The Prediction of Functional Dependency by Lateralized and Nonlateralized Neglect in a Large Prospective Stroke Sample.

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Abstract:

***Background* —** Lateralized and nonlateralized impairments in visual attention have been identified as important components in patients with visuospatial neglect. This study investigated the course of these two phenomena across time in relation to neurological symptoms and functional outcome in a large consecutive and prospective stroke sample.

***Methods:* —**375 consecutive stroke patients were divided into three groups (lateralized, nonlateralized, or no visual inattention) acutely and three months post-stroke using the Star Cancellation test. Neurological impairments, localization of brain damage, asymmetry in clinical symptoms and functional outcome were assessed. Possible group differences were analysed and stepwise logistic regressions were performed to examine the relative importance of predictors of functional dependency.

***Results:* —**Participants with acute lateralized inattention differed ($p \leq 0.05$) from the other two groups by more often exhibiting severe neurological symptoms, functional dependency, and persisting visual inattention. The regression analyses selected acute lateralized inattention as an important and independent predictor of functional dependency following right hemisphere damage, but not following left hemisphere damage.

***Conclusions:* —** The results emphasize the prognostic value of lateralized inattention and the importance of separating lateralized and nonlateralized symptoms of visual inattention at the commencement of rehabilitation.

Signs of visual inattention are common in patients suffering from stroke. One frequently observed symptom is visuospatial neglect (VSN) [1-3]. At the clinical setting, tests of visual cancellation such as the Star Cancellation test [4] are often used to screen for neglect. Among the paper-and-pencil tests, this type of assessment has proved to constitute a fairly sensitive screening of VSN [5, 6]. In visual cancellation, the inattentive performance across the test sheet can be lateralized towards one side, or it can be nonlateralized. One important observation regarding visuospatial neglect is that both lateralized and nonlateralized impairments seem to have a central role in this phenomenon [7-9]. Kotila and colleagues [10] have reported results in a stroke sample which suggest that lateralized and nonlateralized symptoms of neglect is related to different levels of functional outcome. Kotila and co-workers investigated 66 patients younger than 65 years. They found that 10.5% had lateralized omissions and 7.5% had inattention at neuropsychological testing three months post stroke. None of the patients with lateralized omissions were able to live independently during the four year follow-up, whilst all but one of the patients with inattention lived independently at three months. These results suggest that lateralized and nonlateralized impairments in test performance at an early stage after stroke may predict different functional outcomes, with a lateralized impairment predicting an inferior outcome. Thus lateralized and nonlateralized symptoms at the early clinical screening of neglect may indicate different prognostic information. It is well known that occurrence of neglect, alone or together with other variables, often predicts an inferior outcome [11]. However, to our knowledge have no investigations, except the study by Kotila and colleagues, focused on the tentatively different prognostic value of lateralized and nonlateralized symptoms.

The present study investigated lateralized and nonlateralized impairment in a large prospective and consecutive sample. The main aims were to describe if a simple screening of lateralized and nonlateralized symptoms of visual inattention can provide prognostic valuable information. Also, the study describes the occurrence and course of these two phenomena and the pattern of neurological symptoms and neuroradiological findings in the groups with lateralized and nonlateralized neglect symptoms.

Methods

Participants

The participants were recruited from the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS), a large consecutive and prospective stroke study in Western Sweden. 375 patients under the age of 70 years, admitted during August 1998 to December 2003 to the neurological department at the Sahlgrenska University hospital, were included according to the following criteria: (a) acute onset of clinical symptoms of suggestive stroke, and (b) no haemorrhage on computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain. Patients were included regardless of previous cardiovascular or cerebrovascular events. Patients were excluded if (a) the following evaluation showed aetiology other than ischemic stroke, and (b) they had a diagnosis of cancer at an advanced stage, infectious hepatitis or HIV.

The study was approved by the Ethics Committee of the University of Gothenburg. All participants provided written informed consent prior to enrolment. For participants who were unable to communicate, consent was obtained from their next-of-kin.

