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"Dov'è la sinistra?"
HEMISPATIAL NEGLECT IN STROKE

by
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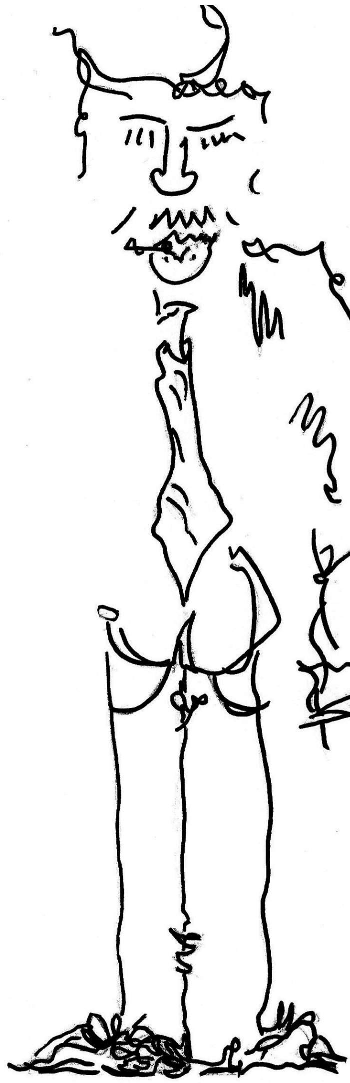
It is neither too late nor too far.

The island called Here is everywhere.

-Wislawa Szymborska



Self portrait of a patient with hemispatial neglect

ABSTRACT

As long as the incidence of stroke continues to grow, patients with large right hemisphere lesions suffering from hemispatial neglect will require neuropsychological evaluation and rehabilitation. The inability to process information especially that coming from the left side accompanied by the magnetic orientation to the ipsilesional side represents a real challenge for rehabilitation. This dissertation is concerned with crucial aspects in the clinical neuropsychological practice of hemispatial neglect.

In studying the convergence of the visual and behavioural test batteries in the assessment of neglect, nine of the seventeen patients, who completed both the conventional subtests of the Behavioural Inattention Test and the Catherine Bergego Scale assessments, showed a similar severity of neglect and thus good convergence in both tests. However, patients with neglect and hemianopia had poorer scores in the line bisection test and they displayed stronger neglect in behaviour than patients with pure neglect.

The second study examined, whether arm activation, modified from the Constraint Induced Movement Therapy, could be applied as neglect rehabilitation alone without any visual training. Twelve acute- or subacute patients were randomized into two rehabilitation groups: arm activation training or traditional voluntary visual scanning training. Neglect was ameliorated significantly or almost significantly in both training groups due to rehabilitation with the effect being maintained for at least six months.

In studying the reflections of hemispatial neglect on visual memory, the associations of severity of neglect and visual memory performances were explored. The performances of acute and subacute patients with hemispatial neglect were compared with the performances of matched healthy control subjects. As hypothesized, encoding from the left side and immediate recall of visual material were significantly compromised in patients with neglect. Another mechanism of neglect affecting visual memory processes is observed in delayed visual reproduction. Delayed recall demands that the individual must make a match helped by a cue or it requires a search for relevant material from long-term memory storage. In the case of representational neglect, the search may succeed but the left side of the recollected memory still fails to open.

Visual and auditory evoked potentials were measured in 21 patients with hemispatial neglect. Stimuli coming from the left or right were processed differently in both sensory modalities in acute and subacute patients as compared with the chronic patients. The differences equalized during the course of recovery.

Recovery from hemispatial neglect was strongly associated with early rehabilitation and with the severity of neglect. Extinction was common in patients with neglect and it did not ameliorate with the recovery of neglect. The presence of pusher symptom hampered amelioration of visual neglect in acute and subacute stroke patients, whereas depression did not have any significant effect in the early phases after the stroke. However, depression had an unfavourable effect on recovery in the chronic phase.

In conclusion, the combination of neglect and hemianopia may explain part of the residual behavioural neglect that is no longer evident in visual testing. Further research is needed in order to determine which specific rehabilitation procedures would be most beneficial in patients suffering the combination of neglect and hemianopia. Arm activation should be included in the rehabilitation programs of neglect; this is a useful technique for patients who need bedside treatment in the acute phase. With respect to the deficit in visual memory in association with neglect, the possible mechanisms of lateralized deficit in delayed recall need to be further examined and clarified. Intensive treatment induced recovery in both severe and moderate visual neglect long after the first two to first three months after the stroke.

ABSTRAKTI

Oikean aivopuoliskon laajoihin vaurioihin liittyvä neglect-oireisto tulee tulevaisuudessakin olemaan neurologisen kuntoutuksen keskeisiä haasteita, ellei aivoverenkiertohäiriöiden määrää saada vähenemään. Neglect-potilaat eivät pysty tietoisesti prosessoimaan vaurion vastakkaisella puolella olevia ärsykkeitä. Sen lisäksi vartalon, pään ja silmien etsiskelyliikkeet kääntyvät voimakkaasti vaurion puolelle. Tässä tutkimuksessa paneuduttiin kliinisen käytännön kannalta keskeisiin neglect-oireiston neuropsykologisiin ongelmiin.

Ensimmäisessä tutkimuksessa kartoitettiin kahden erilaisen neglectiä mittaavan testistön vastaavuutta. Seitsemäntoista potilasta täytti perinteisen visuaalisen Behavioural Inattention Testin konventionaaliset testit ja toimintaterapeutti arvioi neglectin esiintymistä toimintatilanteissa Catherine Bergego Scale-arviointiskaalaa käyttäen. Yli puolella potilaista Neglect todettiin vaikeusasteeltaan jotakuinkin samanlaiseksi. Neglect näyttäytyi kuitenkin arkisissa toiminnoissa ja jananjakotehtävässä vaikeampana niillä potilailla, joilla todettiin neglectin lisäksi myös näkökenttäpuutos.

Toisessa tutkimuksessa selvitettiin, kuntoutuuko neglect pelkästään käden aktivoinnin metodilla ilman visuaalisen skanneerauksen kuntoutusta. Kaksitoista potilasta, joiden sairastumisesta oli kulunut alle puoli vuotta, satunnaistettiin perinteiseen tahdonalaisen visuaalisen skanneerauksen kuntoutukseen tai käden aktivoinnin kuntoutusohjelmaan, joka oli mukailtu pakotetun käden käytön kuntoutusohjelmasta. Neglect kuntoutui molemmilla metodeilla merkitsevästi tai lähes merkitsevästi kolmen viikon kuntoutusjakson jälkeen ja vaikutus säilyi kuuden kuukauden seurannan ajan.

Tutkittaessa neglectin vaikeusasteen heijastumista potilaiden visuaalisen muistin suorituksiin, verrattiin potilaiden suorituksia myös vastaavien terveiden koehenkilöiden suorituksiin. Alkuvaiheen vaikea neglect heikensi merkittävästi vasemmanpuoleisen materiaalin mieleen painamista ja välitöntä mieleen palauttamista. Neglectin lievittymisen myötä välitön mieleen palautus normalisoitui kuormittavinta tehtävää lukuun ottamatta, mutta viivästetyn mieleen palautuksen häiriö vasemmalla säilyi. Representationaalisen neglectin kyseessä ollessa hakuprosessi kyllä käynnistyy, mutta vasemman puoleiset yksityiskohdat eivät siitä huolimatta ole palautettavissa.

Visuaalisia ja auditiivisia herätevasteita mitattiin 21 neglect-potilaalta kuntoutumisen eri vaiheissa. Vasemmalta ja oikealta tulevien ärsykkeiden prosessoinnissa oli selkeitä eroja akuutti- ja subakuuttivaiheen potilailla molemmissa aistijärjestelmissä verrattuna kroonisen vaiheen potilaisiin. Erot kuitenkin tasoittuivat kuuden kuukauden seurantajakson aikana neglectin lievittyessä.

Neglect-kuntoutus lievensi niiden potilaiden oireita, joiden sairastumisesta oli kulunut vain vähän aikaa ja joilla oli todettu vaikea-asteinen neglect. Taktiilinen ekstinktio oli potilailla yleinen, eikä se lieventynyt neglectin kuntoutumisen myötä. Pusher-oire hidasti visuaalisen neglectin kuntoutumista akuutti- ja subakuuttivaiheen potilailla. Depressio ei haitannut potilaiden kuntoutumista akuuttivaiheessa, mutta kroonisessa vaiheessa sillä oli epäedullinen vaikutus kuntoutumiseen.

Yhteenvetona voidaan todeta, että näkökenttäpuutos yhdistyneenä neglectiin saattaa selittää sitä, miksi osalla potilaista neglect näkyy käyttäytymisessä kauemmin kuin paperitehtävissä. Jatkotutkimusta tarvitaan selvittämään, millaiset menetelmät soveltuvat neglectin ja hemianopian yhdistelmän kuntouttamiseen. Käden aktivointi tulisi sisällyttää neglectin kuntoutusohjelmiin visuaalisen kuntoutuksen ohella. Menetelmä soveltuu hyvin niille akuuttivaiheen potilaille, jotka eivät vielä pysty osallistumaan kuntoutukseen istuen. Viivästetyn visuaalisen mieleen palautuksen ja neglectin välisten yhteyksien ja mekanismien tutkimiseksi tarvitaan jatkotutkimusta. Vaikea-asteisen ja kohtalaisen neglect-oireen intensiivinen kuntoutus on tuloksellista vielä kauan ensimmäisten kuukausien jälkeen.

CONTENTS

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I appreciate the constructive and detailed criticism of my official reviewers, Docent Mervi Jehkonen and Docent Marja Hietanen. I also highly respect the insightful reviews that I have received while processing the individual articles for publication. These suggestions have substantially improved my thinking and advanced the results and quality of the study. Professor Ewen MacDonald patiently corrected the language of the articles and this thesis.

The project demanded a lot of work from the personnel of Neuron. Fortunately, research has been a part of our activities and our personnel is used to the extra work that it demands. They have shown a positive and encouraging attitude throughout the project.

Patients and control subjects have undergone hours of assessments and I thank them for their interest, patience and efforts. Psychologist Susanna Suomalainen was in charge of the actual visual scanning rehabilitation of our patients and occupational therapist Auli Miettinen assessed neglect in their behaviour by the Catherine Bergego Scale. I thank both professionals for their devoted and meticulous work. Physiotherapist Anne Ruokonen kindly translated the Scale for Controversive Pushing for the study, thank you! My colleagues Marja Äikiä from the Kuopio University Hospital, Mervi Kinnunen and Saija Moilanen from the Joensuu Central Hospital deserve special thanks for helping in recruiting patients.

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Riitta Luukkainen-Markkula

ABBREVIATIONS

AA	Arm Activation training
ADL	Activities of Daily Living
AEP	Auditory evoked potentials
BDI	Beck Depression Inventory
BIT	Behavioural Inattention Test
BIT C	Conventional subtest of the BIT
BN	Basal nuclei lesion
BTT	Baking Tray Test
CBS	Catherine Bergego Scale
CIMT	Constraint Induced Movement Therapy
CT	Computed Tomography
EEG	Electroenchephalography
EI	Edinburgh Inventory
EP	Evoked potentials
F	Frontal lesion
FES	Functional Electric Stimulation
FIM	Functional Independence Measure
Gr	Group therapy
hc	health care center ward
HH	Homonymous hemianopia
IP	Individually Planned rehabilitation program
iReach	video screen program from the VS
LAD	Limb Activation Device
LBT	Line Bisection Test from BIT
MMAS	Modified Motor Assessment Scale
MMN	Mismatch Negativity
MRI	Magnetic Resonance Imaging
mp	multi-professional stroke unit
NP	Neuropsychological rehabilitation
O	Occipital lesion
OT	Occupational Therapy
P	Parietal lesion

PT	Physiotherapy
SCP	Scale for Contraversive Pushing
SCT	Star Cancellation Test from BIT
SD	Standard Deviation
SPSS	Statistical Package for Social Sciences
TA	Temporal Anterior lesion
TDSS	Tactile Double Simultaneous Stimulation test
Th	Thalamus lesion
TP	Temporal Posterior lesion
VEP	Visual evoked potential
VFD	Visual Field Deficit
VR	Visual Reproduction subtest of the WMS-R
VS	Visual Scanning training
WAIS-R	Wechsler Adult Intelligence Scale Revised
WMFT	Wolf Motor Function Test
WMS-R	Wechsler Memory Scale Revised

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the four published original articles and one submitted article. These articles are referred to in the text by their Roman numerals.

I Luukkainen-Markkula, R., Tarkka, I.M., Pitkänen, K., Sivenius, J. & Hämäläinen, H. (2011). Comparison of the Behavioural Inattention Test and the Catherine Bergego Scale in assessment of hemispatial neglect. Neuropsychological Rehabilitation, 21, 103-116. **

II Luukkainen-Markkula, R., Tarkka, I.M., Pitkänen K., Sivenius, J. & Hämäläinen, H. (2009). Rehabilitation of hemispatial neglect: A randomized study using either arm activation or visual scanning training. Restorative Neurology and Neuroscience, 27, 665-674. *

III Luukkainen-Markkula, R., Tarkka, I.M., Pitkänen, K., Sivenius, J. & Hämäläinen, H. (2011). Hemispatial neglect reflected on visual memory. Restorative Neurology and Neuroscience, 29. 321-330.*

IV Tarkka, I.M., Luukkainen-Markkula, R., Pitkänen, K. & Hämäläinen, H. (2011). Alterations in visual and auditory processing in hemispatial neglect: An evoked potential follow-up study. International Journal of Psychophysiology, 79, 272-279. ***

V Luukkainen-Markkula, R., Tarkka, I.M., Pitkänen, K., Sivenius, J. & Hämäläinen, H. (Submitted). Determinants of recovery from hemispatial neglect after stroke.

1. INTRODUCTION

A clinical neuropsychologist needs proper tools for diagnosing symptoms, a profound understanding of functional networks and syndromes and effective methods to rehabilitate patients suffering neuropsychological deficits. Hemispatial neglect represents one of these challenges. Patients with neglect may be magnetically drawn to the ipsilesional space and automatic movements of eyes, head or trunk to the contralateral side are inhibited in severe forms of neglect. When information from the other half from one's own body and from the surrounding world does not reach awareness, patients live in a different reality from the therapist. Trying to push patients towards the half of the world that for them does not exist can be a frustrating task both for the patient and the therapist and thus any involuntary method that would ameliorate neglect would be most welcome.

Stroke is today and will continue to be the most frequent cause of chronic disability in adults in the western world (Husain and Rorden, 2003; Feigin et al., 2008). Nearly half of the stroke survivors display neuropsychological deficits acutely after stroke and one in three stroke patients is diagnosed suffering from hemispatial neglect (Desmond et al., 1996; Ringman et al., 2004). Although many recover spontaneously within the first months, ten percent of these patients still display neglect three months after the cerebral accident (Ringman et al., 2004, Farnè et al., 2004). Neglect patients are often encountered in neurological rehabilitation units and unfortunately neglect after a right hemisphere stroke often predicts a poor functional outcome (Jehkonen et al., 2000a; Buxbaum et al., 2004).

Hemispatial neglect, the right hemisphere syndrome, is a heterogeneous set of symptoms which vary significantly from one patient to the next depending on the extent and localization of the lesion (Stone, Halligan and Geenwood, 1993; Kerkhoff, 2001; Hillis, 2006). The most frequent etiological causes of neglect are large infarctions of the right middle cerebral artery territory encompassing several cerebral lobes (Vallar, 1993; Maguire and Ogden, 2002). Patients with neglect typically have larger lesions than right hemisphere patients without neglect (Leibovitch et al., 1998). Subsequently they suffer more motor and sensory impairments than patients without neglect (Buxbaum et al., 2004). At the heart of the syndrome is the inattention to the contralesional hemispace. Lateralized visuo-spatial and sensory deficits have been thought to localize mainly in the posterior temporoparietal junction, the crucial area being around the inferior parietal area. Other crucial areas of damage include the right dorsolateral prefrontal cortex (exploratory visuo-motor components), and subcortical regions such as thalamus, the basal ganglia and the white matter tracts connecting these areas (disconnection syndrome) (Husain and Rorden, 2003; Bartolomeo, Thiebaut de Schotten and Dorrichi, 2007; Verdon et al., 2010). Mesulam (2000) concluded that thalamus and cingulate cortex were essential in neglect, bringing aspects of regulation of arousal and motivation into the syndrome. Karnath and Dietrich (2006) have shown that superior temporal area, insula and temporoparietal junction form a vestibular connection to the spatial orientation. These areas integrate vestibular information from the body with auditory and visual information coming from the surrounding space into a multimodal spatial representation.

