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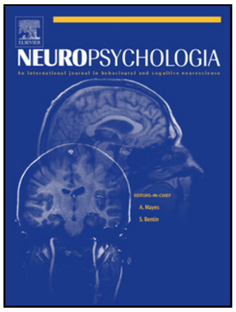

Title: Non-Spatial Neglect for the Mental Number Line.

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A within-subject double dissociation between physical and number-space neglect is described

This double dissociation extended to ordinal sequences and was non-spatial in nature

The number-space neglect was associated with a position-based deficit in working memory

Pointers towards a new theory for the relation between numbers and space are discussed

Running head: NUMBERS AND SPACE

Non-Spatial Neglect for the Mental Number Line.

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Abstract

Several psychophysical investigations, expanding the classical introspective observations by Galton, have suggested that the mental representation of numbers takes the form of a number line along which magnitude is positioned in ascending order according to reading habits, i.e. from left to right in Western cultures. In keeping with the evidence, pathological rightward deviations in the bisection of number intervals due to right brain damage are generally interpreted as originating from a purely spatial-attentional deficit in the processing of the left side of number intervals. However, consistent double dissociations between defective processing of the left side of physical and mental number space have called into question the universality of this interpretation. Recent evidence suggests a link between rightward deviations in number space and defective memory for both spatial and non-spatial sequences of items. Here we describe the case of a left brain-damaged patient exhibiting right-sided neglect for extrapersonal and representational space, and left-sided neglect on the mental number line. Accurate neuropsychological examination revealed that the apparent left-sided neglect in the bisection of number intervals had a purely non-spatial origin and was based on mnemonic difficulties for the initial items of verbal sequences presented visually at an identical spatial position. These findings show that effective position-based verbal working memory might be crucial for numerical tasks that are usually considered to involve purely spatial representation of numerical magnitudes.

KEYWORDS: numbers, space, attention, working memory, SNARC, neuropsychology

Non-Spatial Neglect for the Mental Number Line

In 1880 Galton published two papers in which he described people who report vivid spatial experiences when processing numbers, forming what he called “natural lines of thought”(Galton, 1880a, 1880b). This observation supported the intuitive idea that the processing of number and space are tightly linked. It is only in the last two decades, however, that the relation between numbers and space has become the subject of systematic investigation and now, about 100 years after Galton’s classical observation, it is widely accepted that the processing of numbers is intimately related to the processing of spatial information at both functional and anatomical levels (e.g. Dehaene, Piazza, Pinel, & Cohen, 2003; Fias & Fischer, 2005; Hubbard, Piazza, Pinel, & Dehaene, 2005; Umilta, Priftis, & Zorzi, 2007).

One of the most convincing and robust phenomena that demonstrate the interaction between numbers and space is the SNARC-effect. When asked to indicate whether a number is odd or even with a left or right key press, participants tend to react faster to relatively small numbers (e.g. 1) with their left hand than with their right hand side, while they are faster to relatively large numbers (e.g. 9) when the responses are executed with the right hand side. Dehaene et al. (1993) called this finding the *s*patial-*n*umerical *a*ssociation of *r*esponse *c*odes (SNARC) effect and postulated that it was attributable to the mental organization of numbers, taking the form of a horizontally oriented mental number line (MNL) with small numbers located on the left and large numbers on the right. Since then, this effect has been replicated in a wide variety of experimental tasks, for example, magnitude comparison (Brysbaert, 1995) or phoneme monitoring (Fias, Brysbaert, Geypens, & d'Ydewalle, 1996), for a review see Fias & Fischer (2005).

Besides psychophysical investigations in healthy subjects, neuropsychological studies have provided important additional evidence for the spatial nature of number processing. For instance, patients with left neglect following right hemisphere lesion fail to, report, orient to, or verbally describe, stimuli in the contralesional left hemispace (for a review see Halligan, Fink, Marshall, & Vallar, 2003). When these patients have to indicate the midpoint of a visual line positioned in front of them, they systematically locate the subjective midpoint to the right of the true midpoint as if they ignore the leftmost part of the line (Marshall & Halligan, 1989). Similar observations are made in the representational domain. When asked to describe a familiar scene from a mental image, many patients who neglect the left side of physical space also omit details pertaining to the left side of the image (Bisiach & Luzzatti, 1978). Zorzi, Priftis and Umiltà (2002) recently extended these observations on representational neglect to the numerical domain. They showed that, when asked to indicate the midpoint of numerical intervals, patients neglecting the left side of space systematically shift the midpoint of larger intervals rightward (e.g. they indicate 7 as the midpoint of the interval ‘1-9’), as if they neglected the left part of the MNL. This overestimation was observed irrespective of the presentation order of both numbers comprising the endpoints of the to-be-bisected interval, suggesting that the MNL is canonically oriented in a left-to-right manner. After the initial observation, this pattern of errors in the number interval bisection task has been replicated in several studies using different and unselected groups of neglect patients (e.g. Cappelletti, Freeman, & Cipolotti, 2007; Priftis, Zorzi, Meneghello, Marenzi, & Umilta, 2006; Zamarian, Egger, & Delazer, 2007; Zorzi, Priftis, Meneghello, Marenzi, & Umilta, 2006). Additional evidence of altered number processing in neglect was provided by Vuilleumier and colleagues (2004). They asked neglect patients to perform several magnitude comparison tasks and observed that these patients were slower to respond to the numbers just smaller than (and hence immediately to the left of) the reference number. For example, when asked to compare a centrally presented number with the reference number “5”, neglect patients were slower to respond to the number "4", than to the number "6", while they were slower to respond to the number "6" than to the number "8" when the reference number was "7".

Altogether, the above-mentioned observations intuitively suggest a tight functional link and causal relationship between the attentional deficit observed in perceptual space and the representational deficit observed with numbers. In other words, both the SNARC-effect and the number bisection bias in neglect, would be behavioral signatures of a common numerical-spatial representational system, conceivable as a mental number line (MNL), in which the spatial coding overlaps with or at least is very similar to the way perceptual space is represented and processed (Hubbard, et al., 2005; Zorzi, et al., 2002).

Although the MNL hypothesis provides a coherent and parsimonious account for a variety of observations suggesting a link between numerical and spatial processing, recent evidence has fundamentally questioned the idea of a simple functional equivalence between the MNL and the representation of physical space. Whereas the isomorphic MNL hypothesis predicts a strong correlation between neglect severity in physical line and MNL tasks, no such correlation has been reported in the studies cited above. In contrast, consistent double-dissociations between both types of tasks have been reported (Cappelletti, Freeman, & Cipolotti, 2009; Doricchi, Guariglia, Gasparini, & Tomaiuolo, 2005; Doricchi, Merola, Aiello, Guariglia, Bruschini, Gevers, Gasparini, & Tomaiuolo, 2009; Loetscher & Brugger, 2009; Loetscher, Nocholls, Towse, Bradshaw, & Brugger, 2009; Rossetti et al., 2004) suggesting that different cognitive mechanisms are involved in the two domains. This functional dissociation was further supported by the study of the anatomical correlates of number interval bisection bias in brain damaged patients (Doricchi, et al., 2005; Doricchi, Merola, Aiello, Guariglia, Bruschini, Gevers, Gasparini, & Tomaiuolo, 2009). These studies showed that the patients who established a rightward number interval bisection bias showed a maximal lesion overlap in the prefrontal area's that are associated with short term working memory, whereas those showing a rightward bisection bias both in physical and number space had supplementary lesion involvement of the temporal-parietal junction, an area that can be relevant for attentional neglect (Corbetta & Shulman, 2002; Vallar & Perani, 1986) but not for number processing. These anatomical results were complemented by the finding of significant correlations between rightward deviations in the bisection of numerical intervals and impairments in the recall of spatial and verbal ordinal sequences (Doricchi, Merola, Aiello, Guariglia, Bruschini, Gevers, Gasparini, & Tomaiuolo, 2009; for a discussion on this issue see Rossetti et al., in press).

