The 'side effect':

The influence of left versus right sided spatial neglect at functional outcome measures

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Abstract

The aim of the current study was to investigate the influence of the side (left versus right) and distance (near versus far) at which spatial neglect (SN) occurs, on the life of patients. In total, 277 stroke patients were screened within the first two weeks after their admission to a rehabilitation center. A Line Bisection Test and an Object Cancellation Test were used to measure the presence of SN. Rehabilitation data were used to research the functioning of patients in various areas: the Motricity Index of Arm and Leg for motor function, the Barthel Index and Catherine Bergego Scale (CBS) for independency in activities of daily living, the Stichting Afasie Nederland-scale for communication and the Mini-Mental Status Examination for cognitive functioning. RSN+ patients had significantly less motor functioning problems in the lower extremities than patients with LSN+. Furthermore, LSN+ patients had higher scores on the CBS, which indicated more SN behaviour, in comparison with patients without SN. There was no significant difference between LSN+, RSN+ and SN- patients on other functional outcome measures. The frequency of patients within the near, far or near/far neglect group did not differ significantly between LSN+ and RSN+ patients. A follow-up study which includes side of hemisphere and the specific lesion location is recommended. Concerning the CBS we recommend a replication of the study with larger groups and an expansion of it with a factor or cluster analysis. This may lead to more insight of possible differences in SN behaviour between LSN+ and RSN+ patients and can lead to more customized observation and treatment in hospitals and rehabilitation centers.

Keywords: stroke, spatial neglect, side, distance, left and right neglect, near and far neglect.

1. Introduction

Spatial neglect (SN) is a neurological disorder that is often seen after a stroke (Yang, Zhou, Chung, Li-Tsang, & Fong, 2013). SN is characterized by a deficit in lateralised attention, which results in diminished or delayed responses to, generally, contralesional stimuli (Nijboer et al., 2013a). SN patients are physically able to move their head and eyes into any direction, but exhibit a contralesional bias in eye and head orientation (Karnath & Rorden, 2012). SN is heterogeneous in nature, and can, for example, be found in the visual, tactile and/or auditory domain (Yang et al., 2013). Further on, there are at least two dissociable forms of SN, namely ignoring the contralesional body side (egocentric SN) and ignoring the contralesional side of objects (allocentric SN) (Marsh & Hillis, 2008). The latter form is irrespective of the items location from the patients' viewpoint (Rorden et al., 2012). A patient with egocentric SN might for instance ignore his contralesional leg when stepping out of bed, or forget to shave the contralesional part of his face. A patient with allocentric SN might draw only one half of a clock. Additionally, region-specificity in SN has been described, with patients showing SN in peripersonal (near), but not in extrapersonal (far) space, and vice versa (Van der Stoep et al., 2013; Aimola, Schindler, Simone & Venneri, 2012). Patients with near (N+F-) or near-far SN (N+F+) showed more SN behaviour during basic daily activities (as measured with the Catherine Bergego Scale), while far SN patients (N-F+) were more comparable to patients without SN (SN-) with the exception of way finding (Nijboer, Ten Brink, Kouwenhoven & Visser-Meily, 2014a). Further, SN is associated with anosognosia, a deficit in which the patient is unaware of the existence of his disability (Dai et al., 2014).

It is known that SN has a strong negative influence on the independence in daily life activities as e.g. mobility and self-care (Nijboer et al., 2013b). SN patients show slower recovery of motor impairment (Nijboer, Kollen & Kwakkel, 2014b) and are longer admitted in rehabilitation centres (Gillen, Tennen, & McKee, 2005; Jehkonen, Laihosalo, & Kettunen, 2006). The incidence and severity of SN is influenced by the amount of elapsed time since the stroke; SN often resolves within weeks to months (Karnath & Rorden, 2012). In a study of Nijboer, Kollen and Kwakkel (2013a), more than half of the initial group of SN patients demonstrated no longer SN as measured with a standard cancellation task, 12 weeks after their stroke. In another study, about two thirds of the patients who showed SN during the acute phase, recovered within 16 months (Karnath, Rennig, Johannsen & Rorden, 2011). SN is mostly seen after right hemisphere damage (RHD) (Yang et al., 2013; Suchan, Rorden & Karnath, 2012). It is thought to be more severe after RHD, compared to left hemisphere damage (LHD) (Mesulam, 1981, as cited in Duecker, 2013; Stone et al., 1991 as cited in Nijboer, Van de Port, Schepers, Post & Visser-Meily, 2013b). Recovery of SN is slower for RHD patients and more persisting (Stone, Patel, Greenwood & Halligan, 1992).