Space in hemispatial neglect can be perceived and organized from several references of frame. Left can be defined according to the patient's own body midline or subjective straight ahead, or even from the fixation point of the eyes (egocentric frame, personal neglect). The surrounding space can be divided into arm reaching space (peripersonal neglect) or eye reaching space (extrapersonal neglect). The frame of reference can also be object centred, left from the centre of an object, face or a drawing at which a person is looking. The left side can be neglected even from memories and mental images (representational neglect). These different subtypes of neglect may appear together or they can be dissociated in individual patients. (For reviews, see Mesulam, 2000; Kerkhoff, 2001).

Hemispatial neglect has been characterized not only by inattention to stimuli on the contralesional side but also by hyperactive or magnetic orientation to the ipsilesional side (Na et al., 1999). Another way of expressing the classification of these symptoms of neglect is through defective and productive manifestations (Vallar, 1998). The inability to describe sensory events coming from the contralateral side of the lesion and impaired exploration of contralesional side would represent defective or negative manifestations of neglect. Active avoidance from contralesional targets, hyperattention of ipsilesional targets as well as perseverative responses on the ipsilesional side refer to positive or productive manifestations of neglect.

During the history of studying neglect, several mechanisms have been postulated to explain the attentional dysfunction. Early theories suggested that neglect results from a deficit in sensory or perceptual processing of neglected stimuli. Heilman and Van Den Abell (1980) proposed a right hemisphere dominance for attention: the right parietal lobe attends to stimuli presented to both the right and left sides whereas the left parietal lobe only attends to ipsilateral stimuli. However, according to the Kinsbourne model (1993), attention does not remain intact in either hemispace in neglect: the disinhibited overactive healthy hemisphere biases the attention to the most right-sided stimuli. Mesulam (1985) first introduced a network model of neglect, which included posterior parietal cortex, frontal eye fields, cingulate gyrus and subcortical areas like thalamus, striatum and superior colliculus in right hemisphere. Lesions in any component of the network or in its interconnections can result in contralesional neglect.

Recently, nonlateralized mechanisms of attention have been found to exacerbate or even to be a central part of the lateralized bias in hemispatial neglect. The overall ability to sustain attention is diminished independently of neglect and has been found to improve with the recovery from neglect (Robertson et al., 1998b; Husain and Rorden, 2003). The latest neuroanatomical model of attention is presented by Corbetta, Patel and Shulman (2008) and is based on their activation studies by functional MRI. The dorsal attention network including the intraparietal sulcus and the frontal eye field areas is believed to function bilaterally. This network enables the selection of sensory stimuli based on internal goals and expectations (goal-driven attention). The ventral attention network is localized around the temporoparietal junction and ventral frontal cortex in the right hemisphere. This network detects behaviourally relevant stimuli in the environment (stimulus-driven attention). The dorsal attention network directs the attention to the contralateral extrapersonal space, whereas the ventral attention network is needed if one wishes to target detection and reorienting towards salient unexpected stimuli in either hemispace. Strokes that cause neglect often damage the right hemisphere ventral attention network but spare the bilateral dorsal network. The spatial bias in neglect will then depend on the imbalance between left and right dorsal parietal cortex: a lesion in the area of the right ventral network induces hyperactivity in the left parietal area. This hyperactivity is associated with the severity of neglect and mitigates with amelioration of neglect. At the same time, the functional imbalance between the parietal areas in left and right hemisphere diminishes (He et al., 2007; Corbetta, Patel and Shulman, 2008). Thus the ventral network damage causes both nonlateralized deficits directly and lateralized deficits indirectly through the connections between the two attention networks (He et al., 2007).

The theoretical background of the present study derives from the functional imbalance of the left and right hemispheres causing inattention to the left hemispace and the hyperactive orientation towards the right hemispace. Also the multimodal sensory processing in neglect has been an important theoretical aspect in this work. The term hemispatial neglect was chosen to represent unilateral or spatial neglect as a syndrome. The term visual neglect is used when referring to the neglect measured by the conventional paper and pencil test of the Behavioural Inattention Test. The term behavioural neglect refers to the neglect assessed by the Catherine Bergego Scale in everyday situations.

1.1. Assessment of hemispatial neglect

Irrespective of the multisensory nature of hemispatial neglect, the visual aspects of the syndrome have been studied most extensively with tasks such as line, letter or star cancellation, figure copying or drawing, line bisection, reading and writing tasks (Halligan and Marshall, 1993). Pizzamiglio et al. (1992) used a test battery including a line bisection test devised by Albert, Letter Cancellation Test devised by Diller et al., the sentence Reading Test of Pizzamiglio et al. and the Wundt-Jastrow Area Illusion Test in their rehabilitation studies to assess neglect. They also developed a Semi-structured Scale for the Functional Evaluation of hemineglect examining the patients' behaviour in situations similar to those encountered in daily life. The six conventional subtests of the Behavioural Inattention Test battery (BIT; Wilson, Cockburn and Halligan, 1987) were developed out of these conventional visual tests: Line cancellation, letter cancellation, star cancellation, figure and shape copying, line bisection and representational drawing. The test battery was first standardized in a group of 80 stroke patients with both left and right hemisphere lesions and in 50 age-matched controls with the patients being assessed on average three months after their stroke (Halligan, Marshall and Wade, 1989). Thirty patients showed signs of neglect, 26 of them had a right sided lesion, whereas only four patients had a lesion in the left hemisphere. All correlations between the conventional subtests of the BIT were significant and loaded on one single factor. However, there was variation in the sensitivity of the subtests in measuring neglect: the star cancellation test was the most sensitive subtest and identified all patients when the cut-off point was less than 130/146, whereas the representational drawing subtest only detected 37% of the patients with neglect. Subsequently, nine practical tests, also assessed as table tests, were added into the battery: Picture scanning, telephone dialling, menu reading, article reading, telling and setting the time, coin sorting, address and sentence copying, map navigation and card sorting (Halligan, Marshall and Wade, 1989). Jehkonen (2002) also demonstrated significant intercorrelations between the conventional subtests in 20 patients with neglect acutely after right hemisphere stroke in her verification study of the BIT in Finnish neglect patients. However, the line bisection subtest correlated significantly only in the responses from three of the six subtests. The internal consistency and the reliability of the BIT C were good in these patients with moderate or severe neglect. The best single test for detecting neglect was the star cancellation and the best combination of three tests was obtained with line crossing, letter cancellation and line bisection (Jehkonen et al., 1998).

Interestingly, physiotherapists and occupational therapists often report neglect in behaviour even though the signs of neglect have disappeared from paper and pencil tests (Buxbaum et al., 2004). This residual neglect may restrict the patients in activities of daily life after discharge from rehabilitation (Jehkonen et al., 2000a). The Catherine Bergego Scale (CBS) was specifically developed by Azouvi et al. (1996) to assess the presence of neglect in everyday life situations. This is a standardised checklist to be used by an occupational therapist to observe hemi-inattention in the following ten functions: grooming or shaving, dressing, eating, mouth cleaning, gaze orientation, knowledge of the left side of the body, auditory attention, collisions into objects on the left while moving, finding one's way, and finding personal belongings in the rehabilitation unit. In this scale, the severity of neglect is rated from 0 to 3 points for each item: 0 = no neglect, 1 = mild, 2 = moderate and 3 = severe neglect. One version of the scale is also completed by the patient. A kind of anosognosia score can be calculated by subtracting the score observed by the occupational therapist from the patient score: if the remainder is positive, the patient is not aware of his/her dysfunctions; if the difference is negative, the patient is overestimating his/her difficulties.

The CBS has been validated in three studies with patients who had right hemisphere lesions and who were, an average, three to four months post-stroke (Azouvi et al., 1996, 2002, 2003). Most patients in these studies had moderate or severe motor impairments; 28–33% had visual field deficits and on average patients displayed mild or moderate neglect as assessed by the CBS. The CBS total score correlated significantly with the traditional neglect tests that were used (Bells test, line cancellation, drawing and copying, reading and writing). In addition, the internal consistency of the scale was found to be good: each individual item of the scale correlated significantly with the total score. The most sensitive items for detecting neglect were dressing, knowledge of left limbs and collisions while moving. In fact, the behavioural assessment was found to be more sensitive than the traditional tests in detecting neglect (Azouvi et al., 2002, 2003). However, there were individual dissociations: few patients showed moderate to severe neglect in the CBS and displayed no sign of neglect in the traditional tests. In one study, almost 20% of patients showed no visual neglect in traditional tests but demonstrated mild behavioural neglect in the CBS (Azouvi et al., 2003).

The CBS has correlated well with individual traditional tests of visual neglect but until now it has not been compared with the test battery based on the traditional visual neglect tests, the conventional subtests of the BIT.

1.2. Rehabilitation of hemispatial neglect

Behavioural treatments of hemispatial neglect try to help patients to track stimuli from the neglected side in a voluntary manner. The first comprehensive neglect training program which attempted to train patients to turn towards the contralesional side was developed by Pizzamiglio et al. (1992). Their program was found to be effective in a group of 13 chronic patients with severe hemispatial neglect. The patients' recovery was confirmed by their performance in several neglect tests. The positive effect was also evident in activities of daily living and persisted for the follow-up period of several months. The 40 hours of visual scanning training during eight consecutive weeks included four different procedures: optokinetic scanning from a large screen, reading and copying training, copying of line drawings on a dot matrix and figure description. This initial finding was soon confirmed by Antonucci et al. (1995), who compared the recovery of two groups of ten patients with left neglect about two months after the stroke. Both groups improved significantly, but only after having received the special neglect training for the substantial amount of hours.

A variety of non-volitional sensory treatments such as caloric vestibular or optokinetic stimulation as well as neck muscle vibration have been applied in the rehabilitation of neglect (for review, see Pierce and Buxbaum, 2002). Sensory stimulation has generally ameliorated neglect but only transiently without achieving long term effects. The prism adaptation method has shown relatively long lasting gains from comparatively short term usage, although the effect is seen in some neglect patients but not in others (Serino et al., 2006).

The left limb activation method was created from the observations that spatial neglect was less severe when the patient was pointing at targets with the arm contralateral to the lesion (Robertson, 1991). The first trials to demonstrate the effect of the left limb activation method on the visual neglect were realized by doing cancellation tasks simultaneously with voluntary left arm or leg movements (Robertson, 1991; Robertson and North, 1992 and 1993; Làdavas et al., 1997; Brown and Walker, 1999). Robertson and North (1992) concluded that only active left finger movements in the left hemispace, visible or invisible, significantly reduced the neglect during cancellation tasks. Left-sided movements did not serve as visual cues, but the effect was thought to derive from either the movement itself or from the spatial location of the arm in the left half space. Gainotti et al. (2002) confirmed the result with seven acute neglect patients: only left hand movement in the left half space produced a significant reduction in the severity of neglect. Robertson et al. (1998a) introduced a limb activation device (LAD) and used it in a large randomized study comparing limb activation combined with perceptual training to perceptual training alone (Robertson et al., 2002). Nine hours of LAD treatment with perceptual training over nine weeks did not reduce the visual neglect in 17 patients but neither did the perceptual training alone. In addition, passive left finger movements did not reduce the neglect of a patient when the cancellation tasks were performed by simultaneous active right hand movements (Robertson and North, 1993). However, Làdavas et al. (1997) claimed that even passive left finger movements in the left space produced a reduction of neglect, if the contralateral right hand was resting out of sight. Furthermore, amelioration of visual neglect was obtained by large complex passive left arm movements, even when the right hand was actively used in cancellation (Frassinetti et al., 2002). Evidently, not only active, but also passive left arm movements could strengthen the activation of the left personal and peripersonal space enough to result in the modulation of the left extrapersonal visual neglect (Làdavas et al., 1997). Passive movement induced by functional electric stimulation (FES) also reduced visual neglect while doing cancellation tasks (Eskes et al., 2003, Eskes and Butler, 2006). The effects of limb activation on neglect have also been measured distinct from the impact of the activation itself. Samuel et al. (2000) reported a significant and long lasting reduction of visual neglect and neglect behaviour in two patients, one with mild and the other with severe stable neglect. These patients received a substantial amount of voluntary left shoulder activation combined with different therapies and activities of daily living during two fourteen-day rehabilitation periods. Brunila et al. (2002) activated the left arm of their patients in conjunction with twelve hours of traditional perceptual training, whereas Bailey et al. (2002) provided ten hours of arm activation to two patients while they were playing games, doing daily activities and motor tasks. In the above studies, ten to twelve hours of left arm activation produced an improvement in five out of six acute neglect patients. For more detailed information of the arm activation studies see Table 1.

In conclusion, an adequate amount of active or passive left arm activation in the left half space combined with simultaneous visual tasks or while doing daily activities is likely to ameliorate neglect, if the right arm is held immobile. The treatment effects have been documented mostly during the limb activation or immediately after the intervention. The question remains if left arm activation alone, without any traditional visual or other simultaneous functional training, could be sufficient to produce a long lasting amelioration of neglect comparable to the effect obtained with traditional visual scanning training. Visual scanning training has been shown to be effective in ameliorating neglect after 40 hours of training during eight weeks although most of the recovery has taken place dur-

Table 1. Studies of arm or limb activation in rehabilitation of neglect during the years 1991 - 2011

Study	**Type of study**	**N time post stroke**	**Tests for neglect**	**Intervention**	**Control test or group**	**Intensity**	**Follow-up**	**Results**
Robertson, 1991	Experiment	6 2 – 7,5 mps	LCT ACT	Pressing a response key with the left hand aided by the right hand in body midline		12 times 20 reaction blocks , each about 30 minutes		No significant reduction of neglect of left arm or right–arm-aided- left arm reaction to stimuli in the body midline.
Robertson and North, 1992	Series of experiments AB1B2	1 3 mps	BIT C (54/146)	B1: Moving fingers of the left hand for 1 sec every 8 sec while doing the LCT. B2: Anchor to the left arm before starting to cancel	A: Same tests without motor activity	While doing the tests, 10 administrations of each condition		Left finger movements significantly reduced neglect in comparison to the normal perceptual anchoring condition.
	AB3B4			B3: Left finger movement in left hemispace out of sight B4: Left finger movement out of sight in right hemispace.				A significant reduction of neglect in left hand activation in left hemispace even when invisible. No effect of left hand activation in right hemispace. Left hand activation redused neglect significantly.
	AB3B5			B5: Visual cueing before cancellation				Visual cueing had no effect.
	AB3B6			B6: invisible right hand movement in left hemispace while reading.				A significant reduction of neglect in invisible left hand movement in left hemispace compared to no movement condition. No effect in invisible right hand / left hemispace condition.

Study	Type of study	N time post stroke	Tests for neglect	Intervention	Control test or group	Intensity	Follow-up	Results
Robertson and North, 1993	Experiments AB1B2	1 3 mps	BIT C (54/146)	B1: Active invisible left hand movement in left hemispace. B2: Passive invisible left hand movement in left hemispace.	A: Tests without motor activity	While doing the tests (LCT), 10 administrations of each condition		Significant reduction of peripersonal neglect in invisible left hand and leg active movement condition compared to the no movement condition. No effect in passive hand movement condition. The reduction of far space neglect was also significant in invisible left hand movement in left hemispace.
	B3B4			B3: Active invisible left leg movement in left hemispace. B4: Simultaneous stimulation of face with left finger response.				Left hand responses did not reduce extinction of tactile stimuli under double simultaneous stimulation conditions. Single left stimulus detection was significantly poorer under the move condition than under no-move condition.
Làdavas et al., 1997	Experimental group (N+) control group (N-)	20 <1-10 mps 9 1-12 mps	LCT Bells test	Name drawings or objects in the mirror while the index finger of the left or right hand was passively moved, out of sight. Visual cueing before starting the naming was required. Each hand was positioned in the left, centre or right space from body midline.	Same procedures for the control group.	While naming the drawings or objects.		Patients were more accurate in reporting stimuli in the mirror when the left hand was located in the left space. When the patients named objects in the left side of the mirror, they were more accurate when the left stimulated hand was located in the left space. There were no significant effects or interactions in the analysis of the variance in the control group.

