op het motorisch functioneren. Daarnaast moet het onderzoek naar de relatie tussen cognitie en motoriek worden verbreed, door ook cognitieve tekortkomingen te evalueren die verder gaan dan spatieel neglect, en moet er worden onderzocht hoe de misperceptie van verticaliteit een rol kan spelen in de relatie tussen spatieel neglect en posturale controle.

CURRICULUM VITAE

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General information

Name: Elissa Embrechts

Date of Birth: 16 February 1994

Education

2012 – 2013	Karel de Grote Hogeschool, Belgium *Bachelor in Midwifery*
2013 – 2016	University of Antwerp, Belgium *Bachelor in Rehabilitation Sciences and Physiotherapy* Graduated with Distinction
2016 – 2018	University of Antwerp, Belgium *Master in Rehabilitation Sciences and Physiotherapy* Graduated with Great Distinction
2018 – Current	University of Antwerp, Belgium Doctor In Medical Sciences (PhD thesis: Gaining insight into the cognitive-motor relationship after stroke: Attentively moving rehabilitation forward; submitted)

Continuous Professional Development Courses

April 2019	Excel database management and pivot tables, STATUA, UAntwerpen, Belgium
April 2019	Writing Academic Papers, UAntwerpen, Belgium
June 2019	Basic Principles of Statistics, STATUA, UAntwerpen, Belgium
June 2019	Multiple Linear Regression, STATUA, UAntwerpen, Belgium
April 2019	Developing a publication strategy in the physical and life sciences, UAntwerpen, Belgium
September 2019	Interactive Gait Analysis Seminar, ESMAC, Amsterdam, The Netherlands
September 2019	Motor Learning and Gait Training Seminar, ESMAC, Amsterdam, The Netherlands
January 2020	Analysis of Grouped and Longitudinal Data using Linear Mixed Models, STATUA, UAntwerpen, Belgium
May 2021	Mindmapping, UAntwerpen, Belgium

October 2021	European Stroke Organisation Summer School, Caen, France
May 2023	Spring School Towards @home Motor Rehabilitation after Stroke, Maastricht, The Netherlands
May 2023	Statistical Parametric Mapping for Biomechanics workshop, KU Leuven, Belgium

Teaching Experience – overview courses

- Rehabilitation Technology (MA level, UAntwerpen)
- Neurokinesitherapie 2 (BA level, UAntwerpen)
- Supervising Master Thesis (MA level, UAntwerpen)

Research Experience – overview stays

Universiteit Utrecht, Helmholtz Institute - August 17-22 2022

Universiteit Utrecht, Helmholtz Institute – October 5-7 2022

Universiteit Utrecht, Helmholtz Institute – September 3 - 15 2023

Membership of board or committee

2020 – 2023 Bureau Vakgroepsraad – effectief stemgerechtigd lid

2020 – 2023 Vakgroepsraad – effectief stemgerechtigd lid

Services

September 2018	SuperNova, Antwerpen, Belgium
November 2019	Dag van de Wetenschap, Antwerpen, Belgium
March 2020	Wetenschapsbattle, Schoten, Belgium
October 2021	PROEFKOT, UAntwerpen, Wilrijk, Belgium
April 2023	Slimmer meten is beter weten? De mogelijkheden van mixed reality bij mensen met een hersenletsel, Thomas More Hogeschool (bijscholing), Belgium

Awards

June 2020	De Luca Foundation – Equipment Donation Initiative: selected as a recipient of a 2-Sensor Trigno AvantiMobile ElectroMyoGraphy (EMG) System
October 2021	Session Award YSPR: received the session Award
May 2023	Winner of the BOF UAntwerpen Post-Doc Challenge

Grants

Travel Grants

- FWO Travel Grant - kort verblijf: Research stay Utrecht
- SMALLL Travel Grant - Research stay Utrecht

Funding

Co-writer/co-proposer

- STIMPRO entitled "Attentional deficits and postural alignment: providing new insights in the interaction betweencognition and motor function after stroke" under Prof. Dr. Nick Gebruers and Prof. Dr. Wim Saeys. This grant wassuccessful.
- DOCPRO4 entitled "Spatial inattention and motor functioning after stroke: an in-depth analysis of the influence ofvisuospatial neglect on motor recovery". This grant was successful.
- COST Action Proposal OC-2023-1-26364 " Extended Reality Neurorehabilitation of Spatial Neglect and Related Disorders After Brain Injury "