Robertson (1993) raised the hypothesis that the slower recovery of RHD SN patients (Stone et al., 1992) is caused by damage to the vigilance system, which is dominated by the right hemisphere (Helton et al., 2010). Heilman, Watson and Valenstein (1980, as cited in Beis et al., 2004) hypothesized that the right hemisphere directs attention to both ipsilateral and contralateral hemispace, while the left hemisphere concentrates attention to almost exclusively the contralateral right hemispace (see figure 1). This would explain left sided neglect (LSN+), but this theory cannot explain right sided neglect (RSN+).

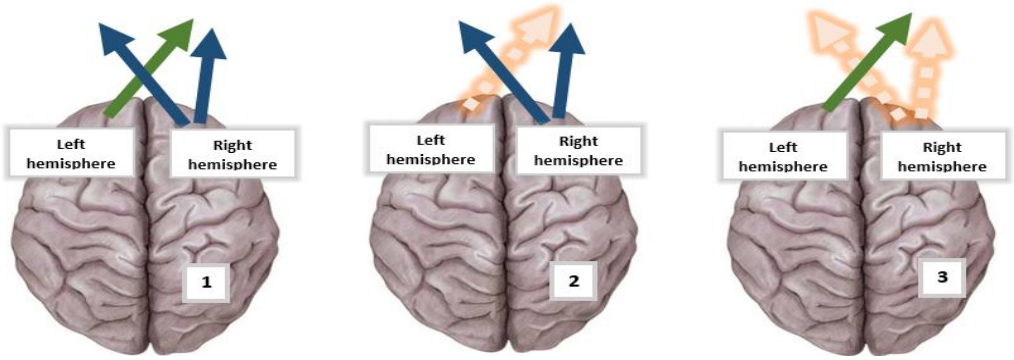

Figure 1: In an undamaged brain (1), the right hemisphere directs attention to both left and right hemispace, while the left hemisphere concentrates attention to almost exclusively contralateral right hemispace (Heilman et al., 1980). After damage to the left hemisphere (2) the patient will still be able to attend both the left and right visual hemispace. However, after damage to the right hemisphere (3), there is no back up from the left hemisphere to cover for the left side of hemispace. The patient will neglect the left half of space (Figure adapted from Mayo Foundation for Medical Education & Research website, 2000).

The primary aim of the current study was the investigation of potential differences in functioning between stroke patients with LSN+ and RSN+. Due to the studies of Mesulam (1981) and Stone and colleagues (1991), we expected worse functional outcomes for LSN+ patients in the current study. However, these studies compared patients with LHD and RHD, while the current study compares LSN+ and RSN+ patients. It is unknown whether the neglected side has a differential functional outcome than the hemispherical side of damage. As such it is of relevance for rehabilitation to explore this. The patients were admitted in an inpatient rehabilitation center. The control group consisted of SN- stroke patients. The following outcome measures were examined: motor function, independency in activities of daily living, communication and cognitive functioning. The strength of this study is the combination of important rehabilitation outcome measures with neuropsychological data, in a large sample of stroke patients. As a secondary aim, the current study investigated the relation between side of SN and region-specific SN (N+F-, N-F+, N+F+). We examined whether the distribution of the various distance groups differs for LSN+ and RSN+ patients.

