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Balance recovery after supratentorial stroke
Influence of hemineglect and the effects of somatosensory stimulation

Ilse van Nes
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I. van Nes
Thesis, Radboud University Nijmegen, with summary in English and Dutch


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Chapter 1
General introduction
Introduction

Stroke is a common cause of death in the western world and it may lead to severe limitations in daily functioning and social participation of the survivors. The stroke syndrome is clinically defined as a rapid development of focal neurological deficits of vascular origin. In pathophysiological terms, infarction can be distinguished from hemorrhage. About 80% of all stroke patients suffer from an infarction, whereas 20% is affected by a hemorrhage. In the Netherlands, the incidence of stroke is approximately 40,000 per year for the whole population (0.25%) and the mortality rate is about 30%.1 Fifty percent is admitted to an acute hospital, whereas approximately 6,000 (14%) patients die before admission.2 A six month follow-up study of van Exel et al.3 showed that, of the 598 patients admitted to several hospitals in the Netherlands, 18% died in the hospital, 40% was discharged back to home, 31% to a nursing home, 9% to a rehabilitation center and 2% was hospitalized for the full six month period.

The majority of the patients with stroke suffers from (a combination of) sensory, motor, cognitive and emotional impairments, leading to difficulties in the performance of activities of daily living (ADL), such as standing and walking.4 Impaired postural control is a frequent feature after stroke and appears to be an important determinant of ADL-dependence and disturbed standing and walking skills in the (sub)acute phase post-stroke.5-10 The risk of falling is substantially enhanced in stroke patients with impaired postural skills,2,9,11-13 which may lead to severe additional injuries and high extra costs.14 Patients may also develop fear of falling, which seriously hampers the progression of their rehabilitation and social integration.15 Hence, the recovery of postural control is a crucial factor in the rehabilitation of patients with stroke.

Postural control

Postural control can be defined as a continuous process that regulates the body’s position in space for the purposes of orientation and stability.16 Body orientation is usually defined as the ability to maintain an appropriate
relationship between the body segments, and between the body and the environment during a particular task. Generally, we perform most tasks in a vertical orientation, thereby using multiple sensory references, including gravity (vestibular system), the support surface (somatosensory system) and the relationship of our body with respect to the ‘remote’ environment (visual system). Postural stability is often defined as the ability to maintain the Center of Mass (COM) between certain limits of the area of contact with the support surface, i.e. the Base of Support (BOS). The COM is the virtual center of the total body mass and believed to be one of the main variables that is regulated by the postural control system. The center of the resulting ground reaction forces is called the Center of Pressure (COP). The COP continuously moves around (the vertical projection line from) the COM to keep the COM within the BOS. The relative contribution of the orientation and stability components in each task depends on the task characteristics as well as on the environmental constraints. Postural control may be organized predominantly ‘top-down’ or ‘bottom-up’, mainly depending on whether destabilization is an active or a passive process. Both orientation and stability are very important for postural control during walking. However, in walking the COM does not stay within the BOS, thereby causing an ongoing state of ‘imbalance’. By taking steps the BOS is continuously adapted to the changing position of the COM, taking into account the inertial forces of the moving body. From a balance perspective, stepping reactions may contribute to feet-in-place equilibrium reactions by adapting the BOS to the moving COM, as is the case during walking.

The neural components essential to postural control include: a) motor processes, which organize the activation of muscular activity throughout the body into so-called ‘muscular synergies’; b) sensory processes, which integrate signals from visual, vestibular and somatosensory systems; and c) cognitive processes, which are essential for mapping sensation to action, and ensuring anticipatory and adaptive aspects of postural control. It is still poorly understood how all these processes contribute to postural control during e.g. sitting, standing and walking.

**Motor control of posture.** The action systems underlying the motor control of posture include systems for the planning (frontal and motor cortex), coordination (brainstem and spinal networks coordinating muscular synergies), and generation (motor neurons and muscles) of forces that produce movements. To counteract balance perturbations, several strategies can be applied which may consist of (a combination of) different muscular synergies. A ‘muscular synergy’ can be defined as a functional coupling of groups of muscles for the purpose of efficient coordination (i.e. reducing degrees of freedom). The task-specific selection of one or more muscular synergies to deal with a postural challenge can be regarded as a ‘postural strategy’.

In the sagittal plane, the most important strategies are the so-called ‘ankle’ (torques and movements mainly about the ankle joints) and ‘hip’ (torques and movements mainly about the hip joint) strategies. Ankle strategies are preferred during quiet standing and to counteract relatively small body perturbations, whereas (additional) hip strategies are needed when the body perturbation is strong and/or when the support surface does not allow sufficient generation of vertical ground reaction forces for an effective ankle strategy. To be effective, hip strategies require the generation of shear forces at the support surface. When both ankle and hip strategies fail, it will be impossible to keep the feet in place, so that one has to rely on stepping strategies. These different strategies are not an ‘all or nothing’ matter, but rather part of a continuum under progressively changing external constraints.

In the frontal plane, during normal biped standing, the control of posture is mainly regulated at the level of pelvis and hips by using the so-called ‘weight-shifting’ strategy. Weight-shifting between the legs is regulated by alternating contractions of the hip abductors and adductors. Indeed, active control at the ankles in the frontal plane is minimal when the distance between the ankles (stance width) is greater than 8 cm. Nevertheless, when the BOS becomes smaller, and particularly during one-legged standing, ankle mechanisms come into play, similar to the ankle strategy in the sagittal plane.

It is important to realize that, besides the lower extremity muscles, the muscles of the trunk and the head continuously contribute to postural control during both sitting, standing and walking. In addition, postural control may constitute reactions to sensory stimulation (‘feedback’ control), or be largely anticipatory to the
demands of a predictable (often voluntary) task. During normal circumstances, balance will be greatly determined by feedforward control mechanisms, allowing smooth and flexible movements with a high degree of automaticity.

**Sensory control of posture.** In order to calculate when and how to generate restoring forces, the nervous system has to know where the body is in space and whether it is standing still or moving. To obtain this information, visual, somatosensory and vestibular systems are used. The visual input is used for a sense of (visual) verticality, while it also reflects motion of the head with respect to the (visual) environment. The somatosensory system provides information about the position of the body with respect to the supporting surface and about the relationship of the body segments with respect to each other. The vestibular system gives information about the position of the head with respect to gravity and about linear and rotational accelerations of the head. To be able to integrate these different types of information, the nervous system needs to be well informed about the relation between the head and the body through proprioceptive information from the neck. A lot of research has been conducted to determine the relative contribution of each sensory system to postural control, e.g. by the use of the Sensory Organization Test. It appears that during quiet stance all three systems more or less equally contribute to postural control, but when balance is perturbed, the contribution of one system may become more important than the other. According to the ‘sensory weighting’ hypothesis, the sensory systems are constantly reweighted depending on the task, the environment and the age of a subject. In some clinical conditions, information from one or more sensory systems may be impaired. For instance, after stroke, somatosensory input from the affected leg is often disturbed. As a consequence, patients have to rely more on visual and vestibular input and will probably experience balance problems when the information from one of these systems is reduced (e.g. when standing with eyes closed). Hence, for unmasking disorders in the sensory control of posture one should use sensory manipulations, e.g. standing on foam or without vision.

**Cognitive control of posture.** The control of posture is usually a well automated task requiring a minimum of attention. However, it has been argued that under certain conditions postural control may demand significant attentional resources. The attentional demands vary depending on the complexity of the task being performed, age and possible neuromusculoskeletal impairments. In studies of attention and postural control, a dual-task paradigm has often been used. In this paradigm, a postural task (which is considered the primary task) and a cognitive task (which is considered the secondary task) need to be performed simultaneously. If both tasks do not use the same motor or sensory systems, a decrease in the performance of either task suggests an interference based on a competition for generalized attentional resources. It has been shown that the attentional demands for walking are greater than those for standing, and that the demands for standing are greater than those for sitting. In young healthy adults, concurrent cognitive task performance may increase postural sway in some instances, but merely when the task complexity is high. Interestingly, when a subject has to focus on a visual secondary task, the postural sway may decrease, probably because vision is used for postural control. Compared to postural control in healthy young subjects, in healthy elderly or in patients with disorders of the nervous system (e.g. patients with stroke), postural control requires more attentional resources, resulting in increased postural sway, even during relatively simple tasks. Hence, to estimate the level of automaticity, it is important to always compare dual-task with single-task performance of postural skills.

In conclusion, postural control is a complex interplay between motor, sensory and cognitive processes that ultimately coordinates the activity of body muscles into effective sitting, standing and walking balance strategies.

**Recovery of postural control in stroke**

From the former paragraph, it follows that, after supratentorial stroke, disturbances in sitting, standing and walking balance may be caused by a ‘unique’ combination of motor, sensory and cognitive impairments. Postural control can be assessed by clinical measures such as the Trunk Impairment Scale, the Berg Balance Scale and the Functional Ambulation Categories, or by using instrumented methods, e.g. force-platform technology. Clinical studies have shown the importance of trunk control for the outcome of
The cancellation task is larger than the cut-off score based on the performance of healthy subjects. There may, however, be some inherent problems with this way of assessing neglect. Most importantly, there may be generalized (non-lateralized) attention deficits due to stroke, which often coincide with the neglect syndrome, that negatively influence cancellation task performance, resulting in an overestimation of (patients with) neglect. Second, paper-and-pencil tasks are relatively simple and often used in daily clinical practice, which may readily lead to ‘spontaneous’ compensation of neglect in test situations, especially in the subacute and chronic phases. Third, paper-and-pencil tasks do not take into account the reaction time of responses, even though time seems to be a critical factor in both spatial and non-spatial attentional deficits. These latter characteristics of paper-and-pencil tasks might lead to underestimation of neglect.

Perhaps related to the diagnostic criteria used, or the methods of subject selection, the literature examining the influence of visuospatial hemineglect on postural control in the subacute and chronic phases of supratentorial stroke is rather inconsistent, whereas studies in the very acute phase are lacking. Studies of sitting balance in selected subacute stroke patients have demonstrated a profound negative influence of visuospatial neglect on postural stability and body orientation, characterized by a contralesional tilt of the active postural vertical. On the other hand, a study in ‘unselected’ subacute stroke patients did not find an association between visuospatial neglect and balance disability. In other studies on standing balance after stroke, the influence of hemineglect appeared not to be unambiguously strong. Hence, it can be concluded that our knowledge of the influence of visuospatial hemineglect or other attention deficits on postural control is still limited, especially concerning unselected patients in the acute phase of stroke. In addition, there is no detailed information about the effect of hemineglect on the recovery of postural control after stroke.

Visuospatial hemineglect and postural control

Of all the cognitive impairments due to supratentorial stroke that may affect postural control, visuospatial hemineglect has been proposed as the most important. Visuospatial hemineglect is a cognitive disorder, due to which patients fail to orientate themselves toward or attend to stimuli on the side contralateral to their lesion. It occurs more frequently after right hemisphere (RH) than after left hemisphere (LH) stroke, but an exact rate of occurrence is hard to derive from the literature. In various studies, the reported frequencies cover a range from 13 to 82 percent in RH patients and from 0 to 76 percent in LH patients, perhaps partly depending on the test which is used to diagnose patients with neglect. In the literature, the Behavioral Inattention Test (BIT) is most often used to assess the presence of visuospatial hemineglect. Patients are classified as having neglect, e.g. when the total number of omissions on a cancellation task is larger than the cut-off score based on the performance of healthy subjects. There may, however, be some inherent problems with this way of assessing neglect. Most importantly, there may be generalized (non-lateralized) attention deficits due to stroke, which often coincide with the neglect syndrome, that negatively influence cancellation task performance, resulting in an overestimation of (patients with) neglect. Second, paper-and-pencil tasks are relatively simple and often used in daily clinical practice, which may readily lead to ‘spontaneous’ compensation of neglect in test situations, especially in the subacute and chronic phases. Third, paper-and-pencil tasks do not take into account the reaction time of responses, even though time seems to be a critical factor in both spatial and non-spatial attentional deficits. These latter characteristics of paper-and-pencil tasks might lead to underestimation of neglect.

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Somatosensory stimulation and postural control

Since half a century, many studies have demonstrated neurochemical and neuroanatomical plasticity in the cerebral cortex of adult animals. It is also
known that cortical representation areas are modified by sensory input, experience and learning, as well as in response to brain lesions. In this perspective, several studies have been conducted in patients with stroke to evaluate the effect of somatosensory stimulation on motor recovery and rehabilitation outcome. Somatosensory stimulation has been applied by (electro) acupuncture, transcutaneous electrical nerve stimulation (TENS) and by vibration therapy. Studies that used acupuncture or TENS have claimed beneficial effects in terms of motor functions, balance and activities of daily living.\textsuperscript{59,62} However, subsequent randomized controlled trials\textsuperscript{61,62} and reviews\textsuperscript{63,64} failed to confirm these results. Vibration therapy can induce brain plasticity by stimulating the Ia and II afferents from (large) muscle groups.\textsuperscript{64} The application of whole-body vibration has shown positive effects on postural control and mobility in patients with multiple sclerosis,\textsuperscript{65} on motor performance in patients with Parkinson’s disease,\textsuperscript{66} and on postural steadiness in healthy elderly.\textsuperscript{68} In addition, sensory stimulation of the superficial cervical plexus has shown to (momentarily) reduce neglect-related postural instability after stroke.\textsuperscript{53} Against this background, it seems worthwhile to determine the influence of whole-body vibration on (the recovery of) postural control following stroke, and compare possible effects between patients with and without neglect.

Objective of this thesis

Based on the above-mentioned background, this thesis will address three main topics in patients who have sustained a first supratentorial stroke. These topics are (1) the recovery of sitting and standing balance, (2) the influence of visuospatial neglect on (the recovery of) sitting, standing and walking balance, and (3) the effect of somatosensory stimulation by whole-body vibration on standing balance and ADL. All studies presented in this thesis have been conducted within the first national rehabilitation research program stimulated and granted by the Netherlands Organisation for Health Research and Development (ZonMw). The present work was part of the subprogram ‘Cognitive rehabilitation’, more specifically the research line ‘Interaction of motor control with cognition’. As such, it formed a bridge with the subprogram ‘Recovery of walking ability after stroke’ within the same ZonMw program.

The following research questions will be addressed in the subsequent chapters:

**Part I. Recovery of sitting and standing balance after stroke**

1. What is known in the literature about the mechanical and physiological mechanisms underlying balance recovery from stroke? What is known about the influence of cognition on balance recovery? And what do we know about different interventions that can be applied to enhance balance recovery from stroke?

Chapter 2 focuses on studies published in the medical and paramedical literature dealing with the recovery of standing balance following stroke. It is subdivided into five major sections on unperturbed stance, stance perturbations, voluntary weight displacements, sensory control, and cognitive control of posture. In the discussion, clinical implications as well as blind spots in the existing literature are highlighted.

2. What are the characteristics of the recovery of sitting balance in the subacute phase of stroke using force-platform technology? What is the influence of vision and sensory manipulations on sitting balance (recovery) after stroke?

Chapter 3 identifies characteristics of the recovery of quiet-sitting balance in 16 patients with a first-ever supratentorial stroke during their inpatient rehabilitation. Three sitting balance assessments are performed at intervals of 6 weeks and the results are compared with those obtained from healthy elderly. The influence of an unstable surface and of visual deprivation are determined.

**Part II. Influence of visuospatial hemineglect on balance after stroke**

3. What is the best way to assess the presence of visuospatial hemineglect in patients with stroke? Is it sensible to use an asymmetry-index to enhance the sensitivity and specificity of the Behavioral Inattention Test? Or is it better to use a computerized reaction time task to determine the presence of neglect?

Chapter 4 is an introduction focusing on the assessment of visuospatial hemineglect. The performance of 20 patients with left hemispheric stroke is compared to the results of 26 patients with right hemispheric stroke on the Behavioral Inattention Test as well as on a computerized reaction time task. Asymmetry indexes are calculated to control for the confounding influence...
of non-lateralized attention deficits. In addition, for the computer task, reaction times are added and compared to the numbers of omissions.

4. Does visuospatial hemineglect independently contribute to balance in the acute phase of stroke?
Chapter 5 compares the influence of visuospatial hemineglect to that of other possible biological and clinical determinants on postural control in 78 patients within 2 weeks after a first-ever supratentorial stroke. Several clinical measures of sitting, standing and walking balance are related to age and measures of muscle strength, sensibility, hemianopia, generalized attention and visuospatial hemineglect, respectively.

5. What is the influence of visuospatial hemineglect on functional and motor recovery during the rehabilitation of stroke patients in the subacute phase?
In chapter 6, by means of multilevel regression analysis, the independent influence of visuospatial neglect on sitting, standing and walking after stroke is re-examined in a longitudinal analysis using three repeated assessments obtained at 6 weeks intervals from 53 patients during their inpatient rehabilitation.

Part III. Effect of somatosensory stimulation on standing balance after stroke
6. Is it possible to influence standing balance control, as measured with force-platform technology, by means of one session of whole-body vibration in chronic stroke patients?
In chapter 7, the influence of one session of whole-body vibration on the control of quiet-standing balance is assessed in chronic stroke patients. Besides the momentary physiological effects, we were interested in the feasibility of this intervention with regard to repeated applications and long-term effectiveness.

7. What are the long-term effects of 6 weeks whole-body vibration on balance recovery and activities of daily living in the postacute phase of stroke?
In chapter 8, the results of a randomized controlled trial including 53 patients are presented. Patients are included within 6 weeks after a first-ever supratentorial stroke and stimulated 5 days a week, during 6 weeks. The total follow-up period is 12 weeks. In this period, three assessments of balance, gait and ADL skills take place. We were especially interested in the possible effects of vibration therapy in patients with visuospatial hemineglect.

The thesis ends up with a general discussion (chapter 9), which emphasizes the implications and limitations of the reported studies, and gives some directions for future research.
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Part I
Recovery of sitting and standing balance after stroke
Abstract

Recently, interest in the mechanisms underlying balance recovery following stroke has grown, because insight into these mechanisms is necessary to develop effective rehabilitation strategies for different types of stroke. Studies dealing with the recovery of standing balance from stroke are, however, limited to rehabilitation inpatients with a unilateral supratentorial brain infarction or haemorrhage. In most of these patients, stance stability improves in both planes as well as the ability to compensate for external and internal body perturbations and to control posture voluntarily. Although there is evidence of true physiological recovery of paretic leg muscle functions in postural control, particularly during the first 3 months post-stroke, substantial balance recovery also occurs in patients when there are no clear signs of improved support functions or equilibrium reactions exerted through the paretic leg. This type of recovery probably takes much longer than 3 months. Apparently, mechanisms other than the restoration of paretic leg muscle functions may determine the standing balance recovery in patients after severe stroke. No information is available about the role of stepping responses as an alternative to equilibrium reactions for restoring the ability to maintain upright stance after stroke. The finding that brain lesions involving particularly the parieto-temporal junction are associated with poor postural control, suggests that normal sensory integration is critical for balance recovery. Despite a considerable number of intervention studies, no definitive conclusions can be drawn about the best approach to facilitate the natural recovery of standing balance following stroke.

Introduction

Stroke is one of the major causes of permanent disability with an incidence of approximately 1.75 ‰ per year. Although approximately two thirds of the affected patients are above 65 years, a stroke may occur at all ages, even in very young children, and can have many causes. A majority of the survivors from stroke have a combination of sensory, motor, cognitive and emotional impairments leading to restrictions in their capacity to perform basic activities of daily living (ADL). Of all possible sensorimotor consequences of stroke, impaired postural control probably has the greatest impact on ADL independence and gait. In addition, among many biological and functional characteristics, postural control is the best predictor of achieving independent living and shows the highest correlation ($r_p = 0.70$) with person-perceived disability after discharge from rehabilitation. Loss of postural control has been recognized as a major health problem in individuals with stroke resulting in a high incidence of falls both during rehabilitation and thereafter, particularly in those patients with both motor and sensory deficits. Rapid and optimal improvement of postural control in patients with stroke is, therefore, essential to their independence, social participation and general health. However, no general physiotherapy approach has proven to be superior for promoting balance recovery from stroke. There is also limited evidence of the effectiveness of sensory stimulation by acupuncture or transcutaneous electrical nerve stimulation, functional electrical stimulation, electromyographic feedback, force feedback or body-weight supported treadmill training on balance and related ADL in patients with stroke.

It is necessary to have optimal understanding of the potential mechanisms underlying ‘natural’ balance recovery and compensatory mechanisms to provide interventions to improve the speed and extent of balance recovery following stroke. The site of the brain lesion will also affect the type and extent of postural reorganisation after stroke. This review focuses on studies using instrumented methods to obtain quantitative information about sensory, motor and cognitive processes involved in the recovery of postural control from stroke.
Recovery characteristics

One of the first studies to address balance recovery from stroke was published by Sackley, who investigated 90 inpatients, all participating in a regular rehabilitation programme, from the moment they were able to stand independently for 30 seconds. Balance was assessed on average 11.5 weeks after stroke as well as 18 weeks later. Small but significant improvements in absolute weight bearing (2-4% of body weight) were found and a relative reduction (7-30%) in the variability of weight bearing as a measure of lateral stability. A major problem of this study was the drop out of 21 patients from the first to the second assessment, making these assessments invalid for comparison. Mizrahi et al. reported a trend towards spontaneous sway reduction in 16 post-acute patients with stroke during 15 weeks, but in this study only 6 patients were followed for at least 10 weeks making their regression analysis suspect. Sackley and Lincoln found even greater improvement of absolute weight bearing (11% of body weight) and lateral stability (40%) in a study with 26 patients over a time period of 4 weeks on average 20 weeks post-stroke. Accordingly, Dickstein et al. reported improved loading on the paretic leg (9.7%) during a 3-week follow up of 23 post-acute inpatients with stroke. In both of the latter two studies, however, patients were probably aware of the fact that loading symmetry was an important outcome, which may have caused measurement bias. More recently, Laufer et al. followed a cohort of 104 patients with a first stroke in the anterior brain circulation who had been admitted to a geriatric rehabilitation centre. Balance was first assessed 3-6 weeks post-stroke (on average 26 days) and re-assessed 6-9 weeks (on average 53 days) later. In the 30 patients in the sample whose standing balance could be assessed twice, small and insignificant reductions in weight-bearing asymmetry and postural sway (RMS COP amplitude normalised to body weight) were found, even though they still exhibited substantially more weight-bearing asymmetry and higher sway values at the second assessment compared to age-matched healthy control subjects. The same group, however, recovered considerably in terms of independence in walking and ADL.

In contrast, other studies have found significant improvement of postural stability in the post-acute phase of stroke. In a study without differential

Unperturbed stance

Although many survivors from stroke regain the ability to stand unsupported during the first days post-onset, approximately 50% of the patients with a total anterior circulation infarction will not have reached independence in this respect 6-9 weeks after stroke onset. Maintaining an unperturbed two-legged standing position, a simple task for healthy individuals, may be quite an achievement for individuals with stroke who need prolonged inpatient rehabilitation care. Once they are able to maintain standing balance, weight-bearing asymmetry in favour of the nonparetic leg as well as increased spontaneous postural sway, most prominently in the frontal plane, are among the most characteristic consequences of incompletely recovered hemiparesis. Improvement of weight-bearing symmetry is traditionally regarded as a primary goal in rehabilitation and has been associated with better motor functioning and greater ADL independence in the post-acute phase of stroke.

Many studies of unperturbed stance in individuals with stroke have used force-plate technology to assess weight-bearing and sway characteristics based on positional and movement characteristics of the ‘centre of pressure’ (COP) of the ground reaction forces. The COP data so obtained, however, reflect not only actual body sway, but also the stabilising moments of force exerted through the lower leg muscles active about the ankle joints (‘ankle mechanisms’). As shown after strokes, increased COP movements during quiet standing seem partly related to increased body sway as assessed with kinematic recordings of the lower legs and pelvis and partly to exaggerated corrective ankle mechanisms as assessed by analysing the higher frequency COP components (>0.4Hz). The ecological validity of such ‘static’ posturography may be questioned in view of the dynamic complexity of postural control in daily life. Yet, several studies of patients with stroke have demonstrated moderate to high associations of selected force-platform parameters derived from quiet-standing registrations, in particular the mean COP velocity, with several functional measures of balance and gait in both the post-acute and chronic phase (r ranging from -0.52 to -0.91). Hence, equilibrium control during the ‘simple’ act of standing still can explain on average 50% ($r^2$) of the variance of several functional balance and gait measures in patients with stroke.
effects of force-feedback training, Walker et al. 42 included 46 inpatients on average 5-6 weeks after their first stroke, who had been admitted to a stroke unit for rehabilitation and were able to stand unassisted for at least 60 s. They were all reassessed on average 5 weeks later with functional measures of balance and gait (Berg Balance Scale, Timed Up & Go Test, gait velocity) as well as by posturography. All functional measures improved considerably, which coincided with a 45% decrease in the sway area relative to the theoretical limits of stability, both with eyes opened and closed. One month after the intervention period, the sway values had decreased further by another 25%.

De Haart et al. 41 followed 37 inpatients during their rehabilitation starting from the time they were able to stand independently for at least 30 s, on average 10 weeks post-stroke, and then 2, 4, 8 and 12 weeks later. A dual-plate force platform was used to determine weight-bearing asymmetry and postural instability (RMS COP velocity). During the rehabilitation period, the patients clearly improved their independence of walking (increase in median Functional Ambulation Categories score from 2 to 4 [range 0-5]) and showed a gradual decrease in lateral (33%) and AP (18%) postural instability. Weight-bearing asymmetry decreased from 13.5% to 10% overloading on the nonparetic leg, with the greatest amount of change noted during the first 4 weeks. Hence, a substantial degree of weight-bearing asymmetry persisted during the 8 weeks thereafter, most prominently in a subgroup of patients with disturbed sensibility or ankle clonus. Patients also showed abnormal static forefoot and lateral foot edge loading on the paretic side (‘pes equinovarus’) as well as substantial asymmetry in the kinetic regulation activity of each leg, without clear signs of restoration of these abnormalities (figure 1). The analysis of kinetic regulation asymmetry was based on the comparison of the RMS COP velocity under each foot separately, which was on average twice as high in both directions on the nonparetic as on the paretic side. Asymmetry in kinetic regulation activity of the legs in patients with stroke has already been described by Mizrahi et al. 26 in terms of greater horizontal ground reaction forces in both directions under the nonparetic compared to the paretic foot. As body sway is relatively greater on the hemiparetic side, based on kinematic analysis of the lower legs and pelvis, 33 the kinetic regulation asymmetry must reflect the use of compensatory ankle mechanisms generated by the nonparetic leg. Because de Haart et al. 41 found little evidence of restoration of symmetry with regard to either equinovarus loading or kinetic regulation asymmetry, the observed functional recovery and improved postural stability must, at least partly, be related to mechanisms other than the restoration of support functions and equilibrium reactions exerted through the paretic leg. Even though they included patients earlier after stroke, Laufer et al. 22 arrived at a similar conclusion, namely that improvement in ADL and gait dependence occurred in their patients without significant improvement in weight-bearing symmetry.

