

Incidence, Risk Factors and Anatomy of Peripersonal Visuospatial Neglect in Acute Stroke

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Key Words

Stroke · Peripersonal visuospatial neglect · Anatomy · Epidemiology · Risk factors

Abstract

Aim: The study aims to describe the epidemiology and the neural correlates of peripersonal visuospatial neglect (PVN) in patients admitted to the Geneva Stroke Unit for an acute stroke or a transient ischemic attack (TIA). **Methods:** Eligible subjects were tested for PVN using both the Ota's discriminative cancellation task and a line bisection task. Brain lesions were identified on diffusion-weighted imaging. A multivariate analysis was performed to identify risk factors of PVN. **Results:** Ninety-eight consecutive patients (40.8% females) were recruited: 64 cases of ischemic stroke, 9 cases of hemorrhagic stroke and 25 cases of TIAs. The mean age was 61.9 ± 2.86 years. The incidence of PVN was 23.5% (95% CI 15.5–33.1) and was not significantly different between patients with right and left hemisphere stroke. There were 5 cases of ipsilesional neglect. There was no association between PVN and age, sex, stroke severity, handedness, lesion type, lesion volume and time to first examination. Lesions of temporal

and parietal lobes were the most frequent in patients with PVN. **Conclusion:** PVN has a low incidence in the acute stroke settings and there is no particular predictor of its presence. It is most often associated with temporo-parietal lesions.

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Introduction

Neglect is a behavioral disorder characterized by failure to report, respond or orient to novel meaningful stimuli presented in a specific location, when this failure cannot be attributed to either sensory or motor defects [1]. It should be viewed as a puzzling syndrome made up of several behavioral manifestations including extinction, neglect, anosognosia and anosodiaphoria. Extinction of sensory stimuli appears on double simultaneous stimulation and can be either unimodal (tactile, visual or auditory), multimodal or cross-modal while neglect can be sensory, visuospatial, motor, representational or personal [2, 3]. In patients with visuospatial neglect, the target of the behavioral disorder is the surrounding space. Patients typically exhibit impaired spatial awareness and most of

ten fail to respond or react to stimuli located on the contralesional side of the body. Visuospatial neglect can be further divided into 2 categories: peripersonal visuospatial neglect (PVN) referring to neglect behaviors occurring within reaching space (near space) and extrapersonal visuospatial neglect referring to neglect behaviors occurring in far space [4, 5]. Most studies of PVN available in the literature have been conducted on selected patients with subacute and chronic brain lesions [6–8]. The few studies that included acute stroke cases and evaluated risk factors only focused on patients with right hemisphere lesions and some did not evaluate allocentric neglect [9–13]. Our aim was to study the epidemiology and the neural correlates of PVN in the acute stroke settings with inclusion of both right and left hemisphere strokes while testing for both perceptive, exploratory and allocentric components of PVN to increase sensitivity [10, 13–15]. Comparing these data with those obtained in patients with subacute and chronic brain lesions might provide some insights on the pathophysiology of PVN.

Materials and Methods

Study Design, Setting and Selection of Participants

This prospective cohort study was conducted on patients with acute stroke or transient ischemic attack (TIA) admitted to the Stroke Unit of the Geneva University Hospital, from September 2012 to March 2014. Our exclusion criteria were very stringent including pre-existing alterations of visual or cognitive functions, past history of stroke, admission occurring more than 15 days after stroke onset and contraindications for MRI. Patients with symptoms strictly related to retinal ischemia or infarction were not included. Patients with altered level of consciousness were not systematically excluded but rather examined later depending on their capacity to cooperate.

Clinical Evaluation of Patients

Patients were clinically tested for PVN on the first day of admission. We also recorded data on factors potentially related to PVN: age, gender, handedness, stroke severity assessed with the National Institute of Health Stroke Scale (NIHSS), lesion volume (voxels), stroke type (ischemic/hemorrhagic) and location on diffusion-weighted imaging sequences obtained with on a 3T MRI device within 15 days of onset.

Two paper-and-pencil tests were used to test for PVN: the Ota's gap detection task [14] and a line bisection task [8].