Tests and measures

Nonlateralized Visual Impairment: Visual neglect was measured by the Star Cancellation (SCT) subtest of the Behavioural Inattention Test (BIT) [4]. Cut-off for a nonlateralized visual impairment (VI) was a score ≤ 52, based on the performance of 25 controls (*median:* 57 years, *range*: 29-70 years) in an earlier study [12]. Scores above cut-off were classified as "no visual impairment" (NoVI).

Lateralized Visual Impairment: Lateralized impairment was assessed in the same sample of controls as described above. Using the formula described by Friedman [13] none of the

controls exhibited an asymmetry index score below 0.48 or above 0.52. Patients were classified as having “lateralized visual impairment” (LVI) if they exhibited index scores of ≤ 0.47 and ≥ 0.53. Also, a lowest level for classifying the performance as lateralized was used: an omission of at least three more targets at one half of the SCT.
Visual Field Deficit (VFD): VFD was rated as present or absent using the conventional confrontation technique. In 136 patients the classification was based on retrospective information from the medical records, examined by a neurologist (CB).
Scandinavian Stroke Scale (SSS) [14]: The SSS have shown good reliability [15] and was used to assess neurological deficits acutely and at follow-up. The SSS sub-scales are seen in table 2.
Modified Rankin Scale (mRS) [16]: The mRS is a validity and reliability tested [17, 18] disability scale which investigates general functional activity level on a scale from 0 to 6. The mRS was administered at follow-up and scores were dichotomized with ≤2 coded as functionally independent and >2 coded as dependent [19].
Localisation of brain damage: A neurologist (KJ) reviewed the patients MRI/CT reports to classify the brain damage as involving the right or left side of the brain, right or left cerebellum, and/or the brainstem. Previous infarcts or lesions of different origins were also recorded according to the above classification.
Lateralization of clinical neurological symptoms: The neurological clinical symptoms described in the medical records were coded as either lateralized (right- or left- sided) or nonlateralized symptoms.

Procedure
The SSS (within the first 7 days) and the SCT were administered by a neurologist and a research assistant. Follow-up testing (the SSS, mRS, and SCT) was done three months post stroke. Inattention in patients with missing data on the SCT was classified based on a retrospective examination of the symptoms described in the medical records by experienced neurologists, neuropsychologists and occupational therapists. Based on this information the patients were classified as having LVI, VI, or NoVI. Information regarding the reasons for missing data was also gathered from the examination of the records. The examination was made separately by a neurologist (CB) blinded for the outcomes of the other data of the study.

Statistical analyses
Kruskal-Wallis one-way analysis of variance (continuous data) and Chi-square (categorical data) with post-hoc two-group comparisons (Mann-Whitney U test and Fisher’s exact test) were used for the group comparisons (LVI, VI, and NoVI). When Chi-square was found to be inappropriate due to small cell values the scores of the LVI and VI groups were collapsed and compared to the NoVI group with the Fisher’s exact test. If only 2 or less patients were identified in two groups no significance tests were performed. To examine whether the inclusion of retrospectively classified patients produced a different outcome in the present study the comparisons were run both including and excluding these patients. At the post-hoc comparisons Bonferroni-Hochberg corrections for multiple comparisons were used.

Sub-items of the acute SSS, VFD, age, and classification of visual attention were included in forward stepwise logistic regression analyses to assess predictors of dependency as measured by the dichotomized mRS score. The SPSS package, version 14.0 was used.

Results

Results from the acute assessments
The SCT assessment was done, in median, 8 days after admission to the hospital (*range:* 1-51 days). Of the 375 participants 53 were not tested on the SCT; 29 due to severe impairments, 12 with recovery in the first few days without further need for hospital care or outpatient rehabilitation,, and two were admitted to another department or hospital. The reasons for missing data could not be established in 10 participants and there were insufficient data to

allow for retrospective classification of visual inattention in 11 participants. Thus, 364 patients were classified with regards to attentional performance, 287 (78.8%) had no sign of visual inattention (NoVI), 37 (10.2%) had nonlateralized visual inattention (VI), and 40 (11%) had lateralized visual inattention (LVI) (see Table 1). In the LVI group 11 (27.5 %) had right visual neglect and 29 (72.5%) had left visual neglect. The LVI group was tested on the SCT significantly later after stroke onset compared to the VI group ($p<.001$) and NoVI group ($p<.001$).The VI group was significantly older than the NoVI group ($p=.002$).