**Figure 1**

The COP trajectory for each foot separately and for both feet together (‘overall COP’) during unperturbed standing with eyes open for 30 s in a 48-year old male, who had sustained an infarction in the right hemisphere one month before (A). Note the weight-bearing asymmetry reflected in the lateral deviation of the overall COP trajectory towards the nonparetic leg. Also note the asymmetry in terms of forefoot overloading at the paretic side and compensatory regulation activity at the nonparetic side (RMS AP COP velocity 29.8 mm/s vs. 7.9 mm/s at paretic side). After a 12-week training period (B), weight-bearing asymmetry had disappeared, but overloading of the paretic forefoot was still present. Although postural stability had improved substantially in terms of a decrease in overall COP velocity in both planes, the asymmetry in AP regulation activity was still a factor 3.75.

**Effects of force feedback**

Shumway-Cook et al. 43 provided preliminary evidence of a beneficial effect of ‘static’ COP feedback on weight-bearing symmetry during quiet standing. Sixteen post-acute patients with stroke were randomly allocated to either 2
the control group. Moreover, it is unclear whether the experimental group received an equal amount of therapy compared to the control group. Sackley and Lincoln\textsuperscript{40} conducted a randomised controlled trial (RCT) to compare the effect of a similar dynamic weight-bearing feedback protocol with a placebo programme in 26 patients who had been admitted to a hospital stroke unit on average 20 weeks post-stroke onset. They reported more improvement of stance symmetry, gross motor function and ADL in the experimental group directly after the 4 weeks of training, but these differential effects were lost after a follow up of 8 weeks. Other RCTs that investigated the effect of COP feedback training while actively shifting weight during various standing activities did not find specific treatment effects on postural stability (sway area)\textsuperscript{42} or functional measures (Timed Up\&Go Test, Berg Balance Scale, gait velocity)\textsuperscript{18,42} in the post-acute phase of stroke. Hence, the overall evidence of a persistent or functionally relevant effect of static or dynamic force-feedback training on weight-bearing symmetry or stance stability in patients with stroke seems to be rather weak.

Effects of aids

In contrast to the ambiguous results of force-feedback training on weight-bearing symmetry during quiet stance, the use of simple aids may have rather dramatic effects in this respect. The addition of a 10 mm shoe lift under the nonparetic leg resulted in a 10% increment in weight bearing on the paretic leg in eight patients in the chronic phase of stroke who bore on average 38% weight on this leg. This improvement showed a significant carry-over effect immediately after the shoe lift had been removed.\textsuperscript{47} Such compelled weight bearing was also achieved by placing a pronating wedge under the shoe of the nonparetic leg in nine post-acute patients with stroke. A shoe wedge with an angle of just 5° resulted in a shift from 40% to 51% weight bearing on the paretic leg, whereas greater angles resulted in overloading of the paretic leg. Again, a significant carry-over effect of approximately 44% weight bearing was found immediately after removal of all wedges.\textsuperscript{48} An even more dramatic increase in weight bearing on the paretic leg (from 41-42% to 65-68%) has been reported in post-acute patients with hemiparesis when placing their nonparetic foot on a step, regardless of step height (10 cm or 17 cm),\textsuperscript{23,49} although such compelled weight shifting may not directly improve gluteus medius activation at the
perturbations, particularly towards the paretic side; (2) delayed, temporally disrupted and weakened short-latency as well as medium- and long-latency leg muscle responses at the paretic side in reaction to movements of the support surface; (3) delayed and reduced leg muscle activation particularly on the paretic side in anticipation of rapid, self-paced arm movements and (4) compensatory activation of nonparetic leg muscles in reaction to movements of the support surface or prior to self-initiated disturbances. As a result, individuals with stroke will avoid large passive body mass displacements and rely excessively on their nonparetic leg muscles to stabilise their posture. These phenomena have been referred to as ‘stabilisation’ strategies.

**Recovery characteristics**

With regard to the recovery of externally perturbed standing, Kirker et al. were able to show changes in compensatory hip muscle activity in response to standardised sideways perturbations in 13 selected patients who were tested 3-15 weeks post-stroke (the moment they were able to stand unsupported) and retested 10-38 weeks later, depending on the speed of functional recovery. They found that initially 12 patients showed abnormal hip muscle activation, of whom eight gradually developed a more physiological pattern. Although most subjects improved their hip muscle recruitment within 12 weeks post-stroke, in two subjects recovery was observed even after 13 and 21 weeks. In the most severe cases, there were no responses in the hip muscles to perturbations in either direction (‘pattern 1’). In the case of some recovery, the nonparetic gluteus medius became active when perturbed in this direction as well as the non-paretic hip adductor on perturbations towards the paretic side (‘pattern 2’). If recovery continued further, also the paretic gluteus medius became active on perturbations in this direction (‘pattern 3’). Eventually, the paretic adductor became active when perturbed towards the nonparetic side (‘pattern 4’). Whereas pattern 2 revealed compensatory adductor activity of the nonparetic leg, patterns 3 and 4 were regarded as evidence of true physiological recovery, which always occurred in this order. EMG latencies of the paretic gluteus shortened in seven recovering

**Stance perturbations**

The ability to withstand external perturbations in an upright position is essential to the safety of standing and walking. In addition, internal perturbations caused by self-initiated movements must be counteracted as smoothly as possible to maintain balance during voluntary activities. Cross-sectional stance perturbation studies comparing patients with stroke, often in the chronic phase, with age-matched healthy control subjects have found evidence of the following: (1) a generally impaired ability to withstand external perturbations, in particular towards the paretic side; (2) delayed, temporally disrupted and weakened short-latency as well as medium- and long-latency leg muscle responses at the paretic side in reaction to movements of the support surface; (3) delayed and reduced leg muscle activation particularly on the paretic side in anticipation of rapid, self-paced arm movements and (4) compensatory activation of nonparetic leg muscles in reaction to movements of the support surface or prior to self-initiated disturbances. As a result, individuals with stroke will avoid large passive body mass displacements and rely excessively on their nonparetic leg muscles to stabilise their posture. They will also limit the speed and amplitude of self-initiated movements causing internal perturbations of posture compared to healthy age-matched individuals. These phenomena have been referred to as ‘stabilisation’ strategies.

**Recovery characteristics**

With regard to the recovery of externally perturbed standing, Kirker et al. were able to show changes in compensatory hip muscle activity in response to standardised sideways perturbations in 13 selected patients who were tested 3-15 weeks post-stroke (the moment they were able to stand unsupported) and retested 10-38 weeks later, depending on the speed of functional recovery. They found that initially 12 patients showed abnormal hip muscle activation, of whom eight gradually developed a more physiological pattern. Although most subjects improved their hip muscle recruitment within 12 weeks post-stroke, in two subjects recovery was observed even after 13 and 21 weeks. In the most severe cases, there were no responses in the hip muscles to perturbations in either direction (‘pattern 1’). In the case of some recovery, the nonparetic gluteus medius became active when perturbed in this direction as well as the non-paretic hip adductor on perturbations towards the paretic side (‘pattern 2’). If recovery continued further, also the paretic gluteus medius became active on perturbations in this direction (‘pattern 3’). Eventually, the paretic adductor became active when perturbed towards the nonparetic side (‘pattern 4’). Whereas pattern 2 revealed compensatory adductor activity of the nonparetic leg, patterns 3 and 4 were regarded as evidence of true physiological recovery, which always occurred in this order. EMG latencies of the paretic gluteus shortened in seven recovering
patients, but normalised only in three subjects. Of the five patients that did not show evidence of improved hip muscle responses (two with pattern 1 and three with pattern 3), functional recovery in terms of independent mobility was relatively poor. However, temporary compensatory muscle activation did not necessarily prevent recovery of physiological muscle patterns at a later stage.

Garland et al.21 used an internal perturbation protocol and found additional evidence for compensatory activity of the nonparetic leg as a basis for functional recovery in a subgroup ('IIb') of 12 post-acute patients. These had recovered relatively slowly and reached independent standing ability on average 6 weeks post-stroke. Although this subgroup showed similar improvements of mobility and gait speed at 1 month follow up as did the other 15 patients, they did not show the same significant decrease in the latency of anticipatory ipsilateral (nonparetic) and contralateral (paretic) hamstrings activation on rapid forward flexion of the nonparetic arm while standing. Instead, they merely tended to increase the activity in the ipsilateral (nonparetic) hamstrings as compensation. In contrast, the 15 patients who were less severely affected or had regained more function before the initial assessment showed a clear improvement of bilateral anticipatory hamstrings activity which could not be explained by an increase in acceleration of the flexing arm. Because these latter patients improved their anticipatory paretic hamstrings activity by at least 20 ms (on average 80 ms), this result was interpreted as evidence of true physiological recovery. Remarkably, only subgroup IIb showed a significant increase (19%) in postural stability (decrease in RMS COP velocity) at 1-month follow up, which was less obvious in the other patients, perhaps due to ceiling effects. The muscular activation pattern in this subgroup indicates that improved postural stability during internal perturbation may be related to compensatory use of the nonparetic leg muscles instead of physiological recovery of the paretic leg muscle functions. This conclusion seems coherent with ‘pattern 2’ responses to external perturbation reported by Kirker et al.70

Effects of perturbation training
One study has reported beneficial effects of dynamic platform training in 13 inpatients with stroke undergoing rehabilitation compared to 11 matched control patients.21 Only the experimental group was trained to sustain increasing amplitudes in the AP and lateral directions of a moving support surface during 10 min of daily exercise time for 3 weeks. After the intervention period this group exhibited more than a two-fold increase in the maximally sustainable movement amplitude (MMA) with the greatest improvement in those patients who were initially most impaired (five- to seven-fold improvements of MMA). In addition, the experimental group showed more improvement in stance symmetry compared to the control group. It remained unclear, however, to what extent both groups were comparable at baseline. The results may also have been biased by different intensities of treatment. The same researchers found no favourable immediate effects of laterally moving platform exercises on the asymmetric recruitment of gluteus medius or medial gastrocnemius muscles in the chronic phase of stroke.56 Hence, definitive conclusions about the possible effects of perturbation training on dynamic postural stability in patients with stroke cannot be drawn.

Voluntary weight displacements
The capacity to voluntarily transfer body weight while maintaining standing balance over a fixed base of support or to actively change the base of support and adopt a different stance position is a prerequisite for safe mobility. Cross-sectional studies of the voluntary weight-shifting capacity in patients with stroke when compared to age-matched healthy control subjects have provided evidence of the following: (1) multidirectionally impaired maximal weight shifting during bipedal standing,72,73 in particular towards the paretic leg,23,74-76 (2) slow speed, directional imprecision and small amplitudes of single and cyclic sub-maximal frontal-plane weight shifts, most prominently towards the paretic side,45,56,62,77-80 (3) bilaterally impaired transitions from bipedal to single-limb stance due to insufficient hip muscle recruitment at the paretic side81 or failure to maintain single-limb support, in particular on the paretic leg,63,87 and (4) abnormal loading asymmetry as well as reduced kinetic energy and rising speed during sit-to-stand transfers.84-88 As a consequence, patients with stroke will only use a small part of their base of support for voluntary weight displacements, which is probably compensated by the early
use of change-in-support strategies or stepping responses, which appear to be relatively preserved.81

Recovery characteristics
De Haart et al.78 studied the restoration of weight-shifting capacity in 36 patients on average 10 weeks post stroke and 2, 4, 8 and 12 weeks thereafter. Patients had to make ‘rhythmic’ lateral weight shifts using visual COP feedback from a computer monitor, on which two stationary blue squares (30x30 mm) were presented at either side of the vertical midline. The position of the squares was individually adjusted so that 65% of body weight had to be borne on either leg to bring the COP in the middle of the corresponding square. Subjects had to maintain their COP within a highlighted target square for 1 s to make a ‘hit’, after which the contralateral square became the target. Subjects were instructed to make as many weight shifts as fluently as possible in 30 s (see figure 2).

During the first 8 weeks, patients’ weight-shifting speed improved from 6.9 to 9.2 hits (33% increase) to stabilise thereafter at a level still significantly slower than that of healthy elderly. At the same time, the imprecision of weight shifting, reflected by the average lateral COP displacement per weight shift, gradually decreased by 25% and reached normal reference values after 12 weeks. During the rehabilitation period patients showed a constant asymmetry in weight-transfer time with weight shifts towards the paretic leg being 23% slower than weight shifts towards the nonparetic leg. Hence, patients with stroke increased their speed of weight shifting by a proportionate decrease in weight-transfer time towards either leg, which underscores the notion that these patients experience difficulties with weight shifting bilaterally. Nevertheless, the moderate asymmetry in weight-transfer time suggests that problems with controlling the terminal phase of a weight shift onto the paretic leg are relatively great compared to problems with initiating the beginning of a weight shift from the paretic leg or controlling the terminal phase of a weight shift onto the nonparetic leg.82,83 Because nonparetic hip muscles can compensate for the lack of hip muscle function at the paretic side70 and because recovery of paretic hip muscle function may occur as well,81 it is possible that the constant degree of weight-transfer time asymmetry reflects a perceptual rather than a motor problem. Indeed, patients with hemi-neglect exhibited a relatively high degree of asymmetry.78

Effects of force feedback
Ustinova et al.89 examined the learning of voluntary weight shifts based on visual COP feedback in patients with different types of stroke in the territory of the middle cerebral artery, on average 10 months post-onset. Forty-three patients received force-feedback training on 10 consecutive days in addition to traditional rehabilitation. They first had to move their COP onto a randomly
sit-to-stand performance has been demonstrated by applying strength training to the lower limbs in patients with chronic stroke. After a 12-week, two times per week progressive resistance strength training programme, Weiss et al. observed a 21% decrease in repeated sit-to-stand time and a 12% improvement in functional balance (Berg Balance Scale) in seven elderly patients, living at home, on average 1 year after stroke. Hence, biofeedback training and perhaps also strength training may promote dynamic balance skills, especially during sit-to-stand transfers, in patients with stroke both in the post-acute and chronic phase.

Sensory control

Patients in the post-acute phase of stroke tend to rely more on visual information for postural control in both planes than healthy age-matched individuals. Deprivation of vision provokes increased COP amplitudes and velocities during unperturbed standing, whereas it does not seem to affect weight-bearing characteristics. The excessive reliance on vision for standing upright may decrease during rehabilitation, most prominently for frontal-plane balance, but can still be found in the chronic phase under more challenging conditions. Indeed, Bonan et al. reported balance problems in a group of 40 ambulatory patients who had suffered a first stroke at least 1 year before using the Sensory Organization Test (SOT), the protocol of the Equitest. Significantly poorer equilibrium scores were found compared to normal reference values only when patients were standing with the eyes closed on a sway-referenced support surface (SOT 5) and, most prominently, when they experienced a conflict between visual and vestibular information while standing with both sway-referenced vision and sway-referenced support (SOT 6). Additionally, many falls were recorded in these two conditions. Several patients were able to perform relatively well during SOT 5 compared to SOT 6, suggesting excessive reliance on visual input despite intact vestibular pathways. Similar results have been reported earlier when comparing stance duration in 10 hemiparetic patients balancing on a compliant versus stable support under different sensory conditions. On the other hand, when standing on a stable support, even elderly persons in the chronic phase of...
Cognitive control

Another non-specific strategy in persons with impaired postural stability is to allocate more attention to their standing balance than usually required by healthy age-matched individuals. There is ample evidence of increased interference of postural control with a secondary attention-demanding task in older adults compared to the young, particularly in elderly with a history of falls. The degree of dual-task interference may depend on the complexity of either task. However, it is less clear to what extent such interference uniquely reflects the enhanced attention demands for motor control due to ageing (or subtle pathology) or whether it is also determined by age-related deficits of divided attention. Against this background, Brown et al. recently compared six patients in the chronic phase of stroke with six age-matched elderly with regard to their attention demands for static postural control. They used a simple reaction-time task in which subjects had to respond as quickly as possible with a verbal response ('top') to a visual stimulus (illumination of a light). Reaction times were recorded in both groups while sitting, standing with the feet comfortably apart and with the feet together. Only the persons with stroke showed a progressive increase in reaction times (10-15%) from sitting to standing with a narrow support base. Although this study did not compare balance performance between groups and task conditions, it was controlled adequately for possible age-related attention deficits. It has provided initial evidence of increased attention demands for standing compared to sitting balance as a consequence of stroke.

As for standing balance recovery, de Haart et al. examined the influence of a concurrent arithmetic task in 37 patients in the post-acute phase of stroke. While maintaining an upright standing position for 30 s, subjects had to respond verbally with either ‘good’ or ‘fault’ to varying auditory sets of eight single-digit additions. While standing upright, the patients made the same number of arithmetic errors (25%) as when sitting. During the dual task, no consistent evidence was found of increased postural instability. However, patients further reduced the spontaneous weight loaded on their paretic leg, which was already at least 10% deviating from an equal weight distribution during quiet standing as a single task. They also increased the relative forefoot loading on the paretic side, which was already abnormal during simple upright
standing. Thus, it appeared as if they were ‘pushing themselves away’ from stance symmetry. This effect of attention distraction on foot loading asymmetry did not diminish over the course of rehabilitation, indicating that weight bearing on the paretic leg during normal standing tends to remain under cognitive control and may not easily become ‘spontaneous’.

Influence of attention deficits
Considering the possible effects of attention on standing balance, it is important to recognise that attention deficits might influence the recovery of both postural symmetry and stability from stroke. Among the first to specifically address this question were Stapleton et al., who tested 13 patients for attention deficits, balance impairments and incidence of falls at a median of 34-days post-stroke as well as 6 weeks later. Visual selective attention, auditory sustained attention, and auditory selective attention were examined using three subtests of the Test of Everyday Attention (TEA). Visual inattention was assessed with the star cancellation test and balance was assessed with the Berg Balance Scale. Although high levels (46-92%) of attention deficits were found at initial assessment and seven patients (54%) showed visuospatial hemi-neglect, only auditory selective attention was associated with balance ($r = 0.67$). Due to the small sample size, a possible relationship between attention deficits and falls could not be observed. It also remained unclear whether the presence of auditory selective attention deficits affected the rate of balance recovery. The same research group recently reported about the relationship between attention deficits (now also including a TEA subtest for divided attention), balance, ADL and falls in 48 community-dwelling ambulatory patients on average 46 months post-stroke. In these patients moderately high levels (19%–44%) of attention deficits were found. Only five patients (10%) showed visuospatial hemi-neglect. Both divided attention and auditory sustained attention were associated with balance and ADL ($r = 0.40–0.54$) and fall status ($r = -0.37–0.41$). Despite the associations found, it remains to be elucidated whether such attention deficits may interfere with balance recovery in the post-acute phase of stroke.

Influence of hemineglect
Instrumented studies of sitting balance in post-acute patients with severe stroke have demonstrated a profound negative influence of visuospatial hemi-neglect on postural stability and body orientation characterized by a contralesional tilt of the active postural vertical. However, the influence of hemi-neglect on standing balance does not appear equally strong once patients are able to maintain an independent upright position. Yet, some studies have indicated more severe loading asymmetry and postural instability in patients with right compared to left hemisphere lesions, most probably related to the presence of visuospatial hemi-neglect. As for voluntary lateral weight-shifting capacity, post-acute patients with hemi-neglect performed 10-20% slower than those without hemi-neglect which coincided with a relatively long weight-transfer time towards the paretic leg. Because there was no influence of the severity of the primary sensori-motor impairments, the greater weight-transfer time asymmetry may have been related to slower central processing of somatosensory information while loading the paretic leg. On the other hand, relative slow processing of visual information from the corresponding side of the feedback monitor must also be considered as an explanation for the observed asymmetry, since the applied weight-shifting task requires a considerable amount of concurrent visual attention. The presence of hemi-neglect did not influence the recovery of weight-shifting capacity in terms of speed or precision.

Discussion
Although numerous studies have identified many pathophysiological aspects of standing balance control in patients with stroke, relatively few studies have dealt with the recovery of standing balance to provide information about which of these aspects are likely to improve during the post-acute phase of rehabilitation. Nearly all of the published longitudinal studies have focused on relatively severely affected patients with a single supratentorial brain infarction or haemorrhage who had been selected for admission in a rehabilitation centre. Although these patients are probably most relevant to clinical rehabilitation in terms of patients’ needs and professional efforts required, little can be said about balance recovery in less severe affected patients with hemispheric stroke, or in patients with infratentorial stroke, e.g. of the brainstem or the cerebellum. The same is true for patients with bilateral
In patients with stroke, there is evidence of bilaterally impaired trunk muscle strength during voluntary movements of the trunk and of impaired voluntary and automatic trunk muscle activations during active movements of the trunk and limbs, respectively, most prominently at the paretic side. As for standing balance, it has been shown that voluntary trunk extensor torque is substantially associated with the Berg Balance Scale score in the post-acute phase of stroke (r_p = 0.51-0.64) at discharge from rehabilitation. Nonetheless, improvement of efferent trunk control while sitting or standing as a relevant factor in balance recovery from unilateral stroke has yet to be determined. Cognitive deficits such as hemi-neglect and a biased subjective postural vertical may be equally important causes of seated postural asymmetry and instability, particularly in those patients who have not yet reached standing ability. Reduction in hemi-neglect may, thus, lead to balance recovery, although this assumption needs to be underscored by empirical evidence as well. Of several intervention studies, only one trial has demonstrated that voluntary trunk control training coupled to visuospatial exploration training while sitting may result in beneficial effects on sitting and standing balance in patients with initially poor trunk control due to stroke, beyond the effects attributable to spontaneous recovery and conventional training.

Stepping responses

The use of relatively small force platforms may be the reason for another neglected aspect of standing balance recovery from stroke, which is the ability to make fast and multidirectional stepping responses to unexpected perturbations. In the case of a gross disturbance of the body’s vertical orientation, and in the absence of external support to the trunk or the arms, the posture-control system may no longer be able to rely on equilibrium reactions to keep the centre of mass well within the limits of the actual base of support. Instead, it may need to execute a stepping response to adjust the base of support to the movement of the centre of mass to prevent a fall. Under normal circumstances healthy subjects often prefer automatic stepping responses to fixed-support strategies when they are perturbed in various directions, even if maintaining a fixed base of support would theoretically be possible, perhaps because stepping requires relatively little muscle force. It is possible...
that stepping responses are even more vital to persons who suffer from impaired equilibrium reactions and muscle force, such as patients with a stroke. It has been reported in patients with chronic stroke that the initiation of paretic hip muscles while taking a voluntary step is relatively preserved compared to the same muscle activity during automatic equilibrium reactions.91 It might be that the ability to train of multidirectional stepping responses is greater than the possibility to influence the efficacy of basic equilibrium reactions following stroke. This hypothesis needs to be corroborated by empirical studies.

Influence of stroke location

Whether balance recovery from stroke is influenced by the location of the brain lesion is an important question, but has not been studied extensively. Laufer et al.22 found that patients with a right-hemisphere stroke of the anterior brain circulation had 37% chance of reaching independent standing after 2 months versus 60% chance for patients with comparable left-hemisphere lesions. However, such an effect of lesion side was not found by Sackley.91 From the moment patients have reached independent standing, no consistent differences in the recovery characteristics of right- versus left-hemisphere lesions have been reported,22,41,78 although Sackley91 reported more improvement of lateral postural stability in patients with left-hemisphere (30%) compared to right-hemisphere (7%) lesions. Ustinova et al.89 found that right-hemisphere patients had somewhat more problems during the initial learning of a voluntary weight-shifting task using visual COP feedback. Many cross-sectional studies have also indicated relatively severe balance problems in patients with right-compared to left-hemisphere lesions, particularly related to visuospatial cognitive deficits.27,88,103,106,124,125,133,134 However, others reported less marked or no effects of lesion side6,36,40,93 or even better static and dynamic balance in the case of right-hemisphere lesions.77 Perhaps more important than the side of stroke is the specific site of the brain lesion. The few studies that have investigated this issue in patients with unilateral supratentorial stroke indicated that involvement particularly of the parieto-temporal junction is associated with poor static and dynamic balance89,23,102 and more specifically lesions of the parieto-insular vestibular cortex.93,108 This association suggests that sensory integration deficits or disturbances of spatial cognition play a major role in the causation of severe standing balance problems after stroke.