Study	Type of study	N time post stroke	Tests for neglect	Intervention	Control test or group	Intensity	Follow-up	Results
Robertson et al., 1998	Case, 18 daily measures	1 trauma 18 mps	Personal neglect: HCT Peripersonal neglect: BTT Far space neglect: Navigation Task	Turn off the "Neglect Alert Device" every 8 seconds		18 days of training during all routine treatments	9 days	Significant improvement in body space, far space and reaching space measures after 18 days of training. Only reaching space improvement was maintained during 9 days of follow-up.
Brown et al., 1999	4 experiments AB1B2	4 1-2 mps	LBT Cancellation Scene copying Clock and flower drawing Reading	B1-left limb movement in left space (LL) B2- right limb movement in left space (RL)	A: Tasks without limb activation	Minutes, while doing the tests		No improvement in scanning or saccadic eye movements in LL or RL conditions, but reduction of errors in reading in both LL and RL methods, even 2,5 minutes prior to reading.
Samuel et al., 2000	Single cases, ABAB 4 weekly measures	1 4 mps 1 7 mps	Bells Test LBT CBS (21and 24/30) (severe neglect + HH)	B: Cued shoulder movement if the patient did not find the target	A: Traditional visual training	A and B each 12 hours	1 month	Significant improvement in LBT after shoulder movement treatment. Positive change in CBS after shoulder movement. Improvements were maintained over 1 month follow-up.
Frassinetti et al., 2001	Several experimental tasks	6 1-5 mps 2 10-30 mps	LCT Bells test LBT Reading Drawing	Left arm complex passive movement by Artomod-E instrument	Baseline test without arm movements	While performing the tests in near space and in far space		A significant reduction of omissions in object naming task in left arm movement as compared to baseline or right arm movement condition. Left arm movement significantly reduced neglect in the LBT. The complex passive movement was strong enough to compete with the activation of the right limb induced by reaching or pointing responses.

Study	Type of study	N time post stroke	Tests for neglect	Intervention	Control test or group	Intensity	Follow-up	Results
Robertson et al. , 2002	Blinded and randomized trial with a control group	40 mean 5 mps	BIT TEA CBS Landmark test Comb and razor test	Limb Activation Treatment (LAT) in left wrist, shoulder or leg + perceptual training (19 patients)	Perceptual Training = lessons from the right brain workbook (21 patients)	12 x 45 min = 9 hours	18-24 months	No significant effects in neglect tests. Only the motor function of the left arm and leg showed a significant treatment effect with LAT. The effect persisted over 18-24 month follow-up.
Brunila et al., 2002	Single cases, weekly measurements	4 2 mps	SCT LCT Line cancellation test LBT Reading Rey Osterrieth figure Two part picture	8 kinds of visuo-spatial tasks with lifting of shoulder every 5 seconds	No control group	12 hours during 3 weeks	3 weeks	3 out of 4 patients showed significant effect in article reading, letter cancellation and Rey Osterrieth figure copying also over the follow-up period. The more movement in the left arm, the better the recovery.
Bailey et al., 2002	Single subject, randomized experimental trial A1BA2	5 19-46 dps 2 13-20 dps	LBT SCT BTT (moderate to severe neglects included)	B: 5 patients visual scanning with visual and verbal cueing, 2 patients left limb activation	A1: first baseline A2: second baseline	10 hours of practice during 4–2 weeks,		Both subjects in left limb activation and 3/5 scanning/cueing subjects demonstrated reduction of neglect ($p<.05$) between baseline and intervention phases in one or more of the 3 tests. No evidence of generalization to non trained tests.

Study	Type of study	N time post stroke	Tests for neglect	Intervention	Control test or group	Intensity	Follow-up	Results
Gainotti et al., 2002	Single subject design, AB1B2	7 7-90 dps	LCT LBT Overlapping figures Copy of a figure (2 mild neglects 3 moderate neglects, 2 severe neglects, all with spared ability to move left hand)	B1:left limb movement in left space, B2:right limb movement in left space	A: neutral condition= cancellation without limb activation	Time required to complete the tests		Left hand movements in left space produced a significant reduction in the severity of neglect in overall number of omissions, in left-sided omissions and in the center of attentional field. Right hand movement in left space had no significant influence on the severity of neglect.
Maddicks et al., 2003	Single case, ABABA-design	1 2 mps	Personal neglect: Beard Trimming Task Peripersonal neglect: Coin Task Far space neglect: Shapes Task on the wall	B: Limb Activation Therapy by left foot	A: No treatment	B: 7 hours	5 days	No significant change in any of the measured neglect assessments.
Eskes and Butler, 2003 and 2006	Experimental design AB1B2	8 1-4 mps 1 13 yps	SNB: Drawing LBT LCT Digit Span	B1: Passive Movement (by FES, 8 patients) B2: Active Movement (turn off the buzzer, 3 patients)	A: No movement condition	6-9 hours of movement treatment		Significant increase in finding left side targets during both FES (6/8 patients) and active movement (1/3 patients) conditions compared to the no movement condition.
O'Neill and McMillan, 2004	Single case, AB-design	1, 2 mps	BIT: Star Cancellation Line Bisection	B: LAT	A: traditional visual treatment by occupational therapist	A and B 12 hours each in 4 weeks	1 month	No effect in Line Bisection test. Significant improvement in Star Cancellation test and total Motoricity Index after LAT. Changes persisted over 1 month follow-up.

Abbreviations: ACT= Albert cancellation test; BIT C= Behavioural Inattention Test, conventional tests; BTT= baking tray task; CBS= Catherine Bergego Scale; dps= days post stroke; FES= functional electrical stimulation; HCT= hair combing task; HH= homonymous hemianopia; LAT= limb activation treatment; LBT= line bisection test; LCT= letter cancellation test; mps= months post stroke; LL= left limb movement in left space; N+= with neglect; N-= without neglect; RL= right limb movement in left space; SCT= Star cancellation test; SNB= Sunnybrook bedside neglect battery; TEA= test of everyday attention; yps= years post stroke.

ing the first weeks of rehabilitation (Pizzamiglio et al., 1992). This raises the question of whether fewer hours of visual scanning training would be sufficient.

1.3. Visual memory and hemispatial neglect

What we cannot see, we cannot remember? Exactly what does a patient with hemispatial neglect see? How much of what a patient sees, is he/she aware of, and how much of what he/she sees and is aware of, can he/she remembers. The concept of perceptual awareness and its relation to working memory has been discussed in the article of Driver and Vuilleumier, (2001). Working memory has become a crucial overlapping function between visual or spatial perception and awareness through the attention modulating function of the right hemisphere prefrontal areas. Recent studies have revealed that patients with neglect display impaired spatial working memory: neglect patients frequently revisit items already visited in visual search tasks as if they had never seen them and cancelled them previously (Husain et al., 2001; Wojiulic et al., 2001). This revisiting behaviour is associated with a dysfunction of the posterior parietal and frontal eye field network in the right hemisphere which causes a deficit in the spatial working memory. Malhotra, Coulthard and Husain (2009) have proposed that the initial deficit in performing spatial tasks might be related to an impairment of spatial working memory in patients with neglect, and that the demand to sustain attention for a longer time (three to four minutes) increases the working memory load, leading to decreased vigilance and poor performance. The deficit in sustaining attention to spatial locations appears to be particularly apparent in patients with right posterior parietal lesions.

According to Ciaramelli et al. (2008), the memory trace in the medial temporal lobe structures may be accessed through direct recognition by a retrieval cue or indirectly through a search strategy mediated by the prefrontal cortex. The direct retrieval technique is based on familiarity as well as the global strength of the memory trace and occurs via the inferior parietal area and its connections to the medial temporal lobe. However, strategic monitoring by the dorsolateral prefrontal cortex is needed to evaluate the relevance of the memory. If the memory is uncertain, a top-down attention network is needed to start the search for cues and to discriminate whether the memory has been accurate or not. In the process of memory retrieval, the dorsal attention network allocates attention to whatever network is needed in the strategy of retrieval. Olson and Berryhill (2009) have claimed that the parietal network is also associated with memory maintenance: if the parietal attention network has been disturbed during the delay period, then memories will be disturbed.

In their model for spatial memory and imagery, Byrne and Becker (2007) discussed the working memory in association with the egocentric system (related to the parts of the body) and the allocentric spatial reference, related to the external world. In this model, the egocentric system is associated with the frontal parietal spatial working memory network and with the short term memory and imagery within a time window of 20 seconds. The allocentric system is associated with the parahippocampal-dependent medium term memory system in a time frame of up to five minutes as well as with the hippocampal-dependent long term memory system (over five minutes). The long term spatial memory involves the generation of allocentric representations in the hippocampus and parahippocampal areas which receive inputs from both dorsal and ventral visual streams. According to this model, representational neglect, the lack of awareness of the contralateral side of internal representations derived from memory, results from a damaged egocentric window into an intact long term spatial memory system (Byrne and Becker, 2007).

Most clinical memory tests include a trial of encoding, a trial of immediate and a trial of delayed recall of stimulus material. The visual reproduction subtest (VR) of the Wechsler Memory Scale Revised (WMS-R, Wechsler, 1987) and its successor the Wechsler Memory Scale III (WMS-III) are the most commonly used clinical test for assessing visual memory. The immediate visual reproduction has been shown to associate with visuospatial problem solving, whereas the delayed recall has a stronger association with other visual memory components (Lezak, 2004). The Rey Osterrieth complex figure test has been considered to be a test of visuospatial, constructional and executive impairments as well as a test of visual memory. The Rey Osterrieth complex figure can be scored separately for the left and right sides and patients with neglect tend to lose and distort more elements from the left of the figure while copying as well as in the delayed recall trial (Rapport et al., 1996). The object memory test was introduced in the study of Lindell et al. (2007) which evaluated several clinical tools for diagnosing hemispatial neglect. In the object memory test, stimuli from the left and right sides are coded separately in trials of naming, immediate recall and delayed recall.

Neglect is known to disturb encoding of visual material and visual working memory. This raises the question about the nature of delayed recall of visual material? Traditionally visual memory tests have not been included in the test batteries proposed for use in the acute diagnosis of the neglect syndrome (Azouvi et al., 2003 and 2006; Lindell et al., 2007). At present there are no comprehensive reports of how patients with neglect perform in traditional visual memory tests which include the trial of encoding as well as the immediate and delayed recall of visual material. This raises several questions; how do patients with neglect differ from comparable healthy subjects in their performances of visual memory tests; does neglect affect immediate and delayed memory performances in different ways; are the visual memories of neglect patients lateralized?

1.4. Alterations in visual and auditory processing in patients with hemispatial neglect

The unilateral neglect and its evolution in time have not been extensively investigated using electrophysiology. In particular, very few investigations have been conducted of both visual and auditory processing in the same patients. Delayed visual evoked potential (VEP) latencies were examined by Angelelli et al. (1996) in stroke subjects with neglect but not in those without neglect. A recent analysis of moving pattern elicited VEPs suggested that the defective stages in neglect occurred early, within 220 ms from stimuli (Di Russo et al., 2008). Correspondingly, the early auditory processing, especially the pre-attentive components, i.e., the N1 and the automatic deviance detection component (mismatch negativity, MMN), has been studied in neglect. Deouell et al. (2000b) reported that MMN had larger amplitude when the stimuli occurred on the right of the subject whereas the left-sided stimuli elicited a smaller amplitude response. A contrary finding with large amplitude MNN for the left sided stimuli has also been reported, though that finding may be explained by the fact that in those subjects in the early acute stage of stroke, the presence of edema may still distort scalp electrical recording (Hämäläinen et al., 1998; Deouell et al., 2000a).

The previous studies are controversial and it is not clear if auditory attention and visuospatial processing are both affected or whether the defects occur pre-attention or during later processing. Brozzoli et al. (2006) as well as others have suggested that the cerebral damage may influence a higher information-processing level which might consequently produce deficits in all sensory modalities.

1.5. Determinants of recovery from hemispatial neglect

Neglect has a negative effect on long-term outcome: these patients take longer to recover and they are left with more functional disability than patients with right hemisphere lesions without neglect (Kalra et al., 1997; Katz, Hatman-Maeir et al., 1999; Jehkonen et al., 2000a; Paolucci et al., 2001). Severe disabilities often lead to a lack of co-operation and inadequate assistance acutely after stroke; dementia and attention deficits increase the probability of late failure in recovery (Musicco et al., 2003). Early admission to rehabilitation clearly decreases long-term adverse outcomes (Musicco et al, 2003; Paolucci et al., 2001). Hemispatial neglect and depression are associated with an increased risk of a poor response on ADL, but not on mobility (Paolucci et al., 2001). Desmond et al. (1996) found that the patients who improved most at one year follow-up were those with larger lesions and a more generalized cognitive impairment at baseline.

Even though sensory impairments are not the cause of neglect, in this syndrome they frequently co-occur with lateralised and nonlateralised spatial deficits (Stone, Halligan and Greenwood, 1993; Vallar, 1993; Husain and Rorden, 2003). Visual field deficits are common in patients with neglect whose lesions reach the occipital cortex, the optic tract or the subcortical geniculo-striate pathway (Cassidy et al., 1999). Patients with only hemianopia learn to compensate for the field loss by eye movements to the blind hemifield, whereas patients with neglect fail to compensate for the deficit because of their inability to orient searching movements of eyes, head and body towards the contralesional side (Müller–Oehring et al., 2003; Doricchi et al., 2005). Curiously, visual fields have not been routinely examined in the studies of rehabilitation of neglect. In a selected sample of 27 such studies which were scrutinized for this study, visual field deficits were reported in only 17 studies (see Table 2). In this sample of 150 patients, there was a rather high incidence of visual field deficits i.e. 62% of patients had impairment.

Primary sensory functions may also be intact and patients may still exhibit neglect of left sided stimuli especially when there are competing stimuli on the ipsilateral side. Extinction, i.e. unawareness of the lateralized stimuli in double simultaneous stimulation situations, is observed in vision, hearing or touch and even between elements in different sensory modalities (Mattingley et al., 1994; Driver and Vuilleumier, 2001; Brozzoli et al., 2006). Neglect and extinction can affect all sensory modalities separately or all of them, as well as the motor domain. Extinction is often present with focal parietal lesions and may or may not be detected with neglect. Both symptoms appear to involve attentional competition between objects in situations with multiple stimuli trying to reach awareness (Driver and Vuilleumier, 2001). For example, tactile extinction or inattention to the contralesional stimulus occurs in a competitive situation, where a patient is simultaneously touched on the contralesional and ipsilesional sides in hands, face or neck, symmetrically or asymmetrically. Brozzoli et al. (2006) reviewed several studies where multisensory stimuli simultaneously and in the same location have enhanced processing of the stimuli; the cross-modal stimulation amplifies the strength of the stimuli to reach the threshold of reaction. However, if areas of multisensory integration are disrupted as occurs in large

Table 2. Documentation of visual field deficits in a sample of rehabilitation studies of hemispatial neglect.

Study	**N**	**VFD+**	**HH / partial**	**% VFD**
Robertson, 1991	6	5		83
Zoccolotti & Judica, 1991	26	not reported		
Pizzamiglio et al., 1992	13	13	11 / 2	100
Robertson et al., 1994	6	4		66
Làdavas et al., 1994	12	9		75
Antonucchi et al., 1995	20	not reported		
Bergego et al., 1997	7	3	3/0	43
Làdavas et al., 1997	10	not reported		
Wiarth et al., 1997	22 +5	4+1	4+1/0	19
Guariglia et al., 1998	9	not reported		
Brown & Walker, 1999	4	2		50
Harvey & Milner, 1999	2	1		50
Samuel et al., 2000	2	2		100
Frassinetti et al., 2001	8	2		25
Rode et al., 2001	2	2		100
Rorden et al., 2001	10	not reported		
Bailey et al., 2002	7	not reported		
Brunila et al., 2002	4	2		50
Frassinetti et al., 2002	13	4		31
Gainotti et al., 2002	7	not reported		
Robertson et al., 2002	36	not reported		
Schindler et al., 2002	20	17		85
Eskes et al., 2003	9	8		89
Bartolomeo et al., 2004	24	not reported		
Schindler & Kerkhoff, 2004	5	4	4 / 0	80
Kerkhoff et al., 2006	10	10		100
∑	299	93/150		62

cerebral lesions, the cross-modal stimulation fails to enhance the process. For example, Frassinetti et al. (2005) described defective integration of sensory stimuli in patients with both neglect and hemianopia, but not in patients with either hemianopia or pure neglect.

Perseveration is often present in the acute phase after the stroke but may remain even longer. Sandson and Albert (1984, 1987) differentiated three distinct types of perseveration in neurological patients: (a) continuous perseveration implied compulsive repetition of a once initiated movement, (b) stuck-in-set perseveration which appeared as an inability to switch strategies, when task requirements changed and (c) recurrent perseveration was depicted as unintentional repetition of a previously emitted response after cessation. The stuck-in-set type of perseveration was found in patients with Parkinson's disease, recurrent perseverations were common in patients with left hemisphere damage and aphasia, whereas continuous perseveration was significantly more frequent in patients with right hemisphere damage.