In the present paper we elaborate on this discussion and provide further evidence that supports the idea that number and line bisection depend on dissociable mechanisms. We describe a left-brain damaged female GG, who showed a within-subject double dissociation between right-sided neglect for physical and representational space and left-sided neglect for number space. Detailed neuropsychological testing revealed that this left-sided neglect had a pure non-spatial origin and was also present for other ordinal sequences. Given the hypothesis that defective spatial and/or verbal working memory could be a relevant functional component of the rightward number interval bisection bias observed in left neglect patients (Doricchi, et al., 2005; Doricchi, Merola, Aiello, Guariglia, Bruschini, Gevers, Gasparini, & Tomaiuolo, 2009), we evaluated her verbal and spatial working memory functioning thoroughly. Remarkably, GG didn’t show any abnormality in spatial working memory but suffered from position-based working memory capacity/accuracy problems for the initial items of verbal sequences.

Patient GG

GG (born in 1955), a retired saleslady with 10 years of formal education had a sudden onset of neurological deficits after plastic surgery in July 2007. CT scans (depicted in Fig. 1) revealed a massive ischemic left hemisphere lesion due to an obstruction of the left middle cerebral artery. In the acute phase, she was right hemiplegic. In the course of the investigations, motor control of the leg was partially regained. General neuropsychological assessment was carried out one month after the cerebral vascular accident (for an overview of the results see Table 1). These investigations did not reveal visual agnosia or general language difficulties. Further testing showed mild impairments in executive functioning and more pronounced difficulties in visuo-spatial attention. The visuo-spatial difficulties were more pronounced for the right side of space, indicating the presence of extrapersonal neglect. Assessment of her (working) memory functions revealed a deficit in the visual and verbal modalities, and an intact visuo-spatial working memory capacity. At the onset of the experimental investigations, one month later, she was co-operative and oriented in space and time. She was able to keep track of appointments and to schedule them efficiently in-between the different therapeutic sessions. She could easily recognize familiar faces, showing no evidence of prosopagnosia. Although her medical file reported possible indications for hemianopia of the lower quadrant of the right visual field, this was never confirmed during the course of the study by GG herself or noticed during experimentation. GG showed a 100% right-hand preference on the Dutch handedness questionnaire (Van Strien, 2002). Before participation in the study, she signed an informed consent form. All investigations were approved by the local ethical committee and took place between October 2007 and June 2008.

--- INSERT FIGURE 1 HERE ---

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Special Neuropsychological Assessment

In the present study, we further investigated the relation between performance on number interval bisection and hemi-spatial neglect. To meet this aim, special neuropsychological investigations were carried out to shed more light on GG’s performance on physical line bisection, to check for the presence of representational neglect and neglect dyslexia and to verify her skills on several verbal and numerical tasks. Here and in the remaining part of the paper, we used the one-tailed significance test (ST) to compare her individual score to a small normative sample (Crawford & Howell, 1998) and the two-tailed[1] unstandardized difference test (UDT) to verify whether her discrepancy in performance between two task conditions was significantly different from those observed in our control samples (Crawford & Garthwaite, 2005). Because the study developed stepwise, we recruited different groups of healthy participants (HC) to serve as controls in the different experimental investigations. Specifications of each group are given in the method section of the corresponding tests.

Neglect assessment

Physical line bisection

To investigate the presence of extra-personal neglect, the physical line bisection task was administered in two variants. In the first, the instruction was to manually indicate the midpoint of individually printed lines centered on a (landscape) A4 sheet. Lines of 2, 10, and 20cm (5 trials per length) were administered. All lines were aligned to the head-body midsagittal plane. Due to right hemiplegia, GG used her non-dominant left hand. Thirteen age and sex matched HC (age range: 52-58 years; mean=53 years) also participated using their dominant hand.

To evaluate the response, the position of the indicated midpoint was determined with 0.5mm precision. In terms of accuracy, GG's performance was in the normal range (ST:p=0.14). She bisected 1 line correctly and the healthy controls on average 3.15 (SD=1.86) lines. To evaluate the nature of the errors, every erroneous trial was categorized as being a left or right neglect specific misplacement (LNS and RNS). In this context, RNS misplacements

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[1] For a discussion on the use of one- and two-sided tests in neuropsychological single case studies see Crawford, Garthwaite and Gray (2003)

are rightward shifts for the 2cm lines (cross- over effect) and leftward shifts for the 10 and 20 cm lines (and vice versa for the LNS misplacements). GG was very consistent in her response pattern as all of here errors were RNS (see Figure 2). The control subjects made on average 5.92 (SD=3.01) RNS and 5.85 (SD=2.85) LNS misplacements. In comparison to these controls, GG made more RNS (ST:p<.01) and a lower amount of LNS misplacements (ST:p=0.04). Furthermore, to get an idea of the consistency of her bias, we compared the discrepancy between the amount of RNS and LNS misplacements in GG with the average observed in the control group. As can be seen in Fig. 2, this discrepancy in GG (14) is significantly larger compared to the discrepancy observed in the HC (0.08 (SD=5.53); UDT:p=0.03).

After the consistency, the magnitude of the bias was further evaluated. To quantify the magnitude, the distance from the left side of the line to the subjective mark was measured for each line separately (with 0.5mm accuracy) and converted into a deviation score using the following formula (Schenkenberg, Bradford, & Ajax, 1980):

$$Deviation = \frac{\text{measured left half} - \text{true half}}{\text{true half}} \text{ X } 100$$

In this way, a negative value is obtained when the subjective midpoint was located on the left of the objective midpoint, which (for long lines) is assumed to reflect inattention towards the right part of the line. GG's average deviation score for the 2cm lines was 5% (SD=4%), for the 10cm lines -9% (SD=3%), and for the 20cm lines -6% (SD=2%). Subsequent testing showed that for all line lengths the deviations (marginally) differed from the results of the control subjects (2cm, ST:p=.039; 10cm, ST:p=.007; 20cm, ST:p=.067).

To ascertain that the bisection bias observed in manual line bisection was not caused by the use of her left hand (for a review see Jewell & McCourt, 2000), GG was also subjected to a bisection verification task. For this purpose, the bisected lines of the manual bisection task were re-administered for verification. In addition, to rule out the possibility that her putative visual field deficit mediated the observed leftward bias (Barton & Black, 1999) both extremities of the line had to be indicated to guarantee that the entire line was perceived. When an error was detected, she was instructed to correct it manually. Although GG made corrections to 8 lines, this had no influence on the consistency of her bias since in this variant; she again made 14 RNS and no LNS misplacements. GG's average deviation score for the 2cm lines, was 5.0% (SD=3.5%), for the 10cm lines -5.4% (SD=2.5%), and for the 20cm lines -5.2% (SD=1.8%). Altogether, the results of the physical line bisection task corroborate the findings collected during the general neuropsychological screening, indicating that GG suffers from right sided physical neglect.

--- INSERT FIGURE 2 HERE ---

Representational neglect

Several additional tests were administered to test whether GG's attentional deficit extended to the representational domain.

Imaging map of Flanders

GG and 11 healthy controls (8 female; Range: 50-72; Average: 60) were asked to mentally visualize the map of Flanders as presented during the weather forecast with Brussels located at the bottom and Antwerp on top and to name as many places as possible within two minutes (for a similar task see Rode, Rossetti, Perenin, & Boisson, 2004). All subjects, including the patient, were living in the same province (Antwerp).

In total, GG mentioned 10 places while the control group reported on average 20.82 places (SD=5.15; ST:p=0.03). To evaluate the presence of representational neglect, all mentioned places were plotted on a map and coded according in terms of the number of times they were mentioned. To statistically validate the results, the map was divided in three equal parts and for each the average amount of mentioned places was calculated.

The HC mentioned on average 4.91 (SD=2.66) places on the left, 7.36 (SD=3.23) places in the middle and 8.55 (SD=2.11) places on the right side of the map, and a repeated measures ANOVA confirmed this rightward bias (F(2,20)=5.75, p<.011). In line with the hypothesis that GG suffers from right representational neglect, she mentioned 3 places on the left, 7 in the center and 0 on the right side of the map. A direct comparison with the control group revealed that GG's performance only differed in the amount of items mentioned on the right side of the map (ST:p<.01). To evaluate the significance of this left/ right asymmetry observed in GG, these scores were transformed into a laterality quotient (LQ) by means of the following formula and compared to the LQ observed in the HC (see Piccardi, Bianchini, Zompanti, & Guariglia, 2008, for a similar approach):

$$LQ = 100 * \frac{\text{correct (or amount)on left side} - \text{ correct (or amount) on right side}}{\text{correct (or amount)on left side } + \text{ correct(or amount) on right side}}$$

GG's LQ was 100, a value which was significantly different compared to the average LQ of the HC (-30 (SD=25); ST:p<0.001). This observation clearly indicates that GG's right-sided neglect was not limited to external space but also extends to the representational domain, at least when information from long term memory needs to be retrieved. In the next task, we further evaluated GG's representational abilities in a task where the mental representation depends less on long term information.