Clinical implications

Based on the available evidence, no firm conclusions can be drawn about the best therapeutic approach to influence the speed or extent of standing balance recovery in the post-acute phase of stroke. There is little evidence of the efficacy of ‘static’ or ‘dynamic’ force-feedback training on either weight-bearing symmetry or postural stability during unperturbed stance. There is preliminary evidence of the efficacy of repetitive sit-to-stand training using biofeedback on dynamic standing balance skills, especially sit-to-stand transfers.91 The possible efficacy of lower-limb strength training on making sit-to-stand transfers needs further support.92 In addition, targeted balance training during visual deprivation may be more effective to improve stance stability under complex sensory conditions than the same training with full vision.97 Similarly, it may be that balance training under dual-task and complex sensory conditions may help to regain sufficient automaticity and flexibility of the various balance skills required in daily life; however, this notion needs to be corroborated by empirical evidence. When balance recovery attenuates, mechanical aids such as canes may improve both weight-bearing characteristics and postural stability during unperturbed standing,75–73 although their influence on dynamic balance skills and gait may be quite different. Hence, with regard to the many possible therapeutic options, the literature is still far from extensive or conclusive. It is expected that this review will help researchers interested in the rehabilitation of patients with stroke to select challenging new study objectives.
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Chapter 3

Posturographic assessment of sitting balance recovery in the subacute phase of stroke

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Abstract

Although early sitting balance is a well-known predictor of functional outcome after stroke, it is still unknown which aspects of normal upright sitting balance are most sensitive to subsequent recovery. This study used an adjustable chair mounted on a force platform to assess the recovery of quiet-sitting balance in 16 patients with a first supratentorial stroke during their inpatient rehabilitation. The patients underwent three posturographic assessments at 6-week intervals from the moment of their admission, on average 5.6 weeks after stroke. Each quiet-sitting balance assessment consisted of 2 series of four 30-s test conditions: sitting with eyes open and closed, on both a stable and unstable (air cushion) surface. The RMS of the center-of-pressure (COP) velocities was used as the primary measure of lateral and anteroposterior balance control. It was found that, compared to 10 healthy elderly, lateral balance was more affected by stroke than balance in the anteroposterior direction, especially during visual deprivation, and most sensitive to subsequent functional changes induced by spontaneous recovery or rehabilitation. Furthermore, lateral balance control showed the strongest association with the Berg Balance Scale as a clinical measure of balance capacity. Hence, (lateral) trunk control seems to be a primary target for rehabilitation. Since an unstable support was necessary to obtain significant effects of stroke, recovery and visual deprivation, it may be important to use an unstable support during sitting balance training as well.

Introduction

Many studies have shown that early sitting balance is an important prognostic factor for functional recovery after stroke. Studies regarding sitting balance have typically used global clinical measures that combine basic activities related to trunk control, such as the Trunk Control Test (TCT), the Trunk Impairment Scale and (the trunk control items of) the Postural Assessment Scale for Stroke Patients. Studies that have used instrumented methods to study sitting balance have focused on the analysis of spontaneous weight-bearing asymmetry (WBA), on the limits of stability during voluntary weight shifting, on the angular dispersion of the support oscillations while maintaining balance on a laterally rocking platform, and on the activation of trunk muscles during voluntary movements of the trunk and arm. Only the study by Nichols et al. examined sitting balance recovery in the subacute phase of stroke and found that, of all outcomes, the forward leaning capacity showed improvement in time.

A recent study by Genthon et al. described, for the first time, the use of a force platform to measure sitting balance in ten stroke patients. They reported increased area of sway and center-of-pressure (COP) velocities, especially in the anteroposterior direction, and indicated the need for longitudinal studies using force platform technology to investigate recovery of sitting balance. In addition, a recent review emphasized the lack of information about the recovery of trunk control in the subacute phase of stroke, based on quantitative instrumented techniques.

In this perspective, we used an individually adjustable chair positioned on a force platform to accurately assess the changes in ground reaction forces during various sitting tasks in stroke patients undergoing rehabilitation. In the first phase of this study, repeated sitting-balance measurements were done in healthy subjects to assess the intra-subject variability of selected force-platform parameters (‘repeatability study’). It was assumed that the most stable parameters would not only be most reliable, but would have the greatest validity as well, because they are probably best related to the neural control processes. In the second phase of this study, these balance parameters...
were evaluated in a cohort of patients shortly after stroke under various mechanical and sensory conditions to assess which aspects of sitting-balance control are most sensitive to the functional consequences of stroke and the subsequent restorative mechanisms (‘cohort study’). We hypothesized that, based on the results of previous studies of standing balance, lateral balance would be most responsive to recovery, especially during visual deprivation.

**Methods**

**Subjects**

In the repeatability study, 14 healthy young individuals (mean age 29.0 ± 3.8 years) were included. In the cohort study, 16 consecutive patients who had been admitted to a rehabilitation center with a first supratentorial stroke (mean age 62.7 ± 7.6 years) were included on average 5.6 ± 1.7 weeks post onset. Patients were eligible when they had a Berg Balance Scale (BBS) score less than 40 within a post-stroke interval of 6 weeks, but were able to sit unsupported on a bed with their feet touching the ground for one minute. This criterion was used to include patients able to perform the posturographic assessment, but who were still sufficiently affected in their balance capacity to show subsequent functional improvement. All patients were included within 3 days after admission. Patients with non-stroke related sensory or motor impairments or using drugs affecting motor control were excluded.

The stroke cohort was compared to 10 healthy elderly volunteers recruited among the relatives of the patients (mean age 57.0 ± 4.8 years). All healthy subjects included in both phases of the study were active in daily life and no one suffered from any neurological or orthopedic disorder. The regional medical-ethical committee approved the study protocol and all participants gave their oral and written informed consent.

**Posturography**

Subjects were placed on a specially designed chair, which was fixed on an AMTI force platform (Model: OR6-7MA-1000) through the legs of the chair. The platform recorded forces in three orthogonal directions and the moments around these direction axes. Signals were processed by a personal computer after a 16-bit AD-conversion at a sampling rate of 500 Hz and the point of application of the resultant of the ground reaction forces (COP) was calculated. The height of the chair was compensated in the moment-of-force calculations, resulting in a COP located in the plane of the seat of the chair. The calculations were done for each sample, with a maximum error of ± 1 mm in the lateral and anteroposterior (AP) directions. The coordinates of this COP were passed through a digital, low-pass filter (Zero Phase Butterworth, cut-off frequency 6 Hz) to eliminate high-frequency components arising from noise.

The chair (figure 1) consisted of a transparent sitting surface, built in a square aluminum frame (40 x 50 cm) positioned on four aluminum legs. The chair had two foot rests that could individually be adjusted in height and depth. The distance between the foot rests was 15 cm. They were positioned in an angle of approximately 5° exorotation from the sagittal midline. For the

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1 Advanced Mechanical Technology Inc., Watertown MA, U.S.A.
The subjects were placed barefooted on the chair with their tubera ischiadica on a fixed line in the frontal plane. A correct position was confirmed through a mirror, which was placed below the transparent sitting surface. The foot rests were individually adjusted to such a height and depth that the hips and knees were in 90° flexion and the ankle joints in a neutral position and were kept constant at consecutive assessments. Subjects were verbally instructed to sit as quietly as possible with an erect spine and with their hands folded on their lap. They looked straight ahead during the EO conditions, whereas they wore a pair of closed dark goggles during the EC conditions.

Analysis
For each registration, the RMS of the COP amplitudes (A_COP) and, after a first-order differentiation, the RMS of the COP velocities (V_COP) in the lateral and AP directions were calculated as balance parameters. Since we were primarily interested in the dynamic aspects of sitting balance control, positional parameters were not calculated. In the repeatability study, coefficients of variation (CV) were determined over the six tests of the healthy young to compare the intra-subject variability of the balance parameters. Based on this analysis, the most stable parameter was identified for each condition in each direction of sway. These selected balance parameters were averaged over the 2 test series within each assessment for every individual in both phases of the study. In the repeatability study, a three-way ANOVA of Time (three assessments) x Vision (eyes open vs. closed) x Surface (stable vs. unstable) was then performed to exclude any systematic trend across the three assessments. In the cohort study, we first compared the baseline data of the stroke patients with those of the healthy elderly using a three-way ANOVA of Group x Vision (eyes open vs. closed) x Surface (stable vs. unstable). Then, a three-way ANOVA of Time (three assessments) x Vision (eyes open vs. closed) x Surface (stable vs. unstable) was done for the stroke patients. Finally, we used Pearson correlation coefficients to associate age, MI and neglect as important determinants of postural control in the acute phase of stroke with the posturographic parameters and the clinical balance measures (BBS and TCT). All statistical analyses were performed with SPSS 12.0.1 for Windows.
Results

Repeatability study
The V\textsubscript{COP} values consistently proved to be much more stable over 6 repeated tests than the A\textsubscript{COP} values with CVs varying between 11.3% and 23.1% (see Table 1). The V\textsubscript{COP} values in the AP direction were generally more stable (CVs 11.3%-14.8%) than those in the lateral direction (CVs 13.8%-23.1%). As for the absolute balance performance, the healthy young showed on average 23% higher V\textsubscript{COP} values when sitting on an unstable surface (lateral: F(1,13)=9.28, p<0.01; AP: F(1,13)=8.95, p<0.01) compared to sitting on a stable surface. No main or interaction effects of time or vision were found.

Table 1 Mean, standard deviation (SD) and coefficient of variation (CV) of all balance parameters for 4 different conditions (n=14).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Condition</th>
<th>Mean</th>
<th>SD</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A\textsubscript{COP}</td>
<td>EO / stable</td>
<td>0.27</td>
<td>0.06</td>
<td>30.9</td>
</tr>
<tr>
<td></td>
<td>EC / stable</td>
<td>0.30</td>
<td>0.07</td>
<td>33.7</td>
</tr>
<tr>
<td></td>
<td>EO / unstable</td>
<td>0.93</td>
<td>0.25</td>
<td>31.2</td>
</tr>
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<td></td>
<td>EC / unstable</td>
<td>0.99</td>
<td>0.33</td>
<td>32.7</td>
</tr>
<tr>
<td></td>
<td>EO / stable</td>
<td>0.50</td>
<td>0.13</td>
<td>30.6</td>
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<tr>
<td></td>
<td>EC / stable</td>
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<td>31.3</td>
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<tr>
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<td>EO / unstable</td>
<td>0.78</td>
<td>0.22</td>
<td>35.7</td>
</tr>
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<td></td>
<td>EC / unstable</td>
<td>0.71</td>
<td>0.25</td>
<td>39.0</td>
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<tr>
<td></td>
<td>EO / stable</td>
<td>1.71</td>
<td>0.57</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>EC / stable</td>
<td>1.73</td>
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<td>15.5</td>
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<td></td>
<td>EO / unstable</td>
<td>2.19</td>
<td>0.68</td>
<td>21.1</td>
</tr>
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<td></td>
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<td>39.0</td>
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<tr>
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<td>0.69</td>
<td>11.9</td>
</tr>
<tr>
<td></td>
<td>EC / stable</td>
<td>3.17</td>
<td>0.64</td>
<td>11.3</td>
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<tr>
<td></td>
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<td>3.54</td>
<td>0.61</td>
<td>14.4</td>
</tr>
<tr>
<td></td>
<td>EC / unstable</td>
<td>3.56</td>
<td>0.70</td>
<td>14.8</td>
</tr>
</tbody>
</table>

AP=anteroposterior; EO= eyes open; EC= eyes closed.

Cohort study
Patient characteristics and clinical measures are shown in Table 2. Figure 2 shows the mean V\textsubscript{COP} values for the healthy elderly and the patients with

stroke at their first assessment. Compared with the healthy elderly, the patients showed higher V\textsubscript{COP} values, but this effect was significant only for the unstable conditions (Group x Surface interaction: lateral: F(1,24)=12.54, p<0.01; AP: F(1,24)=6.19, p<0.05). In addition, there was a Group x Surface x Vision interaction indicating increased reliance on vision during unstable sitting for the stroke patients (lateral: F(1,24)=6.97, p<0.05; AP: F(1,24)=4.48, p<0.05). Figure 3 shows the mean V\textsubscript{COP} values for the stroke patients at the 3 assessments during their rehabilitation. There was an interaction effect of time by surface in both directions (lateral: F(2,14)=6.00, p<0.05; AP: F(2,14)=6.56, p<0.01), indicating that only the unstable condition showed

<table>
<thead>
<tr>
<th>Table 2 Patient characteristics and clinical measures (mean, standard deviation and range (between brackets) for the patients with stroke at the 3 assessments (n=16).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
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<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Age</td>
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<tr>
<td>Gender</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Type of stroke</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Location of stroke</td>
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<tr>
<td></td>
</tr>
<tr>
<td>MI (0-100)</td>
</tr>
<tr>
<td>Somatosensory Threshold*</td>
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<tr>
<td>Neglect (asymmetry index %)</td>
</tr>
<tr>
<td>TCT (0-100)</td>
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<td></td>
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<td></td>
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<tr>
<td>BBS (0-56)</td>
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</tbody>
</table>

*The median and range are given.
MI = Motricity Index, TCT= Trunk Control Test, BBS= Berg Balance Scale.
Discussion

This is the first study that used force-platform technology to assess the recovery of quiet-sitting balance control in the subacute phase of stroke. With the use of an adjustable chair mounted on a force platform it was found that, compared to healthy elderly, $V_{\text{COP}}$ values were abnormally high in both directions of sway during unstable sitting and that these values improved over time. In young healthy subjects it was found that the $V_{\text{COP}}$ values consistently showed better stability than the $A_{\text{COP}}$ values and that these $V_{\text{COP}}$ values did not show any learning effects at 2-week intervals.

When the baseline performances of stroke patients were compared to the performances of healthy elderly, abnormally high $V_{\text{COP}}$ values were found in both directions of sway, although somewhat more pronounced in the lateral compared to the AP direction, and only while sitting on an unstable surface. Moreover, in both directions, a significantly increased reliance on vision was observed after stroke, again most prominently in the lateral direction. These results are in accordance with those of Perennou et al.,8,9,26 who found pronounced lateral postural instability, both with and without vision, in subacute stroke patients during improvement in time. Figure 3 clearly demonstrates that this improvement was reached during the first 6 weeks of follow-up and that, thereafter, the level of postural instability remained twice as high as in the healthy elderly. Only in the lateral direction a Surface x Vision interaction was found ($F(1,15)=10.95, p<0.01$), implicating an increased reliance on vision during unstable sitting across the 3 assessments. Although this influence of vision seemed to diminish during the first 6 weeks, the interaction effect with time was not significant (Surface x Vision x Time interaction: $F(2,14)=1.24, p=0.32$).

The results of the clinical assessments are depicted in table 2. In contrast to the small and gradual changes in the TCT, the BBS showed a major improvement within the first 6 weeks of follow up. This pattern is congruent with the posturographic results presented above. Indeed, of both clinical balance measures, only the BBS was significantly associated with the lateral $V_{\text{COP}}$ values in the unstable condition. The EO condition of the first assessment explained 44% of the BBS variance at the last assessment ($r = -0.66, p<0.01$).

The EC condition of the first and last assessment explained 37% and 42% of the BBS variance at the last assessment ($r = -0.61, p<0.05$ and $r = -0.65, p<0.01$, respectively). Posturographic parameters were not significantly associated with age, MI, or hemineglect.
The fact that no association was found between posturographic parameters and clinical characteristics is in contrast with previous studies indicating a relationship between e.g. hemineglect and balance in patients with stroke. This discrepancy can most likely be attributed to the relatively low number of subjects in this study. Another limitation of this study is the fact that the results apply to a rather severe subgroup of stroke patients who had been selected for inpatient rehabilitation and who suffered from major initial balance problems. Hence, no conclusions can be drawn with respect to less severe or other types of stroke patients.

**Conclusion**

With regard to normal upright sitting, lateral balance control appears most critically affected by stroke, especially during visual deprivation, and most sensitive to functional changes induced by spontaneous recovery or rehabilitation. Furthermore, lateral balance control in sitting is best associated with clinical balance performance. As a consequence, (lateral) trunk control seems to be a primary target for rehabilitation. Since an unstable support seems necessary to stress the posture control system to obtain significant effects of stroke, recovery and visual deprivation, it may be important to use an unstable support during sitting balance training as well.

**Acknowledgements**

The authors would like to thank Fanny Schils, physical therapist, for her help in the posturographic assessments. We are indebted to all participants for their willingness to take part in this study. This study was financially supported by the Dutch Organisation for Health Research and Development (ZonMw) grant no. 14350009.
References


References


Part II
Influence of visuospatial hemineglect on balance after stroke
Chapter 4

Visuospatial asymmetry and non-spatial attention in subacute stroke patients with and without neglect

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Ilse JW van Nes
Wiebo H Brouwer
Alexander CH Geurts
Luciano Fasotti

Revised version submitted to Cortex
Abstract

Asymmetry in performance and an association with non-lateralized attention are often mentioned as two important aspects of the clinical manifestation of visuospatial neglect. Both these aspects were investigated in 21 left (LH) and 24 right hemisphere (RH) stroke patients and in 20 healthy subjects. The letter and star cancellation subtests of the Behavioral Inattention Task (BIT) and a computerized simple visual reaction time task (CVRT) with stimuli presented either left, central or right in extrapersonal space were administered. In LH patients, the calculation of BIT asymmetry scores allowed a better distinction between patients with and without neglect than raw omission scores. However, in RH patients, raw and asymmetry scores led to similar classifications. In the CVRT, raw and asymmetry scores for the number of omissions also produced identical classifications. Thus, the computation of omission asymmetry scores did not substantially refine the diagnosis of neglect. On the other hand, more patients were classified as neglect patients by using CVRT reaction time (RT) asymmetry scores than by using BIT or CVRT omission scores. Ipsilesional RTs were chosen as a measure of general, non-lateralized attention. The ipsilesional RTs of the LH and RH patients did not differ from the healthy subjects’ lateral RTs. However, within the RH group, patients with both RT asymmetries and BIT scores above cut-off level showed longer ipsilesional RTs than patients with defective RT asymmetries but normal BIT scores. This supports the idea of an interaction between lateralized and non-lateralized attentional components in neglect, in which the presence of general attentional deficits exacerbates the severity of neglect symptoms due to visuospatial bias. RT tasks may contribute to the detection of asymmetries in visuospatial attention in patients with subclinical neglect symptoms, who might compensate for their lateralized deficit in paper-and-pencil tasks thanks to intact general attention.

Introduction

Visuospatial neglect refers to a disabling disorder in spatial attention. It occurs more frequently after right hemisphere (RH) stroke than after left hemisphere (LH) stroke, but an exact rate of occurrence has been hard to derive: in different studies, reported frequency rates range from 13 to 82 percent in RH patients and from 0 to 76 percent in LH patients. The moment and method of assessment turn out to play an important role in this variability (see Bowen et al. for a review).1

A common definition of visuospatial neglect is: ‘a disorder whereby a patient fails to explore the half-space contralateral to the cerebral lesion’.2 The asymmetry in performance levels on the contralateral as compared to the ipsilesional side is indeed the most central and distinctive feature in the clinical manifestation of neglect. Even the unsophisticated observer can notice the left-sided difficulties of RH stroke patients with neglect in everyday tasks such as dressing, eating, reading or writing. Given this definition, one would expect that the degree of asymmetry in responses to stimuli on the left and the right side is somehow taken into account in the assessment of this disorder. This is the case in a study by Azouvi et al.,3 who report not only the number of omissions, but also the difference between left sided and right sided omissions on different tasks, for instance the Bells Test.4 It has also been suggested that the location of the first item which was identified in cancellation tasks could indicate the exploration strategy used by the patient.5,6 However, in many of the standard paper-and-pencil tests employed to assess neglect, the most specific characteristic of neglect, i.e. the presence and degree of asymmetry in task performance, is not considered. An important example is the Behavioural Inattention Test (BIT),7 a widely used test battery for neglect in which only the total number of errors is considered. As a result, scores may be confounded by general attentional deficits or other cognitive disorders that are common in stroke patients.

Besides asymmetry in performance, another clinically evident feature of visual neglect is that symptoms in neglect patients do not have an all-or-nothing character. According to Anderson et al.,8 neglect does not reflect an irreparably damaged cognitive system, but rather an inability to consistently detect and respond to stimuli. These authors suggest that neglect patients may not ignore
all contralesional stimuli, but detect some, whilst their neglect is mainly reflected in a slowing of their responses. According to Bartolomeo and Chokron, in RH neglect patients, exogenous attention for the contralesional side is impaired, whereas endogenous attentional processes seem to be relatively preserved, although slowed. This idea fits well within the clinical picture of neglect: patients do not explore left space automatically, but can be instructed to do so on a conscious level. Therefore, it may be expected that in some instances, patients are able to compensate for their neglect by means of endogenous attention, resulting in a slowing in their contralesional response, but not necessarily in omissions.

To investigate the varying degree of responsiveness in neglect patients, other measures than the traditional ones are needed. As Schendel and Robertson point out, unlimited exposure time of the stimuli allows patients to enhance their primary performance level by checking, so that the severity of neglect becomes difficult to quantify and tests lose sensitivity. Thus, when paper-and-pencil detection tests are used, conclusions about the results of the cognitive processes of visuospatial scanning and attention in neglect can only be drawn in terms of the presence or absence of responses. Schendel and Robertson as well as Deouell suggest that in studying neglect, reaction time data could yield important information about the status of visuospatial attention in this disorder.

In the present study, performance on the star- and letter-cancellation subtests of the BIT is analyzed in patients with a subacute supratentorial LH or RH stroke. Regular scores (in which the degree of asymmetric performance is not taken into account) are compared with newly computed asymmetry scores. In addition, the same comparison between raw omission scores and asymmetry scores will be made in a more ecological task, namely a computerized visual reaction time task (CVRT), in which a large visual car driving scene is employed. It is expected that computing the degree of asymmetric test performance might increase test specificity in the diagnosis of neglect.

The CVRT is also used to investigate reaction time patterns. Given the abovementioned varying degree of responsiveness in neglect, it is expected that in patients who do not show defective omission scores, asymmetries in ipsilesional vs. contralesional RTs still might reveal the presence of attentional biases. Thus, RT data could further enhance the sensitivity of asymmetry scores.

Finally, it is generally accepted that impaired general, non-spatial attentional difficulties modulate spatially lateralized neglect phenomena and may even aggravate them. As Husain and Rorden point out, attentional deficits can occur in stroke patients independently of neglect, but when combined with a lateralized bias, these deficits may exacerbate the severity of neglect and reduce the potential for recovery from neglect. Robertson suggests that the general attentional deficits in unilateral neglect may be relatively low-level arousal deficits. These might be deficits in the third and last major function of attention in the Posner and Petersen attentional taxonomy: the function of self-maintaining a vigilant or alert and ready-to-respond state. According to Duncan et al, besides the association of neglect with lateralized bias, it is also strongly associated with processing capacity.

In the present study, general non-spatial attentional processes will be investigated by means of ipsilesional RTs on the CVRT, since it was assumed that at this position, interference between spatial and non-spatial attentional problems would be reduced to a minimum. As the basic attentional processes of arousal and selective attention are often associated with the right hemisphere, it may be expected that RH patients show slower ipsilesional RTs than LH patients, although both patient groups might be slower than healthy controls, as found in a RT study by Kaizer et al. The interaction of general, non-spatial attentional processes with neglect symptoms will be investigated by studying the relation between ipsilesional RTs and RT asymmetries in the RH neglect patients. It is expected that the degree of asymmetrical performance is associated with the presence of general attentional deficits.

Methods

Participants
Three subject groups were examined: 20 healthy subjects, 21 patients with a left hemisphere (LH) stroke and 24 patients with a right hemisphere (RH)
stroke. The healthy subjects were recruited by publishing an advertisement in a local paper, in which healthy elderly were invited to participate. For the patient groups, all patients with a first intracerebral infarction or hemorrhage admitted to the Sint Maartenskliniek rehabilitation centre in the period from June 2003 until February 2005 were eligible. Patients with severe concomitant behavioural or psychiatric problems were excluded. Furthermore, no patients with severe aphasia were included. Although some language problems may have been present in the selected patient group, it was observed that by offering repeated instruction and demonstration, all patients included were able to perform the tests. Patients with visual field deficits like hemianopia and quadrantanopia as diagnosed by means of Donders’ confrontation method were excluded. All patients were examined within nine weeks post-stroke. One of the LH patients was left-handed, all other patients were right-handed. Research was completed in accordance with the Declaration of Helsinki. All subjects gave their informed consent to participation in this study. In Table 1, medical and demographic data of the subjects are presented.

Table 1 Medical and demographical data of the three subject groups.

<table>
<thead>
<tr>
<th></th>
<th>LH patients (N=21)</th>
<th>RH patients (N=24)</th>
<th>Healthy controls (N=20)</th>
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</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>59.8 (34-80)</td>
<td>61.2 (38-72)</td>
<td>60.4 (38-81)</td>
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<tr>
<td>Days post-onset (range)</td>
<td>35.3 (15-48)</td>
<td>36.8 (20-62)</td>
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<tr>
<td>Motricity Index1 (range)</td>
<td>50.1 (0-83)</td>
<td>45.9 (0-77)</td>
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<td>Lesion Location</td>
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</tr>
<tr>
<td>- 6 medial cerebral artery area</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- 3 capsule interna</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- 2 parieto-occipital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 1 subcortical, not specified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 1 multiple lacunar infarctions</td>
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</tr>
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<tr>
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<td>RH Ischemia (N=17):</td>
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<tr>
<td>- 1 basal ganglia</td>
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<td></td>
<td></td>
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<tr>
<td>- 1 fronto-temporal</td>
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<td></td>
<td></td>
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<tr>
<td>- 1 paraventricular</td>
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<td>LH Hemorrhage (N=5):</td>
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</tr>
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<td>- 2 parietal</td>
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<td>- 1 temporo-parietal</td>
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<td>- 1 fronto-temporal</td>
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<td>- 1 thalamic</td>
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<tr>
<td>- 3 medial cerebral artery area</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>- 1 temporal/subcortical</td>
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<td></td>
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</tbody>
</table>

1 Motricity Index25,26 scores are given for the contralesional lower extremity. Scores of 27 and below on this 99-point rating scale indicate a severe hemiparesis/hemiparalysis.

ADMINISTERED TASKS

Two kinds of tasks were administered to all the patients: the Behavioural Inattention Test (BIT)7 and a computerized reaction time test (CVRT). To the healthy controls, only the CVRT was administered. The conventional subtests of the BIT (i.e. line crossing, letter cancellation, star cancellation, figure and shape copying, line bisection and representational drawing; see for further details Wilson et al)7 were administered to all patients. Of these subtests, only the letter and star cancellation data were used to compare raw and asymmetry scores. As Halligan et al.27 point out, letter cancellation and star cancellation are the most sensitive subtests of the BIT and the combination of these two subtests can provide a short neglect screening that can be easily applied in clinical practice. Furthermore, besides the line cancellation subtest (which however often shows ceiling effects), none of the other subtests of the BIT are suitable for the computation of an exact asymmetry index.

