Neuropsychological and neuroanatomical correlates of perseverative responses in subacute stroke

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Patients with left-sided neglect frequently show repetitive behaviour on the ipsilesional side, such as re-markings on cancellation tasks or extensive elaboration on drawings. It is unclear whether these perseverative responses occur as a symptom of hemi-neglect or inattention in general, and/or whether they are related to anatomical brain correlates such as lesion location, lesion side or volume. In a first study, we examined the prevalence and neuropsychological correlates of perseverative responses in 206 subacute stroke patients and 63 healthy controls. Perseverative responses were considered present when there was at least one re-marking on the Star Cancellation, and both the degree and spatial distribution of re-markings were examined. A distinction was made between hemi-neglect and non-lateralized inattention. Spatial and verbal working memory were assessed with the Corsi Block Span and the Digit Span. Verbal and non-verbal executive function was assessed with the Visual Elevator and Letter Fluency. Stroke patients without inattention demonstrated re-markings that were related to executive performance, and the degree of perseveration was equally distributed across the sheet. Hemi-neglect patients but not patients with generalized inattention demonstrated more re-markings than controls, suggesting that a lateralized spatial attention bias triggers the perseverative responses. Patients with left and right hemi-neglect showed the same prevalence of perseveration, but the distribution of re-markings was more lateralized towards the ipsilesional side in patients with right-hemispheric stroke. The degree of perseveration in patients with hemi-neglect was related to the severity of the neglect. The goal of the second study on a subset of patients (n = 127) was to determine the neuroanatomical correlates of perseverative responses in the early phase of stroke. Lesion anatomy was administered by indicating involvement of frontal, parietal, temporal, occipital lobe, caudate nucleus, lenticular nucleus and/or thalamus. Lesion volume was calculated using a manual tracing technique. Lesion analyses indicated that perseverative behaviour is strongly associated with lesions involving the caudate nucleus or the lenticular nucleus, independent of lesion volume. The caudate nucleus was an important correlate of perseveration independent of the presence of hemi-neglect. No association was found between lesion side and perseverative responses, in contrast to previous studies. In conclusion, a stroke involving the basal ganglia and the presence of (left- or right-sided) hemi-neglect are two important associates of perseverative responses in the subacute phase of stroke.

Keywords: neglect; perseverative responses; stroke; structural imaging

Abbreviations: GI = generalized inattention; LN = left-sided hemi-neglect; RN = right-sided hemi-neglect

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Introduction

Unilateral neglect (UN) is a multifaceted disorder, with varying aspects of the disorder depending to a great extent on the location and volume of dysfunctional brain tissue (Mort et al., 2003; Hillis et al., 2005; Karnath et al., 2005). Patients with UN typically fail to act or detect stimuli in the contralesional hemifield. Other frequently related deficits are visuospatial
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distortion in general (Lexak et al., 2004), disturbed size estimation (Irving-Bell et al., 1999; Dijkerman et al., 2003), biased gaze exploration (Ishiai et al., 1992; Karnath and Fetter, 1995) and impaired insight (anosognosia) (Buxbaum et al., 2004; Vuilleumier, 2004).

One of the associated symptoms that has received less attention in the literature are the repetitive motor actions that are sometimes observed in patients with neglect, for example, the re-marking of items in cancellation tasks, the extensive elaborations in drawing or automatic recurrent writing behaviour (Evpanyan and Kumral, 2001). This condition has been called 'motor perseveration', although it remains largely unsolved whether the mechanism(s) driving such behaviour are always related to an impairment of motor control. Moreover, it should be noted that perseverative responses in tasks with visual feedback (e.g. cancellation or drawing) might be dissociated from re-visitings in tasks in which no visible mark is made (e.g. visual search paradigms, invisible cancellation, daily life). For example, Husain et al. (2001) have reported a parietal patient who demonstrated no perseverative responses on standard cancellation but many re-visitings (i.e. re-fixations) in a visual search task without visual reminders. Whereas the latter have been related to an impaired spatial working memory in combination with a spatial attentional bias (e.g. Husain et al., 2001; Driver and Husain, 2002; Wojciulik et al., 2004; Mannan et al., 2005), the neuropsychological and neuroanatomical mechanisms underlying repetitive responses on tasks with visual feedback remain less clear, despite the fact that this concerns a very common clinical observation.