Description of a novel scene from memory

To investigate GG's ability to generate and access mental images from a newly learned scene, GG and 8 age and sex matched healthy controls (age range: 55- 64; average 58 years) received a previously unseen picture of a bedroom and were asked to describe its content in as much detail as possible with the intention to memorize it (see Denis, Beschin, Logie, & Della Sala, 2002 for a similar task). No time constraints were imposed and when hinted to be ready, a retention interval of 10 minutes was initiated. Afterwards, the picture had to be described from memory. During the memorization phase, the midpoint of the picture was aligned to the subjects' body midline.

In total GG mentioned 35 elements of the picture during the description phase, an amount which is in the normal range (average of HC: 39.5 (SD=10.81); ST:p=0.35). During the memory phase, she only recalled 63% (i.e. 22) of those described elements whereas the controls on average recalled 82% (SD=9%) of them (ST:p<.04). Further analyses showed that this lower overall recall was due to a significant lower memory recall for the elements on the right side of the picture. Whereas her left- sided performance was within the normal range (81% vs. 81% (SD=0.11); ST:p=0.50), she recalled only 47% of the described elements on the right side of the picture (HC: 83% (SD=12); ST:p=0.01). The left-right asymmetry observed in GG was again significantly larger compared to the HC, as her LQ of 26.34 was significantly larger compared to that of the HC (-0.94 (SD=9.18); ST:p=0.01).

GG's right sided representational neglect can thus also be observed in newly acquired mental images. Numbers however, are more abstract in nature than the evoked mental scenes of the previous tasks. For this reason, we further investigated whether the representational deficits also extends to a more abstract domain of knowledge. For this reason we also administered the O'clock task (Grossi, Modafferi, Pelosi, & Trojano, 1989) which is a frequently used tool to screen for the presence of representational neglect.

The O'clock task

GG and 13 age and sex matched HC (age range: 52-64; average: 56 years) were asked to imagine pairs of orally presented clock faces and to report in which of both faces the hands of the clock made the greatest angle. Stimuli were pairs of hours, involving full and half hours. In total, 32 pairs were presented. In half of the trials, both hands of the clock were located in the right hemifield (e.g. 1:30 and 5:00) and in the other half of the trials, in the left hemifield (e.g. 11:30 and 8.00). The test was administered in a quiet and dimly lit room. For the hours with the clock hands on the left, 11 of the 16 trials were correctly answered by GG, whereas only 7 of the 16 trials were correct for the hours with the hands on the right. Both for the left as for the right side, her performance was lower compared to the HC (both ST's:p<=0.01) who on average responded 14.14 (SD=1.14) and 14.69 (SD=1.25) of the left and right sided hours correctly. Importantly, GG's LQ was 22.22. A statistical comparison with the LQ of the control group further confirmed the presence of right representational neglect as her LQ was significantly larger compared to the average of the control group (-1.84 (SD=5.75); ST:p<0.001).

Verbal abilities

GG and the same group of 8 age and sex matched healthy controls (age range: 55- 64; average 58 years) participated in reading, writing and spelling.

Reading

To evaluate her reading abilities, and the possible presentation of neglect dyslexia, GG and the HC were instructed to read 40 words and 40 non-words consisting of 3, 5, 7, and 9 letters (10 each), presented on a computer screen. Presentation time was limited to 600ms to have a sensitive measure for abnormalities. During word reading, GG made 2 errors and the HC made on average 0.1 (SD=0.35) errors (ST:p<0.001). In non-word reading she made 15 and the HC on average 2.63 (SD=1.41) mistakes (ST:p<0.0001). Importantly, in line with her right-sided neglect, the majority of those errors, in both words (2 of the 2) and non-words (11 of the 15), were related to the right side of the stimuli.

Writing

24 words were selected from the list used in the word bisection task (6 trials of each word length; see Experimental Investigation 1). The instruction was to write down the words spoken by the experimenter. GG wrote 23 of the words correctly, a score within the normal range (HC: 23.25 (SD=1.04); ST:p=0.41).

Spelling

GG was asked to spell out loud 35 words (from 3 to 9 letters). 26 words visually presented, 9 words were spoken by the experimenter. In both variant, GG's performance (resp. 26/26 and 8/9) was within the normal range (visual: HC: 25.5 (SD=0.53); ST:p=0.20; Oral: HC: 8.75 (SD=0.46); ST:p=0.08).

Numerical abilities

For the numerical tests, two different control groups were sampled. A first group of 8 age and sex matched controls (age range: 55- 64; average 58.25 years) participated in counting and calculation and a second group of 12 healthy controls (8 females, age range: 51 – 80; average 68 years) computed averages.

Forward and backward counting

GG and the HC were asked to count forward and backward with the numbers 1 to 20 as the starting point without time constraints. Both GG and the HC were flawless.

Calculation

To evaluate her arithmetical abilities, simple and complex calculation problems were administered. For simple arithmetic, 24 problems were randomly selected from the possible single digit problems of each arithmetic operation (with the exception of operand 0 problems and operand 1 problems in multiplication). Addition and subtraction problems were administered first, multiplication and division afterwards. Subsequently more complex addition and subtraction problems were presented. These consisted of a two-digit number as the first operand and a single digit number between 3 and 7 as the second operand. Problems were created such that in half of the cases the decade was crossed and the result never exceeded 99. All problems were presented on a computer screen and remained visible until responding. GG correctly solved 24, 23, 24 and 23 of addition, subtraction, multiplication and division problems correctly, a performance which is comparable (all ST's:p>=0.08) to that of the HC who responded correctly in 23.88 (SD=0.35), 23.75 (SD=0.46), 22.25 (SD=2.25), 23.63 (SD=0.52) of the corresponding trials. In the complex calculation tasks, GG was correctly solved 23 and 21 of the addition and subtraction problems, which is again comparable to the score of the HC who were correct in 23.63 (SD=0.52) and 23.13 (SD=1.36) of the cases (both ST's:p>=0.09).

Computing average

GG was instructed to compute the average of the number pairs used in the number interval bisection task (see Experimental Investigation 1). In total, 48 pairs were presented on a computer screen and remained visible until a response was given. GG made 4 mistakes, an amount comparable to the HC who on average made 2.66 errors (SD=1.83; ST:p=0.25).

Parity judgment

This task was used to investigate presence of the SNARC-effect (Dehaene, et al., 1993) to verify whether she associates numbers spatially in a in a left to right manner as a function of number magnitude. Digits ranging from 1 to 9 (excluding 5) were presented randomly in the center of a computer screen and had to be judged on their parity (odd or even). GG was asked to press the left mouse button for odd and right button for even numbers (e.g. Priftis, et al., 2006). Each digit was presented 12 times. A trial started with a fixation mark (700ms), immediately followed by the target number which remained visible until responding. To get used to this procedure, 8 practice trials were performed. Erroneous responses and responses outside the range of 150 – 2500ms were excluded from the analyses. In total, 75/96 trials met the inclusion criteria. SNARC-congruent trials were defined as small numbers (<5) responded to with left responses and large (>5) numbers with right responses. The average reaction time for the congruent trials (n=40) was 1247ms (SD=467) and for the incongruent trials (n=35) 1472ms (SD=503). An independent t-test showed that those reaction times differed from each other (t(73)= 2.01, p=.049), indicating the presence of a SNARC-effect and thus a normal left to right association between numbers and space in line with many earlier reports in healthy individuals (e.g. Dehaene, et al., 1993; Fias, Brysbaert, Geypens, & G., 1996).

---- INSERT TABLE 2 HERE ----

EXPERIMENTAL INVESTIGATION 1: Bias in Number, Letter and Word Bisection Tasks

Based on the idea that the mental representation of numbers takes the shape of a canonical left-to right oriented number line that is functionally isomorphic to the way physical space is represented and processed (e.g. Hubbard, et al., 2005), the hypothesis was examined whether GG's extrapersonal and representational neglect generalizes to the mental representation of numbers. For this purpose, a number interval bisection (Zorzi, et al., 2002) was administered. In addition, since it has been shown that neglect also affects the mental representation of other ordered sequences, a letter interval (Zamarian, Egger, & Delazer, 2005; Zorzi, et al., 2006) and a word bisection task were also examined.