Oral presentations

November 2021	Kinekring Voorkempen: *Balanscontrole her-leren na een beroerte: implicaties voor lopende onderzoeksprojecten en de revalidatie.* Westmalle, Belgium
October 2021	Joint European and World Stroke Organization Conference – ESO WSO: Young Stroke Physicians and Researchers Workshop (YSPR). An in-depth analysis of the influence of spatial neglect on motor recovery post-stroke: study protocol. Online.
September 2021	OPSYRIS (Organisation for Psychological Research into Stroke): Functional balance and mobility in patients with visuospatial neglect: preliminary data of a longitudinal clinical cohort study. Durham, England (Hybrid).
May 2022	OPSYRIS (Organisation for Psychological Research into Stroke): *recovery of spatial neglect after stroke.* Leuven, Belgium

May 2022	Nederlandse Vereniging voor Neuropsychologie ‘focus op aandacht’: *preliminaire data van een longitudinale cohort studie.* Nijmegen, The Netherlands.
May 2023	NeuroDay UAntwerpen *Spatial neglect and postural control after stroke*
Dec 2023	Revabeurs Gent – ZieZo vzw *Visuospatieel neglect na een niet-aangeboren hersenletsel*

Poster presentations

May 2019	Neurorehabilitation and Neural Repair, Maastricht, The Netherlands *Lower limb muscle synergies during walking after stroke: a systematic review*
September 2019	Annual Meeting of the European Society of Movement Analysis in Adults and Children *The impact of exposure to immersive virtual reality on spatiotemporal gait parameters in healthy participants*
October 2020	World Congress of Neurorehabilitation, virtual *The association between visuospatial neglect and balance and mobility post-stroke: a systematic review*
November 2020	Joint European and World Stroke Organization Conference *An in-depth analysis of the influence of spatial neglect on motor recovery post-stroke: study protocol*
September 2021	European Stroke Organisation Conference *Motor and functional consequences associated with personal neglect after stroke: a systematic review*
September 2021	Organisation for Psychological Research into Stroke Conference *Misperception of verticality: a key characteristic of hemispatial neglect after stroke? A systematic review*
May 2022	Nederlandse Vereniging voor Neuropsychologie Voorjaarsconferentie *Delayed acquisition of functional motor milestones in people with visuospatial neglect after stroke: preliminary data of a longitudinal cohort study*
May 2022	Organisation for Psychological Research into Stroke Conference *Cognitive-and-Motor Therapy after stroke is not superior to Cognitive and Motor Therapy alone to improve motor and cognitive outcomes: a meta-analysis*
May 2022	Organisation for Psychological Research into Stroke Conference *Upper limb activity trackers for quantifying spontaneous movements in stroke patients with spatial neglect: a protocol for a pilot study*
May 2023	NeuroDay UAntwerpen *Does visuospatial neglect contribute to standing balance within the first 12 weeks post-stroke? A prospective longitudinal cohort study*

May 2023 Neurorehabilitation and Neural Repair Conference
Does visuospatial neglect contribute to standing balance within the first 12 weeks post-stroke? A prospective longitudinal cohort study

A1 Publications

2023

- **Elissa Embrechts**, Jonas Schröder, Tanja C.W. Nijboer, Charlotte van der Waal, Christophe Lafosse, Steven Truijen, Wim Saeys. Does visuospatial neglect contribute to standing balance within the first 12 weeks post-stroke? A prospective longitudinal cohort study. BMC Neurology. Accepted. DOI : 10.1186/s12883-023-03475-1.
- **Elissa Embrechts**, Thomas B. McGuckian, Jeffrey M. Rogers, Chris H. Dijkerman, Bert Steenbergen, Peter H. Wilson, Tanja C.W. Nijboer. Cognitive-and-Motor Therapy After Stroke Is Not Superior to Motor and Cognitive Therapy Alone to Improve Cognitive and Motor Outcomes: New Insights From a Meta-analysis. Archives of Physical Medicine and Rehabilitation. 2023, ISSN 0003-9993, https://doi.org/10.1016/j.apmr.2023.05.010.
- **Elissa Embrechts**, Renata Loureiro-Chaves, Tanja C.W. Nijboer, Christophe Lafosse, Steven Truijen, Wim Saeys. The Association of Personal Neglect with Motor, Activities of Daily Living, and Participation Outcomes after Stroke: A Systematic Review. Archives of Clinical Neuropsychology. 2023, ISNN 1873-5843, DOI: 10.1093/arclin/acad063.
- Jonas Schröder, Wim Saeys, **Elissa Embrechts**, Ann Halleman, Laetitia Yperzeele, Steven Truijen, Gert Kwakkel. Recovery of Quiet Standing Balance and Lower Limb Motor Impairment Early Poststroke: How Are They Related? Neurorehabilitation and Neural Repair. 2023;37(8):530-544. doi:10.1177/15459683231186983.
- Charlotte van der Waal, **Elissa Embrechts**, Renata Loureiro-Chaves, Nick Gebruers, Steven Truijen, Wim Saeys. Lateropulsion with active pushing in stroke patients: its link with lesion location and the perception of verticality. A systematic review. Topics in Stroke Rehabilitation. 2023. 30:3, 281-297, DOI: 10.1080/10749357.2022.2026563.
- Charlotte van der Waal, **Elissa Embrechts**, Steven Truijen, Wim Saeys. Do we need to consider head-on-body position, starting roll position and presence of visuospatial neglect when assessing perception of verticality after stroke?. Topics in Stroke Rehabilitation. 2023. DOI: 10.1080/10749357.2023.2253622.