The CVRT was administered in the two patient groups and in the healthy controls. This task was an adaptation of an older driving simulator test in which attention had to be divided between dynamic lane tracking and a continuous
CVRT procedure

Rectangular patterns of square dots (±50 cm x 15 cm) were projected successively at three positions just above the ‘horizon’ on the screen, with the centre of the stimuli at a vertical position of approximately 10º below the level of the eyes and a horizontal visual angle of approximately 105º between the left side of the left stimuli and the right side of the right stimuli (see Fig. 2).

In total, 36 of these patterns were projected: 12 on the left, 12 on the middle, and 12 on the right position in random order. Before the assessment trial, six stimuli were presented in a practice trial, consisting of two stimuli at each position in a random order.

Subjects had to press a button on the steering wheel as fast as possible when detecting a rectangle. Patients used the upper button on the ipsilesional side with their ipsilesional (nonparetic) hand, healthy subjects used the upper right button with their right hand. The task was self-paced: stimuli disappeared directly after the subjects’ response or (in the case of an omission) after a
maximum presentation time of 6000 ms. Between the disappearance of one stimulus and the presentation of the next one there was a random interstimulus interval of 800 to 1200 ms. The first stimulus appeared 2000 ms after the start of the task.

Data analysis

For both the BIT and the CVRT, raw scores as well as asymmetry scores were computed. To determine cut-off levels that would be indicative of neglect, the data of healthy subjects were used.

In case of the BIT subtests, norm data for raw scores were available from the test manual. Cut-off scores (the lowest score that occurred in healthy subjects minus one) are defined for the total of the six subtests (cut-off 129) and for all subtests separately. In this study, the sum of detected stimuli on the letter and star cancellation subtests was used. The cut-off scores of these two subtests are 33/40 stimuli for the letter cancellation subtest and 52/54 stimuli for the star cancellation subtest. Thus, the maximum score for both subtests together is 94 and the cut-off score was set at (33 + 52 =) 85. For the computation of asymmetry scores, the following formula was used:

\[
\frac{\text{ipsilesional score} - \text{contralesional score}}{\text{ipsilesional score} + \text{contralesional score}} \times 100\%
\]

Using the abovementioned BIT norm data (cut-off scores: 33/40 and 52/54, respectively), the highest asymmetry score that still should be considered ‘normal’ was calculated by filling in the formula, based on the hypothetical healthy case in which an optimal (i.e. errorless) performance occurred on one side and all omissions were made on the other side. This results in 20 ‘ipsilesional’ vs. 13 ‘contralesional’ detections in the letter cancellation and 27 ‘ipsilesional’ vs. 25 ‘contralesional’ detections in the star cancellation task (for the statistical analysis, absolute values were computed from the asymmetry scores, so that the exact side would not be very important in this example). Thus, the highest BIT asymmetry score that should be considered ‘normal’ would be:

\[
\frac{(20 + 27) - (13 + 25)}{(20 + 27) + (13 + 25)} \times 100\% = 10.6\%
\]

BIT asymmetry indexes higher than 10.6% were interpreted as indicating the presence of neglect.

For the CVRT, the number of omissions (i.e. stimuli that were not detected) as well as mean RTs (ms) were recorded for each position (left, middle, right). Cut-off scores were based on the performance levels in the healthy subjects group. In the healthy subjects, no omissions occurred in the CVRT. Nevertheless, in patients, it was reasoned that one omission could occur by chance. Therefore, a cut-off level of two or more omissions was chosen.

In the computation of the mean RT scores, omissions (see results) and responses faster than 150 ms were dropped. Thus, only valid RTs were used. Early responses occurred in six LH patients (17 early responses in total) and in two RH patients (both one early response). No cut-off level for mean RTs was defined.

Asymmetry scores for CVRT omissions and RTs were computed using the same formula that was used for the BIT. Asymmetry indexes for omissions were only calculated for patients who made two or more omissions. Regarding the spatial distribution of the omissions, any sign of asymmetric test performance was considered indicative for neglect. Thus, for the omissions, all asymmetry indexes greater than zero were considered above cut-off. The maximum asymmetry in right and left RTs that occurred in the healthy subjects was 21.4%. Thus, this score was set as the RT asymmetry cut-off score.

After computing BIT and CVRT asymmetry scores, these scores were converted into absolute (positive) values. This was necessary to compare the RT scores of both patient groups to those of the healthy subjects. For reasons of homogeneity, also for the BIT and CVRT omissions, absolute values were computed.
Results

BIT
In Table 2, mean raw scores as well as mean asymmetry scores (absolute values) on the BIT letter and star cancellation subtests are displayed for both patient groups. Furthermore, for both the raw and the asymmetry scores, the number of patients that respectively scored below and above cut-off level is displayed.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>BIT letter and star cancellation: raw and asymmetry scores for both patient groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raw scores Max. = 94 Cut-off ≤ 85</td>
</tr>
<tr>
<td></td>
<td>LH (N=21)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>87.33 (9.50)</td>
</tr>
<tr>
<td>N of patients below / above cut-off</td>
<td>4</td>
</tr>
</tbody>
</table>

Overall, RH patients had lower raw BIT letter and star cancellation sum scores than LH patients. However, when tested using a one-way ANOVA, this difference was not significant ($F(44)=3.36$, $p=ns$). According to the summed letter and star subtest cut-off scores (i.e. $≤ 85$ indicates neglect), four patients in the LH group and eight patients in the RH group could be classified as neglect patients. These patients were exactly the same patients who had total BIT scores within the ‘neglect’ range (i.e. $≤ 129$).

Most BIT asymmetries were in the expected direction. That is, LH patients made more omissions at the right side, whereas RH patients made more left omissions. The absolute BIT asymmetry scores, computed from the letter cancellation and star cancellation subtests did (in contrast with the raw scores) show significant differences between RH and LH patients ($F(44)=4.97$, $p<0.05$). Using the cut-off score of 10.6%, one LH and eight RH patients could be classified as neglect patients. Thus, compared with the classifications based on raw scores, three LH patients were no longer classified as neglect patients. These LH subjects made 14/40, 21/40 and 31/40 omissions in the letter cancellation task, but only 2/54, 1/54 and 0/54 omissions in the star cancellation task, respectively. This considerable difference in lateralized omissions between letter and star cancellation suggests the presence of a subtle verbal information processing problem rather than visuospatial neglect in these LH patients.

CVRT omissions
The patterns of left, middle and right omissions for the three subject groups are displayed in Figure 3. Visual inspection reveals that RH patients made most of their omissions on the left side, whereas LH patients mostly made omissions on the right side.

In Table 3, the mean number of omissions in the CVRT and the mean absolute CVRT omission asymmetry scores for both patient groups are displayed.
The healthy subjects’ scores are not represented, since no omissions occurred in this group. Ten patients missed two or more stimuli, of whom eight were RH patients. All these RH patients had asymmetry scores of 100%. Of the two LH patients with two or more omissions, one made three omissions on the right and none on the left side and thus had a maximum asymmetry score. The other LH patient made four omissions on the right and one on the left, and thus had an asymmetry score of 60%. In general, all patients who had two or more omissions on the CVRT, also had abnormal (> 0) asymmetry scores. For this reason, the number of patients who scored above cut-off was the same for raw and asymmetry scores.

A one-way ANOVA for both patient groups and the healthy subjects showed a significant group effect ($F(64)=4.74$, $p<0.05$) for the total number of omissions (L+R). Post-hoc tests (Bonferroni) revealed a significant difference between the healthy subjects and the RH patients ($p<0.05$). Also, for the asymmetry in omissions, a significant group effect occurred ($F(64)=6.47$, $p<0.01$). Post hoc tests showed significant differences between the healthy subjects and the RH patients ($p<0.01$) and between the LH and RH patients ($p<0.05$).

**CVRT reaction times**

The patterns of left, middle and right RTs for the three subject groups are displayed in Figure 4. As can be seen, both patient groups showed a contralesion slow of their RTs.

RTs of the three subject groups at each horizontal position were compared using a MANOVA. At the left side, there was a significant group effect, ($F(2)=9.10$, $p<0.001$), with significant post-hoc (Bonferroni) differences between the RH patients and the healthy subjects ($p=0.001$) as well as between both patient groups ($p<0.005$). RTs at the middle position showed also a significant group effect ($F(2)=6.32$, $p<0.005$). Post-hoc test showed that RH patients were significantly slower than healthy subjects ($p<0.005$). Also at the right position, there was a significant group effect ($F(2)=3.94$, $p<0.05$), that resulted from a significant ($p<0.05$) difference between the LH patients and the healthy subjects. Notice that the patients’ ipsilesional RTs, that were considered a measure of general attention, did not differ significantly from the healthy subjects’ RTs at the matching positions.

For the patient groups, a GLM repeated measures analysis was performed with Group (RH, LH) as a between-subjects factor and Side (ipsilesional, middle, contralesional) as a within-subjects factor. Since for healthy subjects no ‘ipsilesional’ and ‘contralesional’ side could be defined, they were not included in this analysis. Group and Side effects were both significant.

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**Table 3** CVRT omissions: raw and asymmetry scores for both patient groups.

<table>
<thead>
<tr>
<th></th>
<th>Raw omissions L+R</th>
<th>Asymmetry scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Max. = 24</td>
<td>Max. = 100 %</td>
</tr>
<tr>
<td></td>
<td>Cut-off &gt; 1</td>
<td>Cut-off &gt; 0 %</td>
</tr>
<tr>
<td>LH (N=21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SD)</td>
<td>0.52 (1.66)</td>
<td>7.62 (24.88)</td>
</tr>
<tr>
<td>RH (N=24)</td>
<td>2.21 (3.62)</td>
<td>33.33 (48.15)</td>
</tr>
<tr>
<td>N of patients above cut-off</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>SD: standard deviation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Figure 4** Mean CVRT reaction times at each position for the three groups.
asymmetry scores for the RTs are displayed on the y-axis. The horizontal line indicates the cut-off score of 21.4%.

Table 4  CVRT RTs: asymmetry data.

<table>
<thead>
<tr>
<th></th>
<th>Asymmetry scores</th>
<th>Max. = 100 %</th>
<th>Cut-off &gt; 21.4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LH (N=21)</td>
<td>8.77 (10.08)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>RH (N=24)</td>
<td>28.65 (23.45)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Healthy (N=20)</td>
<td>5.98 (5.02)</td>
<td></td>
</tr>
</tbody>
</table>

CVRT: computerized visual reaction time task; RT: reaction time; SD: standard deviation

Figure 5  Patient classifications based on BIT asymmetries and CVRT RT asymmetry scores.

Visual inspection reveals that seven patients are classified as neglect patients using the criteria of both BIT and CVRT. However, in seven other cases,
patients were split up in three groups:
- N++ patients (N=7): patients classified as neglect patients by both BIT asymmetry scores and CVRT RT asymmetry scores (i.e. patients in the upper left and lower right quadrant in Figure 5) is discussed in further detail below.
- N+ patients (N=4): patients that were only classified as neglect patients using the CVRT RT asymmetry scores, but not using the BIT (i.e. patients in the upper left quadrant of Figure 5)
- N- patients (N=12): patients who were not classified as neglect patients using either one of both measures (lower left quadrant of Figure 5).

Since only one RH patient was classified as a neglect patient using the BIT but not the CVRT (patient C), this category was not included in the analysis.

The RT patterns of the healthy subjects and the three RH groups are represented in Figure 6. As can be seen, RH patients who were classified as neglect patients by both the BIT and the CVRT (N++) showed slow overall and ipsilesional RTs and a clear asymmetry in left vs. right RTs, whereas RH classifications by means of both tasks do not correspond. Test performance of the patients who were differently classified according to the BIT and CVRT asymmetries in RTs (i.e. patients in the upper left and lower right quadrant in Figure 5) is discussed in further detail below.

**Patients T, G, K:** Whereas these patients did not show defective BIT scores (raw nor asymmetry scores), they all made contralateral omissions on the CVRT and showed clearly asymmetrical RTs, which showed a systematic pattern over the stimuli and were not the result of a few incidentally long RTs. Furthermore, they showed clinical signs of neglect as observed by their therapists and therefore were later referred for further neglect screening by their neuropsychologist in a later stage of rehabilitation treatment. These results seem to point toward the presence of a mild form of neglect.

**Patients I, U:** These patients showed almost optimal BIT scores and no CVRT omissions. However, clearly asymmetrical RTs occurred, which showed a systematic pattern over the stimuli. These results seem to point toward the presence of a spatial attentional bias.

**Patient W:** This LH patient showed obvious asymmetries in both the letter and star cancellation subtests of the BIT and also in the number of CVRT omissions (four right, one left). Furthermore, raw CVRT RT data were clearly asymmetrical (left 1204 - middle 1269 - right 1600 ms). However, due to the fact that all RTs were very slow, the asymmetry score did not reach the cut-off level.

**Patient C:** This RH patient showed obvious asymmetries in both the letter and star cancellation subtests of the BIT. However, CVRT omission and RT asymmetry scores were in the normal range. This could not be explained by a general slowing of RTs.

**Correlation between CVRT RT asymmetry scores and ipsilesional RTs**

Pearson correlations between RT asymmetry scores and ipsilesional RTs were not significant for the LH nor for the RH patient group, although for the RH group, there was a trend toward significance ($r = 0.386, p=0.063$).

**CVRT RT time patterns in RH patients and healthy subjects**

To explore the role of the combination of lateralized and non-lateralized attention components in neglect instead of in RH patients in general, the RH patients were split up in three groups:

**Figure 6** Mean CVRT reaction times at each position for the three RH subgroups and the healthy subjects.
patients who were classified as neglect patients only by the CVRT (N+) had slow RTs on the left, but not on the right. The RT patterns of N- patients and healthy subjects were very similar.

Because of the small and different group sizes, the RT patterns of the four groups were analyzed using non-parametrical tests. Kruskal Wallis Tests for left, middle and right RTs as well as RT asymmetries all showed highly significant group differences (X² = 34.18, 30.58, 20.41, 27.25, respectively; p<0.001). Since no post-hoc tests were available, a number of separate Kruskal Wallis Tests were performed, each comparing two groups. RT asymmetry scores of the N++ as compared to the N+ group did not differ significantly (X² =2.00, p=ns), but the difference between the RT asymmetry scores of the N+ and the N- patients was significant (X² =8.47, p<0.05). There was no significant difference between RTs of the N++ and the N+ group at the left position (X² =2.29, p=ns). However, differences between N++ and N+ patients were significant at the middle (X² =7.00, p<0.01) and right (X² =4.32, p<0.05) position. Finally, Kruskal Wallis Tests showed no significant difference between the N++ and N+ groups with regard to age, days post onset, Motricity Index score and number of CVRT omissions.

Discussion

In the present study, two aspects of neglect were evaluated, namely the asymmetry in ipsilesional as compared to contralesional performance levels and the role of non-spatial attentional processes. As Halligan et al.27 have pointed out, the combination of letter and star cancellation provides a short neglect screening that can be easily applied in clinical practice. The results of this study replicate the finding that the letter and star cancellation subtests correctly predict total BIT scores.

In the LH patients, the computation of asymmetry scores for the letter and star cancellation BIT subtests resulted in classifications into ‘neglect’ and ‘non-neglect’ categories that differed from the classifications solely based on raw scores. Three LH patients did not show asymmetric test performance, whilst their raw scores were in the neglect range. In clinical practice, it may not be common to administer the BIT to LH patients, unless visuospatial deficits are presumed to be present. In these cases, clinicians might want to consider the difference between left and right omissions and compare performance on the different subtests. In the RH patients, no differences in classifications emerged using either raw or asymmetry scores on the BIT. Thus, the idea that the computation of asymmetry scores could prevent false-positive neglect diagnoses was not confirmed in RH patients.

With regard to the omissions on a computerized visual reaction time task (CVRT), asymmetry scores seemed more sensitive in discriminating the LH group from the RH group than raw scores. However, this could be explained by the fact that in all subjects but one, asymmetry scores were either 0 or 100%. Thus, abnormal performances seem to have been artificially ‘inflated’ by computing asymmetry scores. To classify patients, just as in the BIT (at least regarding the RH patients), the computation of asymmetry scores in the CVRT did not seem to have any additional value as compared to raw omission scores.

Beside omissions, RTs were recorded in the CVRT task. Asymmetry scores, computed from RTs at both lateral positions, turned out to be highly sensitive in discriminating the RH group from the healthy subjects. Like Deouell et al.,13 we found that by classifying patients using RTs, more patients fell into the neglect category than by using the BIT. Also, more patients were classified as neglect patients when asymmetry scores were computed based on RTs instead of CVRT omissions. This suggests that RT asymmetry scores are more sensitive in detecting spatial attentional bias.

RTs were not only taken into account to study asymmetrical performance, but also to draw some conclusions about the status of non-spatial attention in our patients. Ipsilesional RTs instead of central RTs were chosen as a measure of general, non-spatial attentional processes, since especially in the RH group, a rightward attentional bias was expected.32-35 This would cause a slowing of left and central RTs, that could however not be attributed to general attentional
patients did not reach significance, although it could be expected that this were the case with larger group sizes. Furthermore, it turned out that patients with defective scores not only on the CVRT but also on the BIT, were the ones with the longest ipsilesional RTs. Thus, the finding that ipsilesional RTs in RH were similar to those in LH patients could not be explained by rightward hyper attention.

The main reason for analyzing RT patterns within the RH group was to investigate the role of non-spatial attentional mechanisms in neglect. This topic has been reviewed in several recent studies. For example, as Husain and Rorden point out, deficits in general attentional processes can occur in stroke patients independently of neglect, but when combined with a lateralized bias, these deficits may exacerbate the severity of neglect and reduce the potential for recovery from neglect. Thus, in their conceptualisation of neglect, these authors seem to distinguish ‘lateralized bias’ from ‘neglect’ and view neglect symptoms as an addition of a lateralized bias and general attention problems. The results of the last part of the present study seem to support this notion. Here, RT patterns of the healthy subjects and three subgroups of RH patients were compared, i.e. patients who were classified as neglect patients by both BIT asymmetry and CVRT RT asymmetry scores (N++), patients who were only classified as neglect patients using the CVRT RT asymmetry scores (N+) and RH patients with normal scores on both tasks (N-). The N++ and the N+ patients showed similar asymmetries in their lateral RTs. However, the ipsilesional RTs of the N++ patients were significantly higher than those of the N+ patients. Thus, in concordance with the ideas of Husain and Rorden, the presence of an ipsilesional slowing of RTs, reflecting general attention problems, seems to contribute to the exacerbation of neglect symptoms and the worsening of test performance in RH patients with a lateralized bias.

As Bartolomeo and Chokron have claimed, neglect patients might compensate for their exogenous orienting deficit by relatively intact endogenous searching processes. The current results indicate that apparently, the N+ patients had more general attentional resources to compensate for their lateralized deficit, so that they may have been able to employ compensatory attentional resources successfully in the BIT subtests, although their lateralized attentional bias was
revealed on the CVRT RT task. One could raise the question whether such well-compensated asymmetries should be called ‘neglect’. In clinical terms, we might speak of the N++ patients as patients with a ‘severe’ neglect and call the symptoms of the N+ group ‘mild’ or even ‘sub-clinical’, since these were not obvious on the BIT. Nevertheless, for both therapists and clinicians it might important to recognize attentional bias in patients who do not show obvious signs of neglect on paper-and-pencil tasks. It was postulated that well-compensated or recovered neglect might be detected by increasing attentional load,39 for instance under dual task conditions.40 Thus, patients with attentional asymmetries but no general attentional problems might still show visuospatial attention deficits in the contralesional hemisphere, especially in attentionally demanding situations, like traffic. Future research will aim at investigating the issue of attentional capacity.

Acknowledgements

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References


Chapter 5

Is visuospatial hemineglect really a determinant of postural control following stroke? An acute-phase study
Abstract

Introduction. The purpose of this study was to determine the independent contribution of visuospatial hemineglect to impaired postural control in the acute phase (<2 weeks) of stroke compared to other possible clinical and biological determinants.

Methods. This study was conducted in 4 hospitals in the mid-east region of the Netherlands. A total of 78 consecutive patients with a first-ever acute supratentorial stroke was included. Functional balance was measured with the Trunk Impairment Scale, the Trunk Control Test, the Berg Balance Scale, and the Functional Ambulation Categories. Visuospatial hemineglect was assessed by means of an asymmetry index obtained from the Behavioral Inattention Test. The Motricity Index, vibration threshold, sustained attention and the presence of hemianopia were registered as other possible clinical determinants. Stepwise backward multiple linear regression analysis was performed introducing all selected clinical determinants as well as age and poststroke time as possible biological determinants.

Results. Hemineglect was present in 17 patients (21.8%). The groups with and without hemineglect were different for gender and the proportion of right hemisphere strokes, but not for age, type of stroke or poststroke time. Neglect patients had on average lower scores on all functional balance tests as well as on the clinical assessments. Multivariate linear regression showed that, besides hemineglect, only muscle strength and age independently contributed to impaired balance explaining 65% to 72% of variance of the selected outcomes.

Conclusion. This study showed that hemineglect independently contributes to impaired postural control in the acute phase of stroke.

Introduction

Loss of postural control is a major problem in many patients with an acute stroke and has been identified as an adverse predictor of functional outcome. Motor, sensory as well as cognitive impairments may account for postural imbalance in stroke patients. As for cognitive impairments, hemineglect in particular is regarded as a negative determinant of postural control and functional outcome. However, the results of studies on this subject vary considerably.

Perennou et al. demonstrated decreased postural stability in patients with visuospatial and personal hemineglect in the subacute phase of stroke, which was characterized by an asymmetrical trunk posture deviated towards the affected side. In another study by the same group, it was argued that hemineglect is strongly associated with contraversive pushing, a condition in which patients seem to actively push away from the nonparetic side leading to severe postural imbalance. Consistent with these findings, Taylor et al. reported a midline shift of the trunk towards the affected side during sitting, which occurred mainly in patients with visuospatial hemineglect in the first 6 weeks after stroke. On the other hand, in patients 2 to 4 weeks after stroke, Tyson et al. did not find a relationship between visuospatial hemineglect and balance as measured by the Brunel Balance Assessment (BBA), which consists of 3 subscales (sitting, standing and stepping). In addition, de Haart et al. did not find a clear relationship between visuospatial hemineglect and the control of quiet standing as measured by force-plate posturography during a 3-month follow-up of balance recovery in the subacute phase of stroke. Hence, the results of previous studies concerning the influence of hemineglect on balance in patients in the subacute and chronic phases after stroke are inconsistent, probably due to differences in patient selection, stroke severity, and prevalence or diagnosis of hemineglect. As a consequence, the influence of hemineglect on balance skills in an unselected sample of patients during the acute phase after stroke (<2 weeks) is unknown.

There are several reasons to examine the influence of hemineglect in the acute phase after stroke. Most importantly, the true relationship between hemineglect and balance can be best assessed in the very early phase, because both
hemineglect and postural imbalance are usually more prevalent and severe in the first 2 weeks after stroke. Moreover, the recruitment of patients in the acute phase allows to study this relationship in an unselected sample of patients. Finally, knowledge about this relationship may be important to guide early therapeutic and preventive interventions and, perhaps, influence the choice of discharge destination from the hospital. Against this background, we investigated the independent contribution of hemineglect to impaired postural control in the acute phase after stroke, in relation to the possible influence of other clinical and biological determinants. A secondary goal was to estimate the incidence of hemineglect and contraversive pushing in an unselected sample of acute stroke patients and to compare postural imbalance between these subgroups. We hypothesized that hemineglect would be an important independent determinant of impaired postural control in the acute phase after stroke and that balance impairments would be even more pronounced in patients with contraversive pushing.

**Methods**

**Patients**

This cross-sectional study was conducted in 4 hospitals in the mid-east region of the Netherlands: the University Medical Centre St. Radboud and the Canisius-Wilhelmina Hospital in Nijmegen, the Rijnstate Hospital in Arnhem and the Jeroen Bosch Hospital in ’s Hertogenbosch. All patients who had been consecutively admitted to neurology wards of these hospitals with a first-ever supratentorial infarction or hemorrhage were eligible during the period October 2005 until March 2006. Patients were included if the stroke was proven by computed tomography or magnetic resonance imaging scans and if the time after stroke was less than 2 weeks. Exclusion criteria were 1) diminished level of consciousness, primary visual deficits or severe aphasia, respectively according to the items 1A (not alert), 1C (disturbed performance of level of consciousness commands), 2 (partial gaze paresis or forced deviation) and 9 (severe aphasia or mute) of the National Institutes of Health - Stroke Scale, 2) non-stroke related sensory or motor impairments and 3) concomitant cognitive problems that impaired the ability to follow simple verbal instructions. All patients gave their written informed consent after receiving both verbal and written information about the study. All patients received a ‘best medical treatment’ according to the guidelines of the Netherlands Society of Neurology, ensuring that each patient was given physiotherapy to start mobilization and to improve passive and active range of joint motion as soon as possible. No specific therapy was initiated to improve postural control or hemineglect. The regional medical-ethical committee approved the study protocol.

