Subcortical neglect is not always a transient phenomenon:
Evidence from a 1-year follow-up study

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Abstract

Compared to cortical lesions, spatial neglect following subcortical stroke is most frequently seen as a mild and transient phenomenon. Since this assumption is based on only few observations, we re-examined the prognosis and severity of spatial neglect in patients with circumscribed right-sided basal ganglia or thalamic lesions in the acute and in the chronic phase of the stroke. On average 1.15 years after stroke, spatial neglect had persisted in about 40% of the patients with subcortical lesions. The severity was reduced to about one third. The results argue against the view that spatial neglect following subcortical lesions typically has a favorable prognosis.
Introduction

Spatial neglect is well-known to occur not only with cortical injury but likewise after right-sided subcortical lesions restricted to the basal ganglia or the thalamus (e.g. Caplan et al., 1990; Fromm, Holland, Swindell, & Reinmuth, 1985; Healton, Navarro, Bressman, & Brust, 1982; Karnath, Himmelbach, & Rorden, 2002; Kumral, Kocaer, Ertubey, & Kumral, 1995; Rusconi, Maravita, Bottini, & Vallar, 2002; Vallar, 2008; Vallar & Perani, 1986; Watson, Valenstein, & Heilman, 1981). In comparison to cortical lesions, subcortical neglect is most frequently seen as a mild and transient phenomenon and thus has a favourable long-term prognosis. However, this assumption is based on rather few, usually single case or small group studies. This is mainly because studies on subcortical neglect are constrained by its lower incidence compared to spatial neglect following cortical lesions (Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1997). Some authors concluded that lesions confined to the basal ganglia and adjoining white matter produce mild to moderate neglect that completely recovers after the early phase of stroke (sample size $n = 3$; Samuelsson, Jensen, Ekholm, Naver, & Blomstrand, 1997). Persisting symptoms of spatial neglect were observed in only 18% of a sample of 11 patients with circumscribed lesions of the right thalamus while the remaining portion of acute neglect patients had recovered completely three months post-stroke (Motonura, Yamadori, Mori, Ogura, Saka, & Sawada, 1986). A further study investigated both the recoveries of aphasia and of neglect after basal ganglia lesions (Weiller et al., 1993). One year post-stroke, the prognosis was excellent for patients with initial neglect after right-sided lesions and was slightly reduced for patients with initial aphasia due to left hemisphere stroke. While neglect had recovered completely in all 9 patients with acute symptoms, language disturbances persisted in 20% of the patients with initial aphasia at the follow-up.
However, also contrasting observations were reported. Three months post-stroke, chronic neglect symptoms were observed in three out of five patients (i.e. 60%) with subcortical lesions (Ferro, Kertesz, & Black, 1987). A further study reported symptoms of chronic neglect as tested by simple drawing tests and the Raven's Coloured Progressive Matrices 1 year post stroke in 3 selected patients (1 with thalamic, 2 with basal ganglia lesions; Fromm et al., 1985). Moreover, Cappa, Guariglia, Messa, Pizzamiglio, and Zoccolotti (1991) studied 5 patients with deep lesions who had persistent symptoms of spatial neglect at a one-time examination carried out on average 3 months post stroke (ranging from 3 to 35 months). Likewise, a single case observation on a patient with a thalamic lesion revealed chronic spatial neglect eight months post-stroke (Colombo, De Renzi, & Gentilini, 1982).

Due to the contradicting observations in previous studies, the aim of the present investigation was to study patients with subcortical lesions centering on either the basal ganglia or the thalamus and to re-examine the question whether such lesions lead to only transient neglect symptoms and have a favourable prognosis. In contrast to previous studies (Cappa et al., 1991; Ferro et al., 1987; Motomura et al., 1986; Samuelsson et al., 1997), the present investigation should re-examine patients not before eight months had elapsed after the stroke in order to exclude further marked spontaneous improvement of the disorder.