Perseverative responses on standard cancellation have been reported in 30% (Na et al., 1999) to 90% (Rusconi et al., 2002) of patients with neglect. So far, three mechanisms have been proposed to explain this type of re-markings in patients with neglect. A first account states that the patients’ perseveration on the ipsilesional side of space is related to the amount of information on the contralesional side. The more targets on the contralesional side of space, the more perseveration on the ipsilesional side, suggesting that there is implicit knowledge of the contralesional side (Manly et al., 2002; Bottini and Toraldo, 2003; Toraldo et al., 2005). On the basis of this finding, it has been suggested that the apparent perseverative behaviour occurs because of either (i) a motor deficit or directional hypokinesia (patients cannot perform movements to the contralesional side and therefore make them on the ipsilesional side); or (ii) to a sensory deficit or allochiria (patients misperceive contralesional stimuli as located on the ipsilesional side). A second potential mechanism underlying perseverative responses is that some patients with neglect are also impaired in mental flexibility, resulting in perseveration in general (not specifically in motor perseveration). It has been suggested that the combination of perseveration and neglect may be responsible for recurrent cancellations in some neglect patients, and that the spatial bias explains why perseverative responses are usually confined to the ipsilesional hemifield. A third account states that neglect patients are ‘magnetically attracted’ or become ‘locked’ onto the ipsilesional side of the hemifield, resulting from a deficit in disengaging attention from the ipsilesional side of space (Posner et al., 1987; Mark et al., 1988). Finally, although the working memory account discussed previously does not so much apply to standard diagnostic tests for neglect such as cancellation or copying, neglect patients frequently report that they are marking items for the first time on standard cancellation even when re-marking targets that are clearly visible to the examiner. It has been suggested that patients may have difficulty seeing their own marks because the marks generally are more faint than the printed stimuli on the sheet (Manly et al., 2002). In this case, an impaired spatial working memory might still exacerbate re-cancellations in standard tasks to some extent.

With respect to neuroanatomical factors, perseverative responses have predominantly been related to right-hemispheric damage and have been associated with anterior/ frontal lesions or lesions in the underlying subcortical grey nuclei (Na et al., 1999; Rusconi et al., 2002). In contrast, perseverative responses in stroke patients without neglect have been related to global brain dysfunction rather than localized damage (Annoni et al., 1998; Ruchinskas and Giuliano, 2003). However, the methodologies to assess perseverative responses in these studies were very different from the studies in neglect patients. Only one study (Rusconi et al., 2002) has directly compared perseverative responses in patients with and without neglect, but it is still unclear whether these are associated with any kind of brain damage, with pathological inattention in general, or with hemi-neglect in particular. The relation between perseverative responses and lesion side also has to be elucidated, given that the majority of studies have focused on patients with right-hemispheric damage.

The aim of our first study was to examine whether perseverative responses occur predominantly in patients with a left-sided hemi-neglect (LN) due to right-hemisphere damage, as has been suggested in previous studies (Rusconi et al., 2002; Toraldo et al., 2005). To this end, we compared perseverative responses on standard cancellation between healthy controls, stroke patients without inattention, patients with non-lateralized inattention and patients with hemi-neglect caused by either left- or right-hemispheric stroke. In addition, we examined whether perseverative responses are related to (i) neglect severity; (ii) spatial and non-spatial working memory; and (iii) executive functioning.

**Study 1: Prevalence and neuropsychological correlates of perseverative responses in subacute stroke**

**Subjects**

Two hundred and six subacute stroke patients, recruited from two previous studies from our group on the neuropsychological consequences of subacute stroke (Nys et al., 2003a, b), were included in the present study. Patients without a
neurological, psychiatric or cognitive disorder were included in the early phase of stroke with a maximum of 21 days post-stroke. Across the whole population, 44% of patients suffered a stroke in the left hemisphere, 42% in the right hemisphere, 2% suffered a bilateral stroke and 12% demonstrated infratentorial brain damage in the brainstem and/or the cerebellum. Patients were categorized into four groups by means of a cancellation task (see below): patients without inattention or neglect (N'), patients with non-lateralized (generalized) inattention (GI), patients with LN and patients with right-sided hemi-neglect (RN). In addition, 63 healthy controls without a neurological, psychiatric or cognitive disorder were examined (Con). All subjects gave informed consent for participation in this study. Demographic data are summarized in Table 1.