**Assessment**

All tests were performed bedside by the same investigator – physiotherapist (SL). Outcome measures in this study were the Trunk Impairment Scale (TIS), the Trunk Control Test (TCT), the Berg Balance Scale (BBS) and the Functional Ambulation Categories (FAC). The TIS consists of 3 subscales, including static sitting balance (score range 0 to 7), dynamic sitting balance (score range 0 to 10) and coordination (score range 0 to 6). Thus, the total TIS score ranges from 0 to 23 points. The TCT examines 4 movements: 1) rolling from a supine position to the affected side and 2) to the non-affected side, 3) sitting up from a supine position and 4) sitting balance. The total TCT score ranges from 0 to 100 points. The BBS was used to assess static and dynamic standing balance. This scale comprises 14 tasks (score range 0 to 4) yielding a total sum score of 0 to 56 points. The level of independency of walking was assessed with the FAC (score range 0 to 5). Visuospatial hemineglect was assessed by means of 2 subtests of the Behavioral Inattention Test (BIT), namely, letter cancellation and star cancellation. We selected these particular tests because Halligan et al. found that these are the most sensitive subtests of the BIT, and to minimize the burden of the examination on the patients. To control for nonlateralized, generalized attention deficits, we calculated an asymmetry index, which was introduced by McIntosh et al. to determine personal neglect. An asymmetry index higher than 10.6% (cut-off value based on the lowest scores of the norm data obtained from healthy subjects) was interpreted as evidence of visuospatial hemineglect. Contraversive pushing was investigated using the standardized Scale for Contraversive Pushing (SCP). Patients who scored at least 1 out of 2 points for all 3 items were considered to suffer from contraversive pushing.
Several other clinical and demographic characteristics were addressed as possible determinants of balance, including age, stroke type (infarction/hemorrhage), stroke side (left/right), time after the stroke (days), sustained attention, muscle strength, vibration sense and vision. Sustained attention was tested with the elevator counting subtest of the Test of Everyday Attention (TEA) (score range 0 to 7). Muscle strength of the contralesional leg was assessed using the Motricity Index (MI) with a score ranging from 0 (complete paralysis) to 100 (normal strength). Vibration threshold was measured at the lateral malleolus and at the hallux contralateral to the stroke using a semi-quantitative tuning fork (US neurologicals, Kirkland, WA) with a score ranging from 0 (no vibration sense) to 8 (maximum vibration sense). Vision was tested for the presence of contralesional hemianopia by means of Donders’ confrontation test, which was performed by presenting a moving finger in each of the four quadrants, for each eye separately (present/absent). We chose not to consider stroke volume or specific stroke location as a possible biological determinant, because it is still unclear how stroke volume is associated with clinical stroke severity. Moreover, stroke volume or specific stroke location cannot be reliably assessed on an early CT-scan of the brain, because it takes some time before hypodensity develops.

### Results

A total of 78 consecutive acute stroke patients was included during a 6-month period. Visuospatial hemineglect was present in 17 patients (21.8%). In table 1, all demographic and clinical characteristics and balance outcomes are described. We chose not to consider stroke volume or specific stroke location as a possible biological determinant, because it is still unclear how stroke volume is associated with clinical stroke severity. Moreover, stroke volume or specific stroke location cannot be reliably assessed on an early CT-scan of the brain, because it takes some time before hypodensity develops.
Contraversive pushing was diagnosed in 3 female patients. They all had a right hemispheric infarction and suffered from visuospatial hemineglect. Their biological, clinical and balance characteristics are compared with the N+ patients without pushing behavior in table 1. The 3 ‘pushers’ performed much worse on all balance outcomes compared to the ‘nonpushers’. In addition, they had lower muscle strength and a higher vibration threshold. Two of the three ‘pushers’ suffered from hemianopia. Remarkably, the BIT asymmetry score was only slightly higher for the ‘pushers’ (59%) than for the ‘non pushers’ (50%) and sustained attention was even better in the ‘pushers’.

Discussion

To the best of our knowledge, this is the first hospital-based study that investigated the independent contribution of visuospatial hemineglect to impaired postural control in an unselected sample of patients with a first-ever supratentorial stroke within 2 weeks after stroke onset. According to our hypothesis, hemineglect made an independent contribution to postural imbalance, while age and muscle strength appeared to be independently associated with impaired balance as well. In quantitative terms, the influence of hemineglect was substantial, because it coincided with 25% to 38% lower values on each of the selected balance outcomes that, together, covered the whole spectrum of balance skills during sitting (TCT, TIS), standing (BBS) and walking (FAC). The finding that impaired sustained attention did not independently contribute to balance impairment indicates that the adverse influence of hemineglect was caused by a specific lateralized deficit. The observed incidence of hemineglect was substantial, because it coincided with 25% to 38% lower values on each of the selected balance outcomes that, together, covered the whole spectrum of balance skills during sitting (TCT, TIS), standing (BBS) and walking (FAC). The finding that impaired sustained attention did not independently contribute to balance impairment indicates that the adverse influence of hemineglect was caused by a specific lateralized deficit. The observed incidence of hemineglect was substantial, because it coincided with 25% to 38% lower values on each of the selected balance outcomes that, together, covered the whole spectrum of balance skills during sitting (TCT, TIS), standing (BBS) and walking (FAC). The finding that impaired sustained attention did not independently contribute to balance impairment indicates that the adverse influence of hemineglect was caused by a specific lateralized deficit. The observed incidence of hemineglect was substantial, because it coincided with 25% to 38% lower values on each of the selected balance outcomes that, together, covered the whole spectrum of balance skills during sitting (TCT, TIS), standing (BBS) and walking (FAC).

Perennou et al. previously emphasized the importance of visuospatial hemineglect as a determinant of impaired balance following stroke. They
found that hemineglect explained as much as 56% and 61% of postural behavior during sitting with and without vision, respectively, in 14 selected patients with left-sided hemiparesis who were at least 2 months after stroke.\textsuperscript{6,24} They hypothesized that the observed postural instability in patients with hemineglect could be the result of a problem in the multisegmental orientation of the body in space due to a higher-order disorder in the processing of somesthetic information. This disorder would lead to a disturbed body scheme and would be strongly associated with lesions of the temporoparietal junction, the so-called polymodal sensory cortex.\textsuperscript{25} In the same vein, Kerkhoff provided evidence of multisensory spatial orientation deficits in patients with hemineglect by investigating the visual-spatial and tactile-spatial axis orientation in the chronic phase.\textsuperscript{26} They found that patients with hemineglect showed a significant contraversive tilt of all 3 visual-spatial and tactile-spatial axes and that these deficits were significantly associated with their ambulation performance.

Conversely, others have not confirmed the proposed relationship between hemineglect and postural imbalance after stroke. For instance, Tyson and co-workers did not find such a relationship in patients 2 to 4 weeks after stroke but, instead, found that only muscle strength and somatosensation were independently associated with balance as assessed with the BBA.\textsuperscript{8} They suggested that hemineglect might be related to balance disability due to a possible association with muscle weakness and sensory loss. Yet, in a recent publication by the same group, no association between sensory loss and hemineglect could be determined.\textsuperscript{27} The average time after stroke is an important difference between the study of Tyson et al. (21 days) and our study (5 days). Although the incidence of hemineglect was higher in Tyson’s study (28%), hemineglect might have been less severe due to natural recovery, resulting in a weaker association. Indeed, the spontaneous recovery of hemineglect in the first weeks after stroke is substantial.\textsuperscript{28} Some studies regarding standing balance in the post-acute and chronic phases of stroke\textsuperscript{28,29} failed to show an association between postural instability and hemineglect as well, most likely for the same reason. Perhaps most important, in the present study a BIT asymmetry index was used to determine the presence of visuospatial hemineglect, integrating both the star and letter cancellation test, in order to control for generalized attention deficits. In contrast, Tyson et al.\textsuperscript{8} used a nonlateralized cut-off criterion for (either) the star cancellation test or the line bisection test to identify hemineglect patients. This latter criterion may have led to overestimation of hemineglect and, subsequently, to a nonsignificant association with postural imbalance. Generally, the relatively high incidences of hemineglect reported in some other studies may well be the result of using less stringent criteria for diagnosing hemineglect.\textsuperscript{30,31} Indeed, if in this study the raw cut-off scores of the BIT would have been used, instead of the asymmetry index, 10 more patients would have been classified as suffering from visuospatial hemineglect. Visual inspection of these patients’ test results revealed that their omissions were evenly distributed at both sides. In addition, these 10 patients had a relatively low score on the TEA. Hence, they most probably suffered from a generalized attention deficit rather than hemineglect.

In the present study, the observed incidence of contraversive pushing was 4%, which is lower than the 10% reported by Pedersen et al.\textsuperscript{32} All 3 ‘pushers’ had sustained a right hemisphere infarction (2 patients with predominantly temporal lobe lesions and one patient with a large frontoparietal lesion) and suffered from visuospatial hemineglect. Yet, their average BIT asymmetry index was only 9% higher than in the hemineglect patients without pushing behavior, whereas their average BBS and FAC scores were much lower (1.7 and 0, respectively). The small number of ‘pushers’ in this study does not justify any generalization. Still, the observed pattern of results might be an indication that, although hemineglect and pushing behavior may be related, contraversive pushing may not be simply an extreme form of hemineglect but rather a distinct entity. Indeed, Pedersen et al. did not find a significant difference in the incidence of hemineglect or anosognosia between patients with and without pushing behavior.\textsuperscript{32} Possibly, discrete neural networks encoding the postural vertical must be damaged to observe contraversive pushing.\textsuperscript{7,21,24,33,34}

Our multivariate model showed that, besides hemineglect, muscle weakness independently explained a considerable proportion of the variance in balance control. This result is coherent with the reports by others who found a significant and independent association between muscle weakness and
balance impairment in the post-acute and chronic phases of stroke, respectively. Dietz and Sinkjær suggested that after supraspinal motor lesions regression occurs on the affected side to “simpler” motor performance. Although the monosynaptic reflex responses may be disinhibited, the polysynaptic responses that are most important for postural regulation are reduced. In contrast with the study by Tyson et al., the present study did not find that loss of somatosensation, in terms of increased vibration threshold, independently contributed to impaired balance, whereas aging did. As for sensation, it may well be that Tyson’s study tested this impairment more extensively and sensitively using the Rivermead Assessment of Somatosensory Performance (RASP). On the other hand, the independent adverse influence of older age on balance after stroke that we observed seems to be in line with many other studies investigating postural and gait control in elderly persons. Because older age is generally associated with sensory problems, it may be that in the present study the possible association of somatosensation with balance was to some extent obscured by its association with age. In addition, the number of patients included in the current study was still limited, which may have prevented us from identifying relatively weak associations.

**Conclusion**

The results of this study have shown that visuospatial hemineglect independently contributes to impaired postural control in an unselected sample of patients in the very acute phase of supratentorial stroke. Together with muscle strength and age, the presence of hemineglect can explain 65% to 72% of the variance in sitting, standing, and walking balance. This knowledge is not only important from a neuroscience perspective, but also for guiding preventive measures and therapeutic interventions in the (sub)acute phase of stroke. Indeed, several authors have emphasized the increased fall risk in stroke patients that suffer from visuospatial hemineglect. Future research is needed to determine the influence of hemineglect on the recovery of sitting and standing balance in the various phases after stroke.

**Acknowledgements**

We thank all patients for their willingness to participate in this study as well as the departments of neurology of the Radboud University Nijmegen Medical Centre and the Canisius-Wilhelmina Hospital in Nijmegen, Jeroen Bosch Hospital in ’s Hertogenbosch, and Rijnstate Hospital in Arnhem, for their help in the recruitment of patients.

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References


Chapter 6
Is visuospatial hemineglect longitudinally associated with postural control in the postacute phase of stroke?

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Fanny Schils
Luciano Fasotti
Alexander CH Geurts
Gert Kwakkel

Submitted
Abstract

Introduction. The purpose of this study was to determine the longitudinal association of visuospatial hemineglect with postural control in postacute stroke patients and to establish whether this relationship is confounded by other determinants.

Methods. A prospective cohort study of 53 postacute stroke patients consecutively admitted for inpatient rehabilitation was conducted. Transfers and standing balance were assessed with the Berg Balance Scale (BBS) and walking balance with the Functional Ambulation Categories (FAC). Repeated measurements took place at baseline (36.6 ± 10.4 days after stroke) and after six and 12 weeks. Visuospatial hemineglect was assessed by an asymmetry index, derived from the Letter and Star Cancellation Tests (LSCT asymmetry index). Random coefficient analysis was used to analyze the longitudinal impact of visuospatial hemineglect on the BBS and FAC. The association between hemineglect and outcome was corrected for potential confounders: age, severity of paresis of the lower leg, sensory deficits and presence of hypertonia. A covariate was considered to be a confounder if the regression coefficient of hemineglect on outcome changed by >15%.

Results. Visuospatial hemineglect was significantly associated with BBS and FAC. The relation between hemineglect and both BBS and FAC was confounded by severity of paresis of the lower leg. After correction, hemineglect remained independently associated with BBS, whereas the association with FAC lost significance.

Conclusion. Visuospatial hemineglect is longitudinally and independently associated with postural control after stroke. These findings suggest that hemineglect is an important factor particularly for controlling static and dynamic standing balance during the first months post stroke.

Introduction

A majority of the survivors from stroke suffer from motor, sensory and cognitive impairments resulting in limitations in their activities and social participation. For a substantial number of these patients, the main goals of rehabilitation are to restore independent gait and activities of daily living (ADL). One of the most important factors that determine the independency of gait and gait-related activities is postural control. Although a uniform definition is lacking, postural control or ‘balance’ has been described as the capacity to maintain, achieve or restore a state of equilibrium during any posture or activity. Rapid and optimal recovery of postural control in patients with stroke is a prerequisite for their independence and social participation and will also improve general health by reducing the risk of falling. Therefore, it is necessary to have a good conceptual understanding of the factors that may affect (recovery of) postural control after stroke.

A considerable number of studies suggests that in patients with stroke visuospatial hemineglect is associated with a less extensive recovery of ADL and, recently, several studies have been published about the specific influence of visuospatial hemineglect on postural control. Although some of these cross-sectional studies found an adverse influence of visuospatial hemineglect on postural control, other studies did not corroborate this relationship. Only a few studies controlled for possible confounders of this relationship, such as severity of paresis, hypertonia, loss of tactile sensation and age. Moreover, information about the longitudinal association of visuospatial hemineglect with postural control in patients with stroke remains unclear. Only a prospective study of Kollen et al. investigated, in a repeated measurement design, the quasi-causal relationship of change of visuospatial hemineglect on improvement of walking ability according to the Functional Ambulation Categories (FAC) during the first year post stroke. They found a first indication that a reduction in visuospatial neglect is an independent factor related to improvement of gait as assessed by the FAC in patients with a first-ever stroke, after controlling for postural control assessed with the timed-balance test, severity of paresis assessed with the Fugl-Meyer leg score and motricity index leg score (MI-leg) and time post stroke.
Against this background, the aim of the present prospective study was to investigate the longitudinal, bivariate relationship of visuospatial hemineglect with standing and walking balance in patients with stroke in the postacute phase. Subsequently, we investigated the influence of possible confounders that may affect this relationship in an association model. We hypothesized that the presence of visuospatial hemineglect would be negatively associated with standing and walking balance. Based on the literature and on clinical grounds, we hypothesized that older age, severity of paresis, sensory deficits and the presence of hypertonia might significantly influence the observed association between visuospatial neglect and postural control.

Methods

Design and subjects
This prospective cohort study was based on a randomized, controlled trial (RCT) that investigated the long-term effects of whole-body vibration on postural control after stroke. As this RCT revealed no group differences on any of the outcome measures, we combined the results of both groups in this study. In the present study, 53 patients with stroke participated with a mean age of 61.1 ± 10.3 years. All patients were admitted to one of three participating rehabilitation centers in The Netherlands (i.e., St. Maartenskliniek, Nijmegen; Groot Klimmendaal, Arnhem; Tolbrug, ’s Hertogenbosch). Patients with the diagnosis ‘stroke’ according to the definition of the WHO were included if they met the following criteria: 1) first-ever supratentorial stroke, 2) a poststroke interval less than six weeks and 3) moderate or severe balance impairments defined as a score less than 40 on the Berg Balance Scale (BBS). Exclusion criteria were: 1) nonstroke-related sensory or motor impairments, 2) use of medication that could interfere with postural control, and 3) concomitant cognitive problems that impaired the ability to follow simple verbal instructions. After receiving verbal and written information, all subjects gave their written informed consent to participate in the study. The regional medical-ethical committee approved the study.

Procedure and measurements
Patients were included within three days after admission to the rehabilitation center (mean time post-stroke: 36.6 ± 10.4 days). Measurements took place at baseline (t₀), at 6 weeks (t₁) and at 12 weeks (t₂) follow up. Each entire testing procedure took about two hours, depending on the level of disability. All functional measurements were performed by three independent, experienced physical therapists, who were not involved in the rehabilitation management of the participating stroke rehabilitation wards.

The dependent variables in our model were the Berg Balance Scale and the Functional Ambulation Categories (FAC). The BBS was used to assess postural control during body transfers and static and dynamic standing balance tasks. This scale comprises 14 tasks (score range 0-4) yielding a maximal total sum score of 56 points. The level of independency of walking or walking balance was assessed with the FAC. This instrument distinguishes between six levels ranging from ‘unable to walk’ (i.e. score 0) to ‘able to walk independently anywhere’ (i.e. score 5). Both scales, i.e. BBS and FAC, have been shown to be reliable and valid. Visuospatial hemineglect was the independent variable in our model. To determine the presence of visuospatial hemineglect, we used two subtests of the Behavioral Inattention Test (BIT), which have been proposed by Halligan et al., viz. the letter and star cancellation tests (LSCT). We selected these particular tests because Halligan and colleagues found that these are the most sensitive subtests of the BIT, and to minimize the burden of the examination on the patients. To control for non-lateralized, generalized attention deficits, we calculated an asymmetry index (LSCT asymmetry index), which was introduced by McIntosh et al. to determine personal neglect. An asymmetry index higher than 10.6% (cut-off value based on the lowest scores of the norm data obtained from healthy subjects) was interpreted as evidence of visuospatial hemineglect.

Age was addressed as time-independent possible confounder, whereas severity of paresis, sensory deficits and hypertonia were addressed as possible, time-dependent confounders. For assessment of severity of paresis of the lower limb, we used the Motricity Index of the leg (MI-leg). MI-leg measures muscle strength of hip flexion, knee extension and ankle dorsiflexion by using a weighted score for each part from 0 (i.e., no movement) to maximal 33 points (i.e., normal power). A total of 100 points (3 * 33 + 1) are available for the lower limb. The somatosensory threshold was used to assess sensibility.
in the affected lower limb. It was determined by investigating the pressure sensitivity at the tip of the hallux using five calibrated monofilaments indicated by the log transformation of the applied forces (2.83, 3.61, 4.31, 4.56 and 6.65). Hypertonia was assessed by means of the Modified Ashworth Scale (MAS) for the ankle plantar flexors.23

Data analysis
The longitudinal relationship of visuospatial hemineglect and postural control was investigated by using random coefficient analysis (RCA) (MLwiN, version 2.02).34 RCA takes into account that the repeated observations within one subject are interdependent. In MLwiN the intercept is assumed to be randomly distributed between subjects.

Initially, bivariate longitudinal regression analyses were conducted with the BBS and FAC as the dependent variables and the LSCT asymmetry index as the independent variable. To examine the unique longitudinal association of visuospatial hemineglect on standing balance (i.e. BBS) and walking balance (i.e. FAC), a correction was made for possible baseline differences on BBS and FAC in the association model by taking the initial BBS and FAC values as determinants in the regression model. Subsequently, impact of visuospatial neglect was added to the model and tested, while controlling for time-independent (age) and time-dependent variables (i.e. severity of paresis, sensory deficits and hypertonia) as possible confounders, associated with both the dependent (i.e. BBS or FAC) and independent variables (i.e. visuospatial hemineglect). If the regression coefficient of visuospatial neglect changed beyond 15% after adding the candidate variable in the model, the added covariate was considered to be a confounder.35

Results
Patient characteristics at baseline of all the 53 stroke patients are presented in table 1. Table 2 shows the values of the dependent and independent variables at the three assessments for the whole group as well as for the patients with and without hemineglect, separately. In total, 152 of the 159 scores were available for modeling. Bivariate random coefficient analysis showed that visuospatial hemineglect was significantly associated with both the BBS ($\beta=-0.258, SE=0.065, p<0.05$) and the FAC ($\beta=-0.061, SE=0.024, p<0.05$).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics at baseline.</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>Total 53</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>23/30</td>
</tr>
<tr>
<td>Age, years (mean±SD)</td>
<td>61.1±10.3</td>
</tr>
<tr>
<td>Type of stroke (ischemic/hemorrhagic)</td>
<td>38/15</td>
</tr>
<tr>
<td>Location of stroke (left/right)</td>
<td>25/28</td>
</tr>
<tr>
<td>Time post stroke (days) (mean±SD)</td>
<td>36.6±10.4</td>
</tr>
<tr>
<td>% present based on LSCT asymmetry index</td>
<td>24.5%</td>
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<tr>
<td>LSCT asymmetry index (mean±SD)</td>
<td>11.0±23.0%</td>
</tr>
<tr>
<td>Berg Balance Scale (0-56) (mean±SD)</td>
<td>23.8±16.6</td>
</tr>
<tr>
<td>Functional Ambulation Categories (0-5) (median (range))</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>Barthel Index (0-20) (mean±SD)</td>
<td>10.1±3.4</td>
</tr>
<tr>
<td>Trunk Control Test (0-100) (mean±SD)</td>
<td>72.3±24.9</td>
</tr>
<tr>
<td>Rivermead Mobility Index (0-15) (mean±SD)</td>
<td>5.2±3.0</td>
</tr>
<tr>
<td>Motricity Index of the leg (0-100) (mean±SD)</td>
<td>49.0±28.3</td>
</tr>
<tr>
<td>Somatosensory threshold affected side (0-6.65) (median (range))</td>
<td>6.65 (2.83-6.65)</td>
</tr>
<tr>
<td>Modified Ashworth Scale (0-5) (median (range))</td>
<td>0 (0-2)</td>
</tr>
</tbody>
</table>

SD: standard deviation; LSCT: Letter and Star Cancellation Tests.
Table 3 shows the proportional change in the regression coefficients of the LSCT asymmetry index after inclusion of the possible confounders in the association model for both the BBS and the FAC. Adding MI-leg to both models resulted in the largest proportional change (33% and 39%, respectively) in the regression coefficient of the LSCT asymmetry index. After controlling for MI-leg, the relationship between visuospatial hemineglect and BBS was still significant (ß=-0.173, SE=0.056, p<0.05), whereas the relationship between visuospatial hemineglect and FAC lost significance (ß=-0.037, SE=0.022, p=0.09).

No significant change of the regression coefficient of the LSCT asymmetry index was found after controlling for age, hypertonia or sensory deficits.
Discussion

To the best of our knowledge, this is the first study to show that, longitudinally, the presence of visuospatial hemineglect is significantly and independently associated with postural control after supratentorial stroke. In line with our hypothesis, hemineglect appeared to have an adverse influence on postural control. After controlling for potential confounders, we found that only severity of paresis of the lower limb, assessed with the MI-leg, significantly distorted the longitudinal relationship between the LCST asymmetry index, on the one hand, and BBS and FAC, on the other hand. After controlling for severity of paresis, hemineglect remained significantly and independently related to ‘standing balance’ (BBS) whereas the association between hemineglect and ‘walking balance’ (FAC) lost significance.

As reported before, the observed postural instability in patients with hemineglect could be the result of a problem in the multisegmental orientation of the body in space, due to a higher-order disorder in the processing of somesthetic information, leading to a disturbed body scheme. The results of this study are in line with several cross-sectional studies. An important reason why other studies did not find an independent influence of hemineglect on postural control may well be the different way of determining hemineglect. In the present longitudinal study as well as in our previous acute-phase study an LSCT asymmetry index was used to determine hemineglect, thus, controlling for generalized attention deficits. Using less stringent criteria for diagnosing visuospatial hemineglect, as was done in other studies, may have led to an overestimation of the presence of hemineglect and, subsequently, to a non-significant association with postural control. Another reason for the observed significant relationship between visuospatial hemineglect and postural control may be the robustness of the applied regression model. In our model, we not only analyzed the between-subject relationship, but also the within-subject relationship by including the repeated measurements in time. Analyzing also the within-subjects relationship is important, because it acknowledges that visuospatial hemineglect is a time-dependent covariate that may quickly resolve as a result of spontaneous neurological recovery. Indeed, the results of this study clearly indicate that the severity of hemineglect, in terms of number of contralesional omissions on the letter and start cancellation tests, substantially decreased in time.

Severity of paresis of the lower limb appeared to be a factor that significantly influenced the association between hemineglect and postural control. This finding is in agreement with the reports by others who found a significant and independent association between muscle weakness of the lower limb and balance in various phases post stroke. Sensory deficits, hypertonia and age did not significantly influence the longitudinal association between hemineglect and postural control in our study. Although reports regarding the impact of sensory deficits on the association between hemineglect and postural control are somewhat conflicting in the literature, the absence of influence of hypertonia on this relationship is consistent with previous research. As for the influence of age, several other studies showed an independent adverse influence of older age on balance after stroke. The most likely reason why age did not affect the results of this study is that we included relatively young patients, who had been selected for admission in a rehabilitation center, which reduced the variability in age range.

A limitation of the present study is the limited number of participating subjects and the fact that they had all been recruited in rehabilitation centers. As a consequence, the estimated associations may lack precision and the probabilities to show significant associations may have been reduced. In addition, the 15% change in the β-coefficient of LSCT asymmetry index that we used as a criterion for confounding is an arbitrarily selected value, however, taking 10% or 20% as a criterion would not have changed the decisions made.
References


Part III

Effect of somatosensory stimulation on standing balance after stroke
Chapter 7

Short-term effects of whole-body vibration on postural control in unilateral chronic stroke patients: preliminary evidence

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Jaak Duysens

Abstract

The short-term effects of whole-body vibration (WBV) as a novel method of somatosensory stimulation on postural control were investigated in 23 chronic stroke patients. While standing on a commercial platform (Galileo900), patients received 30-Hz oscillations at 3 mm amplitude in the frontal plane. Balance was assessed four times at 45-min intervals with a dual-plate force platform, while quietly standing with the eyes opened and closed and while performing a voluntary weight-shifting task with visual feedback of center-of-pressure (COP) movements. Between the second and third assessments, four repetitions of 45-sec whole-body vibration were given. The results indicated a stable baseline performance from the first to the second assessment for all tasks. After the whole-body vibration, the third assessment demonstrated a reduction in the root mean square (RMS) center-of-pressure velocity in the anteroposterior direction when standing with the eyes closed (p<0.01), which persisted during the fourth assessment. Furthermore, patients showed an increase in their weight-shifting speed at the third balance assessment (p<0.05), while their precision remained constant. No adverse effects of whole-body vibration were observed. It is concluded that whole-body vibration may be a promising candidate to improve proprioceptive control of posture in stroke patients.