Methods

Sixteen patients consecutively admitted to the Centre of Neurology at Tübingen University were diagnosed as showing spatial neglect due to an acute subcortical stroke in the basal ganglia or the thalamus. All patients had a circumscribed right-sided lesion due to ischaemic or haemorrhagic first-ever stroke demonstrated by diffusion-weighted and T₂-weighted fluid-attenuated inversion recovery MRI or by spiral CT. Patients with previous brain lesions, cerebral atrophy, tumours, diffuse or bilateral lesions were excluded.
Spatial neglect was diagnosed when the patients showed the typical clinical behaviour such as constant eye and head orientation towards the right (Fruhmann Berger & Karnath, 2005), orienting towards the ipsilesional side when addressed from the front or the left, and/or ignoring of contralesionally located people or objects. In addition, each neglect patient further had to fulfil the criterion for spatial neglect in at least two of the following three clinical tests: the “Letter cancellation” task, the “Bells test”, and a copying task. (i) The Letter Cancellation Task (Weintraub & Mesulam, 1985). Sixty target letters 'A' are distributed amid distractors on an A4 landscape paper; 30 targets on the right half of the page and 30 on the left. Patients were asked to cancel all of the targets and were classified as suffering from spatial neglect when they omitted at least five left-sided targets. (ii) The Bells Test (Gauthier, Dehaut, & Joanette, 1989). The task consists of seven columns each containing five targets (bells) and 40 distractors evenly distributed over the sheet. Three of the seven columns (= 15 targets) are on the left side, one in its middle, and three on its right side (= 15 targets) of an A4 landscape paper. Again, patients were asked to cancel all of the targets. More than five left-sided target omissions were taken to indicate spatial neglect. (iii) Copying Task (Johannsen & Karnath, 2004). Patients were asked to copy a complex multi-object scene consisting of four figures (a fence, a car, a house, and a tree), two in each half of an A4 landscape format. Omission of at least one of the left-sided features of each figure was scored as one, and omission of each whole figure was scored as two. One additional point was given when left-sided figures were drawn on the right side. The maximum score was 8. A score higher than 1 (i.e. more than 12.5% omissions) was taken to indicate spatial neglect.

The initial examination was carried out on average 10.5 days (SD = 8.3) post-stroke. To exclude further marked spontaneous improvement of the disorder, patients were re-examined not before 8 months had elapsed after stroke. In this chronic phase, two patients had deceased, one patient developed dementia in the intermediate period and was excluded, two patients denied being examined a second time, and one patient had moved far beyond the
catchment area. Thus, 10 of the initial 16 subcortical patients could be re-examined with the same tests used in the acute phase. This investigation was carried out 1.15 years ($M = 412.6$ days, $SD = 95.7$) post-stroke. Table 1 provides the relevant demographic, clinical, and anatomical data of these 10 patients. All subjects gave their informed consent to participate in the study that has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

--- Table 1 near here ---

**Results**

In the chronic phase, 1.15 years post-stroke, 4 of the 10 subcortical patients (= 40%) still showed spatial neglect in at least 1 of the 3 clinical neglect tests ($median = 1$ test positive, $range = 1$ to 3). Chronic neglect was found in half of the patients with basal ganglia lesions and in 1 of the 4 patients with thalamic stroke. Figure 1 illustrates the lesions of the subcortical patients who had recovered ($n = 6$, left panels) and those who developed chronic neglect ($n = 4$, right panels).

--- Figure 1 near here ---

In the 4 patients with chronic neglect and the 6 who had recovered, we analysed factors age, strength of contralateral hemiparesis, presence of visual field defects, days spent in the rehabilitation unit, weekly amount of physiotherapy and occupational therapy, time of re-examination, aetiology, and lesion volume. Both groups were comparable with respect to the time of re-examination (chronic patients: $M = 424.0$, $SD = 132.4$; recovered patients: $M = 405.0$, $SD = 76.1$; $U = 12$, $p = 1.0$). Patients who developed chronic neglect were older ($M =$
78.1, $SD = 3.0$) than those who had recovered ($M = 61.6, SD = 11.0; U = 2, p = .04$). Further, persisting neglect symptoms were more frequent following ischaemic lesions (Fisher’s exact test: $p = .03$). Particularly in the group with basal ganglia stroke, all ischaemic lesions led to chronic neglect while all patients with haemorrhages had recovered.