**Method**

**Unilateral neglect**

Patients were given a visuomotor exploratory task from the Behavioural Inattention Test (BIT) (Wilson et al., 1987), widely used as a clinical test for the assessment of spatial neglect (Star Cancellation). The patient’s task was to mark 54 small stars among 72 distracters (larger stars, letters and words) printed on an A4 paper sheet. The Star Cancellation is divided into six columns of respectively 8, 8, 11, 11, 8 and 8 targets to examine the lateral distribution of omission and perseveration errors. The sheet was taped to the table so that patients were not able to move it, and aligned with the mid-sagittal plane of the patient’s trunk. Patients received instruction to cancel as many target items as possible with one mark for every target. No restrictions were placed on head or eye movements and patients were asked to declare when the task was finished. Patients who omitted to mark three or more items were classified as having inattention (Wilson et al., 1987). In contrast to previous studies on motor perseveration, we additionally imposed more stringent criteria to identify hemi-neglect, that is, we used the criterion for the absolute difference between left-sided and right-sided omissions to equal or exceed three (Tant et al., 2002; Mark et al., 2004). We chose this approach in order to make a clear distinction between a general scanning deficit and a lateralized scanning deficit.

**Perseverative responses**

The prevalence of patients with perseverative responses was operationalized as the percentage of subjects with at least one re-marking on the cancellation sheet.

The degree of perseveration was defined as the number of re-markings on the Star Cancellation regardless of the degree of neglect [method according to Rusconi et al. (2002)]. However, it could be argued that the greater the number of cancelled targets, the greater the opportunity to re-mark targets (Manly et al., 2002). Therefore, we created a perseveration percentage (number of targets with perseverative marks/total number of targets cancelled × 100) similar to the method applied by Na et al. (1999). Both perseveration measures were recorded because these two studies report contrasting results regarding the relation with neglect severity, perhaps as a consequence of different scoring [this suggestion was also made by Toraldo et al. (2005)].
Working memory
Spatial working memory was assessed by means of the Corsi Block Span (Kessels et al., 2000). We also assessed verbal working memory by means of the Digit Span (WAIS-III).

Executive function
Executive function was assessed by means of the Visual Elevator and Letter Fluency (N and A, 1 min each) (Lezak et al., 2004). The Visual Elevator (Test of Everyday Attention) (Robertson et al., 1994) assesses attentional switching and cognitive flexibility by asking patients to count up and down as they follow a series of visually presented ‘floors’ in the imagined elevator.

Statistical analyses
We performed analyses of variance and χ²-analyses to compare demographic and neuropsychological variables between the five groups. Post hoc contrast analyses were performed to compare patient groups with healthy controls. Differences in the distribution of omissions and perseverations were analysed using ANOVA (analysis of variance) with number of omissions/perseverations as the dependent variable and column position as within-subjects variable. Neuropsychological correlates of perseverative responses were assessed with Spearman correlations.

Results
Neglect and related neuropsychological findings
On the whole, 66 of the 206 subacute stroke patients (32%) demonstrated either generalized or lateralized inattention as defined by more than three omissions on the Star Cancellation. More specifically, 23 of these 66 patients demonstrated LN (more than three omissions on the left versus the right), 12 demonstrated RN (more than three omissions on the right versus the left) and 31 demonstrated no spatial preference and were thus classified as having GI.

Neglect severity and neuropsychological findings adjusted for age, sex and education are shown in Table 1. As expected according to our definition of inattention, a significant difference was observed in the number of targets cancelled across groups \( F(4, 265) = 111.61; P < 0.001 \), with both GI and hemi-neglect patients omitting more items than healthy controls (all \( P < 0.001 \)). No difference was observed between N− patients and controls. Figure 1 shows the distribution of targets cancelled across positions for the five groups (Con, N−, GI, LN, RN). The linear increase in contralesional omissions for LN \( F(1, 22) = 63.9; P < 0.001 \) and RN patients \( F(1, 11) = 21.2, P < 0.001 \) was significant.