Anosognosia, unawareness of illness, hemiparesis, hemianopia or neglect, has been found to co-occur with neglect but it is often double-dissociated in such a way that a patient may show unawareness of the illness or the neglect or the hemiparesis though not necessarily all of them (Jehkonen et al., 2000b). Anosognosia for neglect, although often present in the early phases after stroke, was not prolonging discharge to home in the study of Jehkonen et al. (2001).

The pusher syndrome could be classified as one of the productive manifestations of neglect. Pusher symptom, a pathologically strong pushing-like movement with healthy extremities to the ipsilesional side, is often part of the disturbed body balance encountered in patients with neglect (Karnath et al., 2002; Perennou et al., 2002; Danells et al., 2004). Karnath has considered pusher as part of the neglect syndrome and calls it "gravitational neglect". Both pusher and neglect take a longer time to recover when they occur together.

In the present study, we documented the neurological deficits, the amount and quality of rehabilitation and neuropsychological deficits in patients with hemispatial neglect in the course of recovery from their right hemisphere stroke. We were interested in the role of hemianopia, extinction, perseveration, anosognosia, pusher and depression in the process of recovery from neglect. The aim of this study was to search for determinants of excellent or poor recovery from hemispatial neglect during different phases of recovery.

1.6. Aims of the studies

The aims of the studies focused on five separate aspects of hemispatial neglect:

1. The conventional subtests of the Behavioural Inattention Test and the Catherine Bergego Scale were compared in the assessment of hemispatial neglect. The aim was to find out if the test batteries converge and correlate in assessing the severity of neglect in same patients, as there was no such previous comparison. (Study I)

2. The second aim was to determine whether left arm activation alone, without any traditional visual or other simultaneous functional training, would be sufficient to produce a long lasting amelioration of neglect. (Study II)

3. The third aim was to determine how neglect would be reflected in visual memory and how the severity of neglect would be associated with different processes of visual memory. The associations of recovery of neglect and recovery of visual memory functions were also explored. (Study III)

4. The fourth aim was to examine, if patients with hemispatial neglect displayed any processing deficits in both visual and auditory evoked potentials. The changes in evoked potentials in these two modalities were followed up for over six months. (Study IV)

5. The final aim was to search for determinants of recovery from neglect during the different phases of recovery. (Study V)

2. PATIENTS AND METHODS

2.1. Patients and subjects

The inclusion criteria of the study were as follows: patients with first-ever stroke in the right hemisphere were included into the study. Exclusion criteria for the patients were previous traumas or other brain lesions as well as other diseases causing general cognitive decline or lack of co-operation i.e. dementia, aphasia or mental illness. Left hemisphere neglect was excluded to avoid patients with transient neglect entering the study. Left-handed patients with left inattention were excluded because of the possible reorganization of brain functions that could have conferred uncontrolled variation into the pattern of recovery. Each diagnosis of stroke, haemorrhage or infarction, and the lesion location were based on CT or MRI scans and assessed by a radiologist and a neurologist. Healthy controls were identified to match the acute-subacute patients with respect to age, gender and education from volunteers among the personnel of the rehabilitation center or from their friends and relatives.

Forty patients with right hemisphere stroke, with a suspicion of neglect, who entered the Brain Research and Rehabilitation Center Neuron between February 2004 and February 2007, were examined. The initial plan was to gather at least thirty patients. Finally, after three years of searching, it was decided to be satisfied with a minimal of six acute and subacute patients and ten chronic patients. Some subacute patients were transferred from another central hospital after receiving acute rehabilitation, chronic patients came from all over the country. Eighteen patients were excluded for not fulfilling the inclusion criteria: neglect was not severe enough in 13 patients, one subacute patient did not want to risk the ready set rehabilitation programs because of insufficient previous rehabilitation, one patient was diagnosed with progressive general cognitive impairments, one acute patient was too tired to participate in such a demanding rehabilitation program and finally two patients were found to be left handed. Furthermore, one chronic patient, who entered the arm activation training program, dropped out later because of disabling pain symptoms. The patients' characteristics, areas of lesion, motor disability, sensory impairments, visual field deficits, sensory extinction, pusher and perseverative errors as well as handedness scores before the rehabilitation are presented in Table 3.

Neuropsychological, neurological, occupational and physiotherapeutic examinations were carried out within the first three days after entrance into rehabilitation. The

Table 3. Patient characteristics, neurological data and scores of tactile extinction, pusher, perseveration errors and handedness at pre-rehabilitation examination.

	Age	F/M	Education	Post onset months	Areas of lesion	Motor disability	Sensory impairment	VFD	TDSS	Pusher	Persev. errors left / right	EI
1	62	M	Elementary	<1	F,TA,P	Moderate	No	No	1	1.0	0 / 22	89
2	62	M	Elementary	<1	F,TA	Mod.severe	Severe	No	0	6.0		94
3	62	M	Vocational	1	F,P	Mod.severe	Severe	No	0	-	2 / 6	84
4	70	F	Graduated	3	Th	Mod.severe	Mild	No	2	4.75	0 / 0	84
5	56	F	Elementary	3	F,P	Moderate	Moderate	HH	2	2.75	7 / 8	95
6	45	F	College	6	F	Mod.severe	Severe	No	3	-	6 / 2	84
7	62	F	College	<1	F,TA	Mod.severe	Mild	No	1	4.25	7 / 5	78
8	49	F	Elementary	1	F,TA,TP,P	Mod.severe	Moderate	HH	3	1.5	0 / 8	84
9	60	M	Elementary	2	F, TA	Slight	Mild	No	5	2.0	0 / 8	95
10	40	F	Vocational	3	F,TA,P	Mod.severe	Severe	HH	3	2.75	0 / 2	80
11	74	F	Elementary	5	TP, O	Mod.severe	Mild	HH	4	1.0	6 / 3	80
12	61	M	Elementary	5	F, BN	Moderate	No	No	4	-		95
13	54	M	Elementary	12	F,TA	Mod.severe	Moderate	No	0	0	3 / 5	86
14	59	F	Elementary	15	F,TA,P	Moderate	Severe	No	2	-		91
15	56	M	Elementary	48	BN	Moderate	Moderate	No	3	0	6 / 4	83
16	54	F	University	131	F,TA	Moderate	Mild	No	0	0.25	0 / 0	66
17	51	F	College	16	TP,BN	Slight	No	HH	0	0	1 / 0	80
18	58	M	Vocational	16	TP,O,Th	Slight	Moderate	Partial	0	0	2 / 4	82
19	59	M	College	24	F	Moderate	Mild	Partial	0	-	3 / 7	81
20	58	M	Vocational	24	TP	Mod.severe	Severe	HH	0	-	1 / 3	94
21	57	F	Elementary	47	F,TA,BN	Moderate	Mild	No	4	-	0 / 0	100

Abbreviations: F= female, M= male. Areas of lesion were assessed by a neuroradiologist and were based on CT or MRI: F = frontal, TA = temporal anterior, TP = temporal posterior, P = parietal, O = occipital, Th = thalamus, SC = subcortical, BN = basal nuclei. Motor disability was assessed using Modified Rankin Scale. Sensory impairments were assessed by a four step scale by a neurologist. VFD = confrontational assessment of visual field deficits ; HH = homonymous hemianopia. Tactile extinction was measured by the Tactile Double Simultaneous Stimulation test (TDSS) where 0 = severe extinction and 8 = no extinction. Pusher was measured by the SCP which is scored from 0 to 6: the higher the score, the greater the severity of pushing. Perseveration was assessed by the alternating letters motor fluency test. EI = Edinburgh Inventory of handedness, 100 meaning totally right handed.

same examinations were repeated after the three week rehabilitation and at the six month follow-up examinations.

The first five chronic patients received individually planned rehabilitation and the following five chronic patients were allocated to the arm activation training program. The acute and subacute patients were randomized into the arm activation or the visual scanning training procedure. The method of randomization was carried out as follows: A clerk from the ward held out a pair of brown envelopes to the patient as she/he entered the ward. One envelope registered the patient into the AA group and the other envelope contained information about the VS group. The patient picked one of the envelopes and the next patient entering the study was randomized to the other group automatically. This arrangement of paired randomization was necessary to make efficient use of the resources of the ward.

Patients were between 40 and 74 years old (mean 57.6, SD 7.6), ten male and 11 female. The mean age of the patients was 57. Twelve healthy control subjects were matched to acute and subacute patients in terms gender, age and education. There were four male and eight female subjects ranging from 40 to 73 years of age (mean age 59.25; SD 10.27). Seven control subjects had completed elementary school education, two had attended also vocational schools and three subjects had college education. All twenty-one examined patients, numbered 1-21 in the tables, and control subjects volunteered and provided their informed consent. The study was approved by the Ethical Committee of the Kuopio University Hospital and the Central Hospital of North Carelia.

Different patients were included in the studies I-V: Study I included patients 1, 3-6, 8-11, 13,15-21; patients without a score or with a score less than 5 points in the CBS at baseline (in patients whose BIT C score was below 130) were excluded from this study. Acute and subacute patients 1-12 were included in Studies II and III and in the statistical analyses of pusher. All 21 patients were included in Studies IV and V. The control subjects were included in the Study III.

2.2. Methods

2.2.1. Evaluation of hemispatial neglect and criteria of impairment

The conventional subtests of the Behavioural Inattention Test (BIT C) were chosen for the measurement of visual neglect, because this test battery is well documented, frequently used in neglect studies and it is simple to administer and score. Furthermore, it has been verified for Finnish patients (Jehkonen, 2002). Original cut of points were used in this study to make it comparable with other studies. In any rehabilitation study, a behavioural assessment is crucial to evaluate the generalization of the training into everyday situations. In this study, neglect in ADL was observed and evaluated using the Catherine Bergego Scale (CBS) that had previously been documented and described in the literature. The CBS has been developed specifically for patients with neglect and gives a more detailed estimation of neglect in behaviour than overall ADL measurements. Anosognosia score was calculated from the difference between the CBS patient- and CBS occupational therapist-score.

Since the interest was in the expression and amelioration of neglect in different phases after stroke, differentiated inclusion criteria of neglect for acute, subacute and chronic patients were defined. In this study, all acute patients entered the study at least ten days after falling ill, when most of the spontaneous recovery had taken place, and less than three months from the stroke. The subacute phase was considered from three to six months after the stroke to clearly separate this phase from the chronic phase which was set to start from one year after the stroke.

The criteria for acute neglect were set to be rather severe to exclude any transient symptoms and thus hemispatial neglect was defined by the presence of at least two of the following conditions: a score of 100 or less on the BIT C, at least two of the BIT conventional subtests below the cut-off points, or a CBS occupational therapist evaluation score of 10–30 points. The subacute phase criteria resemble the traditional definitions of neglect in rehabilitation studies and the patients had to fulfil at least two of the following criteria: a score of less than 130 points in the BIT C, at least one of the BIT C subtests under the cut-off point, or a CBS score of two points or more. In the chronic phase, when the post onset time was more than one year, the criteria were defined such that even residual neglect or no neglect at all in the BIT C was allowed if neglect in behaviour was present: a score of 140 or less in the BIT C or the CBS score of 5 points or more. The scores of individual patients in the BIT C and CBS at baseline and the changes from the pre-rehabilitation to the post rehabilitation and to the follow-up assessment are shown in Tables 4a and 4b.

2.2.2. Neuropsychological examination

The neuropsychological assessments were conducted by the research neuropsychologist. Another psychologist undertook the rehabilitation of the patients. Handedness was assessed by the Edinburgh Inventory (Oldfield, 1971) at baseline. All other tests were conducted before rehabilitation, at post-rehabilitation and at follow-up, each time in a stand-

Table 4a. Scores of patients with visual neglect assessed by the BIT C before rehabilitation (1) and the changes in the scores to post-rehabilitation (2) and follow-up (3). Beck Depression Invetory Depression scores (BDI) before rehabilitation (1) and at follow-up (3) are included.

	Months post stroke	**Rehab Group**	**BIT C 1**	**BIT C 1-2**	**BIT C 2-3**	**BIT C 1-3**	**BDI 1**	**BDI 3**
1	0	AA	17	42	68	110	7	0
2	0	AA	35	29	49	78	7	7
3	1	AA	108	27	7	34	17	-
4	3	AA	140	2	3	5	3	6
5	3	AA	108	27	-4	23	3	0
6	6	AA	118	16	-6	10	9	18
7	0	VS	96	36	6	42	4	1
8	1	VS	21	57	36	93	-	8
9	2	VS	129	4	6	10	7	7
10	3	VS	37	28	27	55	21	13
11	5	VS	114	1	9	10	17	9
12	5	VS	136	0	4	4	6	6
13	12	AA	137	0	5	5	8	6
14	15	AA	139	3	-1	2	13	11
15	48	AA	127	17	-1	16	2	6
16	131	AA	128	2	4	6	-	-
17	16	Indiv	130	-9	-2	-11	-	-
18	16	Indiv	119	-13	12	-1	7	10
19	24	Indiv	132	6	-4	2	-	20
20	24	Indiv	97	19	-17	2	12	22
21	47	Indiv	125	6	-24	-18	26	16
m(SD)	17.2(29.7)		104	14.3(17.8)	8.4(21.1)	22.7(34.3)		

Abbreviations: Rehab Group= rehabilitation group; AA= arm activation; VS= visual scanning training; Indiv= individually planned rehabilitation program. BIT C= Behavioural Inattention Test, conventional subtests.

Table 4b. Behavioural neglect of patients assessed by the Catherine Bergego Scale (CBS) before rehabilitation (1), at post-rehabilitation (2) and at follow-up (3) and the change in the scores between the three assessments (1-2, 2-3, 1-3). The anosognosia scores (CBS ANO 1,2,3) are included.

	Months post stroke	**Rehab Group**	**CBS OT 1**	**CBS OT 2**	**CBS OT 3**	**CBS OT 1-2**	**CBS OT 2-3**	**CBS OT 1-3**	**CBS ANO 1**	**CBS ANO 2**	**CBS ANO 3**	**BDI 1**	**BDI 3**
1	<1	AA	11	10	0	-1	-10	-11	3	7	0	7	0
2	<1	AA	-	-	5	-	-	-	-	-	3	7	7
3	1	AA	10	2	1	-8	-1	-9	-2	0	-4	17	-
4	3	AA	11	8	6	-3	-2	-5	4	2	0	3	6
5	3	AA	6	4	4	-2	0	-2	4	-	1	3	0
6	6	AA	9	6	5	-3	-1	-4	-1	-3	-1	9	18
7	<1	VS	-	8	5	-	-3	-	-	1	0	4	1
8	1	VS	23	17	12	-6	-5	-11	13	-	9	-	8
9	2	VS	17	12	5	-5	-7	-12	12	11	1	7	7
10	3	VS	11	8	3	-3	-5	-8	-2	-3	2	21	13
11	5	VS	14	8	11	-6	3	-3	-2	-3	3	17	9
12	5	VS	2	1	5	-1	4	3	-3	-5	0	6	6
13	12	AA	5	3	7	-3	5	2	-1	-2	3	8	6
14	15	AA	2	1	0	-1	-1	-2	-2	0	-1	13	11
15	48	AA	1	-	2	-	-	1	-2	-	-1	2	6
16	131	AA	2	2	4	0	2	2	-2	-	0	-	-
17	16	Indiv	13	13	5	0	-8	-8	5	-	-	-	-
18	16	Indiv	17	-	10	-	-	-7	3	-	-	7	10
19	24	Indiv	15	-	13	-	-	-3	12	-	9	-	20
20	24	Indiv	12	-	12	-	-	0	4	-	-	12	22
21	47	Indiv	6	-	6	-	-	0	-	-	-	26	16
Mean(SD)			9.8(6.0)	6.8(4.7)	5.7(3.9)	-3.07(2.5)	-1.9(4.4)	-4.1(4.8)					

Abbreviations: Rehab Group: rehabilitation group. AA= arm activation; VS= visual scanning training; Indiv= individually planned rehabilitation program. CBS OT= Catherine Bergego Scale assessed by an occupational therapist. CBS ANO= the anosognosia score based on the difference between the evaluation of the Catherine Bergego Scale by the patient and the corresponding assessment by the occupational therapist. BDI= Beck Depression Inventory scores.

ard order (see Table 5). The pencil and paper tests were presented in the patient's midline as instructed. Each testing session lasted about 1.5 - 2 hours depending on the patient.