2. Methods

2.1. Patients

Participants were selected from a stroke patient population, who were admitted for inpatient rehabilitation to rehabilitation center De Hoogstraat in Utrecht, between November 2011 and January 2014. Inclusion criteria for both screening and study were: (1) a stroke; (2) age above 18 years; (3) normal or corrected-to-normal visual acuity and (4) the ability to perform at least the near and far cancellation tasks. Exclusion criteria were: (1) severe deficits in communication and/or understanding (e.g. aphasia).

2.2. Procedure

A SN screening took place within the first two weeks and consisted of the OCT and LBT. SN behaviour of the patients was observed and noted by nursing staff in the same week as the screening took place, using the Catherine Bergego Scale (CBS). Demographic and stroke characteristics were reviewed from the patient's medical record. A review procedure by a medical ethics committee was not needed, due to the fact that the data was already routinely collected for usual care (Nijboer et al., 2014a).

2.3. Outcome measures

The LBT and OCT were used to detect the presence of SN. The tests were conducted on a computer at a distance of 30 cm (i.e. near space) and at a distance of 120 cm (i.e. far space) (Nijboer et al., 2013, 2014; Van der Stoep et al., 2013).

During the OCT, patients were requested to cross 56 target objects among 75 distractors. Objects were arranged in a scattered pattern on the computer screen. The difference in number of omitted targets between the contralesional and ipsilesional side was used to indicate SN. An asymmetry of at least two omissions indicated SN.

The LBT consisted of three horizontally oriented lines that were evenly distributed across the screen in vertical space. The middle line was presented in the exact middle of the screen. The top line was shifted to the right, whereas the bottom line was shifted to the left. Patients were requested to indicate the middle of each line by clicking on the subjective midpoint. Patients performed the task four times in a row (Van der Stoep et al., 2013). Performance on the LBT indicated SN when the deviation from the midpoint was at least three standard deviations higher or lower than the mean deviation of the norm group. The normal range was from -0.55 to 0.55° in near space and from -0.71 to 0.69° in far space. Patients who showed SN in at least one of the two tests were assigned to the LSN+ or RSN+ group. Patients with no SN on both tests were assigned to the SN- group.

The CBS (Azouvi et al., 1996) is an observation scale to assess SN. Caregivers score the degree of SN during ten everyday activities, such as way finding and finding belongings. The CBS measures the patients performance in personal (body parts, body surface), peripersonal and extrapersonal space, as well as in perceptual, representational and motor domains. Scores range from 0 (no SN observed) up to 30 (severe SN observed). In the current study we used the Dutch translation of the CBS (Ten Brink et al., 2013).

Demographical (age, gender) and stroke characteristics (days post-stroke) were reviewed, as well as other relevant measures from the patient's medical record: the Motricity Index (MI) for Arm and Leg, the Stichting Afasie Nederland-scale (SAN), the Mini-Mental State Examination (MMSE) and the Barthel Index (BI).

The MI (Collin & Wade, 1990) assesses motor impairment in stroke patients. There are three items for the upper extremities (MI Arm: i.e. pinch grip, elbow flexion, shoulder abduction) and three items for the lower extremities (MI Leg: i.e. ankle dorsiflexion, knee extension, hip flexion). Minimum score is 0 (no activity, paralysis) and maximum score per subsection is 99 (normal muscle force).

The SAN-scale (Deelman, Koning-Haanstra, Liebrand & Van de Burg, 1987) can be used to detect language- or speech disorders. Minimum score is 1 (no verbal communication possible) and the maximum score is 7 (normal speech and language understanding). A score of 2 or less is considered as a language disorder.

The MMSE (Folstein, Folstein & McHugh, 1975) measures cognitive status (orientation, memory, attention, calculation, language and construction functions). Scores vary from 0 (severe cognitive impairments) up to 30 (no cognitive impairments). A score of less than 24 is considered as cognitive impairment.

The BI (Collin, Wade, Davies, & Horne, 1988) measures the extent to which a patient can function independently in activities of daily life (i.e. feeding, bathing, grooming, dressing, bowel and bladder control, toileting, chair transfer, ambulation and stair climbing). Minimum score is 0 (completely dependent) and the maximum score 20 (completely independent).