Number Interval bisection

GG and the same group of thirteen sex and aged matched healthy controls (age range: 52-58 years; mean=53 years) which participated in the physical line bisection task described earlier, were orally presented with two numbers that defined the to-be-bisected numerical interval and were asked to estimate the midpoint between these two numbers without making calculations. The length of the intervals could be 3, 5, 7, and 9. The number pairs (48 in total, see Appendix 1) were constructed following the method described in Zorzi, Priftis and Umiltà (2002). All number intervals were randomly presented in ascending order. In addition GG performed the task with numbers in descending order in a separate block. No time constraints were imposed and the intervals were repeated if requested. Subjects were not explicitly encouraged to use spatial imagery.

In total, GG made more errors compared to controls (14/48 vs. 3.92/48; SD=2.22; ST: p<.001) in the ascending condition. Similar to a physical line bisection task, the pattern of these errors was evaluated by categorizing them as right neglect specific (RNS; i.e. overestimations in the 3 and underestimations in the 5, 7, and 9 unit intervals) and left neglect specific (LNS; underestimations in the 3 and overestimations in the 5, 7 and 9 unit intervals) misplacements. In contrast to what could be expected on the basis of her right-sided physical neglect, 11 of these errors were LNS and only 3 were RNS. Compared to the healthy controls, GG made more LNS (11 vs. 2.15 (SD=1.72); ST:p<.001) and a comparable amount of RNS misplacements (3 vs. 1.77 (SD=0.19); ST:p=0.19). Importantly she not only made more LNS errors, a discrepancy between the amount of RNS and LNS misplacements as observed in GG (-8) was not found in the healthy controls (-0.38, SD=2.10; USDT: p<.01; see Figure 3), indicating the consistency of her LNS response bias.

Subsequently the magnitude of the bias was quantified by averaging the distance between the observed and correct responses for every number interval length. This results in a positive value when the subjective midpoint is overestimated. When the numbers were presented in ascending order, GG’s average deviation score for the 3item intervals was -0.14 units (SD=0.65), for the 5item intervals 0.00 units (SD=0.53), for the 7item intervals 0.56 units (SD=0.73) and for the 9item intervals 0.67 units (SD=0.58). Importantly, GG’s performance significantly differed from the score of the control group in the 3item (ST:p<.01), 7item (ST:p<.01) and 9item intervals (ST:p=.02). A similar pattern was observed in the descending condition. Here she made 11 errors of which 8 were LNS and 3 RNS and her bias was -0.1 (SD=0.44), -0.7 (SD=0.46), 0.22 (SD=0.67) and 1.67 (SD=0.58) units for the 3, 5, 7 and 9item intervals respectively.

Altogether, these results indicate that, contrary to what would have been expected from the mental number line hypothesis, GG showed a consistent and significant left sided neglect when bisecting numerical intervals. Next, it was verified whether this left sided neglect was also found when GG bisected letter intervals.

Letter interval bisection

Similar to Zorzi et al. (2006), 48 intervals with a length of 3, 5, 7, and 9 letters (twelve trials per length) were constructed. These intervals were selected both from the beginning and the end of the alphabet. The list of used letter pairs is included in Appendix 2. All letter intervals were orally presented in a random and ascending or descending way (e.g. which letter is in the middle of A and I?). No time constraints were imposed and the intervals were repeated when requested. GG and eight sex and age matched healthy controls (age range: 49-64 years; mean=57 years) participated. They were not explicitly encouraged to use spatial imagery and were not allowed to write anything down. During the course of the experiment, GG indicated that she was unable to solve the tasks for intervals with a length of nine letters. Therefore this interval length was not taken into account in the analyses.

In total GG made more errors compared to the healthy controls (18/36 vs 5,75/36 (SD=2.49); ST: p<.001). Of those 18 errors, 12 were LNS and 6 RNS whereas the control subjects on average made 3.50 (SD=1.77) LNS and 2.25 (SD=1.16) RNS misplacements. Subsequent analyses revealed that GG made both more LNS (ST:p<0.001) and RNS (ST:p<0.01) misplacements. Importantly however, a discrepancy as observed in GG (-6) was again not found in the healthy controls (-1.25 (SD=1.67); USDT:p=.03) indicating that she consistently made more LNS misplacements (see Figure 3).

To evaluate the magnitude of the bias, average deviation scores were calculated for each letter interval separately by subtracting the number corresponding with the ordinal position of her response with the ordinal position of the real middle letter. In this way, a comparable deviation score was obtained as in the number interval bisection task. GG’s average deviation score for the 3letter intervals was 0.17 units (SD=1.59), for the 5-letter intervals 0.25 units (SD=0.62) and for the 7-letter intervals 1.08 units (SD=1.68). Similar to the number interval bisection task, the biases were larger compared those observed in the healthy controls. Their average bisection bias for the 3-letter intervals was 0.00 units (SD=0.04; ST:p<.01), for the 5-letter intervals -0.02 units (SD=0.09; ST:p=0.01) and for the 7-letter intervals 0.14 units (SD=0.20; ST=p<0.01).

Based on these findings, we conclude that GG showed a significant rightward bias. Importantly this bias could not be attributed to a deficient knowledge of the alphabet since she was perfectly able to recite it correctly without any effort. This conclusion indicates that her left-sided neglect is not limited to numerical sequences, but is also observed for verbal information. To provide further evidence for this claim, GG was submitted to a task where she had to indicate the midpoint of verbally presented words.

Word bisection

The experimental setup and analyses were similar to the interval bisection tasks described above with the exception that the intervals were replaced by words. These words, (words of 3, 5, 7, and 9 letters; 12 words of each length; see Appendix 3) were chosen based on the following criteria: no compound words, no diphtongues, all letters pronounced and a similar frequency of use. GG, together with 13 healthy controls (age range: 50-72 years; average=60 years) participated in this task.

With 16 errors, GG's performance was worse compared to that of the controls (7.92 errors; SD=4.12; ST:p=0.04). Of her errors, 15 were LNS and 1 RNS misplacements, whereas the healthy controls on average made 4.17 (SD=3.38) LNS and 3.75 (3.36) RNS misplacements. Subsequent analyses showed that GG made more LNS (ST:p<0.01) and an comparable amount of RNS errors (ST:p=0.22). Furthermore, the bias in GG was again more consistent compared to the healthy controls' as the discrepancy found in GG was much larger as the one observed in the control subjects (-14 vs. -0.42 (SD=5.33); UDT:p=0.03; see Figure 3).

To evaluate the magnitude of the bias of each word length, average deviation scores were computed in a similar way as in the letter interval bisection task for each word length separately. GG's did not make any error in the three letter words. Her average deviation score for the five letter words was 0.17 units (SD=0.39), for the 7 letter words 0.50 units (SD=0.52) and for the 9 letter words 0.58 units (SD=0.79). The average deviation scores of the control subjects were 0 (SD=0), 0.03 (SD=0.08), 0.05 (SD=0.15) and -0.06 (SD=0.35) for the 3, 5, 7, and 9 letter words respectively. Importantly, her performance significantly differed from the score of the control group in these words (5letter words: ST:p=0.06; 7letter words: ST;p<.01; 9letter words: ST:p=.05).

Supporting the results of the letter interval bisection task, the findings of the present task corroborate the claim that GG's left sided neglect is not limited to numerical sequences, but extends to verbal information as well. Importantly, her pattern of performance cannot be attributed to neglect dyslexia, as her word reading or writing performance did not show any problems pertaining to the beginning of words (if anything for the rightward side when reading verbal material, see infra).

--- INSERT FIGURE 3 HERE ---

Physical line bisection vs. Number interval bisection

The observation that GG consistently showed a rightward bias in physical line bisection and a consistent leftward bias in number interval bisection suggests that in this single patient, both tasks doubly dissociate from each other. Since in the present study, both tasks were administered in the same control subjects, this idea was objectified by entering the discrepancy between the amount of LNS and RNS misplacements of each task into the DISSOCS-tool (Crawford & Garthwaite, 2005). As described above, this analysis showed that

GG made consistently more RNS than LNS misplacements in physical line bisection (14 vs. 0.08 (SD=5.53); ST:p<0.01) and more LNS than RNS misplacements in number interval bisection (-8 vs. -0.38 (SD=2.10); ST:p<0.01), resulting in a significant discrepancy between both measures (RSDT: p<.01). It is worth noting that in these healthy controls, performance on physical line and number interval bisection did not correlate (r=-0.18;p<.56).