Visual memory was assessed by the visual reproduction subtest (VR) of the WMS-R (Wechsler, 1987), the object memory test (Portin et al., 1995) and the Rey Osterrieth complex figure test (Lezak, 2004). The WMS-R visual reproduction subtest is the precursor of the now most commonly used test of visual memory (WMS-III). The visual reproduction of the WMS-R was administered according to the manual: the patient was asked to draw four previously shown abstract figures, one at a time, from memory immediately after exposure and again after a one hour delay. The immediate memory score was based on the correct units immediately recalled. The delayed score was based on the units recalled 60 minutes later. In the object memory test, presented in the study of Lindell et al. (2007) in patients with neglect, 20 common objects were positioned in an A4-sized box

Table 5. Neuropsychological examination, tests in the order of presentation

	Test
1.	*Wechsler Memory Scale-Revised (WMS-R), visual reproduction (VR)*
2.	*Object Memory test*
3.	*List learning test*
4.	*Rey Osterrieth complex figure*
5.	*Behavioral Inattention Test, conventional subtests (BIT C)*
6.	*Wechsler Adult Intelligence Scale Revised (WAIS-R)*: Digit Span, Picture Completion, Similarities and Block design
7.	*WMS-R vis. reproduction,* delayed recall
8.	*Object Memory test*, delayed recall
9.	*List learning test,* delayed recall
10.	*Rey Osterrieth complex figure,* delayed recall
11.	*The alternating letters motor fluency test*
12.	*The Corsi Block test*
11.	*Tactile Double Simultaneous Stimulation test (TDSS)*

with a cover, with 10 objects on each side. The task was first to name each object. After closing the box, the patient had to draw or write all objects that he/she could recall on the corresponding places of an A4 sheet of paper. The number of objects named or pointed out at encoding and objects recalled from the left and right sides were scored immediately and after a 60-minute delay.

The Rey Osterrieth complex figure is a test of planning, assessing visuo-constructive abilities as well as visuo-spatial memory. The patients had five minutes to copy the Rey figure from the upper part of an A4 sheet of paper to the lower part of the paper set in the patient's midline. After a 60 min delay, the patient was asked to draw the figure from memory. The copied and recalled units were scored according to the manual, and in addition, scores from left and right sides were calculated (Rapport et al., 1996). The Corsi block test (Lezak, 2004) was used to assess the spatial working memory span; two successful trials were demanded for a span. The Corsi block test has been used as a traditional test for visuospatial short term memory in both clinical and experimental research settings (Kessels et al., 2000). It is a spatial analogue to the digit span test as an index of verbal short term memory, but has not been used in patients with neglect to avoid the compounding influence of lateralized inattention on the performance. Right hemisphere patients without neglect performed worse than left hemisphere patients in the standardization study of Kessels et al. (2000) confirming that the Corsi block test can be effectively used for a spatial working memory test. The List Learning Test (Äikiä et al., 2001), a Finnish modification of the Rey Auditory Verbal Learning test, was considered the best alternative to assess verbal learning and recall for reference. This test consisted of the oral presentation of 15 semantically unrelated words, which patients were requested to learn and recall in four consecutive trials. The sum of correctly recalled words in the last trial was scored as the number of learned words on the fourth trial, the number of words recalled after 60 min was scored as the delayed memory score.

Four subtests of the Wechsler Adult Intelligence Scale–Revised (WAIS-R; Wechsler, 1981) were used to evaluate verbal and visual abilities. Digit Span, Picture Completion, Similarities and Block design were conducted according to the manual. The sum of correct answers was calculated in each subtest.

Perseveration was here assessed by the motor learning and fluency test by Luria (Christensen, 1975). The patient had to write the letter S alternating with a mirror image of S for three minutes. The total number of letters, the number of perseveration errors from the left and the right side separately were scored.

Tactile extinction was assessed by the double simultaneous stimulation test (TDSS;

NIH stroke scale). Patients were blindfolded and touched from behind in the area of their head and neck. Four out of eight touches were unilateral and four bilateral stimuli randomly delivered. The bilateral stimuli were delivered in different places on each side. Patients normally identified correctly all unilateral stimuli. If the left-sided stimulus in a bilateral trial was not identified, the score was 0. If the patient identified the left-sided stimulus at the same site with the right sided stimulus, the score was 1. If he/she identified both stimuli correctly, the score was 2 points. Thus severe tactile extinction was defined as 0-1 points, moderate as 2-4 points, mild as 5-7 points and no tactile extinction was defined as 8 points.

2.2.3. Neurological examination and evaluation of functional status and motor functions

An extensive clinical examination was conducted for each patient at some time during the first three days after entering the rehabilitation, after three weeks of rehabilitation and six months after the rehabilitation. Those examinations were conducted by the research neurologist. On admission, patients were given a neurological examination which included the assessment of motor disability using the Modified Rankin Scale (Rankin, 1957) and the confrontational assessment of visual fields. This clinical testing of visual fields has been shown to be nearly as reliable as Goldman kinetic perimetry or visual evoked potentials to contralateral stimuli (Doricchi et al., 1999, 2005). The lesion location was based on CT or MRI and assessed by a neuroradiologist.

General functional status was assessed by nurses on the ward according to the Functional Independence Measure (FIM; Keith et al., 1987) before the rehabilitation and at the follow up assessment. Furthermore, the Beck Depression Inventory was completed before the rehabilitation and at the follow-up assessment.

Motor functions were assessed by a physiotherapist. The Modified Motor Assessment Scale, MMAS (Carr and Shepherd, 1989), was used to estimate the motor recovery of the patients. The eight areas assessed in this test are: from the supine position to side lying, from supine position to sitting on the side of the bed, balanced sitting, from sitting to a standing position, walking, upper arm function, hand movements and advanced hand activities. A physiotherapist evaluated pusher symptoms using the Scale for Contraversive Pushing (SCP) (Karnath, Ferber and Dichgans, 2000). There are three domains assessed for both sitting and standing positions: posture, extension, and resistance. Patients are scored from 0-6 i.e. the higher the score, the greater the severity of pushing. Patients were identified as pushers if they scored >0 on any of the three domains as defined in Danells et al. (2004).

In order to achieve an objective assessment of the changes in the affected hand motor performance, the structured Wolf Motor Function Test, WMFT (Wolf et al., 1989), was used. The WMFT includes 16 timed motor tasks and both the functionality and quality of each movement are scored on a scale 0-5 for each variable. The test includes tasks such as extension of the arm to an indicated line on the table, lifting a pencil from an indicated spot on the table, etc. The WFMT is a well-established test for the assessment of the paretic hand and it provided a sensitive assessment tool also in the present study. One individual conducted the test and the scoring was performed simultaneously by another trained person (not involved in other parts of the study) following published criteria. In addition, the hand-grip force of the affected hand was recorded.

2.2.4. Electrophysiological methods

Twenty one subjects participated in the auditory and visual evoked potential (EP) experiments. Data acquisition and preprocessing were performed with a system manufactured by Electrical Geodesics, Inc., (Eugene, Oregon, USA). Continuous EEG was recorded with a 128-electrode net using Cz as the reference. Only a few channels, different for auditory and visual experiments, and following clinical neurophysiologic convention, were selected for component latency and amplitude analysis. The analysis window was 800 milliseconds from the stimulus onset.

Early auditory processing was studied by eliciting pre-attentive components N1 (N100) and mismatch negativity (MMN). Subjects received 400 standard and deviant tones first separately to the right ear and then to the left ear through earpieces. Standard tones were 1000 Hz (85%, i.e., 340 tones) and deviant tones were 1125 Hz (15%, i.e., 60 frequency deviant tones). The auditory evoked potential (AEP) N1 component peaking usually at about 90 ms and the MMN component at about 210 ms were marked in the individual averaged wave forms. The peak latencies and amplitudes of these components were analyzed separately for the left and right ears for standard and deviant tones and pre- and post rehabilitation and at follow-up in CP3 and CP4 electrode locations for both ipsi- and contralateral responses.

Visual processing was also studied by eliciting pre-attentive components. A plastic curved 1 inch wide bar set with three separate LED lights was placed in front of the subject so that the center light was at 1.5 m distance at the eye level. A total of 400 stimuli were delivered, 340 standard stimuli, 30 bilateral stimuli and 30 unilateral stimuli. Stimuli were delivered separately for the right sided stimulus experiment and then another 400 stimuli for the left sided experiment (each side with its own 30 bilateral stimuli and 30 unilateral stimuli). No voluntary action was required from the subject. From the visual evoked potentials elicited by LED stimuli the major negative deflection were measured. Its peak latencies and amplitudes elicited separately by the right, left, or bilateral stimuli were measured in PO3 and PO4 scalp electrode locations.

2.3. Rehabilitation procedures

Acute and subacute patients were randomized into two rehabilitation procedures: six patients were allocated to the arm activation training (AA) and the other six to the visual scanning training (VS). In addition, four chronic patients received full arm activation training (AA) (one patient interrupted the training) and five other chronic patients received some kind of individually planned rehabilitation (IP) that was designed together with the patient and the multi-professional team to support the aims of the three weeks of rehabilitation. This therapy included either visual scanning or visual memory exercises and/or supportive conversations. The therapies given to the patients before entering the study, therapies they received during the rehabilitation and therapies provided during the six month follow-up period are reported in Table 6. The illnesses of the patients diagnosed before entering the study are also reported in Table 6.

As determined by the individual hand and arm motor status assessed by WMFT, one patient received active arm activation comparable to the constraint-induced movement therapy, CIMT (Miltner et al., 1999). This is a set of rehabilitation techniques where the emphasis is placed on intensive exercise of the affected arm while the movement of the healthy arm is simultaneously restrained with a sling. This CIMT procedure was available in our rehabilitation center at that time of this study and the program was modified to suit the present study by the head of the neurophysiology department. Five patients without sufficient left arm mobility received modified arm activation therapy, which included voluntary shoulder motor training of the left arm in simple push-pull equipment in the left hemispace for about 50% of the training hours with the other 50% consisting of passive arm activation. The passive arm activation included multichannel functional electrical stimulation (FES) induced movement, sensory electrical stimulation of the left hand with a stimulating glove or, specifically in cases of a spastic left arm, stretching exercises aided by the therapist. All exercises were performed by the left arm in the left half space, allowing the right hand to rest on the right side. A study nurse from the CIMT program implemented the arm activation therapies. It has been shown that CIMT effects are ob-

Table 6. Illnesses before the stroke, months post stroke, type of rehabilitation before entering the study, hours of therapies during the rehabilitation and during the six months of follow-up of 21 patients with hemispatial neglect.

	Illnesses diagnosed before stroke	Months post stroke	Rehabilitation before entering the study in weeks	Therapy hours during the three weeks of rehabilitation							Therapy hours during the follow-up		
				AA	VS	PT	OT	Gr	NP	∑	PT	OT	NP
1	Heart bypass surgery	<1	3 in acute neurology ward	21		18	2	9		50	7	0	0
2	Heart bypass surgery, asthma, sleep apnoea, hypertension, hypercholesterolemia	<1	2,5 in acute neurology ward	21		18	0	9		48	29	5	0
3		1	4 in acute neurology ward	21		18	9	6	1	55	85	14	0
4		3	2 in acute neurology ward + 13 in health centre	30		10	5	2		47	36	0	0
5	Hypertension, Hypercholesterolemia	3	11 in multiprofessional stroke unit	30		11	7	0		48	48	0	0
6	Hypothyreosis, hypertension	6	18 in multiprofessional stroke unit + 11 in health center	30		10	6	2		48	48	24	0
7		<1	3 in acute neurology ward		10	18	14	8		50	90	45	5
8	Hypertension	1	7 in acute neurology ward		9	18	9	9		45	50	0	0
9	Type 2 diabetes, Polyneuropathy	2	8,5 in multiprofessional stroke unit		10	18	8	11		47	48	24	0
10		3	6 in acute neurology ward + 8 in health centre		10	18	9	8		45	100	21	8
11	Hypertension,	5	7 in acute neurology		9	18	9	9		45	-	-	-

	heart bypass surgery		ward + 16 in health centre										
12	Hypercholesterolemia, hearth infarction	5	11 in multiprofessional stroke unit		9	16	10	13		48	48	0	0
13	Hearth insufficiency	12	20 in multiprofessional stroke unit + 9 in health centre	30		10	6	4	1	51	48	0	0
14		15	-	20		6	4	3		33	48	24	0
15	Hypertension	48	10 in multiprofessional stroke unit + 2 in health centre	30		3	1	7		41	48	0	0
16		131	Good acute rehabilitation	30		11	5	10		56	48	0	0
17		16	-			7	4	10	5	26	48	0	36
18	Hypertension	16	8 in multiprofessional stroke unit + 12 in health centre			11	7	6	14	38	-	-	-
19	Hypercholesterolemia, type 2 diabetes	24	12 in multiprofessional stroke unit			13	5	7	16	41	72	0	0
20	Hypertension, sleep apnoea	24	-			11	3	-	7	-	26	13	0
21	Hyperlipidemia, type 2 diabetes, osteoporosis	47	4 in acute neurology ward			6	4	0	5	15	48	0	0

Abbreviations: AA= arm activation; VS= visual scanning training; PT = physiotherapy; OT = occupational therapy; Gr = group physiotherapy; NP= individually planned neuropsychological rehabilitation tained after about 50 hours of training in chronic patients (Tarkka et al., 2001). However, the present patients, being in the acute and subacute phase, needed extensive rehabilitation including physiotherapy and occupational therapy and thus the amount of arm activation for these patients was set at 20–30 hours taking into consideration the subjective needs of the individual patients. In the study of Samuel et al. (2000) both visual and behavioural improvements were obtained after only two weeks of arm activation when it was combined with all daily therapies. This finding was a motivation to keep the amount of arm activation hours higher than the numbers of hours of visual scanning training.

The visual scanning training was aimed to correspond to the well documented program first described by Pizzamiglio et al. (1992). The visual scanning program was adapted into a Finnish version maintaining the essential features of the authentic program. In the new version of the program, three different procedures were used at each training session: 1. visual scanning from a 1,5 x 2,2 meter-video screen (iReach rehabilitation program); 2. reading and copying written material and 3. copying drawings from a dot matrix model from the left to a similar matrix on the right. The figure description was omitted because the video screen program was extended to cover several different types of visual materials: pictures, facial expressions, words, and calculations. All materials in the visual scanning program became progressively more demanding and complex, i.e. there were three degrees of difficulty: easy, intermediate and demanding. The iReach program also included the three levels of difficulty with bilateral stimuli. The visual scanning training from the video screen comprised the first half of each one hour training session, the second half of the training session was used either for matrix-copying or reading and copying the written materials. At the beginning of the training, an individual starting level was defined. After a short latency of waiting for the answers, scanning was cued by visual anchors or verbal cueing. Each stage of difficulty was trained for as long as about 75% of the items were being completed correctly, before the patient could advance to the subsequent stage. The authentic visual scanning training was realized at an intensity of one hour five times a week during eight weeks (40 hours total) combined with two daily sessions of physiotherapy (Pizzamiglio et al., 1992 and 2006). The patients received one hour of visual scanning training three or four times a week for three weeks (9-10 hours total) combined with two daily sessions of physiotherapy (60 and 30 min) and one hour of occupational therapy or a one hour group physiotherapy per day five days a week. Again, subjective needs were taken into account when planning individual rehabilitation programs.

2.4. Statistical analyses

In a small population like the one in the present study, it is possible to include a lot of primary data in tables. This may be appreciated by clinicians as well as by researchers. Nearly all statistical parameters and results can be calculated back to the basic data in numerous tables. The data were also described as means, standard deviations and range in the individual articles as well as in the results. Non-parametric test were generally used due to the small number of patients, lack of data normality and non-continuous variables. The proportional severity of visual and behavioural neglect was calculated as a percentage from the maximum severity of each test (Study I). The percentages of recovery from the maximum scores or from the baseline scores were calculated in the unpublished data. In order to clarify the difference in verbal and visual performances in the WAIS-R, percentages of maximum scores were calculated in Table 7. In the same table, also percentages of delayed recall of the immediate visual reproduction or copy were calculated and could be compared with the percentage of the verbal recall (unpublished data). The group differences for gender, educational level, motor disability, sensory impairment, visual field deficits and the number of brain areas in lesion were compared using 2-sided Fisher's exact test (Studies I, II, III). The treatment effects and the persistence of the results were analyzed with the nonparametric Friedman rank analysis of variance (exact test) with the Willcoxon signed ranks test (exact test, 2-tailed) used as a post hoc test to determine whether there were any specific treatment effects from pre- to post-rehabilitation, from post-rehabilitation to follow-up and from pre-rehabilitation to follow-up measurement (Study II). Other group differences were analyzed by the nonparametric Mann-Whitney test using exact significance, 2-tailed (Studies I, II, III). Correlations were analyzed using the non-parametric 2-tailed Spearman's correlation (Studies I, II, III, IV and V). The level of significance was set at $p < 0.05$.

In study IV, the measured EP latencies and amplitudes were compared between pre-post and follow-up conditions within the acute/subacute and chronic groups and group comparisons were made using the general linear model. Hemispheric differences in latencies and amplitudes were compared using paired sample t-test. The relationships between BIT scores and EP latencies and amplitudes were analyzed using the Spearman correlation.