2.4 Analysis

LSN+, RSN+ and SN- patients were compared on demographic (age, gender), stroke characteristics (days post stroke onset) and functional outcome measures: MI Arm, MI Leg, BI, SAN, MMSE and CBS using the Kruskal-Wallis test (2-tailed, α=.05). A Mann-Whitney test was used as a post hoc test to follow up these findings. Furthermore, a Bonferroni corrected for multiple testing, wherefore all alpha levels were set on .0167. A Pearson's chi-square test of contingencies was used to evaluate whether the region-specific SN groups (N+F-, N-F+, N+F+) were equally divided for LSN+ and RSN+ patients.

Patients who showed contradictory test results during the screening were excluded from the study, e.g scoring 'LSN+' on the Object Cancellation Test (OCT) and 'RSN+' on the Line Bisection Test (LBT). Data was not split for hemisphere of stroke.

3. Results

3.1 Demographical and stroke characteristics per SN group

An overview of the demographical and stroke characteristics for SN+ and SN- patients is given in Table 1. The group of 277 patients (132 with SN, 145 without SN) had a mean age of 59 years (SD = 12.04). The SN+ group was divided in LSN+ and RSN+. According to a Kruskal-Wallis one-way analysis of variance the groups (LSN+, RSN+ and SN-) did not differ with respect to gender ($H(2) = 1.04$, $p = .59$), age ($H(2) = 2.32$, $p = .31$) or days post stroke onset ($H(2) = 3.77$, $p= .152$).

Average scores on the MI Arm, SAN, MMSE and BI were comparable for both the SN+ groups and the SN- group (all $p > .07$). However, the three groups differed significantly for the MI Leg ($H(2) = 6.71$, $p = .035$), and the CBS ($H(2) = 13.69$, $p = .001$). A significant difference was found for the MI Leg between LSN+ and RSN+ ($U = 1010$, $z = -2.39$, $p = .017$). LSN+ patients had a significant lower score on the MI Leg than RSN+ patients. This indicated more severe impairment of the lower extremities for LSN+ patients in comparison to RSN+ patients. The CBS scores of LSN+ patients were significantly higher in comparison with the scores of SN- patients, ($U = 690$, $z = -3.55$, $p < .001$). This indicated that caregivers observed more SN behaviour from LSN+ patients than from SN- patients. RSN+ patients did not score significantly different on the CBS when compared to LSN+ patients, ($U = 296.50$, $z = -2.07$, $p = .038$), or when compared to SN- patients ($U = 812$, $z = -1.56$, $p = .119$).

3.2 Side of SN and neglected distance

The distribution of SN+ patients over the various distance groups (Table 1) was as follows for LSN+: 45.9% N+F+, 37.7% N+F- and 16.4% N-F+. N+F- was with 38.0 % the most prominent distance group in RSN+ patients, followed by the N+F+ group with 32.4% and the N-F+ group with 29.6%. No relation was found between the side of SN and the distance at which SN was observed (N+F-, N-F+, N+F+), for the distribution of distance groups for LSN+ was not significant different from RSN+, (χ^2 (2, N = 132) = 4.0, $p = .14$).

Table 1 *Demographical, stroke characteristics and functional outcome measures per group (LSN+, RSN+ and SN-)*

Clinical variables	**LSN+ (SD)**	**RSN+ (SD)**	**SN- (SD)**	**Statistics (Kruskal-Wallis)** *LSN+, RSN+ and SN-*	**Statistics (Mann-Whitney)**
Group size	22.0 % n=61	25.6% n=71	52.3% n=145		
Gender (% male)	48.2%	51.8%	57.9%	H(2) = 1.04, p = .593	
Age in years	60.4 (11.9) n=61	59.0 (11.7) n=71	57.8 (12.1) n=145	H(2) = 2.32, p = .313	
Days post stroke onset	37.8 (27.6) n=61	30.2 (21.3) n=68	34.3 (33.3) n=142	H(2) = 3.77, p = .152	
Side of damage					
Contralateral	55.1% n=43	44.9% n=35			*LSN+ vs RSN+:* U= 1207, z=-2.32, p=.020
Ipsilateral ***(Bilateral: n=5)***	32.5% n=13	67.5% n=27			
MI					
Arm (0-99)	56.5 (42.7) n=46	71.6 (34.3) n=58	62.3 (39.7) n=115	H(2) = 2.37, p = .306	
Leg (0-99)	64.7 (35.9) n=47	79.5 (30.2) n=58	68.8 (34.6) n=113	H(2) = 6.71, p = .035*	*LSN+ vs RSN+:* U = 1010, z = -2.39, p = .017**