The Ota's gap detection task is a figure discriminative cancellation task used for assessment of unilateral neglect, which also discriminates between body-centered and object-centered neglect [14]. The Ota's cancellation task is similar to the bells test which is the most sensitive tool to identify patients with unilateral neglect [9]. Patients were instructed to circle every complete circle or to cross out every incomplete circle on the test sheet, using a pencil held in the hand. After the test, we compared the number of left

stimuli missed, and the number of right stimuli missed. The neglected side was the one that had a simple majority of stimuli missed [10]. We considered that such decision criteria would ensure a higher sensitivity. Different decision scores for cancellation tasks have been used by other researchers but there is currently no consensus in the literature with respect to the ideal decision criteria [7, 9]. Results of the Ota's test were also used to compute a center of cancellation score (CoC), which has been proven to be a good measure of neglect severity [16, 17]. We used the procedure and the software provided by Rorden and Karnath [16] (<http://www.mccauslandcenter.sc.edu/CRNL/tools/cancel>).

For the line bisection task, patients were asked to mark the middle of 4 lines of 2 different lengths (5 and 20 cm), presented separately and centered on an A4 size horizontal white sheet or paper. A 20 cm line was presented first, then the two 5 cm lines and lastly the second 20 cm line. Deviation from the true middle was measured in millimeters (mm), positively for rightward deviation, negatively for leftward deviation. A separate score for the 20 cm lines and the 5 cm lines was then obtained by computing the average of signed deviations obtained. The side of hemineglect was opposite to the side toward which the middle of the line is deviated. A negative score lower than -7.2 mm for both 20 cm lines and/or -2.5 mm for both 5 cm lines was considered as right hemispatial neglect. A positive score greater than $+6.5$ mm for both 20 cm lines and/or $+2$ mm for both 5 cm lines was considered as left hemineglect. These cutoffs for maximum acceptable deviation have been validated in previous studies [8]. The acting hand has no effect on the results for the 20 cm lines and the usage of 2 different line types may help to correct the effect on the 5 cm lines test (larger leftward deviation with the left hand) [8].

A patient was considered as having PVN if he had a positive result for at least 1 of the 3 tasks used to screen for unilateral neglect (Ota's test, 5 cm line bisection task and 20 cm line bisection task). It is well known that a combination of tests is more sensitive than using one single test, especially because some patients may have normal results in less sensitive tasks [8].

Anatomical Study of Brain Lesions

An independent anatomical study was done based on MRI findings. The following functional regions of the brain were attributed a score of 1 if they were partially or totally affected by the acute stroke or 0 if not involved at all: frontal, insular, rolandic, parietal, temporal, occipital, thalamic, caudate nucleus, putamen, pallidum, internal capsule, brain stem and cerebellum. The region-specific score (RSS) was defined as the total number of times that a functional region had received a score of 1 after reviewing all MRIs of patients with PVN. The region involvement index (RII) was defined as the ratio of a RSS and the sum of all RSSs. A RII of $\geq 10\%$ was arbitrarily interpreted as a significant association between PVN and the functional region studied.

In addition to the anatomical analysis described above, we performed a complementary voxel-based lesion statistical mapping (VLSM) analysis. We used a procedure previously reported in the analysis of brain lesion-behavior relationships [15, 18, 19]. The location and the extent of brain damage were delineated in each patient, based on their MRI scan obtained with a 3T apparatus. The slices thickness was 2 mm. Lesions identified on diffusion-weighted imaging sequences were manually reconstructed on a standardized brain template with the MRICro software (www.mricro.com) [12]. This was done by a trained neuropsychologist who was blind-

Table 1. Distribution of visuospatial neglect as evaluated on visit 1 with test combination, according to: side of lesion, age, sex, handedness, type of lesion, stroke severity. Number of positive cases = 23

Factors studied	Visuospatial neglect		Total	p value
	yes	no		
Sex				0.2
Male	11	47	58	
Female	12	28	40	
Age	62.3 (56.0–68.6)	61.9 (58.5–65.3)	61.9 (59.1–64.9)	0.9
Side of lesion				0.9
No lesion	6	19	25	
Right	9	27	36	
Left	8	25	33	
Bilateral lesions	0	4	4	
Type of lesion				0.8
Ischemic	16	48	64	
Haemorrhagic	1	8	9	
Stroke severity (NIHSS score)	1.4 (0.7–2.2)	1.4 (1.0–1.9)	1.4 (1.07–1.8)	0.9
Lesion volume (voxels)	2,961 (0–6,027.9)	2,109.1 (977.9–3,240.3)	2,309 (1,211.3–3,406.8)	0.9
Time to first examination	3.5 (2.8–4.3)	3.8 (3.1–4.4)	3.7 (3.2–4.2)	0.7
Handedness				0.7
Right-handed	20	68	88	
Left-handed	3	7	10	

ed to patients' performance (A.S.). All 3D lesion maps were entered into the Matlab-based VLMS code [20] with the corresponding behavioral scores. On a voxel-by-voxel basis, the VLMS separated the subjects into 2 groups according to the presence or the absence of a lesion in the voxel considered. A t test was performed based on behavioral scores of each test individually then on an average of neglect scores obtained with all 3 tests. The resulting statistical measure was used to create a separate map based on each variable. Areas showing significant correlations with PVN were identified using the false discovery rate corrected at $p < 0.05$. Resultant statistics were mapped onto standardized brain templates from the Montreal Neurological Institute.