2022

- **Elissa Embrechts**, Charlotte van der Waal, Dorine Anseeuw, Jessica van Buijnderen, Améline Leroij, Christophe Lafosse, Tanja CW Nijboer, Steven Truijen, Wim Saeys. Association between spatial neglect and impaired verticality perception after stroke: A systematic review. Annals of Physical and Rehabilitation Medicine, Volume 66, Issue 3, 2023, ISSN 1877-0657, DOI: 10.1016/j.rehab.2022.101700.

2021

- **Elissa Embrechts**, Tamaya Van Criekinge, Jonas Schröder, Tanja Nijboer, Christophe Lafosse, Steven Truijen, Wim Saeys. The association between visuospatial neglect and balance and mobility post-stroke onset: A systematic review. Annals of Physical and Rehabilitation Medicine, Volume 64, Issue 4, 2021, 101449, ISSN 1877-0657, DOI: 10.1016/j.rehab.2020.10.003.

2020

- Tamaya Van Criekinge, Jordi Vermeulen, Keanu Wagemans, Jonas Schröder, **Elissa Embrechts**, Steven Truijen, Ann Hallemans & Wim Saeys. Lower limb muscle synergies during walking after stroke: a systematic review. Disability and Rehabilitation, 2020; 42:20, 2836-2845, DOI: 10.1080/09638288.2019.1578421

A1 Publications submitted

- **Elissa Embrechts**, Jonas Schröder, Charlotte van der Waal, Christophe Lafosse, Steven Truijen, Wim Saeys, Tanja C.W. Nijboer. Time Course of Recovery of Visuospatial and Personal Neglect in the First 12 Weeks after Stroke: an Exploratory longitudinal Cohort Study. Neuropsychological Rehabilitation. *Under review.*
- Ivan De Boi, **Elissa Embrechts**, Quirine Schatteman, Rudi Penne, Steven Truijen, Wim Saeys. Assessment and treatment of visuospatial neglect using active learning with Gaussian processes regression. Artificial Intelligence in Medicine. *Under review*.
- Jonas Schröder, **Elissa Embrechts**, Renata Loureiro-Chaves, Steven Truijen, Gert Kwakkel, Wim Saeys. Exoskeletal training for enhancing lower limb motor recovery early poststroke: Does timing matter? A pilot randomized trial. NeuroRehabilitation. *Under review.*
- Renata Loureiro-Chaves, **Elissa Embrechts**, Amber van Hinsberg, Jonas Schröder, Laetitia Yperzeele, Cathy M. Stinaer, Steven Truijen, Wim Saeys. Association between white matter integrity and lower limb motor impairment after stroke: a systematic review. Brazilian Journal of Physical Therapy. *Under review.*

Published conference proceedings

2023

- Visuospatial neglect is associated with standing independence early post-stroke – a prospective cohort study. **Elissa Embrechts**, Jonas Schröder, Tanja C.W. Nijboer, Christophe Lafosse, Steven Truijen, Wim Saeys. Advances in Stroke Recovery Scientific Conference 2023 Abstracts. Neurorehabilitation and Neural Repair. 2023;37(5_suppl):3S-55S. https://doi.org/10.1177/15459683231163223

2019

- The Impact of Exposure to Immersive Virtual Reality on Spatiotemporal Gait Parameters in Healthy Participants: A Preliminary Study. **Elissa Embrechts**, Tamaya van

Criekinge, Jonas Schröder, Nolan Herssens, Ann Hallemans, Steven Truijen, Wim Saeys. Gait & Posture. 2019;73:577-8.

- Are Muscle Synergies Related to Functional Outcome After Stroke? Tamaya Van Criekinge, Ann Hallemans, Nolan Herssens, Jonas Schröder, **Elissa Embrechts**, Willem De Hertogh, Steven Truijen, Wim Saeys. Gait & Posture. 2019;73:156-7.