					LSN+ vs SN- : U = 2452, z = -.784, p = .433 *RSN+ vs SN-:* U = 2652, z = -2.14, p = .033
SAN (1-7)	5.6 (1.6) n=52	5.4 (1.7) n=57	5.4 (1.8) n=120	H(2) = 0.26, p =.877	
MMSE (0-30)	25.8 (4.6) n=43	25.6 (3.6) n=48	26.6 (3.8) n=100	H(2) = 5.51, p =.064	
BI (0-20)	11.9 (5.5) n=52	13.8 (5.6) n=51	12.9 (5.2) n=116	H(2) = 3.56, p =.169	
CBS (0-30)	8.3 (8.1) n=32	3.6 (4.8) n=27	3.1 (4.9) n=75	H(2) = 13.69, p=.001*	*LSN+ vs RSN+:* U = 296.50, z = -2.07, p = .038 *LSN+ vs SN- :* U = 690, z = -3.55, p < .001** *RSN+ vs SN- :* U = 812, z = -1.56, p = .119
Region-specific SN					
N+F-	37.7% n= 23	38.0% n=27			
N-F-	16.4% n=10	29.6% n=21			

	45.9%	32.4%
N+F+	n=28	n=23

SN+ = spatial neglect on Line Bisection Test and/or Object Cancellation Test (LSN+ = left SN, RSN+ = right SN) **SN-** = no spatial neglect

*****=significant ****** = significant after Bonferonni correction

4. Discussion

The first aim of the current study was to investigate possible differences in the functioning between patients with LSN+ and RSN+. The control group consisted of stroke patients without SN. We assessed motor functioning, independency and SN behaviour in activities of daily living, communication and cognitive functioning. The second aim was to study the possible relation between the side of SN and region-specific SN.

Nijboer et al. (2013b) found that SN in general has a strong negative influence on the independence during daily life activities in stroke patients. Because SN is more severe (Mesulam, 1981) and persisting (Stone et al., 1992) after RHD, we expected worse functional outcomes for patients with LSN+. No earlier studies with a focus on the possible differences between LSN+ and RSN+ patients at functional outcome measures were found. Concerning the influence of side of SN at the functional outcome measures, the current study observed no differences between LSN+ and RSN+, except for the functioning of the lower extremities and SN behaviour (as observed with the CBS). More severe motor impairment of the lower extremities was seen for LSN+ compared to RSN+ patients. Nijboer, Kollen & Kwakkel (2014b) studied the influence of SN on the upper extremities and found lower scores on mobility and recovery of motor impairment for SN patients in comparison with SN- patients. Although the mean of the group of LSN+ patients in the current study was lower than the mean of the RSN+ group, we did not find a significant relation between LSN+ and motor functioning of the upper extremities. It may be that LSN+ is more impairing than RSN+ on the functioning of the lower extremities, but the current study needs to be expanded with more precise information, namely side of hemisphere and location of lesion.

LSN+ patients showed more SN behaviour than SN- patients. This is not remarkable and only confirms the quality of the observations of the nursing staff. As for the RSN+ and SN- group it is salient that the mean and SD of the CBS scores were quite alike. The difference between LSN+ and RSN+ patients on the CBS was no longer significant after the Bonferonni correction, but it is recommended to repeat this part of the study with larger groups and to look more specifically to the items e.g. with a factor or cluster analysis.

In a study regarding region-specific SN (Nijboer et al., 2014a) it was found that patients with N+F- or N+F+ scored worse on basic daily activities, while N-F+ patients were more comparable to SN-. We found no relation between the side of SN and region-specific SN. No difference in the distribution of distance groups (N+F-, N-F+, N+F+) was found between the groups of LSN+ and RSN+ patients.