The SPSS for Windows 11.0 and 14.0 were used in the calculations.

3. RESULTS

3.1. Convergence of the BIT C and the CBS in measuring hemispatial neglect (Study I)

In this study, the expression of visual and behavioural neglect in individual patients was examined. Seventeen of our 21 patients had baseline measurements in both the BIT C and the CBS and these patients participated in this study. The patients were 40-74 years old (mean 57 years, SD 8 years) and they were in various stages of recovery after their stroke (mean time from stroke 20 months, SD 32 months). In most cases their lesions were rather large, involving two or more brain areas. Thus most patients had also rather severe motor disabilities and sensory impairments. Eight patients were diagnosed with visual field deficit; most of them had a homonymous hemianopia.

On average, our patients had mild visual neglect in the BIT C and moderate behavioural neglect in the CBS. The correspondence of visual and behavioural neglect was not uniform in individual patients. Even if both types of neglect were present to a rather similar extent in nine of the patients, differences were observed: six patients showed more severe neglect in behaviour than in the visual neglect tests. Furthermore, there were two patients displaying more severe visual neglect than the impairments observed in their behaviour by the occupational therapist in real life situations.

The test batteries were internally coherent. However, the line bisection and figure and shape copy subtests of the BIT were not as consistently and strongly associated with the other conventional subtests of the BIT. Instead, they were strongly linked with the size of the lesion. In the CBS, eating from the left side of the plate was the only item which was not strongly associated with the total score or scores of the other items in our patients. Unfortunately, the items of eating and mouth cleaning from both sides after eating were not observed as often as other items in these patients.

The correlations between the subtest of the BIT C and the items of the CBS were polarized in these two weaker items. The line bisection subtest correlated significantly with four items and the total score of the CBS and the item of eating from the left side of the plate was linked significantly with three out of the six subtests of the BIT C as well as with the total score. The common factor for these items was found in the visual field deficit which was significantly associated with line bisection subtest in the BIT C as well as with the items assessing auditory attention and spatial orientation and the total score of the CBS. Interestingly, gaze orientation, auditory attention and spatial orientation were the three items which had the strongest correlations with the total score of the CBS. In the further analyses, patients with or without visual field deficit were compared. The result confirmed the findings of the correlation analysis: patients with neglect and visual field deficit showed more severe neglect in behaviour (the total score of the CBS), neglected the left space more often while moving in the space and scored significantly worse in the line bisection subtest of the BIT.

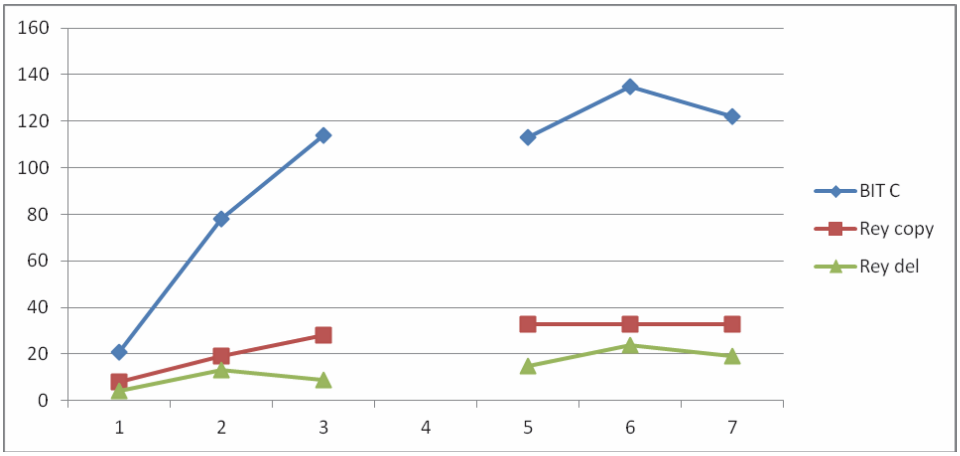
3.2. Amelioration of neglect by arm activation and visual scanning training (Study II)

In Study II, the efficacy of left arm activation alone, without any simultaneous visual scanning training, was examined in the rehabilitation of neglect. Patients were randomized into two rehabilitation groups: Six patients received 20-30 hours of arm activation training (AA) and other six acute-subacute patients received 9-10 hours of visual scanning training (VS, including iReach) for neglect rehabilitation. The specific hours of individual therapies that the patients received during the three weeks of rehabilitation are listed in Table 6. Patients in these two rehabilitation groups were similar in terms of their demographic, neurological and neuropsychological characteristics at the pre-rehabilitation assessment. At baseline, the severity of neglect varied from severe to residual visual neglect. Patients with only residual visual neglect were included if they showed neglect in their behaviour as assessed by an occupational therapist according to the CBS.

At the end of the rehabilitation, both groups had gained significantly in the overall functional independency as measured by the FIM. Visual neglect measured by the BIT C had improved significantly in patients receiving arm activation training already at the post-rehabilitation assessment and the effect remained at the follow-up assessment. In the visual scanning training group, the recovery of visual neglect was almost significant after the rehabilitation achieving statistical significance at the follow-up assessment. Neglect in behaviour alleviated almost significantly by the end of the rehabilitation in both groups, but the result was not preserved as well in the visual scanning group. In addition, the visual scanning group perseverated significantly less in the motor fluency test and copied the Rey Osterrieth complex figure significantly better by the follow-up assessment compared to the baseline. These effects were not seen in the arm activation group.

One of the patients (number 8 in the tables), who first was randomized into the visual scanning training group, after two years was assigned into the arm activation training to explore if more recovery could be achieved through the arm activation program at such a late time after the stroke (i.e. more than two years) (unpublished data). This patient started the visual scanning training program with severe visual neglect (21/146 in the BIT C). After the rehabilitation, neglect was still moderate (78/146) but continued to alleviate so that she scored 114/146 in the BIT C at the follow-up assessment. There had been no change in the BIT C score during the two years between the follow-up assessment and her recruitment into the arm activation program. After the arm activation training, she scored 135/146 in the BIT C, but her progress was not permanent and she regressed to score 121/146 in the BIT C at the two year follow-up assessment (see Figure 1.)

Figure 1. Recovery of visual neglect measured by the BIT C and the performance in the Rey Osterrieth complex figure of a patient who first receieved Visual Scanning training (VS) and Arm Activation training (AA) two years later.



Assessments: 1) 16.2.2005 before the VS training; 2) 9.3.2005 after the rehabilitation; 3) 20.9.2005 at 6 month follow-up; 5) 20.7.2007 before the AA ; 6) 2.3.2007 after the AA and 7) 20.1.2009 at 2 year follow-up.
Abbreviations: BIT C= Behavioural Inattention Test, conventional subtests; Rey copy= the score of the Rey Osterrieth complex figure copy; Rey del= delayed recall of the Rey Osterrieth complex figure.

3.3. Hemispatial neglect reflected on visual memory (Study III)

In study III, the effect of hemispatial neglect on encoding, immediate and delayed recall of visual material was investigated. The visual performances of present patients were markedly compromised as compared with their verbal performances in the subtests of WAIS-R and with the verbal learning test (see Table 7).

Table 7. The sum of raw scores and percentages of maximum raw scores in two verbal (number span, similarities, maximum $\Sigma = 62$) and in two performance subtests (picture completion, block design, maximum $\Sigma = 73$) of the WAIS-R and the scores in the visual and verbal memory tests of the patients with hemispatial neglect before rehabilitation.

Patient number	**Months post stroke**	**WAIS-R verbal Σ (%)**	**WAIS-R performance Σ (%)**	**15 words 4. learning**	**15 words delayed recall (% of immediate)**	**WMS-R, VR immediate**	**WMS-R, VR delayed (% of immediate)**	**Rey copy**	**Rey delayed (% of copy)**
1	<1	34 (55)	0 (0)	8	8 (100)	0	0	1	0 (0)
2	<1	-	-	-	-	-	-	-	-
3	1	37 (60)	15 (21)	7	3 (43)	20	0 (0)	31	4 (13)
4	3	38 (61)	22 (30)	10	3 (30)	16	0 (0)	29	0 (0)
5	3	21 (34)	13 (18)	9	6 (67)	28	0 (0)	17	11 (65)
6	6	41 (66)	29 (40)	10	8 (80)	34	12 (35)	22	6 (27)
7	<1	44 (71)	14 (19)	11	10 (91)	27	13 (48)	7	0 (7)
8	1	40 (65)	14 (19)	8	0 (0)	4	0 (0)	8	4 (50)
9	2	48 (77)	19 (26)	7	2 (29)	33	8 (24)	21	3 (14)
10	3	38 (61)	23 (32)	4	0 (0)	13	0 (0)	9	3 (33)
11	5	13 (21)	10 (14)	11	9 (82)	9	0 (0)	11	0 (0)
12	5	43 (69)	28 (38)	11	6 (55)	36	0 (0)	28	20 (71)
13	12	32 (52)	15 (21)	7	2 (29)	26	0 (0)	9	0 (0)
14	15	35 (56)	22 (30)	7	6 (86)	34	0 (0)	26	12 (46)
15	48	36 (58)	25 (34)	8	0 (0)	25	12 (48)	24	0 (0)
16	131	38 (61)	15 (21)	12	11 (92)	30	5 (17)	32	13 (41)
17	16	37 (60)	25 (34)	7	6 (86)	25	12 (48)	20	9 (45)
18	16	37 (60)	13 (18)	9	8 (89)	12	3 (25)	12	0 (0)
19	24	25 (40)	15 (21)	11	7 (64)	-	-	16	4 (25)
20	24	39 (63)	22 (30)	12	13 (108)	28	21 (75)	25	10 (40)
21	47	40 (65)	14 (19)	8	6 (75)	20	5 (25)	22	0 (0)
Mean(SD)	17.2 (30)	35.8 (8)	17.7 (6)	8.9 (2)	5.7 (4)	22.1 (11)	4.8 (6)	18 (9)	4.9 (6)

Abbreviations: WAIS-R= Wechsler Adult Intelligence Scale Revised; WMS-R= Wechsler Memory Scale Revised; VR= visual reproduction subtest of the WMS-R; Rey copy= the copying of the Rey Osterrieth complex figure; SD= standard deviation.

The correlation analyses revealed that the severity of visual neglect was significantly associated with the encoding phase: naming of objects from the left side or with the copying of the Rey Osterrieth complex figure. In addition, the immediate visual reproduction of the WMS-R was strongly linked with the severity of neglect. However, the delayed visual recall of the patients was not significantly associated with the severity of neglect measured by the BIT C at baseline assessment.

In the second analysis, patients with neglect and matched healthy control subjects were compared in their performances of visual memory tests. Patients and controls were similar in terms of gender, age and education. Healthy controls scored 140-146 in the BIT C whereas the scores of the patients with neglect varied from 17-140, from severe to residual visual neglect at the baseline assessment. Patients named fewer objects and copied fewer details from the Rey Osterrieth complex figure, from both the left and right side. Patients also recalled significantly fewer details from the figures of the WMS-R and less objects from the left side in both immediate and delayed reproduction trials of the object memory test. In the delayed recall trial of the Rey Osterrieth complex figure, healthy controls reproduced both left- and right-sided material significantly better than patients with neglect. Patients tapped a significantly shorter sequence in the Corsi Block test than controls. There was, however, no difference between patients and controls in learning or recalling verbal material or in the immediate or delayed recall of objects from the right side of the stimulus array.

After three weeks of rehabilitation, the delayed visual reproduction of the WMS-R of the patients was no more significantly worse than the reproduction of the controls. Patients named objects from the right side nearly as well as the controls; were able to memorize right-sided objects as well as matched healthy controls in the immediate recall trial and they reproduced objects from the right as well as the control subjects after one hour delay. The delayed recall of the right side of the Rey Osterrieth complex figure had also recovered during the rehabilitation. By the six-month follow-up assessment, neglect had alleviated significantly in the patients: only one of the patients displayed moderate visual neglect, five patients scored mild and six patients showed residual neglect in the BIT C. Patients still scored significantly poorer than the matched controls, however, and they were still impaired in the immediate visual reproduction of the WMS-R. Their immediate recall of objects from the right side and delayed recall of objects from the left side were also significantly reduced as compared with the performances of the control subjects. They continuously copied the Rey Osterrieth complex figure worse from both sides and there was a deficit in the delayed recall which was now lateralized only to the left-sided details. Hemianopia with neglect impaired visual memory performance more than visual neglect alone. At baseline, the difference between patients with or without hemianopia was not significant, but at the end of the rehabilitation, patients with neglect and hemianopia were significantly poorer in the ability to copy the Rey Osterrieth complex figure and in the immediate recall of left-sided objects as compared to patients with neglect alone. At the six month follow-up, this difference had disappeared.

3.4. Alterations of visual and auditory processing in patients with hemispatial neglect (Study IV)

A total of 21 subjects with hemispatial neglect formed two groups, 12 subjects in the acute/subacute group and nine subjects in the chronic group according to the time since the stroke onset. Both groups presented with neglect and impaired functional abilities. At baseline, the severity of neglect, as assessed by the BIT conventional subtests, differed significantly between the groups but no longer at three weeks or the follow-up period of 6 months.

The primary cortical component in the visual pathway, here called the VEP N1 component, was well detected in the occipital scalp area after bilateral LED stimulation and also after unilateral stimulations (right or left visual field). In the acute/subacute group, the left visual field stimuli produced significantly smaller N1 amplitudes in the pre- and post rehabilitation conditions than the bilateral stimuli, but this effect waned by the follow-up. The chronic group did not show significant differences between unilateral and bilateral stimuli. In addition, the right visual field stimulation produced a larger amplitude N1 component at the post rehabilitation time point (three weeks) in the acute/subacute group compared to the chronic group and it was also larger than the N1 elicited by the left visual field stimulation.

In the auditory modality, the N1 and MMN components were elicitable via monaural stimulation in all subjects. N1 component latencies after right or left ear stimulation were within the normal values in both sides in all studied recording times in the acute/subacute group. In the chronic group, N1 latency was significantly longer after the right ear stimulation at the post rehabilitation time point. This hemispheric difference was reflected also in the significant positive correlation of auditory N1 amplitude of the right stimulation (ipsilateral registration) to the change in the BIT C score ($r = 0.76$, significant at the 0.05 level) in the chronic group. This association with the BIT C change was not present with left ear stimulation. In the acute/subacute group, the amplitude of N1 of right ear stimulation compared to the left ear stimulation was significantly smaller only at six months follow-up. By and large, when the right monaural stimulation produced a higher amplitude in the right hemisphere, the BIT C sum score was correspondingly higher at post rehabilitation, i.e., three weeks (r = 0.57, significant at the 0.01 level, all subjects). When the auditory stimuli were analyzed in the contralateral hemisphere to the stimulated ear, the N1 and MNN components were again detected in all subjects. The N1 amplitude was significantly higher in the left hemisphere after right ear stimulation than in the reverse set-up in the acute/subacute group by the follow-up and this kind of tendency was observed already at the three week time point. The chronic group also showed a similar amplitude difference in N1, i.e., higher amplitude in the left hemisphere after the right ear stimulation.

The alterations in the auditory system due to neglect could be observed in the complexity of MMN generation in acute/subacute subjects: the left monaural stimulation elicited the normal N1 component but the generation of MMN was nonexistent in left centroparietal channels (Figure 2 in the original article). Rather unexpectedly, when the monaural stimulation came from the right, both N1 and MMN were distinctively normally generated in the same left centroparietal area in the same subjects.

3.5. Determinants of recovery from hemispatial neglect (Study V)

The mean recovery of our 21 patients in the BIT C from pre-rehabilitation to follow-up was 15% (22.7, SD 34.3) of the maximum score of the BIT C. More than 60% of the recovery had been achieved at the end of rehabilitation. Seven patients showed a remarkable improvement in their visual neglect (>20 points), most patients gained 10-20 points but three patients deteriorated from the pre-rehabilitation to the follow-up assessment (see Table 4a). Neglect in behaviour observed by the CBS was markedly reduced in three patients (decrease > 10 points) and here also, most of the recovery was detected already at the post-rehabilitation assessment (75%). Five patients failed to improve (see Table 4b).

When recovery of visual neglect during the rehabilitation was analyzed, more recovery in visual neglect was associated with less time from stroke, severe motor impairments and severe neglect at the pre-rehabilitation assessment (see Table 8). Pusher symptoms at pre-rehabilitation were linked with less satisfactory improvement in visual neglect during the rehabilitation.

As expected, the total amount of improvement in the BIT C from the pre-rehabilitation to the follow-up assessment was associated with the amount of previous multi-pro-

Table 8. Significant correlations between recovery of visual neglect measured by the BIT C and behavioural neglect assessed by the CBS to other variables assessed in the study.