Table 1. Background Data

	LVI	VI	NoVI	*p* =
Acute assessment		-	-	-
No.	40 / 11%	37 / 10.2%	287 / 78.8%	-
Age	58.5 / 36-69	61 / 36-69‡	56 / 18-69	.002
Gender (m/f)	26/14 – 65/35%	23/14 – 62/38%	180/107 – 63/37%	ns
Retrospectively classified‖	15 / 37.5%*†	5 / 13.5%	22 / 7.5%	.000
Days onset > assessment	12 / 1-45*†	6 / 1-19	7 / 1-51	.002
Follow-up assessment				
No.	12 / 3.4%	37 / 10.6%	301 / 86%	-
Age (years)	65 / 36-69†	61 / 40-68‡	56 / 18-69	.002
Gender (m/f)	19/3 - 75/25%	23/14 – 62/38%	187/114 – 62/38%	ns
Retrospectively classified§‖	2 / 15.5%	7 / 19%‡	13 / 4.5%	.001

Values are given in median/range for ordinal data and number and percentage for nominal data. * = $p\leq 0.05$ between the LVI and VI groups. † = $p\leq 0.05$ between the LVI and NoVI groups. ‡ = $p\leq 0.05$ between the VI and NoVI groups. § = scores of the LVI and VI groups are collapsed and compared to the NoVI group with Fisher's exact test. If significant, individual two-group comparisons were done. ‖ = number of patients in each group that was retrospectively classified on visual inattention. m = male and f = female.

Table 2 show that the LVI group, compared to the NoVI group, had inferior results on total SSS and on all the neurological variables (p<.001 except for language with *p*=.015).

Table 2. Results for the Post-acute LVI, VI, and NoVI Groups on Neurological Symptoms and MRI/CT Scans

Variables	LVI	VI	NoVI	*p* =
SSS	21/0-48*†	39/0-48‡	44 / 0-48	.000
Arm	1 / 0-6*†	6 / 0-6	6 / 0-6	.000
Hand	1 / 0-6*†	4 / 0-6	6 / 0-6	.000
Leg	3 / 0-6*†	5 / 0-6	6 / 0-6	.000
Orientation	6 / 0-6†	6 / 0-6	6 / 0-6	.000
Language	10 / 0-10†	10 / 0-10	10 / 0-10	.011
Facial	0 / 0-2†	2 / 0-2	2 / 0-2	.000
Walk	0 / 0-12*†	9 / 0-12‡	12 / 0-12	.000
VFD	22 / 55%*†	10 / 27%‡	28 / 9.8%	.000
Clinical symptoms				
Non - asymmetric§	2 / 5%	9 / 24.5%	55 / 19%	ns
Right Sided	13 / 32.5%	18 / 48.5%	139 / 48.5%	ns
Left Sided	25 / 62.5%*†	10 / 27%	93 / 32.5%	.001
MRI/CT results				
MRI§	33 / 82.5%	32 / 86.5%	259 / 90%	ns
Normal MRI/CT	0	1 / 2.5%	23 / 8%	-
Acute Infarcts§	40 / 100%*†	30 / 81%	235 / 82%	.041
Left Hemisphere	12 / 30%	17 / 46%	110 / 38.5%	ns
Right Hemisphere	23 / 57.5%*†	8 / 21.5%	71 /24.5%	.000
Bilateral damage	2 / 5%	1 / 2.5%	6 / 2%	-
Brainstem§	3 / 7.5%	4 / 11%	33 / 11.5%	ns
Left Cerebellum	1 / 2.5%	1 / 2.5%	16 / 5.5%	-
Right Cerebellum	0	1 / 2.5%	24 / 8.5%	-
Non-acute infarcts	9 / 22.5%	11 / 29.5%	73 / 25.5%	ns
Left Hemisphere	2 / 5%	0	26 / 9%	-
Right Hemisphere§	5 / 12.5%	4 / 11%	26 / 9%	ns
Bilateral damage§	0	7 / 19%	10 / 3.5%	ns
Brainstem	0	1 / 2.5%	8 / 3%	-
Left Cerebellum	0	0	4 / 1.5%	-
Right Cerebellum§	3 / 7.5%	2 / 5.5%	1 / 0.5%	-

Values in Median/Range for ordinal data and number and percentage for nominal data. * = $p\leq 0.05$ between the LVI and VI groups. † = $p\leq 0.05$ between the LVI and NoVI groups. ‡ = $p\leq 0.05$ between the VI and NoVI groups, §= scores of the LVI and VI groups are collapsed and compared to the NoVI group with Fisher's exact test. If significant, individual two-group comparisons were done. One patient (NoVI) was not assessed with the SSS, and six (4 NoVI, 1 VI, and 1 LVI) was not assessed on all sub-items.