EXPERIMENTAL INVESTIGATION 2: Position-based Deficit in Verbal Working Memory

Until now, we have shown that GG's ipsilesional neglect for ordinal sequences was not due to general difficulties in the processing of numerical and verbal information and completely dissociated from her attentional deficit. Doricchi et al. (2005; 2009) proposed that defective spatial and/or verbal working memory could be a relevant functional component of the rightward bias that is observed in the bisections of number intervals by right brain damaged patients with left spatial neglect. This proposal was based on the observation of significant correlations between the severity of the bias in number interval bisection and the reduction of the spatial and/or verbal working memory span. By itself, however, a reduced working memory capacity is not sufficient to explain the directional consistency of the bisection bias. For this, the reduction of the working memory capacity should be characterized by an unequal distribution of mnemonic efficiency along the sequence of items to be retained. For instance, when the first elements of the sequence are not remembered, a bias towards larger numbers could be observed during bisection. Since in GG spatial working memory capacity (5 elements) is within the normal range but verbal working memory capacity is reduced (3 elements), we predicted that, if working memory indeed contributed to the number bisection bias, GG's verbal working memory deficit would primarily impair the items from the beginning of verbal working memory sequences.

To investigate position-based effects in working memory, we tested performance of GG and healthy controls in a probe recognition and a position recall task tapping verbal and visuo-spatial working memory.

Verbal working memory

Probe recognition task

Methods

To examine position-based deficits in verbal working memory, randomly selected consonants were presented sequentially in the center of the screen for 1000ms with 500ms in between. After a retention interval (2000 or 7500ms) a probe letter appeared, after which the subjects were instructed to indicate whether or not this letter was part of the memorized sequence by pressing a mouse button (response mapping was counterbalanced across subjects). Each consonant appeared only once in one sequence and each position of the sequence was probed an equal amount of times (except for sequences of 5 or 7 items, whose mid positions were not probed). To avoid strategies based on visual information, the letters of the sequence were in lowercase while the probes were in uppercase. Accuracy was stressed and no time constraints were imposed.

Both GG and a group 18 of HC (age range: 18-29 years; average=23.5 years) were tested with sequences of 2 elements above their verbal working memory span. GG performed the task with sequences of 5 consonants (i.e. two above span) with a retention interval of 2000ms and of 7500ms successively (48 trials for each retention interval). The healthy controls performed this probe recognition task with a retention interval of 2000ms (n=15; average span=6.94; SD=1.18) and with a 7500ms retention interval (n=8; average span: 7.5; SD=1.20). Moreover, another group of 10 HC matched for age and sex (age range: 55-61 years; average=57 years) completed the task with sequences of span +1 elements (average span=5.4; SD=1.07).

Results

In the 2000ms retention condition, GG responded correctly in 77% and in the 7500ms retention condition in 81% of the trials, a performance which was comparable to that of the healthy controls (ST:both p's>0.17). They correctly categorized the probes of the 2000ms condition in 85% (SD=8%) of the trials and in the 7500ms condition in 86% (SD=8%) of the trials. The aged matched healthy controls performed correctly in 90% (SD=5%) of the trials in the span+1 condition.

To examine the presence of a selective position-based working memory deficit, the data of the first and last half of the sequence were collapsed and compared. In case the sequence contained an odd number of elements, the middle position was discarded from the analyses. By means of this procedure, three proportions were available for every subject: correctly recognized start and end items, and the correctly rejected no-match items. As can be seen in Figure 4, GG correctly recognized 25% of the start items, 83% of the end items and rejected 100% of the no-match items of the 2000ms retention condition. A comparison with the data of the healthy controls revealed a dissociation between the performance for the start and end items. With 74% (SD=21%) of the start items correctly recognized, the performance of the control group was significantly better than GG (ST: p<.025). On the contrary, no differences (ST: all p's > .09) were observed for the end (90%; SD=10%) and the no-match trials (90% SD=7%). A similar pattern was observed in the 7500ms retention condition. Here she correctly responded in 50% of the start items, 92% of the end items and 92% of the no-match items. Again, a dissociation was observed between the start and end items. The control group correctly responded in 81% (SD=12%) of the start items which is significantly better than GG (ST: p<.025). On the contrary, no differences (ST: all p's > .09) were observed for the end (85%; SD=8%) and the no-match trials (88% SD=11%). Furthermore in both variations of the task, GG's discrepancy in the performance of start and end items was significantly larger than of the healthy controls (UDT: all p's < 0.03), thereby statistically confirming a dissociation between the memory for start and end items. Finally in the aged matched control group, the performance for the start (87%; SD=11%) and end items (85%; SD=15%) did not differ (t(9)=.22, p=0.83), supporting the finding that GG showed an abnormal asymmetry in the recognition of begin and end items.

--- INSERT FIGURE 4 HERE---

Position Recall task

In addition to the probe recognition task, we also tested working memory with a position recall task in which participants have to indicate which item occurred at a given position in the maintained working memory sequence. This task has the advantage that not only the amount but also the nature of the errors is informative.

Method

The experimental setup was identical to the verbal recognition task (2000ms retention) with the exception that a digit was presented instead of a probe. This digit referred to a position in the memorized sequence and the aim of the task was to recall the consonant occupying this position. Each position in the sequence was probed an equal amount of times. In case the sequences contained an uneven amount of items, the amount of middle responses was increased by the question to recall the "midpoint" of the sequence. GG performed this task with sequences of five items (span + 2; 36 trials), while 10 age and sex matched HC (age range: 55-61 years; average=57 years) completed the task (36-60 trials) at span +1 level (average span=5.36; SD =1.07). Accuracy was stressed and no time constraints were imposed.

Results

The different positions were grouped into a start (first 2 positions), middle (3d position) and end condition (last 2 positions; 12 trials each). As can be seen in Figure 5, GG's performance was better for the end than for the start locations. She correctly recognized 2 of the left-sided items, 2 of the middle and 6 of the right-sided items. Although this amount of correct responses only reflects 27% of the trials, a more detailed analysis of the errors revealed that 73% of the erroneous responses were items that belonged to the memorized sequence. A striking finding was that, similar to her performance on the mental bisection tasks, in 89% of these erroneous responses, a shift towards the end items of the sequence was made. In contrast, the control subjects (72% of the trials correct) did not show such an asymmetry in their recall performance (%correct begin items=81%, SD=9%; middle items=74%, SD=21%; end items=69%, SD=14%; F(2, 18)=2.02, p=.16), and although 75% (SD=14%) of the erroneous responses were elements of the sequence, they did not show a shift towards the end or beginning of the sequence since 45% (SD=19%) of those errors were shifted towards the beginning and 55% (SD=19%) were shifted towards the end of the sequence t(9)=-0.84 p=.42).

--- INSERT FIGURE 5 HERE ---

Spatial working memory

Probe recognition

Methods

In this task, performed by GG and 11 age and sex matched HC (age range: 52-58 years; average=54 years) subjects, spatial locations were presented sequentially on a pc-screen for 1000ms with 500ms in between. After a retention interval of 2000ms a probe location appeared and the task was to indicate whether this location was part of the memorized sequence by pressing two mouse buttons (response mapping was counterbalanced across subjects). Spatial locations were indicated by black squares (3 by 2.5cm) which were presented in an imaginary matrix encompassing the entire computer screen. Depending on the sequence length, this matrix could have 5 to 7 columns and 5 rows. To indicate the locations to be remembered, a square appeared in a randomly selected cell of every column. To disentangle presentation order from spatial location, the spatial sequences were presented from left to right on half of the trials and from right to left for the other trials. In half of the trials the probe was part of the sequence. Furthermore it was controlled that each presented probe (corresponding and non-corresponding) was selected from each column with equal probability. Both GG and control subjects performed this task at span + 1 (GG: span level=5; 72 trials, healthy controls: average span=4.55; SD=0.69; 60-72 trials). For all subjects, accuracy was stressed and no time constraints were imposed. The midpoint of the screen was aligned to the body midline of the subjects.