The strength of contralateral hemiparesis did not differ between the patients with chronic neglect ($M = 3.2, SD = 1.0$) and those who had recovered ($M = 2.9, SD = 1.6; U = 10, p = .76$). Moreover, the groups were comparable with respect to the frequency of visual field defects (Fisher’s exact test: $p = 1.0$), days spent in the rehabilitation unit ($U = 11, p = .87$), the weekly amount of physiotherapy ($U = 7, p = .32$) and of occupational therapy ($U = 10.5, p = .86$). We also found no marked differences for lesion location (cf. Fig. 1) or for lesion volume between patients with recovered ($M = 2.4\%$ of right hemisphere volume, $SD = 1.9$) and persistent neglect ($M = 2.1\%, SD = 0.9; U = 11, p = .87$).

Figure 2 illustrates the severity in the three clinical neglect tests observed in the patients with recovered ($n = 6$) and with persistent symptoms ($n = 4$) for both the acute and the chronic phase of the stroke. In the latter, 1.15 years post-stroke, the severity of spatial neglect was reduced to about one third compared to the initial examination.

--- Figure 2 near here ---

We compared the severity of spatial neglect in the acute phase between the patients who recovered later on and those who developed chronic symptoms. Regarding the number of initially positive neglect tests, we found no difference between the patients with persistent ($M = 3.0, SD = 0.0$) and recovered symptoms ($M = 2.5, SD = 0.6; U = 6, p = .20$). Moreover, the two groups were comparable in the acute phase regarding the percentage of targets neglected in the letter cancellation test ($U = 4, p = .11$), the bells test ($U = 8.5, p = .51$), and the copying task ($U = 3, p = .12$).
Discussion

The present study investigated the prognosis and severity of spatial neglect following a right-sided subcortical lesion restricted to either the basal ganglia or the thalamus. Following a first investigation in the acute phase of the stroke, the re-examination was carried out on average 1.15 years post-stroke. Even after this long period, we observed chronic neglect in 40% of the patients who initially showed the disorder. Its severity was reduced to about one third of the neglect behaviour found in the acute phase. Our results are in line with previous reports of patients showing chronic spatial neglect following basal ganglia or thalamic infarcts (Cappa et al., 1991; Colombo et al., 1982; Fromm et al., 1985). They oppose the frequent belief that spatial neglect due to a basal ganglia or a thalamic lesion is a transient phenomenon and typically has a favourable prognosis (Motonura et al., 1986; Samuelsson et al., 1997; Weiller et al., 1993).

What might account for the differences between the recovery rates found in part of the previous and the present investigations? Regarding the overall severity of initial neglect symptoms, it might be that the patients in previous studies were not as severely impaired as the present patient sample. More than two thirds of our acute patients showed marked deficits, regardless of whether they developed chronic symptoms or not. Unfortunately, former studies (Motonura et al., 1986; Samuelsson et al., 1997; Weiller et al., 1993) did not provide information about test scores or the severity of spatial neglect in the acute phase that would allow for a detailed comparison to our data. Nevertheless, the observation that all patients despite one in the sample of Weiller et al. (1993) already had recovered during the hospital stay, points to initially mild symptoms. Also Samuelsson et al. (1997) reported that their patients with a basal ganglia lesion showed mild to moderate neglect at the initial investigation.

The differences to former studies could further be explained by the varying diagnostic procedures. Some patient samples were tested for neglect by simultaneous tactile stimulation
(tactile extinction) and by asking for a verbal description of a complex picture scene (Cooky Theft Picture; Ringman, Saver, Woolson, Clarke, & Adams, 2004), i.e. by very different tasks compared to the present study. Another study mentioned that spatial neglect was assessed during ‘beside examination’ but did not report, which tests were used (Weiller et al., 1993, p. 1510).

Closer attention deserves the aetiology of the subcortical strokes. All patients of our basal ganglia group who suffered from an ischaemic infarct developed chronic neglect while those with haemorrhages in these structures recovered. Also, Hier, Mondlock, and Caplan (1983) found that spatial neglect due to haemorrhage recovers more quickly than following infarction. However, the disorder may also persist after subcortical haemorrhages. This has been shown previously (Motomura et al., 1986) and was again observed in the present group with thalamic lesions. Conversely, subcortical ischaemia does not necessarily lead to chronic neglect, but may recover (Weiller et al., 1993). However, concerning the limited number of currently available follow-up studies on subcortical neglect, conclusions on the consequences of different stroke aetiologies on the prognosis of the disorder need further investigation.