The LVI group also had inferior results to the VI group on total SSS, strength in arm, hand and leg, in ability to walk, and VFD (all *p*-values < .005 except for VFD with *p*=.02). Compared to the NoVI group, the VI group showed inferior results in total SSS score, ability to walk, and VFD (*p*-values <.01). The LVI group had more left sided symptoms, CT/MRI verified acute infarcts, and acute right sided infarcts compared to the VI group (*p*-values <.05) and NoVI group (*p*-values ≤.01). Acute and non-acute brainstem and cerebellum damages were uncommon in the two inattention groups (see table 2).

Functional dependency. Presence of functional dependency three months after stroke was analysed in participants with complete data and no recurring stroke (*n*=364). Participants showing LVI at the acute stage were more frequently dependent compared to the VI group (*p*=.006) and NoVI group (*p*<.001). Also, the VI group contained more functionally dependent patients than the NoVI group (*p*<.003) (see Table 3).

Table 3. Relationship Between Visual Inattention (LVI, VI, and NoVI) and Functional Dependency at the Post-acute and Follow-up Stages

Visual impairment groups	Functionally dependent	OR
Post-acute		
LVI (*n* = 40)	24 / 70.5%*†	17.1
VI (*n* = 37)	11 / 34.5%‡	3.7
NoVI (*n* = 287)	32 / 12.5%	-
Follow – up		
LVI (*n* = 12)	9 / 82%†	22.6
VI (*n* = 37)	15 / 48.5%‡	4.7
NoVI (*n*= 301)	48 / 16.5%	-

OR = Odds ratio between each of the inattention groups and the NoVI group

LVI = lateralized visual impairment, VI = visual impairment, NoVI = no visual impairmant. *n* =number of patients. Values are in number and percentage.

* = *p*≤ 0.05 between the LVI and VI groups, † = *p*≤ 0.05 between the LVI and NoVI groups, ‡ = p≤ 0.05 between the VI and NoVI groups.

Patients identified as having LVI post-acutely was 17.1 times more likely to be functionally dependent three months after the stroke compared to patients in the NoVI group. Patients who had LVI three months after the stroke were 22.6 times more likely to be functionally dependent compared to the NoVI group.

To identify the most important predictors of dependency among the post-acute variables stepwise logistic regression analyses were conducted. The regressions were done only for patients with no recurring stroke and with complete data on all SSS items (*n*=319) (see Table 4). For all participants, the final step of the regression selected LVI and VI as significant predictors of dependency. Among the SSS-variables, arm strength, language and walking ability were selected and the strongest predictor in this analysis was VFD. Additional regression analyses were done for patients with an acute left (*n*=142) - or right (*n*=108) hemisphere damage verified neuroradiologically and/or clinically (Table 4). Among the selected predictors, LVI and arm strength were the most important following right hemisphere damage, whilst VFD and ability to walk were the most important predictors of dependency following left hemisphere damage. The three different models made overall correct predictions in between 86 and 90 per cent of the cases.

Results from the follow-up assessments

Prior to the follow-up 18 of the original 375 participants suffered a new stroke, of which one died, and were excluded from further analysis. Of the remaining 357 patients, 29 were not tested on the SCT; 12 due to severe impairments, 6 declined, and 2 had moved abroad. The reason for missing data could not be established in 9 participants. There were insufficient data to allow for retrospective classification of visual inattention in 7 of these 29 participants. Thus, 350 patients were classified at follow-up, 301 (86%) had NoVI, 37 (10.6%) had VI, and 12 (3.4%) had LVI (Table 1). In the LVI group 4 (33%) had right sided visual neglect and 8 (67%) had left sided visual neglect. The NoVI group was significantly younger than the LVI (p=.007) and the VI (p=.019) groups.