Contrast analyses revealed that all patient groups performed significantly worse than healthy controls on tests of executive function (all \( P < 0.001 \)) and verbal working memory (all \( P < 0.001 \)). On spatial working memory, patients with GI (\( P = 0.03 \)), LN (\( P < 0.001 \)) and RN (\( P < 0.001 \)) performed worse than healthy controls (Table 1).

Perseverative responses
Prevalence of patients with perseverative responses.
With respect to the prevalence of subjects with re-markings, 12.7% Con demonstrated at least one re-marking, 43.6% N−, 35.5% GI, 56.5% LN and 46.2% RN \( \chi^2(4) = 22.9; P < 0.001 \).

Degree of perseveration. The degree of perseveration (applying the methods of both Rusconi and Na) is shown in Table 1. The total number of re-markings was significantly different between the five groups \( F(4, 265) = 6.18; P < 0.001 \), so was the perseveration percentage relative to the degree of neglect \( F(4, 265) = 15.14; P < 0.001 \). The number of re-markings was significantly higher in hemi-neglect patients (both LN and RN) than in healthy controls (post hoc Dunnett analyses: both \( P < 0.001 \)). Similarly, the perseveration percentage was higher in hemi-neglect patients (both LN and RN) than in healthy controls (post hoc Dunnett analyses: both \( P < 0.001 \)). No differences were observed between Con, N− and GI (all \( P > 0.05 \)).

Figure 2 shows the distribution of perseveration percentage across position (left to right) for the five groups (Con, N−, GI, LN, RN). A repeated-measures analysis with position as
within-subject variable and group as between-subject variable revealed a main effect of group \( F(4, 265) = 7.3, P < 0.001 \) and position \( F(5, 1320) = 3.4, P = 0.004 \). A significant interaction effect was found between group and position \( F(20, 1320) = 6.13, P < 0.001 \). Univariate post hoc analyses revealed that a linear position effect was found only in the patients with LN \( F(1, 22) = 8.9, P = 0.007 \).

**Neuropsychological correlates of perseverative responses**

In stroke patients without inattention, a significant Spearman correlation was observed between perseveration percentage and Letter Fluency \( r = -0.17, P < 0.05 \) and Visual Elevator \( r = -0.19, P = 0.02 \), indicating a relation between perseverative responses and executive dysfunction in those patients. In patients with GI, no significant relations were observed between perseverative responses and the neuropsychological measures. Conversely, significant relations were observed between the number of targets cancelled and working memory (Digit Span Total \( r = 0.49, P = 0.006 \); Corsi Block Span \( r = 0.62, P < .001 \)) and between the number of targets cancelled and executive functioning (Letter Fluency \( r = 0.37, P < 0.05 \); Visual Elevator \( r = 0.57, P = 0.002 \)). This indicates that a disturbed working memory and executive dysfunction is related to inattention but not to perseverative responses.

In patients with hemi-neglect (LN and RN patients taken together to obtain sufficient power), an association was found between perseveration percentage and neglect severity \( r = -0.37; P = 0.03 \), while this relation was not found when considering the total number of re-markings [method according to Rusconi et al. (2002)]. Perseverative responses were related neither to verbal working memory nor to verbal executive function. (The relation between perseverative responses and spatial working memory or executive performance relying on a visual task cannot be reliably examined with the current neuropsychological battery.) Conversely, significant relations were observed between neglect severity and verbal working memory (Digit Span Total \( r = 0.44, P = 0.01 \)) and between neglect severity and executive functioning (Letter Fluency \( r = 0.37, P < 0.05 \)).