According to our literature, SN is more severe after RHD, compared to LHD (Mesulam, 1981; Stone et al., 1991) and the recovery of SN is slower for RHD patients and more persisting (Stone et al., 1992). This makes it remarkable that we found only a small amount of differences between LSN+ and

RSN+ patients. What could explain the lack of differences between LSN+ and RSN+ patients on other functional outcome measures than the motor functioning of the lower extremities? A possible explanation can be found by looking at the mean scores per group. The scores of the SN- patients were in-between scores of the LSN+ and the RSN+ group. LSN+ patients had the worst functional outcomes, followed by the SN- group with higher means and the RSN+ group with the best mean scores. If it was left or right sided SN that influenced the outcomes, it would be expected that SN- patients had significant better scores than SN+ patients. However, this was not the case. The SN- group in the current study was not split for hemisphere of stroke. This may have led to its intermediate position between LSN+ and RSN+ patients. The side of hemispherical damage is possibly of greater importance than the side of SN. Robertson (1993) thought of the right hemisphere as of importance for vigilance and Heilman et al. (1980) hypothesized that the right hemisphere can direct attention to bilateral hemispace (contrary to the left hemisphere). Schaefer, Haaland & Sainberg (2007) found that both left and right hemisphere contribute to the functioning of the upper extremities, but have different specializations. We assume that this may also be true for the functioning of the lower extremities, and that the side of hemisphere influences the functional outcome. Devinsky (2000) said that the right hemisphere dominates the awareness of the physical and emotional self. It dominates neural programs for body image and its relations to the environment (Devinsky, 2000). So it seems that the right hemisphere influences both the upper and lower extremities, for it influences the image of the whole body. We expect that a division in the research data for left and right hemisphere will lead to more precise outcomes.

A follow-up study is needed to investigate the influence of hemispherical side because the group with LSN+ patients was not a group of exclusively RHD-patients. This current study also had patients included with ipsilesional SN. Patients with ipsilesional SN show diminished or delayed responses to stimuli on the same side as the side of hemispherical damage (Sacchetti, Goedert, Foundas & Barrett, 2014). So in the current study were also LSN+ patients with LHD instead of RHD. A study with a strict division in left and right hemispherical damage could lead to more clear outcomes. A future study could also include lesion location information. This may lead to more precise results.

Finally, it is important to mention that all included patients in this study were in the sub-acute phase of a stroke. They received inpatient rehabilitation after hospitalization and were (relatively) young and moderately disabled. This may influence the generalizability of the current study. Another remark is that slightly more RSN+ than LSN+ patients were included, while most SN studies have more LSN+ patients. This is probably due to our extensive screening (two SN tests in both a near and far condition). SN is more severe after RHD (Mesulam, 1981) and therefore presumably easier to notice when only a single SN test is used.

In conclusion, we found no influence of the side of SN on most of our functional outcome measures, except for the motor function of the lower extremities. Other functional outcome measures than the motricity for the lower extremities were not significantly influenced by the side of SN, and were possibly more influenced by the place of damage (side of hemisphere and location of lesion). LSN+ patients had more severe motor impairment of the lower limbs than RSN+ patients. It is possible that LSN+ influences the motor function of the lower extremities, but more research is needed for it can also be explained by side of hemisphere or specific lesional location. The right hemisphere dominates the awareness of the physical self and its relations to the environment (Devinsky, 2000). In this way it also influences motor functioning of the lower extremities. After a split for hemisphere of stroke, this relation might also become statistically significant for the upper extremities. Further on, we found no relation between side of SN and the type of region-specific SN. The results of the current study have no direct implications for the rehabilitation of SN patients. However, as said, concerning the CBS we recommend a replication of the study with larger groups and an expansion of it with a factor or cluster analysis. This may lead to more insight of possible differences in SN behaviour between LSN+ and RSN+ patients and lead to more customized observation and treatment in hospitals and rehabilitation centers.

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