Results

Overall GG responded correctly in 67% of the trials, a performance which is comparable to that of the control group (average=74%; SD=16%; ST:p=.34). To identify possible deficits in the retention of (contra-)lesional positions, the data of all subjects were collapsed as a function of the location on the screen (left or right). In case the sequence had an odd amount of elements, the middle element was not included in the analyses. As illustrated in Figure 6, GG correctly recognizes 61% of the left-sided and 56% of the right-sided match probes and correctly rejected 72% of the left-sided and 78% of the right-sided no-match probes. A comparison with the control group did not reveal any difference in performance (ST: all p's > .15). On average they correctly recognized 72% (SD=18%) of the left-sided and 75% (SD=17%) of the right-sided match probes and correctly rejected 75% (SD=13%) of the left-sided and 76% (SD=12%) of the right-sided no-match probes. Finally to investigate abnormalities in spatial working memory related to the sequential presentation order of the items, the data of all subjects were collapsed as a function of the location in the sequence (start items and end items). GG correctly recognized 61% of the start items and 56% of the end items and correctly rejected 83% of the start and 67% of the no-match end items, again, those values did not differ from controls (ST: all p's<0.13). On average they correctly recognized 73% (SD=20%) of the start and 74% (SD=15%) of the end match probes and correctly rejected 72% (SD=11%) of the start and 80% (SD=14%) of the end no-match probes. Thus, even in the case when GG had to remember sequences with an amount of elements exceeding her spatial working memory span, no remarkable asymmetries were found in her recognition performance.

--- INSERT FIGURE 6 HERE ---

Recall of spatial positions

Method

The experimental setup of this task was identical to that of the spatial recognition task with the exception that the probe was replaced by a digit. This digit referred to a position in the memorized sequence and the aim of the task was to recall the location that corresponded to this position. Because the presented sequences consisted of an odd amount of positions, the middle position was additionally requested with the question to indicate the midpoint of the sequence. GG performed this task with sequences of five items (span level; 30 trials; a larger sequence length resulted in chance level performance) while 10 age and sex matched healthy controls (age range: 52-58 years; average=55 years) performed the task at span + 1 level (average span=4.6; SD=0.52; 30-48 trials).

Results

Overall GG responded correctly in 25 of the 30 trials. To investigate possible asymmetries, the data were collapsed as a function of the location on the screen: left, middle or right (10 trials each). She correctly recognized 8 of the left-sided items, 8 of the middle and 9 of the right-sided items. In two of the errors she responded with a position which occurred later in the sequence than the asked position, in one error she shifted her response towards the right and the final two errors were completely unrelated to the presented sequence. This pattern of performance was very similar to that of the control subjects. On average they responded correct in 77% (SD=9%) of the trials. For both the left- and right-sided locations, they responded correctly in 81% (SD=9%) of the trials, while their performance of the middle locations was 68% (SD=13%); 81% (SD=9%). Thus again, GG's didn't show any remarkable asymmetry when recalling positional information from spatial working memory.

General Discussion

The most widely accepted and influential view on the relation between numerical and spatial processing is that its behavioral signatures (e.g. SNARC-effect, number bisection bias in neglect patients) arise from a shared underlying spatially defined representation, taking the form of a left to right oriented Mental Number Line (henceforth MNL). It is believed that from the moment our brain processes a number, its corresponding position on the MNL is automatically activated, accompanied by shifts of spatial attention. These shifts of attention along the MNL are assumed to be mediated by the same parietal neural circuits and cognitive systems as shifts of attention in the external world, leading to the suggestion that the neural spatial representation of the MNL functionally overlaps with the neural representation of equivalent spatial objects, i.e. visual lines, in physical space (e.g. Hubbard, et al., 2005; Umilta, et al., 2007; Zorzi, et al., 2002).

The study reported here offers a body of evidence that is *not consistent* with this hypothesis. We presented the case of GG, a 52 year old right-handed woman, who suffered from *right* extrapersonal neglect after left hemisphere damage. Contrary to the predictions of a purely spatial-attentional interpretation of the MNL, her *left sided* neglect for number space (i.e. affecting small numbers) did not follow, but was directionally opposed to her extrapersonal neglect for the *right side* of visual space. Extensive examination showed that this double dissociation was not confined to numerical information, but extended to the bisection of verbally ordered sequences like letter intervals and words. Further investigations revealed normal basic numerical abilities and no unexpected problems in reading, writing and spelling. Importantly, GG showed a normally oriented SNARC-effect with small numbers associated with the left and large numbers with the right hand side, excluding the possibility that the observed number bisection pattern was caused by a reversal of her MNL. A position-based deficit in verbal working memory was observed to be associated with number and letter bisection performance, with worse performance for items from the beginning of the to-be-remembered sequence of items. This pattern of results was observed across different experimental sessions and was thus not caused by random fluctuations in either attention or motivation.

At first sight, the double dissociation observed in GG is reminiscent of a general dissociation between perceptual and representational neglect (e.g. Beschin, Basso, & Della Sala, 2000; Coslett, 1997; Guariglia, Padovani, Pantano, & Pizzamiglio, 1993). Number space neglect used to be considered as a specific form of representational neglect (e.g. Zorzi, et al., 2002) and observations were described showing that number interval bisection together with other representational neglect tasks can be dissociated from perceptual neglect in the same subject (e.g. Cocchini, Bartolo, & Nichelli, 2006; Priftis, Meneghello, Zorzi, Pilosio, & Umilta, 2005). Current views on neglect do consider it to be a multifaceted syndrome which results from the interplay of damage to several different cognitive systems (e.g. Vallar, 1998). From this perspective, dissociations between representational and perceptual neglect have been explained in terms of a mental generation problem due to selective deficits in visuo-spatial working memory (Beschin, Cocchini, DellaSala, & Logie, 1997; Della Sala, Logie, Beschin, & Denis, 2004; Denis, et al., 2002; Ellis, DellaSala, & Logie, 1996). Along the same lines, the defect in number interval bisection has been attributed to a selective spatial working memory disorder affecting the short term retention of left-sided positions in the MNL (Doricchi, et al., 2005). In GG however, no dissociation was observed between her extrapersonal and representational neglect since in several tasks she clearly showed problems for the contralesional right side in both the extrapersonal and representational domain. Furthermore, a careful examination of her spatial working memory performance, both with regard to her capacity and her ability to maintain specific positions, did not reveal any abnormality.

Altogether, the specific pattern of GG’s deficits, casts doubt on the spatial nature of her ipsilesional neglect for numbers and verbal sequences. This conclusion questions the idea that biases in the bisection of number intervals along the MNL necessarily derive from a functional isomorphism between the MNL and physical lines. The study of GG suggests that neglect for one side of the MNL is not an intrinsic or a necessary part of the spatial neglect syndrome and that neglect for the MNL rather reflects a specific cognitive disorder that co-exists or interacts with spatial neglect.

Although several studies with various experimental paradigms and patient groups have demonstrated the occurrence of joint deficits in physical and number space, none of these studies have demonstrated that the deficits in number space are functionally linked to attentional disturbances. For example, as in neglect, it has been described that schizophrenic patients, suffering from subtle right sided neglect, can demonstrate leftward bias in both number interval (Cavezian et al., 2007) and visual line bisection (Michel et al., 2007). However, these studies reported separate tests of visual line bisection and number interval bisection, without testing the possible correlation between bisection biases observed in both tasks. Conclusions based on a purely phenomenological similarity in the performance of two tasks do not suffice as evidence in favour of a claim that they are functional linked. As a matter of fact, a more recent investigation run in a large sample of 40 schizophrenic patients (Tian et al., 2011), demonstrated that visual and number bisection biases are dissociated (not correlated) in these patients. To conclude that spatial attentional processes operate in a similar way in visual and number-space, positive correlations should be found between the performances on both tasks in patient populations where the attentional system is significantly compromised by localized brain damage or dysfunction. At present, however, no such strong positive correlations have been reported in the neuropsychological literature. To the contrary, in a recent study, Rossetti et al. (in press) observed correlations smaller than 0.1 in a sample of 74 neglect patients.