	Recovery of visual neglect									Recovery of behavioural neglect								
	BIT C 1-2 [1]			BIT C 2-3 [2]			BIT C 1-3 [1]			CBS OT 1-2 [1]			CBS OT 2-3 [2]			CBS OT 1-3 [1]		
Significantly correlating variables	cc	p	n	cc	p	n	cc	p	n	cc	p	n	cc	p	n	cc	p	n
Months from stroke	-.59	.01	21	-.67	.00	21	-.75	.00	21	.64	.01	14				.69	.00	19
Motor impairment	.45	.05	20				.49	.03	20	-.64	.01	14						
MMAS total							-.48	.04	19	.76	.00	13						
SCP total	.61	.03	13															
WMFT, functional scale total										.54	.04	14						
FIM total							-.53	.02	18	.72	.00	14						
BIT C total	-.80	.00	21	-.57	.01	21	-.71	.00	21									
CBS OT total										-.57	.03	14	-.54	.04	15	-.72	.00	19
CBS patient total										-.62	.02	14						
CBS anosognosia score													-.70	.02	11	-.46	.05	19
WMS-R, VR immediate																.51	.03	18
Rey Osterrieth complex figure,copy				-.54	.02	20												
Rey Osterrieth complex figure, delayed recall										.59	.03	14						
Corsi Block span	-.68	.00	20				-.56	.01	20									
15 words, delayed recall										.59	.03	14						
WAIS-R, number span													-.66	.01	15	-.46	.05	19
Perseverations in the motor fluency test							.55	.02	20									
Hours of therapy during rehabilitation							.53	.02	20									
Previous multiprofessional rehabilitation				-.62	.02	14							.64	.03	12	.63	.03	12

[1]= recovery is correlated with the baseline assessment, [2]= recovery is correlated with the post-rehabilitation assessment.

fessional rehabilitation i.e. those subacute patients who had received intensive multiprofessional rehabilitation before entering the study improved less than those who received the comprehensive rehabilitation only during this present study. Good recovery in visual neglect from pre-rehabilitation to follow-up was also associated with the intensity of the rehabilitation. Patients who scored lower overall functional independency measured by the FIM and who made more perseveration errors in the motor fluency test at pre-rehabilitation recovered more. Chronic patients who had already received comprehensive acute and subacute rehabilitation and now were provided with the individually planned (i.e. not so intensive) rehabilitation, improved least, as expected.

The amount of amelioration in behavioural neglect during the rehabilitation was significantly associated with the time from stroke: improvement was better in the acute phase after the stroke. Patients with better functional independence, minor motor impairment and better functioning of the affected arm showed less recovery. The behavioural neglect of patients with good delayed memory performances in the verbal learning task and in the Rey Osterrieth complex figure tests recovered less during the rehabilitation.

The more severe the behavioural neglect was at pre-rehabilitation, the more opportunities there were to improve this symptom by the follow-up assessment. A better number span of the WAIS-R and good immediate visual recall were also linked with good recovery. The anosognosia of neglect in everyday situations calculated from the CBS at pre-rehabilitation seemed to be significantly associated with more alleviation of neglect in behaviour. The severity of visual neglect in the BIT C was not, however, significantly associated with the observed recovery in behavioural neglect.

Hemianopia was significantly associated with a larger lesion size ($r = .479$, $p = .028$, $n = 21$) and with the severity of tactile extinction in these patients ($r = -.461$, $p = .036$, $n = 21$). At the pre-rehabilitation assessment, visual field deficits were linked with the severity of neglect in the CBS ($r = .630$, $p = .004$, $n = 19$). At the six month follow-up assessment, the visual field deficit was associated with the severity of behavioural neglect ($r = .511$, $p = .018$, $n = 21$), with the CBS anosognosia score ($r = .690$, $p = .001$, $n = 19$) and also with the severity of visual neglect in the BIT C ($r = -.531$, $p = .013$, $n = 21$).

Tactile extinction was assessed in all 21 patients by the tactile double simultaneous stimulation (TDSS) test before and after the rehabilitation and at six months. At pre-rehabilitation, ten patients showed severe tactile extinction, ten moderate and one patient displayed only mild extinction in the TDSS. Eleven patients had failed to recover by the follow-up assessment. The TDSS scores were very stable from one assessment to the next (the Spearman correlation coefficient from measurement 1 to 2 was .642, $p = .002$ and from measurement 1 to 3, r = .669, p = .001). In acute-subacute patient group, extinction was more severe in the patients who had more recently suffered their stroke (r = .673, p = .016). The amount of recovery of tactile extinction after treatment was associated with fewer lesioned brain areas (r = -.459, p = .036, n = 21). At the follow-up assessment, the failure of amelioration in extinction was associated with parietal lesions (r = -.454, p = .039, n = 21). The severity of extinction was not associated with the overall recovery of neglect.

Pusher symptom was examined in 14/21 patients at pre-rehabilitation. All patients in acute and subacute phase after stroke displayed pusher at pre-rehabilitation: three patients showed severe, two had moderate and four patients displayed mild pusher (see Table 1). At the first measurement, pusher was significantly associated with a low score in the functional independence measure FIM (r = -.671, p = .012, n = 13). Pusher symptoms were especially disruptive in washing, dressing and in toilet functions. Pusher was also linked with low motor functioning in the MMAS test (r = -.787, p = .012, n = 9) and with better line bisection score in the BIT C (r = .795, p = .010, n = 9). Pusher had alleviated in most patients by the follow-up assessment.

Thirty five percent of the patients reported depression in the BDI at pre-rehabilitation. Two patients reported moderate and four patients described mild depression. At that point, depression was significantly associated with larger lesions (r = .576, p=.016). In addition, patients who evaluated that they were experiencing more neglect in ADL in the CBS patient score at pre-rehabilitation, reported more depressive symptoms (r = .688, p = .003). Two patients reported recovery from depression and in three patients, depression had become more severe. At the follow-up measurement, depression was significantly associated with more severe visual neglect (r = -.497, p = .036), especially in chronic patients (r = .550, p = .018). In contrast, good verbal reasoning in the WAIS similarities subtest was linked with less signs of depression (r = .522, p = .021).

4. DISCUSSION

4.1. Convergence of the BIT C and the CBS in assessment of hemispatial neglect

The purpose of this study was to attend to those aspects of the syndrome of hemispatial neglect that are crucially important in clinical neuropsychological practice. The first of these aspects is diagnosing neglect not only in easily conducted paper and pencil tests but also in everyday behaviour. Since 1988, there has been a well documented test battery for diagnosing visual neglect, the conventional subtests of the Behavioural Inattention Test. In this test battery, behaviour is observed by the BIT B, but this is done in an office manner sitting by the table, not in real-life situations. The methods for observing neglect in real life situations were neither coherent nor specifically directed to observing neglect before the Catherine Bergego Scale was developed. Surprisingly, these two methods, the BIT C and the CBS had not been performed in the same group of patients and consistently compared. In Study I, 17 neglect patients were assessed with the BIT C and the CBS. The analyses showed that these tests were rather congruent in determining the severity of neglect as in the studies of Azouvi et al. (2002, 2003). However, hemianopia combined with neglect was significantly associated with inadequate judgement in the line bisection subtest and with more severe neglect observed in the behaviour of patients. Neglect hampers the compensation of hemianopia by searching eye movements to the contralateral field and thus neglect in patients with hemianopia is evident for longer in ADL than in the narrow space of paper and pencil tasks.

The clinical testing of visual fields by confrontation with fixation point has been shown to be nearly as reliable as Goldman kinetic perimetry or visual evoked potentials to contralateral stimuli (Doricchi et al., 1999 and 2005). The clinical testing of visual fields is easy to conduct and is done routinely in neurological examinations, although visual field deficits are not always documented in neglect rehabilitation studies.

Already Doricchi and Angelelli (1999) found that hemianopia with neglect caused worsening of neglect in the line bisection task but not in cancellation tests. Patients with hemianopia habitually misplace the midpoint towards the blind visual field as if to compensate for the loss, whereas patients with pure neglect bisect lines towards the side of the lesion (Barton and Black, 1998; Kerkhoff et al., 2008). Patients with both neglect and hemianopia show the most severe rightward shift in their judgements of midpoints (Bartolomeo et al., 2003; Doricchi et al., 2005). Azouvi et al. (2002) reported an association between line bisection error and neglect observed in behaviour. These findings were confirmed in the present study. Müller-Oehring et al. (2003) have proposed that patients with neglect and hemianopia do not learn to compensate for the visual field deficit with eye movements and in this respect differ from patients with only hemianopia. Even if neglect patients could resist and overcome the magnetic attraction to the right space in their eye and head movements, the visual field deficit would demand them to exaggerate the leftward move as they attempt to perceive to the left side properly. Schindler and Kerkhoff (2004) reported a differentiated rehabilitation effect in neglect patients with or without hemianopia: the neck vibration method alleviated allocentric neglect in patients without hemianopia. This raises the question if the prism adaptation method would work in patients with neglect and hemianopia to help them in overcompensating for the blind field?

The item of eating from the left side of the plate was the only item of the CBS to significantly associate with the subtests of the BIT C. Unfortunately, it was observed in only eight of our patients and thus the significant association with cancellation subtests of the BIT C remains speculative. One could postulate that the eating item from the CBS could represent the visual neglect observed in the traditional cancellation tests.

4.2. Amelioration of hemispatial neglect by arm activation and visual scanning training

The visual scanning method was the first comprehensive program for training hemispatial inattention. Patients were taught to orient voluntarily to the neglected hemispace in several different types of tasks. The program was effective, but forty hours of training is not cost effective nor is it frequently available. Furthermore, trying to convince patients to observe the naturally neglected side is tiring, frustrating and unrewarding for both the patient and the therapist. The visual scanning training in our study was planned to resemble the original program in its essential features, only the length of the program was shorter. The number of hours of therapy was set to nine or ten hours in three weeks instead of forty hours in eight weeks to examine if less hours would be sufficient for promoting the recovery of neglect. Indeed, any method of neglect training that would work involuntarily would be welcomed in clinical neuropsychological practice. Arm activation methods were processed through a series of detailed case studies and they have been proven to be effective in many trials. Furthermore, constrained-induced movement therapy (CIMT) was developed for intensive training of the affected arm for patients who were expected to show at least minimal movement in their wrist to be able to participate in the exercises. In this study, the concepts of CIMT and arm activation training were combined for the rehabilitation of neglect. In the trial, patients with all kinds of arm mobilities were included, i.e. those who were totally hemiparetic or with some movement in the hand. The CIMT program is a very intensive program of fifty hours or more of exercises and as such is not convenient for comprehensive acute rehabilitation. The CIMT program was here modified to make it more suitable for acute and subacute patients so that they also could attend the necessary physio- and occupational therapies during the three weeks of rehabilitation. For those reasons, the number of arm activation hours in Study II was differentially set to twenty hours for acute patients with lower functional capacity and to thirty hours for those more advanced patients who no more required intensive physio- or occupational therapy. The three aims were to determine 1) whether arm activation would ameliorate neglect alone without visuospatial practice, 2) whether twenty to thirty hours of arm activation would suffice to ameliorate neglect and have some positive effect on the affected arm as well, and 3) whether only nine or ten hours of visual scanning training would be enough to alleviate neglect. Both training methods alleviated neglect significantly or almost significantly in this rather short time. The effect was also observed in everyday life situations, if not as strongly as seen in the paper and pencil tasks. Unfortunately, totally hemiparetic arms did not recover. Nonetheless, the modified CIMT could be successfully used as a rehabilitation program for neglect.

The left arm activation in the left hemispace, active or passive, has been demonstrated to be effective while doing visual tasks (Robertson and North, 1992 and 1993, Làdavas et al., 1997, Brown et al., 1999, Gainotti et al., 2002, Frassinetti et al., 2002). A reduction of visual neglect has also been reported, when the left limb activation has been combined with visual training or everyday tasks (Bailey et al., 2002, Brunila et al., 2002). In the present study, the neglect of arm activation group patients recovered after twenty to thirty hours of active and/or passive left arm activation without any other simultaneous visual training or activity. Furthermore, the effect generalized almost significantly to ADL as assessed by the CBS. Samuel et al. (2000) reported a similar finding in terms of the recovery of both visual and behavioural neglect after a substantial amount of left arm activation in two patients. Previously, Robertson et al. (2002) described an improvement in the motor function alone without any improvement in the visual or behavioural neglect after left arm activation training. However, their patients were more chronic and had milder neglect. Furthermore, their patients received only one third of the arm activation hours compared with the present study.

The time from stroke, the number of hours of physiotherapy and the number of hours of arm activation training were all associated with the amount of recovery in visual neglect in the AA-group. They were also associated with each other in such a way that the more acute patients received more physiotherapy and less arm activation training and recovered more than those patients, who received less physiotherapy and more hours of arm activation and were 3–6 months from stroke. It would have been helpful to standardize the amount of arm activation as the same for all patients in this group to make them comparable.

All patients in the AA- group had sufficient voluntary movement in the shoulder to perform the activation with the push-pull equipment. Three of the six arm activation patients scored 0/80 points in the WMFT at the pre- rehabilitation assessment. Those three patients with some functional movement in the left arm were the only individuals to improve in their arm function due to the activation. The improvement was evident already at the post-rehabilitation assessment and persisted till the follow up. Brunila et al. (2002) considered that the recovery of the visual neglect was better in the patients with better left arm function, but we could not fully confirm that finding in the present study.

Pizzamiglio et al. (1992) found that their 40 hours of visual scanning training was effective in a group of stroke patients with stable severe visual neglect. The intensity of their program included therapy for five hours a week for eight consecutive weeks. Their patients typically showed a rapid improvement during the first week in all four training procedures. Here the significant amelioration of visual neglect was observed after three weeks of rehabilitation in the acute and subacute patients with mild to severe visual neglect. The patients received nine or ten hours of visual scanning training and additional occupational therapy, individual and group physiotherapy for rehabilitation with a total of 47 hours of different therapies, whereas Pizzamiglio et al. (2006) reported two daily sessions of physiotherapy without any mention of training in ADL. With respect to the alleviation of behavioural neglect, this present training effect was only almost significant at the post-rehabilitation assessment. In the CBS assessment, only four of the visual scanning training patients exhibited an improvement with one patient declining in all three personal or body space neglect functions from the pre-treatment to the follow-up measurement in the CBS scores. This failure was not due to any simultaneous change in the sensory functions or depression scores in this patient. When combining the results of all 12 patients in the present study, irrespective of which specific method was used, the training effect in the BIT C was statistically significant and the recovery in the CBS score also was significant both at the pre- and post-rehabilitation assessment and at the follow-up. The visual scanning training may have had a slightly more extensive effect on cognitive functions than the arm activation procedure because those patients showed a significant improvement also in the construction of the Rey Osterrieth complex figure and a significant decrease in the numbers of perseveration errors in the motor learning test at the follow-up measurement.

4.3. Hemispatial neglect reflected on visual memory

The question of how exactly hemispatial neglect impairs visual memory is still largely unanswered. Lateralized tests of visual memory offer a possibility to observe the effects of neglect on memory performances at different latencies. In Study III, the severity of neglect was significantly associated with the encoding phase of the visual memory tasks, such as naming of objects or copying a complex figure. The patients with neglect copied and named fewer details from both the left and, to a lesser degree, from the right side of the materials as compared to their matched healthy control subjects. The present findings agree with the previous observations of Rapport et al. (1996) and He et al. (2007). The spatial working memory deficit occurring in revisiting or re-cancellation behaviour (Malhotra et al., 2004) covers the time window up to 40 saccades. In the test battery used here, this time window would cover all cancelation tasks of the BIT C, the naming of the 20 objects, the Corsi block span, the copying of the figures in the BIT C and the Rey Osterrieth complex figure. The patients performed significantly worse in all these tests compared with healthy matched controls and could be interpreted as displaying a spatial working memory deficit. Neglect ameliorated in the present patients after rehabilitation but did not normalize compared to the healthy control subjects. A spatial working memory deficit over saccades combined with the perceptual bias was still evident in the cancellation tasks as well as in the copying of the Rey Osterrieth complex figure, confirming the results of Husain et al. (2001) and Malhotra et al. (2004). Even after amelioration of neglect, the patients were impaired in their visual search at encoding and in copying, whereas the immediate visual reproduction had improved in the lateralized tests.