**Discussion**

The first important finding of this study is that perseverative responses also occur in healthy controls, patients without neglect and patients with non-lateralized inattention. In these subjects, perseverative responses were equally distributed across the six positions of the Star Cancellation. In patients without hemi-neglect or inattention, a significant relation between perseverative responses and executive functioning was demonstrated. Therefore, perseveration on the Star Cancellation may be used as an indicator of executive performance in patients without neglect. The advantage of the Star Cancellation is that it is easily administered in the subacute phase of stroke and that it is completely non-verbal in nature, whereas most executive tasks require relative complex verbal skills. It is particularly important to assess executive function in a subacute stroke population since it is the most important predictor for long-term cognitive impairment after stroke (Nys et al., 2005b).

In contrast, patients with hemi-neglect but not patients with GI demonstrated significantly more perseverative responses than healthy controls, confirming that a lateralized attentional bias is associated with an increased risk. So far, it has been claimed that particularly patients with LN due to right-hemispheric stroke demonstrate this increased risk (e.g. Rusconi et al., 2002; Toraldo et al., 2005). Our study shows for the first time that patients with RN, on average, demonstrate the same amount of perseveration as patients with left-sided neglect. Since we examined patients in a very early phase after stroke (within three weeks post-stroke), we were able to identify 12 patients with RN. Interestingly, not the degree but the distribution of perseverative responses is different between patients with LN and RN. In general, patients with left hemi-neglect demonstrated a linear increase of perseverative responses towards the ipsilesional side, whereas, on average, this was not the case for patients with right hemi-neglect in which perseverative responses occurred predominantly in central positions. Verbal working memory and executive dysfunction were related to neglect severity but not to perseverative responses. Our study supports the potential usefulness of neglect interventions, which do not only focus on improving the lateralized attentional bias but also on improving executive functioning or working memory. The role of spatial working memory in perseverative responses on standard cancellation remains to be elucidated with a more experimental design.

Interestingly, a relation was found between perseverative responses and neglect severity confirming earlier findings (Na et al., 1999), but only when scoring the repetitive motor actions relative to the number of targets cancelled. This relationship disappeared when we controlled for lesion volume (data not shown), suggesting that neglect patients with larger lesions tend to show a higher number of perseverative responses (see also Study 2). Manly et al. (2002) suggested that neglect patients might be ‘perseverating’ responses because there is implicit knowledge of the contralesional side but the patient is not capable of cancelling those targets owing to either allaesthesia or hypokinesia. These authors used three modified versions of the Star Cancellation in which they reduced the amount of items on the contralesional side, which resulted in a direct reduction of repetitive re-markings on the ipsilesional side. An observation from our group is in agreement with Manly’s theory of either hypokinesia or allaesthesia, that is, two patients with LN repeatedly marked the same locations on the table to the right side of the Star Cancellation rather than on the sheet. They were not changing their behaviour when trying to correct them, and they both indicated ‘I am marking the items as requested’. However, this observation concerned only two patients, and future research is warranted to
disentangle the different accounts of perseveration in patients with neglect with a more experimental design.

Although gender is reported not to affect the frequency of neglect (Ringman et al., 2004), our study demonstrated a significant difference in sex distribution between conditions. Women were more likely than men to demonstrate non-lateralized inattention, but less likely than men to show left-sided neglect. Our findings might suggest a decreased lateralization in women, in line with studies on gender differences with respect to language lateralization (Frost et al., 1999). However, future studies in greater samples are needed to confirm this sex difference in spatial attentional lateralization.

In conclusion, our first study shows that perseverative responses on standard cancellation in patients without neglect is related to executive dysfunction, whereas perseveration in patients with hemi-neglect is related to neglect severity. Although the degree of perseveration is similar in patients with left versus right hemi-neglect, the lateral distribution of perseverative responses is found predominantly in patients with left-sided neglect.

In Study 2, we will compare neuroanatomical correlates of perseverative responses in patients with and without hemi-neglect.

Study 2: Neuroanatomical correlates of perseverative responses in subacute stroke

Introduction

Perseverative responses on standard cancellation have been observed predominantly in neglect patients with anterior lesions (frontal lesions and/or lesions in the subcortical grey matter) (Na et al., 1999; Rusconi et al., 2002). An important potential confounder that has not been taken into account in previous studies is lesion volume. Moreover, neglect has been defined in a different way in these studies, making no distinction between non-lateralized inattention and hemi-neglect. In the study by Rusconi et al. (2002), for example, UN was defined as the omission of at least one target on cancellation. In contrast, we define hemi-neglect as the omission of at least three items on the Star Cancellation, and the difference between right and left also has to equal three or more in order to impose a stricter definition to the lateralized spatial bias (Tant et al., 2002; Mark et al., 2004).