Ethical and Statistical Issues

The study was approved by the Geneva University Hospital Ethical Committee for Research on Human Beings (Authorization number: CER 12-191). All patients included gave an informed consent to take part in the study. Access to patient data and anonymized case report forms was strictly restricted to authorized members of the research team.

Statistical analysis was performed using the statistical software STATA 13. The incidence of PVN and means for quantitative data were computed with a 95% CI. In order to identify variables associated with the presence of PVN in acute stroke or TIA, a univariate analysis was performed using the Pearson's chi-square for categorical independent variables and the Student t test for continuous variables. Fisher's exact test and Mann-Whitney U test were used whenever appropriate. A multivariate logistic regression model was used to adjust for potential confounders in case a significant association was found. Differences between groups of patients with and without PVN were considered statistically significant for p values < 0.05 .

Results

We recruited a total of 101 patients including 41% women. Three of them were further excluded during analysis because the diagnosis at discharge was not stroke (1 case of seizure, 2 cases of migraine with aura). The mean age was 61.9 ± 2.86 years (range 29–87). There were 64 cases of ischemic stroke (65.3%), 9 cases of hemorrhagic stroke (9.2%) and 25 cases of TIA (25.5%). Mean time to first examination was 3.7 days (range 0–15; SD 2.5). The incidence of PVN was 23.5% (23/98, 15.5–33.1) when considering all subjects together and 23.3% (17/73, 14.2–34.6) when excluding patients with TIA. The neglect severity score was higher in patients with right brain lesion than in those with left brain lesion but the difference was not significant (mean CoC 0.005 vs. 0.001; $p = 0.7$). Table 1 summarizes the results of the analyses performed to identify risk factors of PVN.

When considering only the results of the Ota's cancellation task, the incidence of PVN was 15.3% (15/98, 8.8–23.9). There were more cases of left (10) than right (5) PVN but the difference was not significant ($p = 0.5$). According to this task, there were 5 cases of ipsilesional PVN (3 patients with left hemisphere stroke and 2 with right hemisphere stroke) and the mean time to first examination in these patients was 3.2 days (SD 1.8, range 1–6). There was no difference in stroke severity between pa-

Table 2. Neuroanatomy of visuospatial neglect

	Fr	Ins	Rol	Par	Temp	Occ	Thal	CN	Put	Pal	IC	BS	C
RSS (right)	2	2	2	3	5	2	2	0	2	1	1	1	0
RII (right)	0.09	0.09	0.09	0.13	0.22	0.09	0.09	0.00	0.09	0.04	0.04	0.04	0.00
RSS (left)	0	1	1	2	1	0	2	1	1	0	0	3	0
RII (left)	0.00	0.08	0.08	0.16	0.08	0.00	0.16	0.08	0.08	0.00	0.00	0.25	0.00
Global RSS	2	3	3	5	6	2	4	1	3	1	1	4	0
Global RII	0.06	0.09	0.09	0.14*	0.17*	0.06	0.11*	0.03	0.09	0.03	0.03	0.11*	0.00

Fr = Frontal; Ins = insular; Rol = rolandic; Par = parietal; Temp = temporal; Occ = occipital; Thal = thalamus; CN = caudate nucleus; Put = putamen; Pall = pallidum; IC = internal capsule; BS = brainstem; C = cerebellum.

* RII >10%.

Table 3. Neuroanatomy of ipsilesional visuospatial neglect, number of positive cases = 5*

Side of lesion	H	Fr	Ins	Rol	Par	Temp	Occ	Thal	CN	Put	Pal	IC	BS	C
Right	R	0	0	0	0	1	1	0	0	0	0	0	0	0
	R	0	0	0	0	0	0	1	0	0	0	0	0	0
Left	R	0	1	0	1	1	0	0	0	0	0	0	0	0
	R	0	0	0	0	0	0	1	0	0	0	0	0	0
	R	0	0	0	0	0	0	0	0	0	0	0	1	0

H = Handedness (R = right-handed); Fr = frontal; Ins = insular; Rol = rolandic; Par = parietal; Temp = temporal; Occ = occipital; Thal = thalamus; CN = caudate nucleus; Put = putamen; Pall = pallidum; IC = internal capsule; BS = brain stem; C = cerebellum.