DANKWOORD

DANKWOORD

Hier sta ik dan, aan het einde van mijn doctoraatstraject, iets wat onwerkelijk aanvoelt nu ik deze woorden op papier zet. Dit moment markeert het einde van een traject dat ik me bij aanvang moeilijk kon voorstellen.

Mijn diepe dank gaat uit naar de **Universiteit Antwerpen**, mijn bijna tienjarige tweede thuis als student en werknemer. Dank voor de tijd, de mensen, en de ongekende kansen die ik hier heb gekregen. Mijn oprechte waardering gaat uit naar de **Faculteit** en in het bijzonder naar onze **Vakgroep**. Het is een eer om deel uit te maken van dit team. Speciale dank aan het bestuur van onze vakgroep – Mira, Nathalie en Nick – voor de warme ontvangst als Assistentenvertegenwoordiger in de Vakgroepsraad.

Aan mijn promotoren, Wim, Steven, Christophe, en Tanja, mijn diepste dank voor jullie begeleiding, steun, en het vertrouwen in mijn capaciteiten. **Wim**, dank je wel voor de informele opmerking tijdens een masterproefvergadering: "Hey Elissa, als je wilt doctoreren, laat het dan maar weten." Ik herinner me nog hoe ik thuiskwam en dacht: doctoreren, wat betekent dat eigenlijk? Bedankt voor de kansen, de vrijheid en het vertrouwen dat je in mij hebt gesteld. **Steven**, dank je wel dat je me altijd op de juiste momenten hebt aangemoedigd en me hebt gesteund in het opbouwen van mijn netwerk. Ook mijn dank aan mijn begeleider, **Christophe**, voor het mogelijk maken van mijn werk bij RevArte. En natuurlijk, last but not least, dank je wel **Tanja**. Je bent een bron van inspiratie, iemand naar wie ik enorm opkijk, en waarvan ik nog steeds elke dag bijleer.

Aan de **patiënten** die deelnamen aan mijn onderzoek, mijn oprechte dank. Jullie enorme inzet en tijdsinvestering hebben me nog maar eens duidelijk gemaakt waarom ik dit alles doe. Bedankt aan alle betrokken ziekenhuizen: RevArte, UZA, GZA St Augustinus, GZA St Vincentius, AZ Geel en AZ Monica, en uiteraard de artsen en paramedici waarmee ik mocht samenwerken.

En dan zijn we nu aan de *collega's* aangekomen. Eigenlijk is het raar om jullie collega's te noemen, want jullie zijn zo veel meer dan dat. Bedankt aan de Neureca's. Merci **Charlotte**. Ik denk oprecht dat ik geen zachtere persoon op aarde ken dan jij. Merci voor de steun, altijd vlotte samenwerking, leuke belletjes, lachbuien, huilbuien, knuffels, en kleine attenties. Voor alles eigenlijk, dus. Merci, **Jonas**, voor de inspiratie, steun en brainstormsessies, en voor het gezamenlijk includeren en testen van patiënten. Wat een traject hebben we afgelegd... Merci om ook af en toe mijn uitlaatklep te zijn. Thank you **Renata**, for always being there when I could use a second pair of eyes, and for the talks over a casual beer. Bedankt **Amber**, om altijd met een lach de bureau binnen te wandelen, altijd enthousiast te zijn, en mee te vieren bij de kleine en grote overwinningen.

Bedankt ook aan de andere collega's. Danku **Ben**, voor de enorme steun en onvergetelijke momenten samen, waarvan ik nu vaak nog denk: hoe is het mogelijk? Van gsm's zoeken in de sneeuw, naar sleeën op een kapotte zwemband, fietsbanden achterstevoren monteren, en dotje te gaan redden. Merci aan **Timia**. Timi, wij kunnen samen lachen, feesten, dansen, maar

ook zeker en vast *bleiten* 😉. Je hebt er altijd gestaan, op elke moment dat ik het nodig had. Merci voor de retreat, en de weekendjes weg. Binnenkort nog eens gaan fietsen in Epernay, wat denk je? Merci aan **Charlotte J**, voor de casual babbels telkens op de R3, de brainstormmomentjes, maar ook de lunch'kes en festivallekes. Merci aan **Anke**, voor de spontane ochtendkoffietjes in het stad, de steun, en het luisterend oor. Merci ook aan al de rest, en in het bijzonder: Sophie, Sophie, Amber, Rob, Nele, Emily, Suzanne, Valérie-Anne, Eugénie, Lot, Lotte, Lien, … Ook bedankt aan de oud-collega's, **Tamaya** en **Nolan.** Ik kijk nog steeds op naar jullie!