Studies examining neuroanatomical correlates of perseverative responses in non-neglect patients provide no evidence for frontal lobe involvement, and global neurological dysfunction seems more important than localized dysfunction (Annoni et al., 1998; Ruchinskas and Giuliano, 2003). Then again, the methodologies used to assess perseverative responses are very different from the above-mentioned neglect studies. A direct comparison of the associated brain structures between patients with hemi-neglect and those without has not been reported so far.

The aim of this second study was to evaluate the importance of lesion location and lesion side for perseverative responses when correcting for lesion volume in patients with and without hemi-neglect.

Method

Subjects

The same patients were included as in Study 1 with two additional restrictions: (i) patients with a bilateral stroke (n = 3) or a stroke involving brainstem or cerebellum (n = 24); and (ii) patients with unavailable data regarding neuroanatomical characteristics (n = 52) were excluded for Study 2. In total, 127 subacute stroke patients were included, of which 25 (20%) demonstrated hemi-neglect.

Lesion analysis

An experienced stroke neurologist who was blind to the neuropsychological data evaluated the patients’ stroke location at baseline from CT or MRI by means of a brain atlas (Damasio, 1995). He recorded whether or not there was involvement of the frontal lobe, the lenticular nucleus (globus pallidus or putamen), the thalamus (dorsal or ventral), the caudate nucleus, the temporal lobe, the parietal lobe and/or the occipital lobe. He also determined the side of the lesion (left versus right) and lesion site (cortical involvement of the lesion versus exclusive subcortical lesion involvement). Lesion volume was calculated using Leica Q500 MCP image analysis software by manual tracing of the lesion on each slice showing the infarct of haemorrhage, followed by multiplying lesion area by slice thickness in all slices showing the lesion. This method has been shown to have a high inter-rater reliability and is described in detail elsewhere (van der Worp et al., 2001).

Statistical analyses

First, we studied the effect of neuroanatomical characteristics on perseverative responses in patients without hemi-neglect. To this end, a series of univariate ANCOVAs (analyses of covariance) was performed with one between-subject variable, that is, location (patients with damage to target region versus patients without damage in target region) with lesion volume as covariate. Perseveration percentage (Na et al., 1999) served as dependent variable.

Secondly, we studied the effect of neuroanatomical characteristics on perseverative responses in the patient population as a whole. To this end, a series of univariate ANCOVAs was performed with two between-subject variables, that is, location (patients with damage to target region versus patients without damage in target region) and group (hemi-neglect versus no hemi-neglect) with lesion volume as covariate. Perseveration percentage (Na et al., 1999) served as dependent variable.

Results

A significant positive correlation was found between the volume of the lesion and the number of perseverative re-
responses ($r = 0.24, P = 0.001$). All further analyses are therefore performed with lesion volume as covariate.

**Patients without neglect**

First, the contribution of neuroanatomical characteristics was determined in patients without hemi-neglect ($n = 102$). No effect of lesion side nor frontal, parietal, temporal, occipital or thalamic involvement was found on perseveration percentage. However, a strong effect was found of lenticular ($F(1, 99) = 14.7; P < 0.001$) and caudate ($F(1, 99) = 11.1; P < 0.001$) lesion involvement on the degree of perseveration. Finally, no effect of lesion site (cortical involvement of the lesion versus exclusive subcortical lesion involvement) was found on the degree of perseveration.

**Entire patient population**

Secondly, the simultaneous contribution of neuroanatomical characteristics and group (hemi-neglect versus no hemi-neglect) was examined in the whole patient group.

No significant main effect was found between patients with left ($n = 66$) and right-hemispheric damage ($n = 61$) with respect to perseveration percentage. No interaction effect between lesion side and group was found. A significant main effect of group was observed [$F(1, 122) = 15.9; P < 0.001$], indicating that patients with hemi-neglect persevered more often than patients without hemi-neglect.