Introduction

There is a general and strong belief that somatosensory stimulation (SSS) promotes brain plasticity, although the underlying mechanisms are not well known. Studies regarding the functional recovery in stroke patients have suggested beneficial effects of SSS in terms of motor functions, balance and activities of daily living. In 1993, a randomized, controlled trial first indicated that electro-acupuncture applied at the paretic body side facilitated recovery of balance, mobility, and activities of daily living in postacute stroke patients, and some of these effects were shown to persist up to 2 yrs after stroke as assessed by posturography. However, recently, a new randomized, controlled trial from the same research group no longer demonstrated differential effects on motor function, mobility, or activities of daily living of either high-intensity-low-frequency transcutaneous electrical nerve stimulation or electro-acupuncture applied at the paretic body side when compared with sham-transcutaneous electrical nerve stimulation of low intensity and high frequency. These differences in outcome could not be unambiguously explained. Although others have demonstrated potentially strong immediate effects of transcutaneous electrical nerve stimulation applied at the contralesional side of the neck on postural orientation and stability while sitting in postacute stroke patients with spatial neglect, the long-term effects of transcutaneous electrical nerve stimulation or (electro-) acupuncture on functional recovery from stroke are, as yet, equivocal. The effects of other forms of SSS are still unknown.

One form of SSS that shows considerable promises for rehabilitation is vibration therapy. Priplata et al. reported that randomly vibrating insoles could ameliorate age-related impairments in balance control. Apparently, vibration is able to enhance postural stability in persons without specific neurological diseases. It is, therefore, possible that in stroke patients intensive and deep stimulation of muscle afferents using vibration may induce stronger sensorimotor recovery than more superficial stimulation of (sub)cutaneous afferents by electrical stimulation. In addition, based on functional magnetic resonance imaging and positron emission tomography studies showing plastic changes in both cerebral and cerebellar hemispheres after unilateral stroke, it may be that application of SSS
at both sides of the body is more effective than only at the paretic side. Against this background, the purpose of this study was to demonstrate beneficial short-term effects of whole-body vibration (WBV) on postural control in chronic stroke patients and to register any possible adverse effects.

Methods

Subjects
A total of 23 ischemic stroke patients (13 men, 10 women; mean age 58.1 ± 11.4 yrs) with a post stroke interval of at least 6 mos (mean interval 23.3 ± 11.4 mos) were recruited from an outpatient population of a rehabilitation center to participate in this research study. Eight patients had a right-hemisphere lesion, and 15 had a left-hemisphere lesion. To be included, patients must have suffered only one stroke in their lifetime, be able to stand without support for 30 sec, understand the goal and methods of the study, and give their informed consent. Patients with non-stroke related sensory or motor impairments and those with medication that could interfere with postural control were not included. Also patients with contraindications for WBV (pregnancy, recent fractures, gall or kidney stones, malignancies, cardiac pace-maker, recent thromboembolic or infectious disease) and patients already treated with WBV were excluded. To obtain reference values for postural control, 23 healthy, elderly controls (mean age 63.9 ± 9.3 yrs) were recruited, mostly relatives of employees of the rehabilitation center. The Committee on Research Involving Human Subjects, Region Arnhem-Nijmegen, approved the study methods, and all patients gave their written informed consent according to specified guidelines.

Intervention
All patients were subjected to one series of four consecutive repetitions of 45-sec WBV with a 1-min pause between administrations. WBV was provided with a commercially available device (Galileo 900; see figure 1). This apparatus consists of a moveable rectangular platform built within a circular ground surface on which a support bar is mounted at the front. The platform makes fast oscillating movements around a sagittal axis in the middle. Subjects were required to stand on the platform with their feet at an equal and standardized distance from the axis of rotation so that the vibration amplitude was approximately 3 mm. The frequency was set at its maximum of 30 Hz. While standing on the vibration platform, subjects were instructed to maintain a “squat” position with slight flexion at the hips, knees and ankle joints, to damp the vibrations approximately at the pelvic level. They were allowed to hold the support bar in front of them. An experienced therapist guided all WBV administrations.

Assessments
Postural control and symmetry were assessed in terms of center-of-pressure (COP) movement and position registered with a dual-plate force platform connected to a personal computer, sampling vertical ground reaction forces at a rate of 60 Hz. During all balance registrations, patients stood barefoot on the force platform with their arms (if possible) alongside their trunk and their feet against a fixed foot frame with an interheel distance of 8.4 cm and a toeing-out angle of 9 degrees. Every balance assessment consisted of two consecutive test series. Each series incorporated two 30-sec quiet standing tasks (one with eyes open and one with eyes closed) and one 30-sec voluntary weight-shifting task in a fixed sequence (eyes open, eyes closed, weight-shifting task), which was repeated in the reversed order (weight-shifting task, eyes closed, eyes open). During quiet standing with the eyes closed, patients were wearing a pair of closed, dark goggles. From each quiet-standing registration, the overall COP was calculated for every set of force samples from the two plates. Then, the lateral deviation of the mean position of this COP from the sagittal midline, relative to the base of support width, was determined as a measure of weight-bearing asymmetry. The RMS COP velocity in both the anteroposterior and lateral directions was calculated as a measure of

Figure 1 Picture of the Galileo 900.
postural instability, because it integrates changes in COP amplitude and frequency. Indeed, of various posturographic measures, the COP velocity has been shown to be most reliable,\textsuperscript{14} sensitive to task manipulations,\textsuperscript{14} and related to measures of functional balance.\textsuperscript{15,16} During the weight-shifting task, real-time visual COP feedback was provided by a color monitor placed in front of the subject at eye level. Two stationary square goals were presented on the monitor at either side of the virtual vertical through the middle of the screen (corresponding to the sagittal midline of the body), such that approximately 15% extra weight had to be borne on each leg to reach the middle of the corresponding goal. During each registration, always one of the two goals was lit by the computer indicating the target. Subjects had to shift their weight toward this target as fast and fluently as possible and hold their COP within it for 1 sec to make a hit. As soon as a hit was made, the contralateral goal was lit and became the target. In this way, subjects made standardized frontal-plane weight shifts at a self-selected speed. Patients were allowed to practice this weight-shifting task until an optimal performance was reached. From each weight-shifting registration, the number of hits was calculated as a measure of weight-shifting speed, whereas the lateral COP displacement per weight shift was determined as a measure of imprecision, after adjusting for individual differences in the intergoal distance, according to Geurts et al.\textsuperscript{17}

To assess their clinical status, all patients were subjected to a standardized functional evaluation consisting of the Motricity Index of the affected lower limb\textsuperscript{18} as a measure of muscular strength, the Berg Balance Scale\textsuperscript{19} as a measure of functional balance and the Functional Ambulation Categories\textsuperscript{20} as a measure of gait independence.

**Procedure**

Each patient underwent four balance assessments at 45-min intervals at the same part of the day. The first two assessments served to establish a baseline performance. After the first assessment (A), the functional evaluation was completed in approximately 30 min. After the second assessment (B), patients were allowed to rest for about half an hour, which was followed by the four WBV administrations. Then, the third (C) and fourth (D) balance assessments were made. Between the latter two assessments, patients were allowed to rest.

For each of the four balance assessments, identical posturographic measures from the two test series per assessment were averaged into one result to reduce intrasubject variability. Because the balance measures yielded rather skewed distributions across patients, possible differences between balance assessments were identified by means of the (nonparametric) Wilcoxon’s matched-pairs signed-ranks test. First, assessment A (mean of test series 1 and 2) was compared with assessment B (mean of test series 3 and 4) to determine a stable baseline. Then, assessment C (mean of test series 5 and 6) and assessment D (mean of test series 7 and 8) were both compared to the average result of assessments A and B (mean of test series 1-4) in order to determine any immediate or prolonged effect of WBV. The healthy elderly were only tested once using the same methods (one assessment consisting of two test series).

**Results**

The functional measures are presented in table 1 and indicate that all patients could walk independently with or without aids or supervision but had impaired balance skills and motor functions of the affected leg.
All patients were able to tolerate the selected 30 Hz frequency already during the first administration of WBV. No administration of WBV had to be aborted due to immediate adverse effects nor did patients mention any subjective complaints after the vibration.

None of the selected balance measures showed a significant change between balance assessments A and B, indicating a stable baseline performance ($p>0.22$). When quiet standing at assessment C was compared with the average result of assessments A and B, the RMS COP velocity in the AP direction during the eyes-closed condition showed a small but significant decrease in 22 patients (one patient was not able to perform the EC condition) ($p=0.009$). This beneficial effect was still noticeable at assessment D ($p=0.01$) (see figure 3). As for the weight-shifting task, the number of hits showed a small but significant increase at assessment C ($p=0.027$) but no longer at assessment D in 21 patients (two patients were not able to perform the weight-shifting task) (see figure 4). All other balance measures remained stable across the four balance assessments.

To test for possible aspecific learning effects due to repeated testing, we also analysed the four test series (1-4) within the first two assessments (A and B) individually. No systematic improvement was found between any pair of consecutive test series nor between the first and fourth test for any selected balance measure ($p>0.09$). The influence of functional level (Motricity Index, Berg Balance Scale, Functional Ambulation Categories) on the effects of WBV was not tested because of the relatively small number of severely affected patients.

### Table 1

<table>
<thead>
<tr>
<th>Functional measures (maximum range)</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional Ambulation Categories (0-5)</td>
<td>5</td>
<td>3-5</td>
</tr>
<tr>
<td>Berg Balance Scale (0-56)</td>
<td>52</td>
<td>20-56</td>
</tr>
<tr>
<td>Motricity Index (0-100)</td>
<td>75</td>
<td>37-100</td>
</tr>
</tbody>
</table>

Sagittal plane postural instability in the eyes-closed condition, expressed as the root mean square (RMS) center-of-pressure (COP) velocity, for four assessments in 22 stroke patients (group means with 95% confidence intervals). The dotted line indicates the average performance of the 23 healthy elderly subjects with 95% confidence intervals.

Frontal plane weight-shifting speed, expressed as the number of weight shifts (WS) (black line), and weight-shifting imprecision, expressed as the average lateral COP-trajectory per weight shift (grey line), for 4 assessments in 21 chronic stroke patients (group means with 95% confidence intervals). The dotted line indicates the average weight-shifting speed of the 23 healthy elderly with 95% confidence intervals.
Based on recent insights in brain plasticity, it is possible that bilateral proprioceptive stimulation may induce spinal and cortical reorganization both through the affected and nonaffected body sides.26

This study used a within-subject design and not a parallel group design because it was anticipated that the presumably small short-term effects of WBV would be hard to demonstrate in a group comparison due to relatively large within-group variability of balance performance. As a consequence, aspecific learning effects related to repeated testing may have influenced the balance improvements that were found. There are, however, several arguments against this possibility. Most importantly, comparing the first four balance test series did not provide any evidence of aspecific learning effects. Because such effects are usually strongest between the first two or three repetitions, it seems unlikely that they would have played a significant role in this study after the fourth test. Second, with regard to the weight-shifting results, the observed data pattern, in which significance was lost at the last assessment (D), does not match with a learning process in which one would expect further improvement or at least stabilization. We therefore conclude that this study provides preliminary evidence of specific short-term beneficial effects of WBV on postural control in chronic stroke patients.

The finding that no adverse effects occurred and that nearly all patients reported pleasant subjective sensations both during and after the vibration therapy suggests that WBV may also be a safe application of SSS in (chronic) stroke patients. This latter conclusion is further supported by our experiences with postacute stroke patients included in an ongoing randomized, controlled trial investigating the effects of prolonged vibration therapy (daily during 6 wks) on postural control. Nevertheless, further research is needed to determine both the safety, the short-term effectiveness and the long-term effectiveness of WBV in different groups of stroke patients.

Discussion

This within-subject study investigated the occurrence of any short-term effects of WBV on postural control in stroke patients as a novel method of SSS. Indeed, it has been reported that vibration is one of the strongest methods for stimulating proprioception, capable of long-lasting postural effects in healthy subjects.9,21 Only chronic patients were included who had their stroke at least 6 mos previously, because they were assumed to be relatively stable in their balance performance compared with postacute stroke patients. Although all patients could walk independently to some extent, most subjects had a suboptimal, moderate, or poor score on the Berg Balance Scale, indicating substantial balance problems. This result is corroborated by the posturographic balance measures indicating substantially greater COP velocities compared with healthy elderly.

Preliminary evidence was found of short-term beneficial effects of WBV on postural control in stroke patients. As for quiet standing, the COP velocity in the sagittal plane decreased slightly but systematically in most of the subjects, indicating a tendency toward improved postural stability after WBV. The finding that this effect was only significant while standing with the eyes closed may be explained by a relatively great reliance on proprioceptive information during visual deprivation in stroke patients.22 If WBV specifically promotes proprioceptive control of standing balance in stroke patients, one would indeed expect greater functional effects while standing with the eyes closed than with the eyes opened. This reasoning, however, does not explain why no such effect was found for quiet-standing control in the frontal plane. As for the weight-shifting task, the number of hits slightly but systematically increased in most subjects, yielding a tendency to improved weight-shifting capacity after WBV. The fact that the level of weight-shifting precision did not change precludes a possible “speed-accuracy tradeoff”. This positive effect of WBV also on self-paced frontal plane weight shifts may again be related to proprioceptive stimulation because loading and unloading the legs is highly dependent on proprioceptive feedback.23 Indeed, it is assumed that WBV primarily increases proprioceptive input (mainly through Ia-afferents).24,25 thus stimulating a sensory system that is of vital importance to postural control.
Acknowledgements

We thank Sabine Verschuere for inspiring discussions on the use of a vibration platform for elderly and for stroke patients, Jeanine Pluimakers, medical student, for her help with inviting the patients and making the posturographic assessments, and to all patients for their willingness to participate in this study.

References


Chapter 8

Long-term effects of 6-weeks whole-body vibration on balance recovery and activities of daily living in the postacute phase of stroke: a randomized, controlled trial

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Fanny Schils
Ronald Meijer
Annette A van Kuijk
Alexander CH Geurts

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Abstract

Background and purpose. The long-term effects of 6-weeks whole-body vibration, as a novel method of somatosensory stimulation, on postural control and activities of daily living were compared to those of 6-weeks exercise therapy on music of the same intensity in the postacute phase of stroke.

Methods. Fifty-three patients with moderate to severe functional disabilities were randomized within 6 weeks poststroke and within 3 days after admission to a rehabilitation center to either whole-body vibration or exercise therapy on music in addition to a regular inpatient rehabilitation program. The whole-body vibration group received 4 x 45-second stimulation on the Galileo 900 (30-Hz frontal-plane oscillations of 3-mm amplitude) for 5 days per week during 6 weeks. The exercise therapy on music group received the same amount of exercise therapy on music. Outcome variables included the Berg Balance Scale, Trunk Control Test, Rivermead Mobility Index, Barthel Index, Functional Ambulation Categories, Motricity Index, and somatosensory threshold at 0, 6, and 12 weeks follow up.

Results. At baseline, both groups were comparable in terms of prognostic factors and outcome measures. Both at 6 and 12 weeks follow up, no clinically relevant or statistical differences in outcome were observed between the groups. No side effects were reported.

Conclusion. Daily sessions of whole-body vibration during 6 weeks are not more effective in terms of recovery of balance and activities of daily living than the same amount of exercise therapy on music in the postacute phase of stroke.

Introduction

Several studies have claimed beneficial effects of somatosensory stimulation (SSS) in patients with stroke in terms of balance, motor performance, and activities of daily living. These studies described both short-term (<1 hour) and long-term (>6 weeks) results of SSS in different phases poststroke. However, well-controlled randomized, controlled trials and reviews did not show clear evidence of beneficial effects of transcutaneous electrical nerve stimulation or acupuncture on balance in patients with stroke. Yet, these recent insights do not preclude beneficial effects of other forms of SSS in (post)acute stroke rehabilitation.

A relatively novel form of SSS that shows considerable promises for the rehabilitation of stroke patients is whole-body vibration (WBV). To underscore this notion, four important considerations can be given. First, WBV is a deeper way of sensory stimulation compared with the more superficial modes such as acupuncture and transcutaneous electrical nerve stimulation, targeting the Ia and II afferents of (large) muscle groups. Second, WBV provides bilateral stimulation, which may induce plastic changes in both hemispheres after stroke. Third, WBV induces sensory stimulation of foot-sole afferents as well, which afferents are well known to play an important role in postural control. Lastly, WBV research in general has shown promising results in various domains of sports and geriatric medicine. In addition, there is preliminary evidence for short-term effects (<1 hour) of WBV on postural stability in patients with chronic stroke.

Therefore, the purpose of this study was to investigate whether WBV, added to regular rehabilitation, has beneficial effects on balance control and activities of daily living in patients with subacute stroke. We also tested whether such functional benefits coincide with improvements of strength and somatosensation.

Methods

Subjects

All patients with a first supratentorial stroke, confirmed by computed tomography or magnetic resonance imaging scan, admitted to one of three rehabilitation
centers in the Netherlands (St Maartenskliniek, Nijmegen; Groot Klimmendaal, Arnhem; Tolbrug, Den Bosch) between May 2003 and February 2005, were eligible. Inclusion criteria were (1) a poststroke interval less than 6 weeks and (2) moderate or severe balance impairments defined as a score less than 40 on the Berg Balance Scale.16 Exclusion criteria were (1) nonstroke-related sensory or motor impairments, (2) use of medication that could interfere with postural control, (3) concomitant cognitive problems that impaired the ability to follow simple verbal instructions and (4) contraindications for WBV such as pregnancy, recent fractures, gallbladder or kidney stones, malignancies, and cardiac pacemaker. After receiving verbal and written information, all subjects gave their written informed consent to participate in the study. The regional medical-ethical committee approved the study.

**Intervention**

All patients were treated with either WBV or exercise therapy on music (ETM) on each working day during 6 weeks of their admission in the rehabilitation center. Both treatments consisted of four sessions of 45 seconds stimulation interrupted by a 1-minute break between each session. In this way, a total of 120 treatment sessions were given per patient. By selecting this specific intensity of WBV, all patients received a strong stimulation of their proprioceptive afferents10 (in particular Ia and II afferents), whereas muscular fatigue was prevented.17 ETM of this intensity was considered a ‘sham’ treatment.

WBV was provided through a commercially available device.5 This apparatus consists of a moveable rectangular platform built within a circular ground surface on which a support bar is mounted at the front. The platform makes fast oscillating movements around a sagittal axis in the middle. Subjects were required to stand on the platform with their feet at an equal and standardized distance from the axis of rotation so that the vibration amplitude was \( \approx 3 \) mm. The frequency was set at its maximum of 30 Hz. Patients who could stand independently (Functional Ambulation Categories [FAC]= 3 to 5) were instructed to adopt a ‘squat’ position with slight flexion at the hips, knees and ankle joints to damp the vibrations approximately at the pelvic level. They were allowed to hold the support bar (see figure 1A). Patients who could not yet stand independently (FAC 0 to 2) were supported at their buttocks by a height-adjustable bench with their knees and hips in 45° flexion while holding onto the support bar as well (see figure 1B). An experienced physical therapist supervised all the WBV administrations.

During the ETM, patients were instructed to adopt the same standing position as during the WBV. The whole program consisted of regular exercises for the trunk, arm, and leg muscles interrupted by periods of relaxation. ETM was given either individually or in small groups of two to three patients and was supervised by an experienced physical therapist as well. To standardize ETM between the participating rehabilitation centers, five different compact discs were recorded, one for each day of the week, to guide the exercises so that patients in different centers received the same type of treatment.

Before the onset of the study, all treating physical therapists received specific instructions on both interventions to ensure uniformity in the treatment.

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5 Galileo 900, Galileo2000, Enschede, The Netherlands
Outcome measures

The Berg Balance Scale was selected as the primary outcome measure. Secondary outcome variables were the Barthel Index, Trunk Control Test, Rivermead Mobility Index, and FAC. The Motricity Index and somatosensory threshold of the affected leg were also regarded as secondary outcome measures. Possible adverse reactions during or 30 minutes after the treatment sessions were registered as well.

To assess the subjective experience and the success of blinding, patients were asked two questions week after t2: ‘Do you think that the extra therapy (WBV or ETM) you received had a positive effect on your rehabilitation?’ and ‘Which of the two extra therapies do you think is most beneficial?’

Statistical Analysis

The independent samples t test and Chi-Square test were used to compare both groups at baseline. A 2-way analysis of variance (groupxtime) was used to assess the effects of treatment depending on group allocation. We performed an intention-to-treat analysis by carrying the last value forward in the case of missing values at the third assessment. All tests were applied 2-sided with a critical α level of p<0.05.

Results

Fifty-three patients were allocated to either the WBV group (n=27) or the ETM group (n=26). All subjects participated in both the first (t0) and second (t1) assessment. In one patient, the WBV was stopped prematurely because of severe shoulder pain, although these complaints could not be directly related to the WBV. At t2, two patients of the ETM group were lost to follow up: one as a result of a second cerebral infarction and as a result of refusal to further participate (see figure 2).

At baseline, the following patient characteristics were registered: Motricity Index, Modified Ashworth Scale, somatosensory threshold of the affected leg, and the presence of hemineglect. The somatosensory threshold was determined by investigating the pressure sensitivity at the tip of the hallux using 5 calibrated monofilaments (2.83, 3.61, 4.31, 4.56 and 6.65). To determine the presence of neglect, we used a computerized visual reaction-time task. Patients had to respond as quickly as possible to visual stimuli at different locations in both visual hemifields by pressing a button with their nonparetic hand. A bias in the mean reaction time between the left and right visual hemifield greater than 34% indicated the presence of neglect.
Table 3 shows the values of all outcome measures with their standard deviations. Both groups showed a main effect of time on the Berg Balance Scale score ($F(2,50)=56.67, p<0.01$) as well as the BI ($F(2,50)=97.12, p<0.01$), RMI ($F(2,50)=76.20, p<0.01$), TCT ($F(2,50)=11.83, p<0.01$), FAC score ($F(2,50)=76.48, p<0.01$), MI ($F(2,50)=26.85, p<0.01$) and somatosensory threshold ($F(2,50)=3.92, p<0.05$). Table 3 clearly shows that improvements were most pronounced during the intervention period, but patients continued to improve during the follow-up period. There were no groupxtime interactions, indicating similar recovery profiles for both treatment groups.

One week after the follow-up period ($t_2$), 38 of the 51 patients (75%) who participated in the third assessment responded to the questionnaire (18 of the WBV group and 20 of the ETM group). Most patients (74%) were positive or very positive about their treatment. Whereas 72% of the patients in the WBV group believed that WBV was the favourable treatment, 55% of the ETM group believed ETM to be most favourable. No adverse reactions occurred during or directly after treatment in either group.

Table 1  Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>WBV (n=27)</th>
<th>ETM (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>16 (59%)</td>
<td>14 (54%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.7 ± 12.3</td>
<td>62.6 ± 7.6</td>
</tr>
<tr>
<td>Type of stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic</td>
<td>16 (59%)</td>
<td>22 (85%)</td>
</tr>
<tr>
<td>Haemorrhagic</td>
<td>11 (41%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Location of stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>14 (52%)</td>
<td>11 (42%)</td>
</tr>
<tr>
<td>Right hemisphere</td>
<td>13 (48%)</td>
<td>15 (58%)</td>
</tr>
<tr>
<td>Time post stroke (days)</td>
<td>38.9 ± 9.2</td>
<td>34.2 ± 11.1</td>
</tr>
<tr>
<td>Neglect: present</td>
<td>8 (30%)</td>
<td>13 (50%)</td>
</tr>
<tr>
<td>Motricity Index (0-100)</td>
<td>47.4 ± 28.7</td>
<td>50.6 ± 28.4</td>
</tr>
<tr>
<td>Modified Ashworth Scale (0-5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>knee flexion (median/ range)</td>
<td>0 (0-3)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>knee extension (median/ range)</td>
<td>0 (0-4)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>ankle dorsiflexion (median/ range)</td>
<td>1 (0-4)</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>ankle plantarflexion (median/ range)</td>
<td>0 (0-2)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Somatosensory threshold affected side (median)</td>
<td>4.56 (2.83-6.65)</td>
<td>6.65 (3.61-6.65)</td>
</tr>
<tr>
<td>Berg Balance Scale (0-56) (mean ± SD)</td>
<td>23.9 ± 14.8</td>
<td>23.7 ± 18.6</td>
</tr>
<tr>
<td>Barthel Index (0-20) (mean ± SD)</td>
<td>10.3 ± 3.1</td>
<td>9.9 ± 3.7</td>
</tr>
<tr>
<td>Trunk Control Test (0-100) (mean ± SD)</td>
<td>75 ± 25.9</td>
<td>69.5 ± 24.0</td>
</tr>
<tr>
<td>Rivermead Mobility Index (0-15) (mean ± SD)</td>
<td>5.3 ± 2.9</td>
<td>5.2 ± 3.2</td>
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<tr>
<td>Functional Ambulation Categories (0-5) (median/ range)</td>
<td>1 (0-4)</td>
<td>1 (0-4)</td>
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</table>

*chi-square test, † independent samples t-test, SD: standard deviation.

Table 2  Therapies (mean hours).

<table>
<thead>
<tr>
<th></th>
<th>Whole-Body Vibration(n=27)</th>
<th>Exercise Therapy on Music (n=26)</th>
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</thead>
<tbody>
<tr>
<td>Physical Therapy</td>
<td>149.6 ± 58.3</td>
<td>118.0 ± 59.6</td>
</tr>
<tr>
<td>Occupational Therapy</td>
<td>44.9 ± 20.1</td>
<td>41.9 ± 26.6</td>
</tr>
<tr>
<td>Speech Therapy</td>
<td>10.9 ± 12.0</td>
<td>17.2 ± 18.4</td>
</tr>
<tr>
<td>Intervention</td>
<td>26.2 ± 3.9</td>
<td>26.7 ± 1.93</td>
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</tbody>
</table>

*Independent samples t-test; NS indicates not significant.
Discussion

The aim of this study was to examine the long-term effects of repeated WBV on balance and activities of daily living in postacute stroke patients compared with the effects of ETM. No group differences in functional improvement on any of the selected outcome measures were observed, although the WBV group received on average a little (but insignificantly) more rehabilitation treatment than the ETM group. In addition, no group differences in muscle strength and somatosensation were found. Hence, the results of this study do not support the a priori hypothesis that repeated WBV in the postacute phase of stroke would be beneficial and a valuable addition to regular rehabilitation interventions.