Merci aan **Lies** Peeters, die dagelijkse koffie om 8u 's ochtends moet ik gelukkig nog niet missen. Danku om altijd te luisteren, te helpen, maar vooral voor het scheuren van uw broek terwijl je een handstand probeerde. This lives rent-free in my brain forever😉. Ook merci aan **Lies** Durnez. Merci om één van REVAKI's grootste supporters te zijn, om mee te werken aan mijn financieringsaanvragen, en om me aan te moedigen om toch ook maar op de post-doc vacature te solliciteren. Zonder die aanmoediging had ik het misschien niet gedaan... Merci aan **Erik** Fransen, om altijd enthousiast mee te denken over oplossingen voor statistiek, en ook altijd hiervoor klaar te staan.

En dan uiteraard, bedankt aan al mijn *vrienden*. **Céline**, merci om zelfs vanop 50km afstand mij toch het gevoel te geven dat je maar 1 minuut veraf bent. Merci om mij de afgelopen jaren onvoorwaardelijk te steunen en er altijd te staan, ondanks dat je ook een heel druk leven hebt. Dit wordt erg geapprecieerd, love you babe. **Chiara**, merci om mij af en toe uit mijn kot te sleuren, en mij mee op verlof te nemen. Merci om nooit te judgen, altijd te luisteren, en mij te laten zien dat er meer is in het leven dan werken op het unief. Zoals werken op festivals, bijvoorbeeld 😉. Merci aan **Julie**. We go way way way back. En al spreken we mekaar soms weken niet, als we mekaar 1 minuut zien, lijkt het alsof we mekaar nooit hebben moeten missen. Dankbaar hiervoor! Merci aan **Quirine**, voor de wijntjes, babbels en festivallekes. Blij dat gij in mijn Teams zit! Merci **Anne-Nina**, om altijd je gekste zelve te zijn. Dankje **Ann-Sophie,** voor de kaars-avondjes mét champagne. Merci ook aan alle andere vrienden. De **Harde Kern**, merci om mij af en toe ne keer te laten zien dat de Kempen toch wel nog net iets harder kunnen feesten dan die Antwerpenaren hier. Merci ook aan het **A-Team**, en mijn **surfcrew**. Om het met een quote van de Mo te zeggen: *The life, it is like the waves, if you don't catch it, you nosedive!* Van deze schatten een enorm grote vermelding voor **Caroline!** Dank om niet alleen een goede vriendin te zijn maar ook voor het ontwerp van mijn cover. Je bent een fantastische artieste, die me op korte tijd toch zeer goed heeft leren kennen, dat kan je terugzien in de cover.

Merci aan mijn **Edgies**, Nastasia, Senne, Laura, Sven, Wim, Pieter en Tom. Merci om ervoor te zorgen dat ik graag ga sporten, en om vaak mijn uitlaatklep voor frustraties te zijn. Merci om mij mee mijn grenzen te doen verleggen. Ik had <u>nooit</u> van mijn leven deelgenomen aan de Strong Viking, als het niet aan jullie peer pressure had gelegen.

Merci aan mijn **Mama**. Bedankt om altijd achter me te staan. Bedankt om mij de kansen te geven om te kiezen wat ik wou studeren, om mij nadien ook mijn gangen te laten gaan in Antwerpen, en hier vertrouwen in te hebben dat alles zou goed komen. Alles wat jij niet kon doen vroeger, gun je mij, en dat is echt kei knap. Ik ben trots dat ik uw dochter ben. Merci voor alle steun, tijdens mijn opleiding, mijn doctoraat, en de moeilijke momenten de afgelopen jaren. Dankuwel ook aan **Papa**. Merci om altijd te supporteren en te laten zien dat je apetrots bent. Je vroeg steeds achter mijn doctoraat, hoe het vlotte, en wat volgende stappen waren. Je was (en bent) vaak contenter met mijn vooruitgang dan dat ik zelf ben! Merci voor de belletjes, en het luisterend oor.

Deze afgelopen jaren vormden een traject vol hoogtepunten, onvermijdelijk gepaard gaande met enkele hobbels en dieptepunten. Maar bovenal waren ze gevuld met waardevolle momenten, vriendschappen en persoonlijke groei. Ik kijk met trots en enorme dankbaarheid terug op dit traject. Het einde van dit hoofdstuk markeert niet alleen afsluiting maar ook een nieuw begin, vol mogelijkheden. Dus, op naar nieuwe avonturen en uitdagingen!

Liefs,

Elissa