No significant main effect was found between patients with cortical ($n = 66$) versus exclusive subcortical damage ($n = 61$) with respect to perseveration percentage. No interaction effect between lesion side and group was found. A significant main effect of group was observed [$F(1, 122) = 15.9; P < 0.001$], indicating that patients with hemi-neglect persevered more often than patients without hemi-neglect.

No significant main effect was found between patients with frontal lesion involvement ($n = 25$) versus no frontal involvement ($n = 102$) with respect to perseveration percentage. No interaction effect between lesion location and group was found. A significant main effect of group was found [$F(1, 122) = 15.3; P < 0.001$] (see Fig. 3).

No significant main effect was found between patients with lenticular lesion involvement ($n = 31$) versus no lenticular involvement ($n = 96$) with respect to perseveration percentage. No interaction effect between lesion location and group was found. A significant main effect of group was found [$F(1, 122) = 15.8; P < 0.001$].

A significant main effect was found between patients with caudate lesion involvement ($n = 16$) versus no caudate involvement ($n = 111$) with respect to perseveration percentage [$F(1, 122) = 16.5; P < 0.001$]. No interaction effect between lesion location and group was found. A significant main effect of group was observed [$F(1, 122) = 25.1, P < 0.001$] (see Fig. 4).

No significant main effect was found between patients with thalamic lesion involvement ($n = 13$) versus no thalamic involvement ($n = 114$) with respect to perseveration percentage. No interaction effect between lesion location and group was found. A significant main effect of group was found [$F(1, 122) = 19.7, P < 0.001$].

No significant main effect was found between patients with parietal lesion involvement ($n = 36$) versus no parietal involvement ($n = 91$) with respect to perseveration percentage. No interaction effect between lesion location and group was found. A significant main effect of group was observed [$F(1, 122) = 13.1; P < 0.001$].

No significant main effect was found between patients with temporal lesion involvement ($n = 35$) versus no temporal involvement ($n = 92$) with respect to perseveration percentage. No interaction effect between lesion location and group was found, although a trend suggested that neglect patients with temporal lesions demonstrated a higher degree of motor perseverative responses [$F(1, 122) = 3.2; P = 0.08$]. A significant main effect of group was observed [$F(1, 122) = 26.8; P < 0.001$].

No significant main effect was found between patients with occipital lesion involvement ($n = 24$) versus no occipital involvement ($n = 103$) with respect to perseveration percentage. No interaction effect between lesion location and group was found.
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was found. A significant main effect of group was observed \[F(1, 122) = 22.5; P < 0.001]\.

**Discussion and conclusions**

Our study is the first to show that a lesion involving the lenticular and/or the caudate nucleus is associated with a higher degree of perseverative responses, even when correcting for the volume of the lesion. A recent study by Stoffers et al. (2001) demonstrated that motor perseveration may be an early diagnostic marker for Parkinson’s disease, which is caused by a loss of dopaminergic neurons in the nigrostriatal pathway (Corti et al., 2005). Furthermore, the role of the basal ganglia has been confirmed in tasks that assess the inhibition of ongoing responses, such as the stop signal task or the go/no-go task. It has been suggested that the basal ganglia act to inhibit competing motor mechanisms that could potentially interfere with the desired movement (Rieger et al., 2003). When considering the overall stroke population including patients with hemi-neglect, patients with a lesion in the caudate nucleus still demonstrated significantly more perseverative responses than patients without a lesion in the caudate nucleus, independent of the presence of hemi-neglect. The role of the caudate nucleus in (motor) perseverative errors has been demonstrated in a variety of other conditions, for example, in patients with schizotypical personality disorder (Levitt et al., 2002), in patients with Tourette syndrome (Bloch et al., 2005) and even in neuroimaging studies with healthy subjects (Lombardi et al., 1999). All in all, the presence of perseverative errors may be an efficient marker of caudate dysfunction in various neurological diseases.