Before rehabilitation patients showed impaired immediate recall of visual material and this deficit was lateralized predominantly to the left space of the stimulus arrays. The time window in the tasks of immediate reproduction lasted from seconds up to five minutes, corresponding to the medium-term dependent memory system as in the model of Byrne and Becker (2007) and the deficit could be associated with the distractions in memory maintenance during the delay period (Olson and Berryhill, 2009). The immediate recall of objects from the left side alleviated after the rehabilitation, but at the same time the patients omitted more items from the right side, suggesting that their overall capacity of visual working memory was still defective (He et al., 2007; Malhotra, Coulthard and Husain, 2009).

The deficit in delayed recall of visual material from the left side remained as compared to the performances of the healthy control subjects even after the amelioration of neglect. The finding suggests that the patients suffered either from a defective strategy to search from the long-term memory storage (Ciaramelli, Grady and Moscovitch, 2008) or that they displayed a representational neglect in the sense of lacking an awareness of the left side of their internal representations derived from memory (Byrne and Becker, 2007).

Different stages of attention and memory processes are encompassed in the broad range of clinical visual memory tests. Trials of encoding, recognition, immediate and delayed recall can be contemplated in the light of the previous theories of attention and memory in patients with neglect. Each separate trial may include more than one stage of attention or memory process which makes the analysis only a kind of crude estimate compared to the data obtained in experimental research settings. If one considers of the processes encompassed in the test performances, even the first phases such as perceptual search and copying require some type of spatial working memory that involves retention of locations over saccades. Immediate reproduction of figures demands nonlateralized attention capacity in addition to intact saccadic spatial working memory. Delayed recall again requires the individual to make a match helped by a cue or requires a search for relevant material from long-term memory storage. In the case of representational neglect, the search may succeed but the left side of the recollected memory still fails to open. Scoring both sides of visual memory tests definitively provides additional information when patients with neglect need to be evaluated.

This research on visual memory in patients with hemispatial neglect sheds new light on the role of attention in the processes of memory. Unfortunately, the test battery used here did not include a test of visual recognition described by Bisiach et al. (1999), where the familiarity effect studied by D'Ermè and Bartolomeo (1997) would have been most evident. A control group of patients with left homonymous hemianopia without neglect would have been helpful. Patients with both hemianopia and neglect scored worse in nearly all test items of visual memory, even if most of the differences were not statistically significant. The possible effect of motor neglect will need to be controlled in future studies as the retrieval trials of most visual memory tests demand a motor response and.

4.4. Alterations in visual and auditory processing in patients with hemispatial neglect

Neglect can be detected in auditory as well as visual processing and this was explored in Study IV by evoked potentials. Both sensory modalities revealed differences between hemispheres in processing stimuli coming from a unilateral source. Amplitudes of visual and auditory evoked potential components elicited by the left sided stimuli were smaller compared to those elicited by the right-sided stimuli in the acute/subacute group. The main hemispheric differences diminished by the follow-up assessment along with the decreasing severity of neglect in the acute/subacute group.

Neglect research has currently emphasized that the changes in the inter-regional influences, between remote parts of the brain network, likely contribute to neglect and the normal influences are disturbed by the right hemisphere lesion (Corbetta et al., 2005) and as also Brozzolli et al. (2006) pointed out, all sensory modalities may be affected.

Study IV assessed both auditory and visual evoked potentials in these adult subjects with hemispatial neglect in the acute/subacute or chronic phase after right hemisphere cerebrovascular infarction. In these subjects, both sensory modalities revealed hemispheric differences in processing stimuli emitted from a unilateral source. The hemispheric differences were present but not similar in the present groups indicating that the time since stroke plays an important role in the sensory processing in subjects with neglect. This was the case even when the subjects with recent strokes were not markedly acute (mean 3 months post stroke). The explanation for the hemispheric differences observed in the N1 amplitudes in the subjects may be that the previous suggested contralesional hyper excitability contributes to these amplitudes. In fact, the mean N1 amplitudes seemed to be reduced almost throughout on the right hemisphere, though not significantly. In neglect syndrome, the left hemisphere appears to make a major contribution to discriminating the deviant stimulus. Since MMN measures the function of the pre-attentive mechanism of orientation and attention, the data suggests that the automatic orientation and deviant detection are impaired in the right hemisphere.

4.5. Determinants of recovery from hemispatial neglect

Determinants of recovery in neglect were searched in Study V by associating the total amount of recovery in the BIT C and in the CBS from pre-rehabilitation to post-rehabilitation and follow-up assessment with background variables, rehabilitation received and other test variables. Patients who were less time from stroke, with lower functional capacity and with more severe neglect at pre-rehabilitation recovered to the greatest extent as in previous studies (Paoluzzi et al., 1998, Buxbaum et al., 2004). Also early admission to rehabilitation increased the likelihood for better outcome (Musicco et al., 2003; Ringman et al., 2004). Significant recovery in visual neglect is possible at 3-6 months or even later after stroke, especially in patients with severe neglect and who have received insufficient acute rehabilitation. Subacute or chronic patients who had received intensive acute rehabilitation in a multi-professional stroke unit previously showed less progression now.

The patients who recovered most had lesions covering several brain areas and would thus correspond to the persistent neglect described in previous studies (Samuelsson et al, 1997; Maguire and Ogden, 2002; Musicco et al., 2003). In this study, a larger lesion size in chronic patients with mild or residual visual neglect was associated with poor recovery, whereas sufficient rehabilitation provided soon after the stroke was able to induce a significant improvement in patients with large lesions and more severe visual neglect.

The severity of visual neglect was not significantly associated with the amelioration of behavioural neglect and vice versa. In contrast, a more general cognitive impairment in the form of decreased delayed memory power and limited attention span was associated with less recovery in neglect observed in behaviour as in the study of Musicco et al. (2003). In the present data, all patients with only residual or subclinical visual neglect still displayed mild or even moderate behavioural neglect and 50% of the patients with mild visual neglect still had moderate behavioural neglect as assessed by the CBS at pre-rehabilitation (for detailed results, see Luukkainen-Markkula et al., 2011). As in the findings of Jehkonen et al. (2000a) and Azouvi et al. (2003), hemispatial neglect was evident in ADL for longer than it could be detected in the conventional paper and pencil neglect tests. In the present study this was especially true in patients with neglect and hemianopia (Luukkainen-Markkula et al., 2011).

Extinction has long been considered as a residual form of spatial neglect (Brozzoli et al., 2006) and this was why the tactile extinction test was also included in this study. Even though neglect appears without extinction and vice versa, tactile extinction was present in most of the acute-subacute patients in this study. It remained quite stable over the followed time course and was not significantly associated with the recovery of neglect in these patients, which confirms the belief that there are different mechanisms behind these two disorders (Brozzoli et al., 2006; Kerkhoff and Rosetti, 2006). Extinction and neglect may share the same cross modal disintegration reported in Frassinetti et al. (2005) who found defective integration of sensory stimuli in patients with both neglect and hemianopia, but not in patients with either hemianopia or pure neglect.

Anosognosia of neglect, calculated from the patients report and from the evaluation of an occupational therapist in the CBS, was associated with less recovery in behavioural neglect from post-rehabilitation to the follow-up. Unfortunately anosognosia of hemianopia was not assessed as behavioural neglect and hemianopia were closely associated after the acute phase.

All of the present acute or subacute patients displayed some degree of pusher at the pre-rehabilitation measurement and pusher hampered the recovery of visual neglect during the rehabilitation period as. Pusher alleviated in most patients by the six month follow-up measurement. These results confirm the close connection between neglect and pusher acutely after right hemisphere stroke (Karnath et al., 2002; Perennou et al., 2002; Danells et al., 2004).

Depression did not prevent recovery in acute or subacute phase after stroke, but depressed chronic patients did not recover as well as those with less depressive symptoms. In some individual patients the symptoms of neglect became more pronounced with depression. Paolucci et al. (2001) showed that the presence of hemispatial neglect and depression at baseline were associated with an increased risk of low response on ADL. In the present patients, depression was associated with more functional losses and less recovery in visual neglect, but there was no association between the recovery of behavioural neglect and depression. Furthermore no correlation was detected between depression and FIM scores or depression and recovery in FIM scores.

4.6. Critical remarks

There are restrictions and shortcomings in this study that should be considered and borne in mind before drawing any conclusions. The patient sample is small and causes restrictions in the generalisation of results. Information of previous illnesses and rehabilitations were collected and included to increase insight to what kind of patients these results can be generalized. Two patients had suffered an intracerebral haemorrhage, one patient had a subaracnoidal haemorrhage and in 18 patients the lesion was ischemic. Thus the results are valid for ischemic etiology and not for the haemorrhagic etiologies.

The initial plan was to recruit ten acute, ten subacute and ten chronic patients, but after four years of acquisition of patients it was ultimately decided to settle for six acute and six subacute patients. There were enough of chronic patients but recruiting acute and subacute patients was not easy. Only acute and subacute patients were properly randomized into two different rehabilitation groups. Chronic patients, who already had received previous visual scanning type of rehabilitation, should all have been included into the arm activation group. However, because of the time constraint, first five chronic patients were taken in for the individually planned program before the arm activation program was devised. The patients ended up receiving the conventional individually planned therapy and thus served as a control group for those chronic patients, who received an extended number of hours of rehabilitation in arm activation training procedure. Theoretically it would have been ideal to create a control group of patients who did not receive comprehensive stroke unit rehabilitation, but this arrangement would have been unethical in the Finnish health care system i.e. for the patients to be assessed and diagnosed without any further treatment. To conclude, patients were selected of the population of stroke patients who were sent into our rehabilitation center during three consecutive years. The excluded patients did not distort the population of the study in any significant way. Complete blinding of patients' allocation to rehabilitation groups from the research neuropsychologist was not possible in the clinical rehabilitation ward arrangement. The research neuropsychologist did not participate in the rehabilitation of the patients and this was imperative in order to add reliability to this study. A matched control group was ultimately gathered for Study III.

Patients without a baseline score in the CBS were excluded from study I. Only acute and subacute patients were included in studies II and III, because they formed a properly randomized coherent group of patients.

The difference in the number of hours of visual scanning training and arm activation is problematic. The significance of more hours of occupational therapy in the visual scanning training remains unknown. However, the aim of the rehabilitation study was to find out if ten hours of visual scanning training would be sufficient to ameliorate neglect and whether 21 or 30 hours of arm activation training would do the same without any visual scanning training. The aim of the study was not to examine whether the two methods would be efficient with the same number of hours.

The associations of gait, pusher, gravitational neglect and visual and behavioural neglect would have been interesting topics to examine. However, our methods of measuring balance and walking were too demanding for most of the present neglect patients. It would have been beneficial to include a method for measuring balance in the sitting position.

Mainly extrapersonal aspects of space were measured in this study. The paper and pencil tasks in the BIT C have been considered to assess extrapersonal or allocentric neglect as do most of the items of the CBS. However, a few items of the CBS are considered to represent personal or egocentric neglect. These aspects have been discussed in the study. The role of motor neglect remains to be controlled. Cancellation tasks as well as drawing and copying all demand motor reactions as well as the arm activation training. This raises the question of how much this motor component was involved while performing tests and whether it influenced the results of the study.

The clinical observation of test-retest effects was that neglect patients actually were able to learn the kinds of tasks in which they were not impaired, for example in the verbal learning and memory test. This same kind of learning effect was not displayed in those tasks measuring neglect. This was apparent in those chronic patients who received less rehabilitation and had rather stable symptoms. The star cancellation test has been studied in repeated testing sessions and has been found to be reliable and stable in patients with severe neglect (Bailey, Riddoch and Crome, 2004). There was, however, more variation in the performances of patients with moderate or mild neglect.

There is always the possibility of erroneous significant differences or correlations especially in those analyses where the groups are very small. In those cases, the findings are only suggestive and need to be confirmed in future studies. When combined groups were analysed, the statistical significances rose much higher than in smaller groups e.g. in the analyses of the effects of the rehabilitation in the 12 acute-subacute patients irrespective of the method used. In Study V, a multivariate statistical analysis would have been better if the population of patients had been bigger. All analyses were run with exact tests and 2-tailed or, 2-sided exact significances.

4.7. Practical implications and future perspectives

The role of hemianopia in clinical neglect rehabilitation should be reviewed. For example, it would be important to discover if specific rehabilitation methods would be suitable for the amelioration of the combination of neglect and hemianopia. In particular prism adaptation is interesting as the artificially leftward directed visual field might help patients to compensate for both neglect and hemianopia.

A variety of arm activation gadgets are readily available in stroke rehabilitation units and they should be exploited in the rehabilitation of neglect. Training can happen with little guidance and assistance at least for the more advanced and motivated patients, who could also train outside the official therapy hours. Left arm activation can be considered as neglect rehabilitation in any situation where only the left arm is activated in the left hemispace and when the functioning right arm is kept unused in the right hemispace. This kind of practice could also be planned as a part of occupational therapy of these patients. Further investigation will be needed to clarify the combined effect of arm activation and visual scanning training. Fewer hours of arm activation might be sufficient if they were combined with visual scanning exercises.

The mechanisms and processes of visual memory seem to have triggered renewed interest currently. The recognition type of visual memory in patients with neglect needs further exploring and the lateralization of delayed recall and its mechanisms could possibly be examined also in experimental research settings. The analysis of the effect of hemianopia on visual memory of neglect patients also needs to be probed in more patients.

Intensive acute rehabilitation is essential, even though comprehensive program can also be effective later in the rehabilitation of neglect, especially in patients who have not received proper multi-professional and comprehensive rehabilitation during the acute phase. Neglect often follows large right hemisphere lesions and patients have severe motor and sensory impairments as well as possible anosognosia of neglect and pusher in the acute phase. In chronic patients lower functional independency is associated with more depressive symptoms. This depression should not be overlooked in the rehabilitation process. In addition, hemianopia and its effects on ADL should be evaluated even in chronic patients with neglect.

4.8. Concluding remarks

1. The BIT C as a measurement of visual neglect and the CBS as an assessment of neglect in everyday functioning and in real life situations measure the same syndrome. The CBS is useful in the evaluation of generalization of neglect rehabilitation into activities of daily living. However, visual fields should be assessed routinely in patients with neglect as these patients do not learn to compensate for their hemianopia. This combination of deficits may impair chronically the patients' functioning in ADL. Deficits of the combination of neglect and hemianopia are easily diagnosed by the confrontational assessment of visual fields, by the line bisection subtest and it is observable in several items of the CBS. These patients with both neglect and hemianopia may also need specific rehabilitation methods.

2. Arm activation training, modified from the CIMT procedure, appears to be as effective as traditional visual scanning training in treating hemispatial neglect during the first six months after a stroke. In the present study, the effect was achieved after twenty to thirty hours of practice whereas the visual scanning training as a part of a comprehensive rehabilitation program was effective with only ten hours of treatment. However, left arm activation may be the only available bedside method of rehabilitating neglect in patients with limited co-operation in the acute phase after stroke. Neglect patients with some activity in their affected arm benefit from arm activation for both neglect and arm functions simultaneously. In clinical practice,

visual scanning training should be combined with arm activation exercises as part of occupational therapy or as assisted exercises on the ward in order to achieve an even better response in the rehabilitation of neglect.

3. The deficit in spatial working memory due to the dysfunction of the right hemisphere ventral attention network seems to be a part of the overlap of hemispatial neglect and visual memory. Another perspective of neglect affecting visual memory processes is observed in delayed visual reproduction. Delayed recall demands that the individual must make a match helped by a cue or it requires a search for relevant material from long-term memory storage. In the case of representational neglect, the search may succeed but the left side of the recollected memory still fails to open. Scoring both sides of visual memory tests provides additional useful information when patients with neglect need to be evaluated.

4. This present data reveals that the hyper excitability of the left hemisphere can be detected in auditory and visual domains in the acute/subacute stage of the stroke patients with neglect. The dynamic balance and the imbalance between the circuits in the two hemispheres can be demonstrated with evoked potentials elicited in different sensory domains but the varying nature of large lesions causing the neglect syndrome makes it difficult to pinpoint the structures responsible for shifting attention and spatial behaviour to the right side. Nevertheless, the present results provide evidence of defective processing in both auditory and visual domains in the same individuals in the neglect syndrome which mostly fades away by about nine months from stroke onset along with the reduction of the severity of neglect.

5. Recovery from hemispatial neglect is strongly associated with early rehabilitation and the severity of neglect. However, intensive treatment can induce recovery in severe or moderate visual neglect long after the first three months since the patients suffered the stroke. Even chronic patients with moderate or severe visual neglect improve after intensive rehabilitation, if they have sufficient compensatory cognitive and psychological capacity. However, the benefit of even intensive rehabilitation program for patients who had received proper treatment in earlier phases after stroke was not permanent in the chronic phase of recovery. Depression may be associated with large lesions and severe neurological losses in chronic patients with neglect and should be diagnosed and treated even years after the stroke to enhance latent recovery.

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