The LVI group scored significantly inferior compared to the NoVI group on total SSS and on the individual neurological variables (p<.001 except for VFD and orientation with p<.05) apart from language and facial palsy (Table 5). The LVI group also had inferior results to the VI group on total SSS, strength in hand and leg, and ability to walk (p-values <.05)

The VI group scored inferior to the NoVI group on total SSS, strength in arm, hand and leg, and orientation, and VFD (p-values .002 to .035). The NoVI group had fewer participants with acute right hemisphere damages than the VI group (p=.009). Acute brainstem- and cerebellum damages were not found in either of the two inattention groups (see table 5).
Functional dependency. Presence of functional dependency was analysed in participants with complete data on the mRS (*n*= 331). The NoVI group had less functionally dependent participants than the LVI (p<.001) and VI (p<.000) groups (Table 3).

Table 4. Forward Stepwise Logistic Regression Analyses of Predictors of Functional Dependency

	β	*SE* β	χ^2	*p*	OR
All participants*					
LVI	1.616	.611	6.995	.008	5.031
VI	1.203	.529	5.175	.023	3.332
VFD	1.784	.495	12.960	.000	5.951
Arm strength	-.321	.119	7.318	.007	.725
Language	-.176	.062	8.083	.004	.839
Walking ability	-.157	.056	7.937	.005	.854
Left brain damage					
VFD	2.450	.690	12.601	.000	11.589
Language	-.220	.080	7.494	.006	.803
Facial palsy	-.764	.312	6.012	.014	.466
Walking ability	-.254	.063	16.453	.000	.776
Right brain damage					
LVI	3.293	.926	12.655	.000	26.930
VI	2.725	1.107	6.063	.014	15.259
Arm strength	-.720	.177	16.606	.000	.487

OR = odds ratio. LVI = lateralized visual impairment. VI = nonlateralized visual impairment VFD = visual field deficit. * = 319 patients. Patients with incomplete data or recurring stroke were not included.

Table 5. Results for the Follow-up LVI, VI and NoVI Groups on Neurological Symptoms and MRI/CT Scans

Variables	LVI	VI	NoVI	*p* =
SSS	39 / 9-48*†	46 / 19-48‡	48 / 11-48	.000
Arm	4 / 0-6†	6 / 0-6‡	6 / 0-6	.000
Hand	4 / 0-6*†	6 / 0-6‡	6 / 0-6	.000
Leg	5 / 0-6*†	6 / 4-6‡	6 / 0-6	.000
Orientation	6 / 4-6†	6 / 0-6‡	6 / 0-6	.018
Language	10 / 3-10	10 / 3-10	10 / 0-10	.ns
Facial palsy	2 / 0-2	2 / 0-2	2 / 0-2	.040
Walk	9 / 0-12*†	12 / 3-12	12 / 3-12	.000
VFD	3 / 25%	8 / 21.5%‡	16 / 5.5%	.000
Clinical symptoms				
Non-asymmetric	2 / 16.5%	2 / 5.5%	60 / 20%	-
Right sided	4 / 33.5%	18 / 48.5%	145 / 48%	ns
Left sided§	6 / 50%	17 / 46%	96 / 32%	.039
MRI/CT results				
MRI§	8 / 66.5%	30 / 81%	271 / 90%	.012
Normal MRI/CT	0	3 / 8%	21 / 7%	-
Acute Infarcts§	10 / 83.5%	32 / 86.5%	252 / 83.5%	ns
Left Hemisphere	4 / 33.5%	15 / 40.5%	120 / 40%	ns
Right Hemisphere§	6 / 50%	17 / 46%‡	73 / 24.5%	.001
Bilateral damage	0	0	7 / 2.5%	-
Brainstem	0	0	37 / 12.5%	-
Left Cerebellum	0	0	17 / 5.5%	-
Right Cerebellum	0	0	22 / 7.5%	-
Non-acute infarcts§	3 / 25%	9 / 24.5%	79 / 26%	ns
Left Hemisphere	1 / 8.5%	2 / 5.5%	25 / 8.5%	-
Right Hemisphere§	1 / 8.5%	3 / 8%	30 / 10%	ns
Bilateral damage	0	0	16 / 5.5%	-
Brainstem	0	1 / 2.5%	8 / 2.5%	-
Left Cerebellum	0	1 / 2.5%	3 / 1%	-
Right Cerebellum	1 / 8.5%	3 / 8%	2 / 0.5%	-