Frontal involvement was not associated with perseverative responses when controlling for lesion volume, either in patients with hemi-neglect or in patients without hemi-neglect. It should be noted that in the study by Na et al. (1999) anterior lesions were defined as involvement of either frontal lobe or basal ganglia, so no distinction was made. In the study by Rusconi et al. (2002), a distinction was made but no correction was performed for lesion volume, although stroke patients with frontal lesion involvement tend to show larger strokes. A recent more experimental study examining neuroanatomical correlates of revisiting targets in a visual search display found that patients with a lesion involving the inferior frontal and intraparietal sulcus perseverated at a pathological rate (Mannan et al., 2005). There was no visible marking in that study, so that task loaded heavily on spatial working memory, which makes it a fundamentally different task than our standard cancellation. Possibly, different brain areas are involved in those types of perseverations due to working memory deficits. Nevertheless, we cannot exclude the possibility of frontal lobe involvement on the basis of our study. First, we could not evaluate the importance of specific regions within the frontal lobe owing to a lack of power. It is still conceivable that the dorsolateral prefrontal cortex and/or the inferior frontal gyrus are associated with perseverative responses given that this brain area is involved in non-motor perseveration (Konishi et al., 1998; Lombardi et al., 1999). Secondly, even if the frontal lobe may not be structurally involved in motor perseveration, it might still be functionally involved in the subacute stroke phase. For example, a recent study (Karnath et al., 2005) has shown that a lesion involving the basal ganglia causes hypoperfusion in frontal areas. Another recent interesting study showed that the volume of hypoperfusion was related to neglect severity (Hillis et al., 2003). Although these relatively new methods are difficult to implement in clinical practice, future studies examining the functional status of the brain in the subacute phase of stroke might reveal interesting new findings on neuroanatomical correlates of cognitive function.

Although it is often suggested that perseverative responses occur predominantly following right-hemispheric damage, our study shows no difference in the degree of perseveration between patients with right- and left-hemispheric damage (see also Annoni et al., 1998), either in patients without hemi-neglect (Study 2) or in patients with hemi-neglect (Studies 1 and 2). This latter finding contradicts previous findings by Rusconi et al. (2002). However, in that study, only four patients with neglect due to left-hemispheric stroke were included and all four omitted only one target. In the present study, patients with severe hemi-neglect caused by left-hemispheric stroke are included, which may probably explain the different result.

In a previous study, we showed that acute neglect—among several neuroimaging, cognitive and clinical variables—was one of the strongest predictors of poor clinical recovery in the first months post-stroke (Nys et al., 2005b), even though the majority of patients in that study no longer showed neglect at the follow-up assessment. These data suggested that the adverse outcomes in neglect patients are not directly related to the persistence of neglect, and that another variable within the neglect syndrome might be causing the long-term dependence. In a recent study (G. M. S. Nys, M. J. E. van Zandvoort, L. J. Kappelle, E. H. F. de Haan, manuscript submitted), we showed that particularly neglect patients who also showed perseverative responses in the early phase were still impaired in daily life functioning at 6 to 10 months post-stroke (even after controlling for the size of the lesion). In addition, patients without neglect also demonstrated a poorer clinical recovery if they showed perseverative responses in the early phase of stroke. These findings highlight the need for future research on this topic with respect to the underlying mechanisms on how this behaviour affects daily activities. Unfortunately, given that both our studies are retrospective in nature we cannot distinguish between different types of perseveration, such as continuous (abnormal prolongation of a current activity) versus recurrent perseveration (repetition of a previous response to a subsequent stimulus), although distinct brain areas and clinical implications might be involved in both types of perseveration. Future longitudinal studies...
aimed at systematically recording different types of perseverations might shed more light on the underlying neural correlates and clinical significance of the disorder.

In conclusion, perseverative behaviour is strongly associated with lesions involving the caudate nucleus or the lenticular nucleus, independent of lesion volume. In addition, the presence of hemi-neglect is strongly associated with the degree of perseveration on standard cancellation, suggesting that a lateralized attention bias triggers the progressive manifestations. Although there is no difference in the degree of perseveration between patients with left versus right hemi-neglect, the distribution of perseverative re-markings is more lateralized in patients with left-sided neglect.

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