Based on previous studies it can already be concluded that only those patients with right subcortical infarcts suffer from spatial neglect (and only those patients with left subcortical infarcts from aphasia) who have additional perfusion deficits in the ipsilesional cortex (Hillis et al., 2002; Weiller, Ringelstein, Reiche, Thron, & Buell, 1990; Weiller et al., 1993). Such malperfusion is not or is significantly less observed in subcortical stroke patients without the disorder. Right basal ganglia strokes that provoke spatial neglect typically induce perfusion deficits in the superior temporal gyrus, the inferior parietal lobule, and the inferior frontal gyrus (Karnath et al., 2005), i.e. in structurally intact cortical areas that have been previously described to cause the disorder when injured directly by cortical infarction. This implies that spatial neglect due to a right basal ganglia lesion typically results from a dysfunction of (part of) these cortical areas. Future studies investigating the course of the
disorder after subcortical stroke and its relation to cortical malperfusion thus may help to understand the mechanism involved in the recovery from subcortical neglect.

Reports on the course of subcortical aphasia after left-sided lesions offer an interesting parallel to the present observations in right hemisphere stroke patients. Like subcortical neglect, also aphasia has often been reported to have a more favourable prognosis after subcortical than after cortical lesions (Démonet, 1997; Nadeau & Crosson, 1997; Olsen, Bruhn, & Oberg, 1986; Wallesch, Johannsen-Horbach, Bartels, & Herrmann, 1997). However, comparable to our results on subcortical neglect, some reports on aphasia challenged this view (Naeser et al., 1982; Robin & Schienberg, 1990). A study on subcortical lesions and aphasia revealed persistent symptoms in about 84% of those patients who were re-examined not before 8 months had elapsed after the stroke (Robin & Schienberg, 1990). Chronic symptoms also were found in a comparable number of patients who were studied at least 6 months post-stroke (Naeser et al., 1982). Thus, both aphasia after left-sided lesions and spatial neglect after right-sided stroke obviously can persist in a considerable number of patients beyond the acute/subacute phase.

We would like to point out that the present as well as previous studies were based on small sample sizes and that the lesions centering on the basal ganglia and on the thalamus also might have affected adjacent white matter tracts in some cases. Nevertheless, our present results allow a clear and straightforward conclusion that underline previous observations on lasting subcortical neglect. We observed chronic neglect in about 40% of our sample with subcortical lesions centering on either the basal ganglia or the thalamus. While the exact percentage of this proportion still might be unsafe regarding the small sample size, the data undoubtedly suggest a modification of the frequent assumption that subcortical neglect due to such lesions typically is a mild and transient phenomenon and typically has a favorable prognosis.
References


Acknowledgements

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Figure 1.

Brain lesions of the 10 stroke patients with spatial neglect due to right-sided subcortical stroke of either (a) the basal ganglia or (b) the thalamus for those who had recovered (n = 6; left panels) and those who developed chronic neglect (n = 4; right panels). Lesions were mapped using MRICro software (http://www.mricro.com) on slices of a T1-weighted template MRI scan from the Montreal Neurological Institute (MNI) distributed with MRICro. MNI z-coordinates of the transverse sections are given.

Figure 2.

Severity of neglect in the three clinical neglect tests observed in the subcortical patients with recovered (upper panel) and with chronic neglect (lower panel). Performance is illustrated separately for the acute (left bars) and the recovered/chronic phase (right bars) of the stroke.
Table 1. Demographic and clinical data at the acute stage of the stroke of the 10 patients with spatial neglect due to a right-sided lesion of the basal ganglia or the thalamus who could be tested in the acute and in the chronic phase of the stroke.

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*Bg*: lesions restricted to the basal ganglia; *Th*: lesions confined to the thalamus. *Chron*, chronic neglect; *Recov*, recovered neglect; *Sex*: f, female; m, male.
Recovered neglect patients

- Letter canc.
- Bells test
- Copy task

Chronic neglect patients

- Letter canc.
- Bells test
- Copy task

Monika_Neglect-Verlauf_nur Klinik_Figure 2