Given the correlations between the number bisection bias and the working memory span (Doricchi, et al., 2005; Doricchi, Merola, Aiello, Guariglia, Bruschini, Gevers, Gasparini, & Tomaiuola, 2009) and the low verbal working memory span observed in GG, we hypothesized that a specific functional impairment in verbal working memory processes was at the heart of the mental bisection bias in GG. What is common to the bisection of numbers, letters and words, is that positional ordered verbal information needs to be retained in working memory, upon which controlled (attentional) selection mechanisms operate to obtain a correct response. Hence a problem in maintaining or building up this sequential verbal representation may account for the bisection bias with ordinal information. GG showed a reduced verbal working memory capacity limited to three elements. Although in all mental bisection tasks biases were mainly observed when the amount of enclosed items exceeded her span level, a general decline in capacity does not explain their directional consistency. For this reason, we predicted that she experienced selective difficulties in the retention of the earlier items of those verbal sequences, merely showing a “recency” effect. After all, a directional bias towards the end of the list can be expected in those tasks when the items at the start of the sequence are missed and bisection is performed on the remaining items. Further testing with the probe recognition task confirmed this idea and revealed that she was indeed selectively impaired in recognizing the initial items of verbal sequences. Further indications came from the position recall task. In this task, where the mechanisms for recalling the identity of an item at a certain location in the sequence are similar to the way responses are probed in a mental bisection task (viz. determining the midpoint of an internally generated mental sequence), she not only missed more begin items. The large majority of her erroneously reproduced letters were items that were presented at further positions in the list, an observation which is reminiscent of the rightward shift observed in the mental bisection tasks.

Interestingly, the idea that serial working memory is crucial for the spatial representation of numbers receives support from recent investigations of the SNARC-effect. In a series of experiments, van Dijck and colleagues pointed to the importance of available working memory resources for the occurrence of the SNARC-effect (van Dijck, Gevers, & Fias, 2009). In a subsequent study it was shown that information stored in working memory is spatially coded as a function of its ordinal position in the sequence and that the SNARC-effect draws upon this mechanism (van Dijck & Fias, 2011). The hypothesis that position-based coding of working memory is an important determinant of number-space interactions has important theoretical implications. Until now the spatial frame of the MNL was considered to be a long-term memory representation that is triggered automatically when numbers are encountered. In this view, the problems observed in neglect patients were interpreted to reflect difficulties in accessing an intact MNL rather than to a deficit in the representation of the MNL itself (Priftis, et al., 2006). The present conclusion that verbal working memory is important for the generation of an accurate number representation, on the other hand, implies that the mental number line is generated during task execution and thus breaks ranks with the popular account (see Fias, van Dijck, & Gevers (in press) for a theoretical discussion of this issue).

As a whole, the evidence that we have summarized above suggests that in order to properly understand the exact mechanisms involved in number interval bisection, future research on number space associations, should incorporate dedicated instruments that test position-based mnemonic accuracy of sequential information. Because of a possible atypical lateralization of cognitive functions in GG's brain, these investigations should not be restricted to the verbal domain but also be extended to include position-based encoding in spatial working memory. In the absence of such measures it is impossible to evaluate the validity and generality of the working memory and mental number line account. For instance, studies by Pia et al. (2009) and by Cocchini et al. (2006) recently reported left hemisphere lesion patients displaying a pattern of performance that is not the same as that of GG. As these studies did not report working memory performance it is hard to judge the theoretical impact of their results. Our results however, indicate that it is important not to restrict the investigation of number bisection performance to neglect patients and to focus also on patients with working memory impairments in the absence of spatial deficits.

In summary the results of the present study demonstrate that altered performance in unilateral brain damaged patients on the number interval bisection task is not necessarily the consequence of impairments in a spatial-attentional mechanism operating on a mental number line, analogous to physical space. We propose that an impaired working memory system (with a position-specific deficiency) constitutes a viable alternative explanation. Future patient studies are needed to determine whether a position-specific working memory impairment is at the heart of all cases of number bisection bias, or alternatively, is restricted to a subgroup of patients. Whatever the outcome of these future investigations, the present case report adds to the growing list of studies that demonstrate that the link between numbers and space is of a multi-faceted nature and is more complex than is conceived of in the prevailing hypothesis of attentional mechanisms operating on a mental number line.

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Figure Captions

Figure 1

Figure 1A: GG's CT scans, acquired two months after the onset of the stroke, revealed a massive ischemic left hemisphere lesion due to an obstruction of the left middle cerebral artery. These scans show that besides a clear prefrontal involvement, the lesion extends to the very ending part of the descending sector of the intra-parietal sulcus at its junction with the post-central sulcus. This cortical-subcortical area is typically damaged in neglect (e.g. Doricchi & Tomaiuolo, 2003). Figure 1B: The anatomical references are given for the different depicted slices to have a better view on the extension of the lesion.

Figure 2

The magnitude and consistency of the bias observed in the manual variant of the physical line bisection task in GG and healthy controls. The left part of the figure shows the magnitude of the bias in terms of the average proportional differences between the indicated and the true midpoint for each line length separately. The zero value reflects a correct response, negative and positive values indicate respectively a leftward or rightward misplacement of the subjective midpoint. Error bars give the standard error of the mean across trials for GG and across subjects for the control group. The right panel reflects the consistency of GG's bias. Here the difference between the amount of right and left neglect specific (RNS and LNS) misplacements observed in GG and the healthy controls are plotted for each subject individually. The 2 standard deviations cutoff is indicated by means of a black stripe. The number of circles on a specific position is in accordance with the number of times this specific value occurred in the sample.

Figure 3

The magnitude and consistency of the bias observed in the number interval, letter interval and word bisection task in GG and healthy controls. The left part of the figure shows the magnitude of the bias in terms of the average differences (expressed in units) between the indicated and the true midpoint for each interval separately. The zero value reflects a correct response, negative and positive values indicate respectively a leftward or rightward misplacement of the subjective midpoint. Error bars give the standard error of the mean across trials for GG and across subjects for the control group. The right panel reflects the consistency of GG's bias. Here the difference between the amount of right and left neglect specific (RNS and LNS) misplacements observed in GG and the healthy controls are plotted of each subject and task individually. The 2 standard deviations cutoff is indicated by means of a black stripe. The number of circles on a specific position is in accordance with the number of times this specific value occurred in the sample.

Figure 4

The figure shows the results of the verbal item recognition task. The black and the grey bars represent the percentage of correctly recognized letters from the beginning or the end of the memorized sequence. The dotted bars reflect the accuracy to recognize letters not belonging to the sequence. Errors bars give the standard error of the mean across subjects for the control groups.

Figure 5

The results of the verbal position recall task. The black bars reflect the percentage of correctly recalled items for the start, middle or ending letters of the sequence. The dark grey bars, indicate the percentage of newly introduced letters for each part of the sequence. Both lighter grey bars reflect the erroneous responses of which the recalled letter was part of the sequence but was shifter towards respectively the begin or end part of the sequence.

Figure 6

This figure shows the results of the spatial probe recognition task. The bars on the left represent the percentage of correctly recognized left and right presented spatial locations. The bars on the right reflect the amount of correctly rejected left and right presented no-match trials. Errors bars give the standard error of the mean across subjects for the control group.

Table 1

Overview of the general neuropsychological assessment

[1] (Reitan & Wolfson, 1993), [2] (Warrington & James, 1991), [3] (Riddoch & Humphreys, 1993), [4] (Buschke & Fuld, 1974),[5] (Della Sala, Gray, Baddeley, Allamano, & Wilson, 1999), [6] (Vos, 1992), [7] (Smith, 1982),[8] (FEPSY, 1995), [9] (Schenkenberg, et al., 1980), [10] (Albert 1973), [11] (Wilson, Cockburn, & Halligan, 1987), [12] (Gauthier, Dehaut, & Joanette, 1989)* this task was administered at the end of the experimental investigations, [13] (Benton, Varney, & Hamsher, 1978), [14] (Graetz, De Bleser, & Willmes, 1992), [15] (Kaplan, Goodglass, & Weintraub, 1983), [16] (Wilson, Alderman, Burgess, Emslie, & Evans, 1996), [17] (Stroop, 1935), [18] (Heaton, Chelune, Talley, Kay, & Curtiss, 1993), [19] (Lezak, 1995 p. 657), [20] The method and procedure of both the letter and the Corsi-block span are described in van Dijck, Gevers and Fias (2009). For the purpose of this study, data from a age and sex matched control group (age range: 52-58 years; mean=53 years) were collected. A comparison of GG's performance with the performance this control group (verbal span= 5.36, SD=1.03; spatial span=4.55, SD=0.69), using the DISSOCS-tool (Crawford & Garthwaite, 2005), revealed that the verbal and spatial span were dissociated in GG. Her spatial span was within the normal range (ST: p=0.27)

while her verbal working memory span was smaller (ST: p=.027), resulting in significant discrepancy between both spans (UDT: p = 0.04).