In the past, several randomized, controlled trials have reported beneficial effects of additional SSS (eg electroacupuncture) on balance recovery after stroke compared with regular rehabilitation. However, in all the randomized, controlled trials reporting positive group differences, the control group only received conventional rehabilitation without any type of sham or control intervention. As a result, all patients were well aware of group allocation, and it is likely that large differences in the number of patient contacts and subsequent expectations occurred. In the present study, the control group received a sham intervention (ETM) with an equal amount of contact time and attention by the same physical therapists. In this way, potential bias by differences in the amount of professional attention and expected efficacy was prevented. Potential bias by differences in the amount of patient contacts and expected efficacy was prevented in the present study. The beneficial effects of SSS were thus (at least partly) explained by nonspecific mechanisms. However, the beneficial effects of SSS may thus (at least partly) be explained by nonspecific mechanisms. The beneficial effects of SSS in patients in the present study were quite successful in terms of subjective experience and believed efficacy, based on the results from the questionnaires, which indicates reasonably effective patient blinding. The negative results found in the present study are in accordance with other randomized, controlled trials that used sham interventions with similar or identical interventions. They reported poor quality of the randomized, controlled trials in the present study, and the control group received a sham intervention (ETM) with an equal amount of contact time and attention by the same physical therapists. In this way, potential bias by differences in the amount of professional attention and expected efficacy was prevented in the present study. In addition, the selected sham intervention was quite successful in terms of subjective experience and believed efficacy, based on the results from the questionnaires, which indicates reasonably effective patient blinding. The negative results found in the present study are in accordance with other randomized, controlled trials that used sham interventions with similar or identical interventions. They reported poor quality of the randomized, controlled trials in the present study, and the control group received a sham intervention (ETM) with an equal amount of contact time and attention by the same physical therapists. In this way, potential bias by differences in the amount of professional attention and expected efficacy was prevented in the present study. In addition, the selected sham intervention was quite successful in terms of subjective experience and believed efficacy, based on the results from the questionnaires, which indicates reasonably effective patient blinding.

Table 3

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1st assessment</th>
<th>2nd assessment</th>
<th>3rd assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBS</td>
<td>(mean ± SD)</td>
<td>(mean ± SD)</td>
<td>(mean ± SD)</td>
</tr>
<tr>
<td>ETM</td>
<td>23.9 ± 14.8</td>
<td>23.7 ± 18.6</td>
<td>40.6 ± 12.8</td>
</tr>
<tr>
<td>WBV</td>
<td>65.7 ± 22.9</td>
<td>61.2 ± 32.4</td>
<td>49.8 ± 22.0</td>
</tr>
<tr>
<td>BI</td>
<td>(mean ± SD)</td>
<td>(mean ± SD)</td>
<td>(mean ± SD)</td>
</tr>
<tr>
<td>ETM</td>
<td>10.3 ± 3.1</td>
<td>9.9 ± 3.7</td>
<td>15.3 ± 3.9</td>
</tr>
<tr>
<td>WBV</td>
<td>88.9 ± 10.2</td>
<td>88.3 ± 10.8</td>
<td>60.5 ± 21.6</td>
</tr>
<tr>
<td>TCT</td>
<td>(mean ± SD)</td>
<td>(mean ± SD)</td>
<td>(mean ± SD)</td>
</tr>
<tr>
<td>ETM</td>
<td>75.0 ± 25.9</td>
<td>69.5 ± 24.0</td>
<td>80.5 ± 21.6</td>
</tr>
<tr>
<td>WBV</td>
<td>67.9 ± 36.9</td>
<td>67.1 ± 36.9</td>
<td>61.2 ± 32.4</td>
</tr>
<tr>
<td>RMI</td>
<td>(mean ± SD)</td>
<td>(mean ± SD)</td>
<td>(mean ± SD)</td>
</tr>
<tr>
<td>ETM</td>
<td>5.3 ± 2.9</td>
<td>5.2 ± 3.2</td>
<td>8.7 ± 3.6</td>
</tr>
<tr>
<td>WBV</td>
<td>43.4 ± 10.9</td>
<td>43.3 ± 10.9</td>
<td>64.9 ± 26.7</td>
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<td>FAC</td>
<td>(median/range)</td>
<td>(median/range)</td>
<td>(median/range)</td>
</tr>
<tr>
<td>ETM</td>
<td>1 (0-4)</td>
<td>1 (0-4)</td>
<td>3 (0-5)</td>
</tr>
<tr>
<td>WBV</td>
<td>3 (0-5)</td>
<td>3 (0-5)</td>
<td>4 (1-5)</td>
</tr>
<tr>
<td>MI</td>
<td>(mean ± SD)</td>
<td>(mean ± SD)</td>
<td>(mean ± SD)</td>
</tr>
<tr>
<td>ETM</td>
<td>47.4 ± 28.7</td>
<td>50.1 ± 28.3</td>
<td>59.8 ± 25.0</td>
</tr>
<tr>
<td>WBV</td>
<td>59.8 ± 28.7</td>
<td>61.2 ± 25.4</td>
<td>65.7 ± 22.9</td>
</tr>
<tr>
<td>Somatosensory Threshold</td>
<td>(median/range)</td>
<td>(median/range)</td>
<td>(median/range)</td>
</tr>
<tr>
<td>ETM</td>
<td>4.31–4.31</td>
<td>4.31–4.31</td>
<td>4.31–4.31</td>
</tr>
<tr>
<td>WBV</td>
<td>4.31–4.31</td>
<td>4.31–4.31</td>
<td>4.31–4.31</td>
</tr>
</tbody>
</table>

SD = standard deviation.
efficacy of acupuncture. In addition, the limited number of negative trials included in this meta-analysis seemed to indicate publication bias, because negative trials may not have been published. In negative trials, a potential type II error should always be considered as a result of lack of statistical power. As for the present study, such a type II error seems unlikely, because all outcome measures showed not even a trend towards a group difference in recovery profiles. It is, nevertheless, possible that the selected outcome measures were not sensitive enough to detect certain (small) group differences. On the other hand, one might argue the clinical relevance of any group difference obtained with an alternative outcome when there are at the same time no effects on well-established clinical measures such as the Berg Balance Scale, Rivermead Mobility Index, Barthel Index, and the FAC.

Another possible explanation for the absence of group differences in this study may be that both interventions were equally beneficial. This possibility, however, seems unlikely because of 2 reasons. First, the observed improvements on the primary outcome measure (Berg Balance Scale) were comparable with the functional improvements found in longitudinal observational studies. Second, the exercises on music in the control group were given during a relatively short period and did not essentially differ from the regular training during individual and group sessions.

Lastly, it is possible that the selected intensity and duration of WBV were still too low to induce lasting changes in the somatosensory pathways or sensorimotor cortices. Yet, we selected an intensity and duration comparable with previous research in healthy subjects and nursing home residents reporting beneficial effects of WBV. We judged a stronger than this selected intensity in a first study of patients with stroke as unwarranted, particularly because it has been shown that WBV induces early muscle fatigue compared with regular muscle exercises. Even in healthy subjects muscle fatigue already occurs after a few minutes of stimulation.

Conclusion

To our knowledge, this is the first randomized, controlled trial that addresses the long-term effects of WBV on the recovery of balance and activities of daily living in the postacute phase of stroke. Although this treatment was well tolerated and appreciated by most patients, it appeared that daily sessions of WBV during 6 weeks are no more effective in terms of recovery of balance and activities of daily living than the same amount of exercise therapy on music.

Acknowledgments

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Chapter 9
General discussion
General discussion

From the literature, it follows that, after supratentorial stroke, disturbances in sitting, standing and walking balance may be caused by a unique combination of motor, sensory and cognitive impairments. Although most of the patients with stroke show considerable improvements in balance performance during their rehabilitation, they do not reach the performance levels of healthy (elderly) persons. This finding may be related to observations indicating that improvement of balance and gait skills appears hard to explain by restoration of functions of the paretic leg muscles.1-6 Apparently, other mechanisms than the restoration of paretic leg functions may contribute to functional recovery from stroke, of which improved trunk control may be an important one.7 This notion was considered essential when the research of this thesis was started.

From a cognitive perspective, visuospatial hemineglect had been proposed as one of the most important determinants of postural control and recovery after stroke. Studies of sitting balance in selected postacute stroke patients had demonstrated a profound detrimental influence of hemineglect on postural stability.8,9 However, whether this adverse influence would also be present in larger groups of (unselected) patients, even after correcting for confounding by other possible sensorimotor, cognitive and biological determinants, was considered another important question at the start of this research.

As for the improvement of postural control after stroke through rehabilitation, several studies had been conducted to evaluate the effects of somatosensory stimulation, of which some studies showed beneficial effects,10-12 whereas others were not able to confirm these results.13-16 Because sensory stimulation of the superficial cervical plexus had been shown to (momentarily) reduce neglect-related postural instability after stroke,8 it seemed worthwhile to determine the effect of a new form of somatosensory stimulation (i.e. whole-body vibration) on postural control following stroke, and compare the possible effects of this intervention between patients with and without neglect.

Thus, the objective of this thesis was to address three main topics in patients with a first-ever supratentorial stroke: 1) mechanisms of recovery of sitting and...
standing balance, in particular with regard to trunk control, 2) the influence of visuospatial neglect on (the recovery of) sitting, standing and walking balance, and 3) the effect of whole-body vibration on standing balance and ADL.

Recovery of postural control in stroke
The results of chapter 3 provide new information about the recovery of sitting balance in the postacute phase of stroke. It was found that, compared to healthy elderly, stroke patients showed impaired postural control in both directions, however, most prominently in the lateral direction. This instability was most pronounced while sitting on an unstable surface, and with the eyes closed. Since similar results have been reported for frontal-plane standing balance, it appears that deficits in lateral sitting and standing balance are characteristic sequelae of stroke. Where in frontal-plane standing balance the hip abductors and adductors play a key role, the oblique abdominal and lumbar erector spinae muscles may be key muscles in sitting balance, because they are able to control the pelvic orientation in the frontal plane. Especially these lower trunk muscles could be targeted in future studies using surface EMG to longitudinally assess their activity and timing 'in rest' and during lateral perturbations. Indeed, it is well known that trunk muscles have a relatively high potential for recovery of function after brain damage due to their bilateral innervation.

The unstable conditions showed clear improvements of sitting balance, while the effects of visual deprivation on lateral balance showed a tendency to diminish. These improvements may be related to both motor and sensory reorganization and stress the importance of challenging postural control by mechanical and sensory manipulations. Future studies might focus at the use of support-surface instability, combined with visual deprivation, in training trunk control. As an inflatable air cushion appeared too unstable for some patients with very poor trunk control, the use of foam could be a sensible alternative in severe patients. Because most of the observed recovery in our study took place in the first six weeks of follow-up, trunk control training may be most effective in the very (sub)acute phase of stroke. Indeed, several training studies aiming to promote restoration of function point in the direction of an early and relatively limited window of opportunity.

As for the recovery of postural control, an interesting topic for future research could be to further explore the association between the site of the brain lesion and sitting, standing and walking balance. From chapter 2, it follows that a lot of studies have shown that patients with right-hemispheric lesions show worse postural control and subsequent recovery compared to patients with left-hemispheric lesions. Particularly the involvement of the temporo-parietal junction in right-sided lesions seems to be associated with poor static and dynamic balance control as well as with poor recovery. Specific postural disorders might be associated with lesions in this association area or with lesions of the thalamo-parietal projections, such as disturbances in the subjective postural, visual and haptic sense of verticality, as was recently shown by Perennou and others. The use of more detailed ‘brain mapping’ techniques, such as fMRI or TMS, may increase our understanding of the relationships between brain lesions and postural malfunctioning, which is still rather limited. These techniques may also help to understand the spontaneous evolution of the damaged brain as well as the changes induced by balance training. Indeed, a slowly evolving, long-term, experience-dependent reorganization of the adult primary motor cortex has already been shown after daily practice of task-specific hand training.

As argued in chapter 2, another important topic for future research remains the role and recovery of stepping responses in patients with stroke. First, timely stepping responses are essential to prevent a fall in the case of a postural disturbance that cannot be counteracted by feet-in-place balance strategies. Second, it may well be that the ability to train multidirectional stepping responses is greater than the possibility to influence the efficacy of basic equilibrium reactions following stroke. To this end, the development of large force-platforms on which stepping responses can be made, and which can apply multidirectional balance perturbations (such as the Nijmegen Fall Simulator of the Radboud University Nijmegen - Medical Centre), may be of great importance to progress our understanding of postural imbalance and its recovery from stroke and, thus, to find new ‘mechanism-based’ targets for functional balance training in stroke rehabilitation.
Visuospatial hemineglect and postural control

Visuospatial hemineglect is a cognitive disorder, due to which patients fail to orientate themselves toward and/or attend to stimuli on the side contralateral to their lesion. From the results presented in chapter 4, several implications can be derived with regard to the assessment of hemineglect both in clinical practice and in research. First, it is important to compare the visuospatial performance on the left versus the right side instead of calculating a total omission score based on errors at both sides. Due to non-lateralized general attention deficits, the use of a total omission score can lead to an overestimation of hemineglect. Second, the presence of non-lateralized general attention deficits may exacerbate the symptoms of neglect due to visuospatial bias, especially in severely affected patients. Third, to better detect relatively subtle forms of hemineglect in mild patients, one should investigate reaction times to left and right stimuli by using a computerized task. Another option for the detection of subtle hemineglect is to add a secondary attention-demanding task, thus, reducing the capacity to consciously compensate for a (mild) visuospatial bias. Taken together, we conclude that there is a need of optimizing the assessment of visuospatial hemineglect in future studies in order to improve both the specificity and the sensitivity of its diagnosis in stroke rehabilitation.

The results of chapters 5 and 6 clearly indicate that visuospatial hemineglect is negatively associated with postural control in both the acute and postacute phases of stroke. From the results of our longitudinal study (chapter 6), it can be concluded that this adverse influence of hemineglect on postural control persists, even though the severity of hemineglect is likely to decrease during rehabilitation. Still, the magnitude of the impact of neglect on postural control gradually decreases with its severity, due to which patients with resolving neglect have similar perspectives with regard to motor and functional recovery as those without neglect. From a clinical point of view, this notion would imply that the consequences of neglect need to be addressed in the very early phase after stroke for two reasons. First, at this stage the risks of hemineglect with regard to falls and injuries are highest, so that a strict prevention policy is warranted. Trauma prevention should be a key issue for all members of the rehabilitation team, including the family, both with regard to falls and with regard to injurious handling of paretic extremities. In addition to prevention, intensive therapeutic measures such as constrained induced movement therapy (CIMT) are indicated.27,28 In CIMT, by constraining the nonparetic extremity, the use of the paretic extremity is forced, while at the same time interhemispheric inhibition of the damaged hemisphere by the nondamaged hemisphere is reduced.29 By such an intensive rehabilitation program, the natural resolution of hemineglect might be speeded up and, thus, the progress of rehabilitation.

Somatosensory stimulation and postural control

Although our cross-sectional study (chapter 7) showed promising indications of beneficial short-term effects of whole-body vibration (WBV) on postural control in chronic stroke patients, the RCT in postacute patients (chapter 8) did not show any statistically or clinically relevant (persistent) effects of this type of somatosensory stimulation on the selected outcomes, i.e. Berg Balance Scale, Barthel Index, Rivermead Mobility Index and Functional Ambulation Categories. Based on the study of Perennou et al.,8 which showed momentary positive effects of transcutaneous electrical stimulation of the superficial cervical plexus on the affected side, but only in stroke patients with visuospatial hemineglect, we were especially interested in the effects of WBV in patients with hemineglect. The total number of subjects in chapter 7 was too low to perform subgroup analyses, but in the RCT (chapter 8) we did not find any effect of WBV in favour of patients with hemineglect. In the RCT, patients received a daily session of WBV while attending a regular rehabilitation program. The WBV was, however, administered ‘in vacuo’, i.e. without a functional task to be performed. Recent literature suggests beneficial effects of brain stimulation only in combination with intensive task-specific training.30,31 When functional training is preceded by e.g. repetitive transcranial magnetic stimulation of the contralesional primary motor cortex or by peripheral nerve stimulation, greater benefits of training may be expected.31,32 It may, therefore, be important to combine the application of somatosensory stimulation with intensive task-specific balance training in future studies in order to establish surplus value of such stimulation. Besides peripheral stimulation, repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) may be promising candidates to induce cortical excitability and improve brain receptivity with regard to functional training.33-36
In general, there is still no consensus on which specific therapeutic approach should be followed in the rehabilitation of postacute stroke patients. Yet, there is ample evidence of the effectiveness of intensive task-specific functional training. Although some believe such training should be started as early as possible after stroke, animal studies have shown that rehabilitation initiated very early post stroke may also be detrimental. As for postural control, perhaps the most promising road for future research is to focus on training of sitting, standing and walking balance (including transfers), under varying and complex sensory deprivation (e.g. of vision) and dual-task (both cognitive and motor) conditions. Indeed, balance training programs that have implemented additional sensory, cognitive and motor challenges to basic standing and walking tasks have proved to be very effective to reduce falls incidence in the elderly. A next step would be to show that such training is also feasible and effective in patients with stroke to reduce falls and improve balance confidence. In addition, imposing external perturbations during functional mobility tasks might be a promising way to force the neuromuscular system to rapidly and effectively adjust its postural strategies. New generation gait robots, such as the LOver-extremity Powered ExoSkeleton (LOPES) developed at the University of Twente, and platforms such as the Nijmegen Fall Simulator may be very useful for this purpose.

In conclusion, besides intensity and task-specificity, complexity may be a third key characteristic of successful rehabilitation of stroke patients. Still, many studies need to be conducted to find the most effective balance training exercises as well as their appropriate intensity and duration for specific subgroups of patients.

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Summary

Balance recovery after supratentorial stroke
Influence of hemineglect and the effects of somatosensory stimulation

Chapter 1 is an introduction and provides general information on stroke epidemiology and neurophysiological and biomechanical backgrounds of postural control. In addition, it addresses some relevant issues regarding the recovery of sitting and standing balance following stroke, the possible influence of visuospatial hemineglect on (the recovery of) balance and gait, and the use of somatosensory stimulation in the rehabilitation of patients with supratentorial stroke. This chapter ends with posing several research questions, which are elaborated in the following chapters.

The body of this thesis is subdivided in three parts. The first part, 'Recovery of sitting and standing balance after stroke', starts with a systematic review (chapter 2) of the mechanical and physiological mechanisms underlying balance recovery after supratentorial stroke. Chapter 3 focuses on the recovery of sitting balance in postacute stroke patients, measured by force-plate technology.

In the second part of this thesis, 'Influence of visuospatial hemineglect on balance after stroke', we first describe two diagnostic tests to assess visuospatial hemineglect (chapter 4), followed by 2 chapters describing the influence of hemineglect on balance in the acute phase (chapter 5) and in the postacute phase (chapter 6) of supratentorial stroke.

In the third part of this thesis, 'Effect of somatosensory stimulation on standing balance after stroke', we present the results of two studies regarding the influence of whole-body vibration. Chapter 7 addresses the short-term effects in chronic stroke patients, whereas chapter 8 provides information about long-term effects of whole-body vibration in postacute stroke patients.

The thesis ends with chapter 9, which is a general discussion of the most important findings and the main limitations of the presented studies. In addition, some suggestions for future research are given.
Part I. Recovery of sitting and standing balance after stroke

In chapter 2 the literature on the mechanical and physiological mechanisms underlying balance recovery from stroke is reviewed. This review is subdivided in sections about unperturbed stance, stance perturbations, voluntary weight displacements and the sensory and cognitive control of posture. During unperturbed stance, weight-bearing asymmetry in favour of the nonparetic leg as well as increased postural sway appear to be characteristic of patients with an incompletely recovered hemiparesis. Relatively small improvements have been found in spontaneous sway reduction and weight-bearing symmetry during rehabilitation. The evidence of force-feedback training on weight-bearing symmetry and stance stability seems rather weak, whereas aids such as shoe adaptations, ankle-foot orthoses and canes may considerably influence weight-bearing characteristics. The use of canes may also improve stance stability. While standing, internal (self-initiated) and external perturbations are a continuous threat to the maintenance of balance. Patients with stroke choose certain ‘stabilisation’ strategies, i.e. they allow less passive body mass displacement as well as self-initiated movement. Compensatory muscle activation on the nonparetic side is an important mechanism for maintaining postural stability during both unperturbed and perturbed stance, but does not necessarily prevent recovery of more symmetric and physiological muscle patterns at a later stage in rehabilitation. In patients with stroke the capacity to make voluntary weight displacements, a prerequisite for safe mobility, appears disturbed as well. Not only is maximal weight shifting impaired, in particular towards the paretic leg, weight shifts are also performed at a slow speed and with poor precision. Transition from bipedal to single-limb stance is impaired due to insufficient hip muscle recruitment on the paretic side and failure to maintain single-limb support on either leg. Compensation of the nonparetic hip muscles as well as recovery of hip muscle function at the paretic side both contribute to the control and recovery of weight-shifting capacity. There is preliminary evidence that biofeedback training may promote dynamic balance skills, especially the speed and symmetry of sit-to-stand transfers. As for the sensory control of posture, patients with stroke may exhibit an excessive reliance on vision. Various explanations have been posed including difficulty of integrating somatosensory information, an inability to select the pertinent sensory input or a nonspecific strategy to compensate for the loss of other sensory input. A clear relationship between the severity of somatosensory impairment and the degree of visual dependence for postural control has not yet been reported. Although instrumented studies of sitting balance have demonstrated a profound negative influence of visuospatial hemineglect on postural control, the influence of visuospatial hemineglect on standing balance does not appear equally strong. The cognitive control of posture may be aggravated after stroke, which is reflected in increased attention demands for standing. Overall, the influence of motor stage, muscle strength or spasticity of the paretic leg muscles on (the recovery of) static or dynamic standing balance appears less obvious than one would intuitively expect. This finding emphasizes the role of other control and restorative mechanisms. In this perspective, there is a clear lack of knowledge regarding the role of trunk muscles, stepping responses as well as sensory and cognitive reorganization in (the recovery of) sitting and standing balance control following stroke.

Chapter 3 focuses on the posturographic assessment of sitting balance recovery in the postacute phase of stroke. This study used an adjustable chair mounted on a force platform to assess the recovery of quiet-sitting balance in 16 patients with a first supratentorial stroke during their inpatient rehabilitation. The patients underwent three posturographic assessments at six weeks intervals from the moment of their admission, on average 5.6 weeks after stroke. Each quiet-sitting balance assessment consisted of two series of 30-sec test conditions: sitting with eyes open and closed, on both a stable and unstable (air cushion) surface. The root mean square (RMS) of the center-of-pressure (COP) velocities was used as the primary measure of lateral and anteroposterior balance control. We found that, compared to 10 healthy elderly, lateral balance was more affected by stroke than balance in the anteroposterior direction, especially during visual deprivation, and most sensitive to subsequent functional changes induced by spontaneous recovery or rehabilitation. Furthermore, lateral balance control showed the strongest association with the Berg Balance Scale as a clinical measure of balance capacity. Posturographic parameters were not significantly associated with age, motricity index, or hemineglect. Hence, (lateral) trunk control seems to be a primary target for rehabilitation. Since an unstable support was necessary to obtain significant effects of stroke, recovery and visual deprivation, it may be important to use an unstable support during sitting balance training as well.
Part II. Influence of visuospatial hemineglect on balance after stroke

In chapter 4 two different methods to assess the presence of visuospatial hemineglect are compared. Two main aspects of the clinical manifestation of visuospatial hemineglect are considered, i.e. asymmetry in performance and an association with non-lateralized attention deficits. These aspects were investigated in 21 left (LH) and 24 right hemisphere (RH) stroke patients (on average 37.1 ± 9.6 days after stroke) and in 20 healthy subjects. The letter and star cancellation subtests of the Behavioral Inattention Task (BIT) and a computerized simple visual reaction time task (CVRT) with stimuli presented either left, central or right in extrapersonal space were administered. In LH patients, the calculation of an asymmetry index for the letter and star cancellation tests allowed a better distinction between patients with and without neglect than raw omission scores. However, in RH patients, raw and asymmetry indexes led to similar classifications. In the CVRT, more patients were classified as neglect patients by using CVRT reaction time (RT) asymmetry indexes than by using BIT or CVRT omission scores. Ipsilesional RTs were regarded as a measure of general, non-lateralized attention. The ipsilesional RTs of the LH and RH patients did not differ from the healthy subjects’ lateral (left or right) RTs. However, within the RH group, patients with both RT asymmetries and BIT scores above cut-off level showed longer ipsilesional RTs than patients with defective RT asymmetries but normal BIT scores. This finding supports the idea of an interaction between lateralized and nonlateralized attentional components in neglect, in which the presence of general attentional deficits exacerbates the severity of neglect symptoms due to visuospatial bias. RT tasks may contribute to the detection of asymmetries in visuospatial attention in patients with subclinical neglect symptoms, who might compensate for a lateralized attention deficit in paper-and-pencil tasks by an intact general (nonlateralized) attention capacity.

The study presented in chapter 5 was set up to determine the independent contribution of visuospatial hemineglect to impaired postural control in the acute phase (<2 weeks) of stroke, compared to other possible clinical and biological determinants. This study was conducted in four hospitals in the mid-east region of the Netherlands. A total of 78 consecutive patients with a first-ever supratentorial stroke was included (on average 5.5 ± 2.4 days after stroke). Functional balance was measured with the Trunk Impairment Scale (TIS), the Trunk Control Test (TCT), the Berg Balance Scale (BBS) and the Functional Ambulation Categories (FAC). Visuospatial hemineglect was assessed by means of an asymmetry index obtained from the Letter and Star Cancellation Tests of the Behavioral Inattention Test (BIT). The Motricity Index (MI), vibration threshold, sustained attention and the presence of hemianopia were registered as other possible clinical determinants. Stepwise backward multiple linear regression analysis was performed introducing all selected clinical determinants as well as age and poststroke time as possible biological determinants. The results showed that hemineglect was present in 17 patients (21.8%). The groups with and without hemineglect were different for gender and the proportion of right hemisphere strokes, but not for age, type of stroke or poststroke time. Neglect patients had on average 17.5 - 43% lower scores on all functional balance tests as well as on the clinical assessments. Multivariate linear regression showed that, besides hemineglect, only muscle strength and age independently contributed to impaired balance explaining 65% to 72% of variance of the selected outcomes. In conclusion, this study showed that hemineglect independently contributes to impaired postural control in the acute phase of stroke.