* No region involvement index was computed due to the small number of subjects with ipsilesional visuospatial neglect. Multiple sites are indicated when the number 1 appears in more than one functional region (e.g., patient number 1 had both temporal and occipital involvement).

tients with contralesional neglect and those with ipsilesional neglect (mean NIHSS score: 1.1 vs. 2.4; $p = 0.6$). There was also no difference in neglect severity between patients with contralesional neglect and those with ipsilesional neglect (mean CoC 0.02 vs. 0.01; $p = 0.8$).

When considering only the results of the line bisection tasks, the incidence of PVN was 8.2% (8/98, 3.6–15.5) with either the short 5 cm line or the long 20 cm line. There was 87.8% agreement between the conclusions of both line bisection tasks. There was 84.7% agreement between Ota's cancellation task and the short 5 cm line bisection task. The same result was found when comparing Ota's cancellation task to the 20 cm line bisection task (84.7% agreement). When considering both line bisection task together as a single test on one hand (abnormal result for any or both) and Ota's cancellation task on the other hand, we found 82.7% agreement.

The anatomical analysis showed that lesions of the temporal lobe, the parietal lobe, the thalamus and the

brainstem were significantly associated with the presence of PVN according to global region involvement indices (table 2). Results of the anatomical analysis for patients with ipsilesional PVN are shown in table 3. The complementary VLSM analysis did not identify any voxel significantly associated with PVN.

Discussion

We performed a cross-sectional study to gather data on the epidemiology and neural correlates of PVN in the acute stroke settings. This study included all strokes and TIAs. The anatomical analysis was based on DWI sequences. The incidence of PVN in our sample was 23.5%. Age, sex, handedness, lesion side, lesion volume, stroke type, stroke severity and time to first examination were not significantly associated with the presence of PVN. The temporo-parietal region, the thalamus and the brain

stem were the brain regions most frequently involved in patients with PVN.

The incidence of PVN reported in this study is similar to that obtained in previous studies [8, 11, 21, 22]. The lack of association between PVN and the potential risk factors considered in our study have also been previously reported in larger studies [8, 21]. The incidence of PVN was not significantly different between patients with right hemisphere stroke and those with left hemisphere stroke. Previous studies on the association between lesion side and incidence of PVN have yielded contradictory results [8, 21–23]. This might be explained by the heterogeneity of assessment methods [18]. Indeed, studies using discriminative cancellation tasks – known to be more sensitive – frequently report lack of significant difference in the incidence of PVN in patients with right versus left brain damage [22]. This suggests that PVN caused by left brain lesions might be frequently missed if not systematically tested using appropriate tasks because it is usually less severe [17, 21]. The non-significant difference of neglect severity scores between patients with right versus left brain lesions in our study might be explained by the small sample size. Other possible explanations for contradictory results found in literature include subject selection, variable delay between stroke onset and assessment and pattern of lesion localization in a given sample [23].

Confirming previous observations, the anatomical analysis revealed the predominance of temporal and parietal lobe lesions in patients with PVN. There was discordance between results of the anatomical analysis based on region involvement indices and those provided by the VLSM analysis. Two putative hypotheses could explain this discordance. First, the small sample size could have limited the possibility to identify associations using VLSM analysis (decreased power of statistical tests). Second, the statistical approach aiming to identify a single lesion focus underlying PVN does not account for the fact that visuospatial awareness is mostly supported by a network rather than a single right or left hemisphere region [6, 18, 24, 25]. Hence, VLSM analysis, though interesting, could also be sometimes misleading.

Several studies have pointed out the preponderant role of temporal and parietal lobes in spatial awareness [2, 11, 21, 26]. Interestingly, by considering results of the anatomical analysis displayed in table 2, it appears that the cumulative involvement index of the temporal and the parietal lobes is higher in the right hemisphere (around 35%) than in the left hemisphere. In the latter, lesions are more evenly distributed between all functional regions considered. This finding could indicate that the attentional net-

work is concentrated around the temporo-parietal region in the right hemisphere while it is more widely distributed in the left one, involving several cortical and subcortical structures. If this hypothesis is proven true, it might suggest that the attentional network is more vulnerable in the right hemisphere with single strategic lesions of the temporo-parietal region frequently causing severe attentional deficits regardless of their size. A greater vulnerability of the attentional network in the right hemisphere would therefore justify the fact that PVN is more severe with right brain lesions but not more frequent than with left brain lesions as discussed above. Indeed, the wider distribution of the attentional network in the left hemisphere could limit the negative effects of brain lesions on the attentional capacity (greater resistance).