Values in Median/Range for ordinal data, and number and percentage for nominal data. * = $p \leq 0.05$ between the LVI and VI groups. † = $p \leq 0.05$ between the LVI and NoVI groups. ‡= $p \leq 0.05$ between the VI and NoVI groups, §= scores of the LVI and VI groups are collapsed and compared to the NoVI group with Fisher's exact test. If significant, individual two-group comparisons were done. 18 participants were not assessed with the SSS (11 NoVI, 6 VI, and 1 LVI)

Discussion

The substantial differences demonstrated between the LVI group and the VI and NoVI groups suggest that asymmetric inattention is related to severe symptoms and functional dependency following a stroke. Acutely the LVI group differed from the VI and NoVI groups by having more severe neurological deficits and right hemisphere damages with more clinical left sided symptoms. A greater proportion of LVI patients were functionally dependent three months after stroke compared to both the VI and NoVI groups. Patients with LVI at follow-up had more severe neurological deficits and a greater proportion was functionally dependent compared to both the VI and NoVI groups. The patients in the post-acute LVI group also differed from the VI patients by more often having persisting symptoms of visual inattention. Further, the results indicate that clinical symptoms of LVI at a late stage after stroke are relatively uncommon whilst remaining symptoms of nonlateralized inattention are more common. Patients with NoVI at follow-up were younger than the patients who were classified as LVI or VI. However, age was not selected as a predictor of dependency at the multivariate regression analyses.

The current results support previous findings suggesting an independent role of LVI in predicting functional outcome in patients with right hemisphere damage [11]. These observations underline the significance of assessing the asymmetric symptoms of inattention in an early stage after stroke during the initiation of rehabilitation. On the other hand, for the patients with left hemisphere damages the most important predictors of functional dependency were VFD, ability to walk and language difficulties.

In the current study the medical records of patients with missing data were scrutinized to retrospectively classify occurrence of visual inattention. In an additional analysis which excluded patients classified from medical records, the same pattern of significant group differences were obtained although the *p* values were somewhat higher (not reported in this study). The retrospective inclusion of patients resulted in an increased number of patients at both ends of the range of severity of symptoms: the patients with missing data either had severe neurological symptoms (including LVI or VI), or very subtle symptoms (without visual impairment). Thus the retrospective classification probably led to more distinct group differences.

The retrospective examination identified 15 patients with acute LVI and 5 patients with acute VI. At follow-up three patients with LVI and 6 patients with VI were identified. After the thorough examination only 3% of the total number of patients could not be classified acutely and 2% could not be classified at follow-up. In the study by Pedersen and collaborators [2] 35.8% in a series of 938 patients were not tested due to missing scores. The authors reported that patients with aphasia constituted the largest proportion of patients not tested (21.5%). Of the patients classified from the medical records in our study, 18 had aphasia and of these 33% had LVI. Excluding patients with aphasia may lead to an underestimation of the frequency of right-sided neglect following left hemisphere strokes because of the problems relating to testing patients with aphasia.

We are aware that reviewing medical records retrospectively is inferior to the acute assessment of visual inattention. However, we believe that this procedure is better than merely excluding missing cases as it allows for classification of patients with severe aphasia or other severe neurological deficits. Further strengths of the present study are the large consecutive and prospective sample in combination with a longitudinal design. The unselected nature of the sample, together with the age limit of ≤ 69 years, increased the possibility of following-up the patients over time. As the patients represented an unselected consecutive series the current sample included 73 (19,5%) patients with prior strokes. Thus, the results cannot solely be ascribed to the new stroke.

The present study emphasises the prognostic importance of acute signs of LVI. Asymmetry in the inattentive performance seems to be more important than visual inattention per se. Thus, patients with LVI should be treated separately in studies that investigate the consequences of stroke.

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Disclosures
None

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