The purpose of the study in chapter 6 was to determine the longitudinal association of visuospatial hemineglect with sitting, standing and walking in postacute stroke patients and to establish whether this relationship is confounded by other determinants. A prospective cohort study of 53 postacute stroke patients consecutively admitted for inpatient rehabilitation was conducted. Transfers and standing balance were assessed with the Berg Balance Scale (BBS) and walking balance with the Functional Ambulation Categories (FAC). Measurements took place at baseline (on average 36.6 ± 10.4 days after stroke) and after six and 12 weeks. Visuospatial hemineglect was assessed by an asymmetry index, derived from the Letter and Star Cancellation Tests of the Behavioral Inattention Test (LSCT asymmetry index). Random coefficient analysis was used to analyze the impact of visuospatial hemineglect on the BBS and FAC. The association between visuospatial hemineglect and outcome was corrected for potential confounders, i.e. age, severity of paresis of the lower leg, somatosensory deficits and presence of
hypertonia. A covariate was considered to be a confounder if the regression coefficient of visuospatial hemineglect on outcome changed by >15%. Visuospatial hemineglect appeared significantly related to BBS and FAC, however, the relation between visuospatial hemineglect and both BBS and FAC was confounded by severity of paresis of the lower leg. After correction for this confounding by severity of paresis, visuospatial hemineglect remained independently related to BBS. We concluded that visuospatial hemineglect is longitudinally and independently associated with postural control after stroke. These findings suggest that hemineglect is an important factor particularly for controlling static and dynamic standing balance during the first months post stroke.

Part III. Effect of somatosensory stimulation on standing balance after stroke
Chapter 7 focuses on the short-term effects of whole-body vibration (WBV), as a novel method of somatosensory stimulation, on postural control. The short-term effects of WBV were investigated in 23 chronic stroke patients (on average 23.3 ± 11.4 months post stroke). While standing on a commercial platform (Galileo900), patients received 30-Hz oscillations at 3 mm amplitude in the frontal plane. Balance was assessed four times at 45-min intervals using a dual-plate force platform, while quietly standing with the eyes opened and closed, and while performing a voluntary weight-shifting task with visual feedback of center of pressure (COP) movements. Between the second and third assessments, four repetitions of 45-sec WBV were given. The results indicated a stable baseline performance from the first to the second assessment for all tasks. After the WBV, the third assessment demonstrated a reduction in the root mean square (RMS) COP velocity in the anteroposterior direction when standing with the eyes closed (p<0.01), which persisted during the fourth assessment. Furthermore, patients showed an increase in their weight-shifting speed at the third balance assessment (p<0.05), while their precision of performance remained constant. Due to the low number of patients, subgroup analyses could not be performed. No adverse effects of WBV were observed. It is concluded that WBV may be a promising means to improve proprioceptive control of posture in stroke patients.

In chapter 8 the long-term effects of 6-weeks WBV on postural control and ADL were compared to those of 6-weeks Exercise Therapy on Music (ETM) of the same intensity in the postacute phase of stroke. Fifty-three patients with moderate to severe functional disabilities were randomized within six weeks post stroke, and within three days after admission to a rehabilitation center to either WBV (on average 38.9 ± 9.2 days after stroke) or ETM (on average 34.2 ± 11.1 days after stroke) in addition to a regular inpatient rehabilitation program. The WBV group received 4 x 45 sec stimulation on the Galileo 900 (30-Hz frontal-plane oscillations of 3 mm amplitude) for five days during six weeks. The ETM group received the same amount of exercise therapy on music. Outcome variables included the Berg Balance Scale, Trunk Control Test, Rivermead Mobility Index, Barthel Index, Functional Ambulation Categories, Motricity Index and somatosensory threshold at 0, 6, and 12 weeks follow-up. At baseline, both groups were comparable in terms of prognostic factors and outcome measures. Both at 6 and 12 weeks follow-up, no clinically relevant or statistical differences in outcome were observed between the groups. There were no Group x Time interactions, indicating similar recovery profiles for both groups. No side effects were reported. In conclusion, daily sessions of whole-body vibration during 6 weeks are not more effective in terms of recovery of balance and ADL than the same amount of exercise therapy on music in the postacute phase of stroke.
Nederlandse samenvatting

Balansherstel na een supratentorieel CVA
Invloed van hemineglect en de effecten van somatosensore stimulatie

Het eerste hoofdstuk van dit proefschrift (hoofdstuk 1) is een algemene introductie en geeft algemene informatie over de epidemiologie van een Cerebro Vasculair Accident (CVA) en tevens over de neurofysiologische en biomechanische achtergronden van balanshandhaving. Daarnaast worden in dit hoofdstuk enkele belangrijke aspecten betreffende herstel van balansvaardigheid tijdens zitten en staan na een CVA besproken, evenals de mogelijke invloed van visuospatieel hemineglect op (herstel van) balans- en loopvaardigheid en het gebruik van somatosensore stimulatie in de revalidatie van patiënten met een supratentorieel CVA. Dit hoofdstuk eindigt met enkele onderzoeksfragen, welke in de daarop volgende hoofdstukken uitgewerkt worden.

Dit proefschrift is onderverdeeld in 3 delen. Het eerste deel, ‘Recovery of sitting and standing balance after stroke’, begint met een systematische review (hoofdstuk 2) van de mechanische en fysiologische mechanismen die ten grondslag liggen aan het herstel van balansvaardigheid na een CVA. Het volgende hoofdstuk (hoofdstuk 3) richt zich op het herstel van zitbalans, gemeten met een krachtenplatform, bij CVA-patiënten in de postacute fase.

In deel 2 van dit proefschrift, ‘Influence of visuospatial hemineglect on balance after stroke’, worden twee diagnostische testen voor het vaststellen van visuospatieel hemineglect beschreven en vergeleken (hoofdstuk 4). Daarop volgen twee hoofdstukken over de invloed van hemineglect op de balansvaardigheid in de acute (hoofdstuk 5) en postacute fase (hoofdstuk 6) na een CVA.

In deel 3 van dit proefschrift, ‘Effect of somatosensory stimulation on standing balance after stroke’, worden twee studies gepresenteerd die de effecten van ‘whole-body vibration’ beschrijven. Hoofdstuk 7 behandelt de korte-termijn effecten bij chronische CVA-patiënten en in hoofdstuk 8 worden de lange-termijn effecten bij postacute CVA-patiënten beschreven.
Het proefschrift wordt afgerond met hoofdstuk 9. Dit is een algemene discussie, waarin de belangrijkste bevindingen en beperkingen van de gepresenteerde studies worden besproken. Tevens worden enkele aanbevelingen voor toekomstig onderzoek gedaan.

Deel 1. Herstel van zit- en stabalans na een CVA

Hoofdstuk 2 is een overzichtsartikel waarin literatuur wordt besproken betreffende de mechanische en fysiologische principes die ten grondslag liggen aan het herstel van balansvaardigheid na een CVA. Dit hoofdstuk is onderverdeeld in secties over staan met en zonder balansverstoringen en staan tijdens actieve gewichtsverplaatsing. Tevens wordt de invloed van houdingsregulatie en cognitie op de balans vaardigheid besproken. Karakteristiek voor patiënten met een incompleet herstelde hemiparese tijdens rustig staan zijn een toegenomen lichaamszwaai en een asymmetrische gewichtbelasting van de benen c.q. meer gewichtname op het niet-paretische been. Tijdens revalidatie treedt vroegtijdig een vermindering van de lichaamszwaai op als een toename van de symmetrie in de gewichtbelasting. Het effect van drukfeedback-training op de symmetrie van de gewichtbelasting en op de stabalans is zwak, in tegenstelling tot het effect van voorzieningen, zoals schoenaanpassingen, enkel-voet orthesen en krukken. Tijdens staan vormen zowel interne (zelfopgelegde) als externe verstoringen een continue bedreiging voor de handhaving van balans. CVA-patiënten laten daarbij maar relatief kleine passieve en actieve verplaatsingen toe van een lichaamszwaartepunt. Om balans te handhaven tijdens staan met en zonder verstoringen vindt er een toegenomen, compensatoire, activiteit van spieren aan de niet-paretische lichaamszijde plaats, zonder dat dit het herstel van meer symmetrische en fysiologische spieractivatiepatronen in een later stadium van de revalidatie belemmert. Een voorwaarde voor een veilige loopvaardigheid is het actief kunnen verplaatsen van het gewicht tussen beide benen. CVA-patiënten laten tijdens het actief verplaatsen van het gewicht niet alleen een minder grote maximale verplaatsing zien, vooral in de richting van het paretische been, maar ook zijn de snelheid en de precisie waarmee de verplaatsingen worden uitgevoerd geringer. Daarnaast hebben CVA-patiënten ten gevolge van zwakke activiteit in de heupspieren aan de paretische zijde problemen om vanuit een positie waarbij beide benen worden belast te komen tot een positie waarbij slechts één been wordt belast. Zowel compensatie van de niet-paretische heupspieren als het herstel van de paretische heupspieren dragen bij aan het herstel van actieve gewichtsverplaatsing. Er is bewijs dat biofeedbacktraining de snelheid en symmetrie van de zit-tot-stand transfer kan bevorderen, echter vooralsnog berust dit bewijs op preliminaire data. Voor wat betreft de sensore regulatie van de houding is het bekend dat CVA-patiënten een grotere visuele afhankelijkheid tonen. Hiervoor worden verschillende verklaringen gegeven zoals moeizame integratie van somatosensore informatie en onvermogen om de meest relevante sensore input te selecteren. Het zou ook een uiting kunnen zijn van een aspecifieke strategie om te compenseren voor de gestoorde somatosensoriek. Een duidelijke relatie tussen de ernst van de somatosensore stoornis en de mate van visuele afhankelijkheid voor de houdingsregulatie is tot op heden echter niet aangetoond. Naast verhoogde visuele afhankelijkheid kan er ook sprake zijn van een verhoogde cognitieve regulatie, hetgeen tot uiting komt in een toegenomen behoefte aan aandacht tijdens het staan. Hoewel studies naar zitbalans, welke gebruik maakten van instrumentele methoden, een negatieve invloed van visuospatieel neglect hebben gevonden op balanshandhaving, is dit in studies naar balanshandhaving tijdens staan nooit bevestigd. De invloed van de ernst van motorische problemen van de paretische beenspieren op (het herstel van) stabalans blijkt minder uitgesproken te zijn dan men zou verwachten. Deze bevinding benadrukt de rol van andere herstelmechanismen dan het herstel van motorische selectiviteit en kracht of een vermindering van spasticiteit. Onduidelijk in dit geheel blijven vooralsnog de invloed van rompspieren, de betekenis van stapreacties en de rol van sensore en cognitieve reorganisatieprocessen.

Hoofdstuk 3 richt zich op het vaststellen van het herstel van zitbalans in de postacute fase na een CVA, door middel van een krachtenplatform. Voor het meten van het balansherstel in zit werd bij 16 CVA-patiënten tijdens hun revalidatiefase gebruik gemaakt van een in hoogte verstelbare stoel, die met behulp van een aluminium frame was bevestigd op een krachtenplatform. Bij alle patiënten werden drie balansmetingen met intervallen van zes weken verricht, vanaf gemiddeld 5.6 weken na hun CVA. Elke balansmeting bestond uit twee series van 30 sec. tijdens rustig zitten met ogen open en ogen dicht op zowel een stabiele als instabiele (luchtkussen) ondergrond. Als maat voor
balanshandhaving in de voorachterwaartse en zijwaartse richting werd de snelheid van het aangrijpingspunt van de grondreactiekrachten gebruikt. In vergelijking met 10 gezonde ouderen, bleek de balanshandhaving bij CVA-patiënten relatief ernstig gestoord in de zijwaartse richting, meer dan in de voorachterwaartse richting. Dit was het meest duidelijk tijdens het zitten met ogen dicht. Bovendien bleek de balanshandhaving in deze richting het meest gevoelig voor herstel tijdens de revalidatie. Er bleek een sterke associatie te bestaan tussen balanshandhaving in de zijwaartse richting en de Berg Balance Scale als klinische maat voor balanshandhaving. Posturografische data bleken niet significant geassocieerd met leeftijd, spierkracht of hemineglect. Uit deze gegevens blijkt dat het verbeteren van rombalans, met name in de zijwaartse richting, een belangrijk doel kan zijn van revalidatie. Omdat de resultaten het meest evident waren tijdens het zitten op een luchtkussen, lijkt het belangrijk om ook balanstraining te verrichten op een instabiele ondergrond.

Deel 2. Invloed van visuospatieel hemineglect op balanshandhaving na een CVA.

In hoofdstuk 4 worden twee verschillende methoden vergeleken om de aanwezigheid van visuospatieel hemineglect vast te stellen. De nadruk wordt gelegd op twee belangrijke aspecten van de klinische presentatie van hemineglect, namelijk de asymmetrie in taakuitvoering en een mogelijke associatie met niet-gelateraliseerde aandachtsstoornissen. Er namen 21 patiënten met een CVA in de linker hemisfeer (LH) en 24 patiënten met een CVA in de rechter hemisfeer (RH) deel aan het onderzoek (gemiddeld 37,1 ± 9,6 dagen na CVA). Tevens werden 20 gezonde proefpersonen onderzocht. De ‘letter-‘ en ‘star-cancellation’ taken van de Behavioral Inattention Task (BIT) werden bij iedere patiënt afgenomen, evenals een geautomatiseerde visuele reactietijdtaak (computerized simple visual reaction time task, CVRT). In de CVRT werden stimuli links, midden of rechts van de patiënt in de extrapersonele ruimte gepresenteerd. Een asymmetrie-index, berekend uit de scores van de letter- en star-cancellation taken, maakte bij LH patiënten een beter onderscheid tussen patiënten met en zonder hemineglect dan ruwe omissiescores. Dit in tegenstelling tot RH patiënten, waarbij de ruwe omissiescores en de asymmetrie-index leidden tot vergelijkbare classificaties. Bij de CVRT werden méér patiënten met hemineglect geclassificeerd door gebruik te maken van de CVRT reactietijd asymmetrie-index dan door gebruik te maken van CVRT omissiescores. Ipsilaterale reactietijden werden beschouwd als een maat voor algemene, niet-gelateraliseerde aandacht. Er was geen verschil in de ipsilaterale reactietijden van de LH en RH patiënten vergeleken met de laterale (links of rechts) reactietijden van gezonde proefpersonen. Echter, bij RH patiënten die zowel met de reactietijd asymmetrie-index als de BIT asymmetrie-index boven de cut-off score scoorden, waren de ipsilaterale reactietijden langer dan bij RH patiënten die verhoogde reactietijd-asymmetrieën hadden, maar normale BIT-scores. Hierdoor wordt het idee ondersteund dat er een mogelijke interactie bestaat tussen gelateraliseerde en niet-gelateraliseerde aandachtscomponenten bij hemineglect, waarbij de ernst van de symptomen van hemineglect wordt versterkt door de aanwezigheid van algemene aandachtsstoornissen ten gevolge van een visuospatiële bias. Reactietijdtaken kunnen dus een bijdrage leveren aan het vaststellen van asymmetriëen in visuospatiële aandacht bij patiënten met subklinische symptomen van hemineglect, welke in staat zijn geleraliseerde aandachtsstoornissen te compenseren met een intacte capaciteit van algemene (niet-geleraliseerde) aandacht tijdens pen-en-papier taken.

De studie beschreven in hoofdstuk 5 werd verricht om de onafhankelijke bijdrage van visuospatieel hemineglect aan een verzwakte balanshandhaving te onderzoeken en deze bijdrage te vergelijken met de invloed van andere klinische en biologische determinanten in de acute fase (<2 weken) na een CVA. Het onderzoek werd uitgevoerd in vier ziekenhuizen in de midden/oostelijke regio van Nederland. In totaal werden 78 patiënten met een eerste supratentorieel CVA, gemiddeld 5,5 ± 2,4 dagen na het accident, geïncludeerd. Balansvaardigheid werd vastgelegd met de Trunk Impairment Scale (TIS), de Trunk Control Test (TCT), de Berg Balance Scale (BBS) en de Functional Ambulation Categories (FAC). Aan de hand van een asymmetrie-index, berekend uit de scores van de letter- en star-cancellation taken van de Behavioral Inattention Task (BIT), werd de aanwezigheid van visuospatieel hemineglect vastgesteld. De Motricity Index (spierkracht), de drempelwaarde van de vibratiezin, de volgehouden aandacht en de aanwezigheid van hemianopsie werden vastgelegd als mogelijke andere klinische determinanten. Een multipie lineaire regressieanalyse werd uitgevoerd, waarbij alle klinische determinanten werden ingevoerd, evenals de
biologische factoren leeftijd en tijd na CVA. Visuospatieel hemineglect bleek aanwezig te zijn bij 17 patiënten (21,8%). Met betrekking tot verdeling van geslacht en aantal patiënten met rechter hemisfeerletsel was er een significant verschil tussen de groep met en de groep zonder hemineglect. Er was geen significant verschil voor leeftijd, type CVA of tijd na CVA. Neglect patiënten scoorden gemiddeld 17,5 - 43% lager op alle functionele balanstaken en klinische testen. Naast visuospatieel hemineglect waren alleen spierkracht en leeftijd onafhankelijk geassocieerd met verslechterde balanshandhaving. Samen verklaarden zij 65 tot 72% van de variantie van de geselecteerde uitkomstmaten. Er werd geconcludeerd dat hemineglect een onafhankelijke bijdrage levert aan verminderde balanshandhaving in de acute fase na een CVA.

In hoofdstuk 6 werd de longitudinale associatie tussen visuospatieel hemineglect en zitten, staan en lopen bij postacute CVA-patiënten bepaald en tevens werd geanalyseerd of deze associatie beïnvloed werd door andere determinanten. Hiertoe werd een prospectief cohort onderzoek uitgevoerd bij 53 postacute CVA-patiënten welke aansluitend aan elkaar werden opgenomen in een revalidatiecentrum. De Berg Balance Scale (BBS) werd gebruikt voor het vaststellen van balans tijdens transfers en staan en de Functional Ambulation Categories (FAC) voor het beoordelen van balans tijdens gaan. De metingen werden bij opname (gemiddeld 36,6 ± 10,4 dagen na CVA) en na zes en 12 weken verricht. Aan de hand van een asymmetrie-index, berekend uit de scores van de letter- en star-cancellation taken van de Behavioral Inattention Test (BIT), werd de aanwezigheid van visuospatieel hemineglect vastgesteld. Om de invloed van visuospatieel hemineglect op de BBS en FAC te analyseren werd ‘random coefficient analysis’ verricht. De associatie tussen visuospatieel hemineglect en de uitkomstmaten werd vervolgens gecorrigeerd voor potentiële confounders, c.q. leeftijd, ernst van paralysie van de onderste extremiteit, somatosensore stoornissen en aanwezigheid van hypertorie. Een covariaat werd als confounder beschouwd wanneer de regressiecoëfficiënt van visuospatieel hemineglect voor de uitkomstmatrix met meer dan 15% veranderde. Visuospatieel hemineglect bleek significant gerelateerd met zowel de BBS als de FAC. Echter, deze relatie werd voor zowel BBS als FAC beïnvloed door de ernst van paralysie van de onderste extremiteit. Na correctie van deze beïnvloeding bleef er een onafhankelijke relatie tussen visuospatieel hemineglect en de BBS bestaan. Er kon worden geconcludeerd dat er een onafhankelijke en longitudinale associatie bestaat tussen visuospatieel hemineglect en balanshandhaving na een CVA. Deze bevindingen suggereren dat hemineglect een belangrijke determinant is voor het handhaven van statische en dynamische stabalans in de eerste maanden na een CVA.

Deel 3. Het effect van somatosensore stimulatie op stabalans na een CVA

Hoofdstuk 7 richt zich op de korte-termijn effecten van ‘whole-body vibration’ (WBV), als relatief nieuwe methode van somatosensore stimulatie, op balanshandhaving na CVA. De korte-termijn effecten van WBV werden onderzocht bij 23 chronische CVA-patiënten (gemiddeld 23,3 ± 11,4 maanden na CVA). Patiënten kregen, staande op een commercieel triplatform (Galileo900), vibraties toegediend in het frontale vlak met een frequentie van 30 Hz en een amplitude van 3 mm. De balanshandhaving werd vier keer gemeten met intervallen van 45 min., waarbij gebruik werd gemaakt van een krachtenplatform bestaande uit twee gescheiden platen. Er werd gemeten met ogen open en dicht en tijdens het uitvoeren van een gewichtverplaatsingstask met visuele feedback van het aangrijpingspunt van de grondreactiekrachten. Tussen de tweede en derde balansmeting werden vier sessies van 45 sec. WBV gegeven. De resultaten lieten voor alle taken een stabiele basisuitvoering zien tijdens de eerste en de tweede meting. Na de WBV was er bij de derde meting een afname te zien in de snelheid van het aangrijpingspunt van de grondreactiekrachten in voor-achterwaartse richting, terwijl de patiënten met hun ogen dicht stonden (p<0,01). Deze afname was nog aanwezig tijdens de vierde meting. Tevens lieten de patiënten een toename zien van de snelheid van gewichtverplaatsing (p<0,05) tijdens de derde balansmeting, terwijl de mate van nauwkeurigheid stabiel bleef. Door het relatief geringe aantal deelnemende patiënten konden geen subgroepsanalyses worden uitgevoerd. Er werden geen negatieve effecten van WBV geobserveerd. Er werd geconcludeerd dat WBV een potentieel gunstige werking zou kunnen hebben op de proprioceptieve regulatie van de balanshandhaving na een CVA.

In hoofdstuk 8 werden de lange-termijn effecten van zes weken WBV op de balanshandhaving en dagelijkse activiteiten (ADL) vergeleken met de effecten van zes weken ‘Exercise Therapy on Music’ (ETM) tijdens de postacute fase na een CVA.
een CVA. Driënvijftig patiënten met matige tot ernstige functionele beperkingen werden binnen zes weken na hun CVA en binnen drie dagen na opname in een revalidatiecentrum gerandomiseerd voor WBV (gemiddeld 38,9 ± 9,2 dagen na CVA) of ETM (gemiddeld 34,2 ± 11,1 dagen na CVA). Alle patiënten volgden tevens een regulier revalidatieprogramma. De WBV groep ontving tevens 4 x 45 sec. stimulatie op de Galileo 900 in het frontale vlak (frequentie van 30 Hz; amplitude van 3 mm.) gedurende vijf dagen per week, zes weken lang. De ETM groep ontving dezelfde intensiteit extra therapie door te bewegen op muziek. De uitkomstmaten omvatten de Berg Balance Scale, de Trunk Control Test, de Rivermead Mobility Index, de Barthel Index, de Functional Ambulation Categories, de Motricity Index en de somatosensore detectiegrens en werden vastgelegd bij 0, 6 en 12 weken follow-up. Bij aanvang van het onderzoek bleken beide groepen vergelijkbaar op grond van prognostische factoren en uitkomstmaten. Zowel bij 6 als 12 weken was er geen klinisch relevant of statistisch significant verschil tussen de groepen voor enige uitkomstmaat. Er waren geen Groep x Tijd interacties, wat duidt op gelijkwaardige herstelverwachtingen voor beide groepen. Er werden geen neveneffecten gerapporteerd. Geconcludeerd werd dat dagelijkse sessies ‘whole-body vibration’ niet effectiever zijn om de balans- en ADL-vaardigheid te verbeteren dan dezelfde hoeveelheid ‘exercise therapy on music’ tijdens de postacute fase na een CVA.
List of publications


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Mijn traject was dan wel geen officieel AIOSKO-traject, in de praktijk kwam het wel op hetzelfde neer. Om mijn opleiding tot revalidatiearts te combineren met de onderzoeksprojecten die wordt gevoerd is van diverse kanten een flexibele instelling nodig. Met name de ervaren steun van mijn opleiders Dirk van Kuppevelt (St Maartenskliniek), Harmen van der Linde (CWZ) en Sander Geurts (UMC St Radboud) was erg belangrijk. Ik ben dan ook erg blij dat ik in ‘jullie’ circuit kon blijven werken. Ook de instelling van mijn voormalig supervisore(s) en huidige collega’s was en is positief, waardoor delen van de opleiding ook gecombineerd konden worden met onderzoek.

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Ilse van Nes werd op 5 juli 1976 geboren te Drunen. Na het behalen van haar VWO diploma in 1994 aan het d’Oultremontcollege te Drunen, studeerde zij van 1994 tot 2001 geneeskunde aan de Katholieke Universiteit Nijmegen. Tijdens haar keuze co-schap en haar wetenschappelijke stage was zij werkzaam op de afdeling revalidatiedeeskunde en de researchafdeling van de St. Maartenskliniek.


Gedurende haar opleiding tot revalidatiearts heeft zij de mogelijkheid gehad zich 2 jaar fulltime bezig te houden met wetenschappelijk onderzoek. Dit is verricht in het kader van het stimuleringsprogramma revalidatie van ZonMw, binnen het consortium Cognitieve Revalidatie. De resultaten van dit wetenschappelijk onderzoek worden beschreven in dit proefschrift. Op de XVIIIth Conference of the International Society for Postural and Gait Research in Marseille in 2005 ontving zij de ISPGR Poster Student Award en tijdens de VRA vergadering op 5 oktober 2006 ontving zij de TOS AIOS trofee.

Momenteel is zij werkzaam als revalidatiearts in de St. Maartenskliniek met als aandachtsgebied dwarslaesierevalidatie en in het Canisius Wilhelmina Ziekenhuis te Nijmegen.

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