Association between neglect syndromes and lesions of subcortical structures has also been reported as is the case in some of our patients. Subcortical lesions are thought to induce PVN through disconnection of the temporo-parietal cortex [27, 28]. In this study, PVN was found in 6 patients with TIA. This finding has also been previously reported by authors who suggest that several mechanisms of focal brain dysfunction without brain lesion can induce PVN, notably misery perfusion and diaschisis [10, 21, 26].

We found 5 cases with ipsilesional PVN when considering Ota's cancellation task only. This unusual phenomenon has been reported several times since its first description in 1988 [29, 30]. The mechanisms underlying ipsilateral neglect have not been entirely elucidated. Data currently available suggest that it may be the results of an inappropriate approach behavior mediated by a disinhibited ipsilesional parietal lobe leading to a visual grasping directed toward the contralesional side. Indeed, it has been demonstrated that most patients with ipsilateral neglect have lesions in the frontal lobe [31, 32], which is responsible for avoidance behaviors [33]. Therefore, frontal lobe's lesions might disinhibit the ipsilateral parietal lobe and induce the aberrant approach behavior responsible for the attentional and intentional biases. However, none of our patients with ipsilesional neglect had a frontal lobe lesion (table 3). This finding suggests that inappropriate approach behavior might not be the only mechanism accounting for ipsilesional neglect. Other authors have suggested that ipsilateral neglect might also be related to a learned compensatory strategy [34, 35]. It is however difficult to support this hypothesis in our cases for 2 reasons. First, they were evaluated early after the onset of symptoms and probably did not have enough time to develop significant compensatory mechanisms. Second, there was

no difference in either stroke severity or neglect severity between patients with contralesional neglect and those with ipsilesional neglect making it difficult to argue that the latter had become more aware of their deficit and begun to compensate on their own, independently, within the acute setting. Finally, data from more recent studies evaluating attentional bias in subacute stroke patients with ipsilesional neglect [32] suggest a complex mechanism, which probably involve both impairment of perceptual attentional awareness of stimuli in one side of space ('where' bias) and deficits of motor intentional movement preparation ('aim bias').

The main limitation of this study is the small sample size resulting from the use of stringent selection criteria, which has possibly led to an underestimation of the incidence of PVN. Recruitment and evaluation of patients in the acute stroke settings has been hampered by the fact that most of them have altered consciousness – especially those with big lesions – and are less willing to take part in clinical studies (especially if they have to go through complex procedures) or have other complications (blood pressure instability, infections, venous thrombosis, myocardial infarctions, cardiac dysrhythmias, stress cardiomyopathy, hemorrhagic transformation of ischemic brain lesions) whose management have priority over inclusion in clinical studies. This has also obviously led to a selection bias accounting for the low NIHSS scores in this study. Nevertheless, the impact of this selection bias might be at least partially counterbalanced by a better reliability of results obtained in assessing PVN in this study since alterations of alertness in patients with large brain lesions could affect their performance. Another limitation is the fact that we did not systematically perform brain perfusion imaging in all our patients and therefore could not give more details on the pathophysiology of PVN in patients with negative brain MRI. Finally, as a TIA often heralds stroke [36], a follow-up of our patients with TIA to identify those who would subsequently develop ischemic or hemorrhagic stroke could have provided an opportunity to examine the potential prognostic value of PVN in TIA and generate a hypothesis for future clinical studies.

In conclusion, this study provides an estimate of the incidence of PVN in acute stroke and shows that age, sex, handedness, lesion side, lesion volume, stroke type and severity are not predictors of its presence in acute stroke patients. It also confirms that PVN can be found in patients with no DWI lesions thus giving a reason to encourage formal in-depth testing for this behavioral disorder, especially when all other stroke diagnostic tests are

negative. Finally, results from the anatomical analysis performed in this study suggest a different organization of the attentional network between the right (concentration around the temporo-parietal region) and the left (wider distribution involving many cortical and subcortical structures) hemispheres that needs to be tested in further clinical studies.

Author's Contribution

J.K.T. designed the study, performed patients' examination and statistical analysis and drafted the manuscript; G.A., R.S., P.P., A.S. and I.M. provided methodological support throughout the study, supervised patient recruitment and revised the manuscript; T.B. took part in patients' examination, prepared the database for statistical analysis, performed analysis on MRIcro and revised the manuscript. All authors approved the final version of the manuscript.

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Disclosure Statement

The authors declare that they have no competing interest.

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