Table 2

Overview of the data collected during the assessment of neglect, the verbal and the numerical abilities. Values in italic reflect a significant difference with the control group.

Figure 1

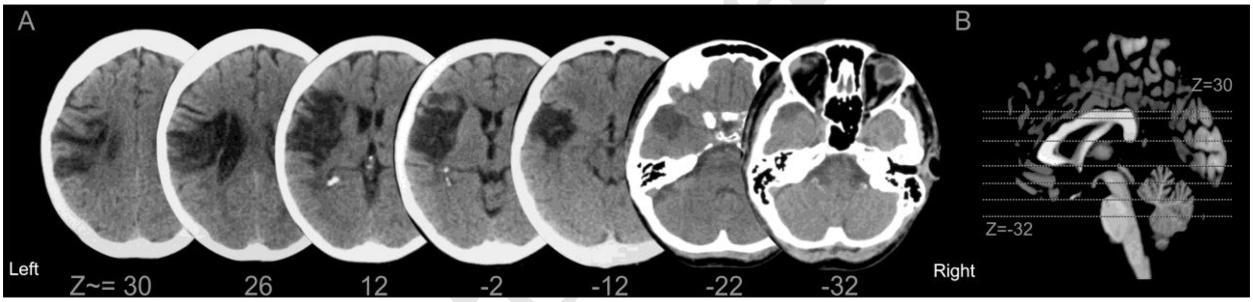

Figure 2

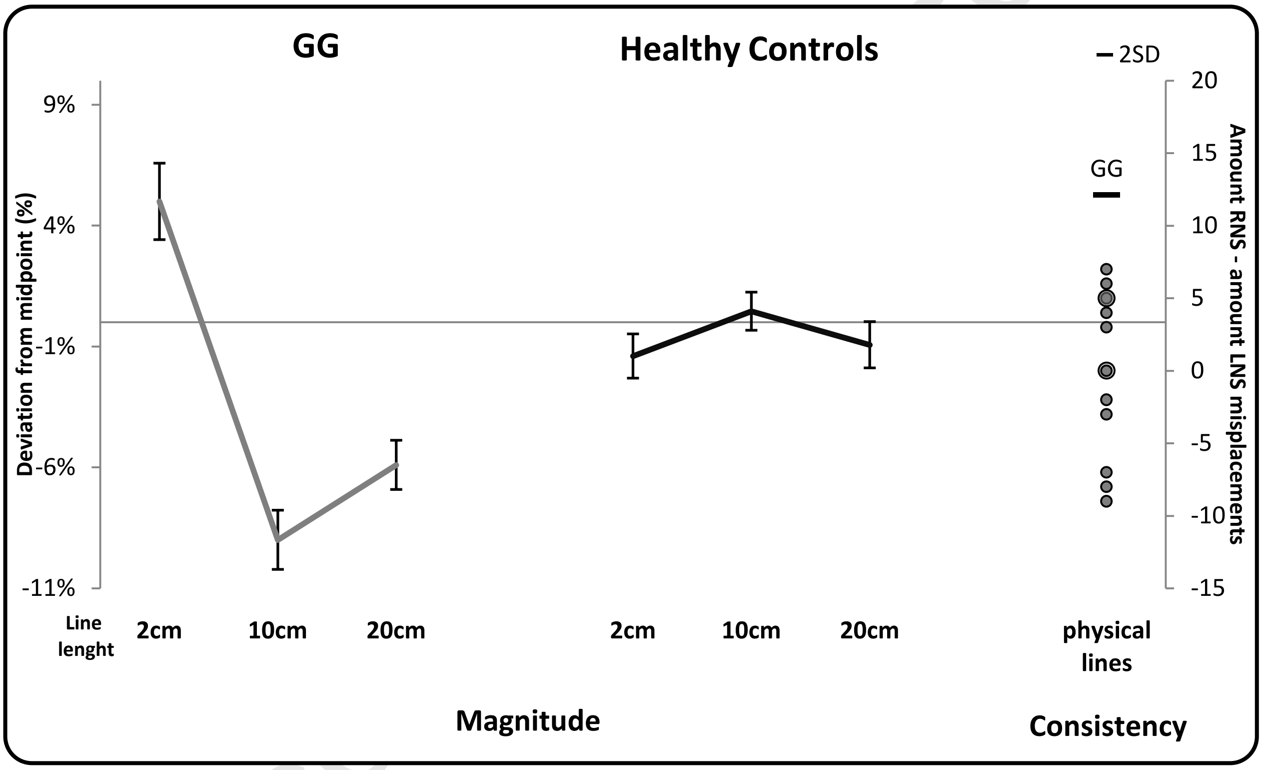
GG
Healthy Controls
2SD
GG
9%
4%
-1%
-6%
-11%
Deviation from midpoint (%)
20
15
10
5
0
-5
-10
-15
Amount RNS - amount LNS misplacements
Line lenght
2cm
10cm
20cm
2cm
10cm
20cm
physical lines
Magnitude
Consistency

Figure 3

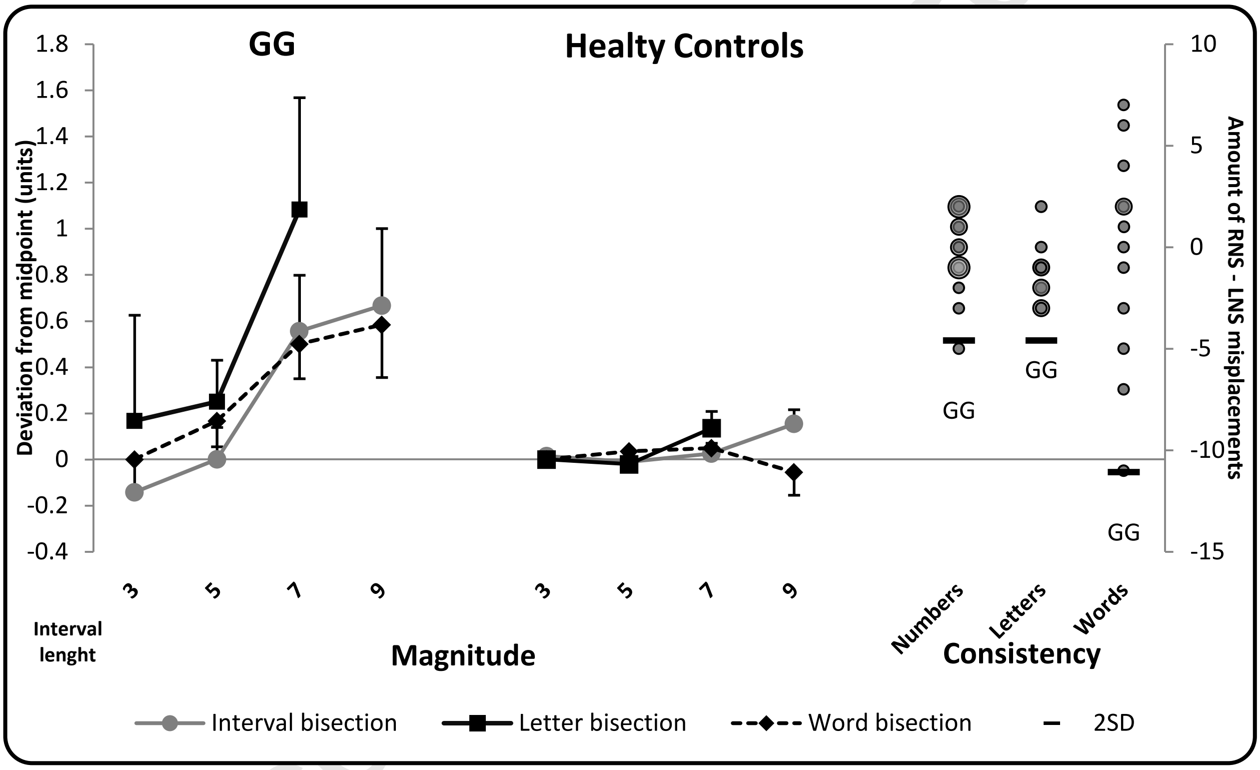
GG
Healty Controls
Deviation from midpoint (units)
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
Amount of RNS - LNS misplacements
10
5
0
-5
-10
-15
GG
GG
GG
3
5
7
9
3
5
7
9
Interval lenght
Magnitude
Numbers
Letters
Words
Consistency
Interval bisection
Letter bisection
Word bisection
2SD

Figure 4

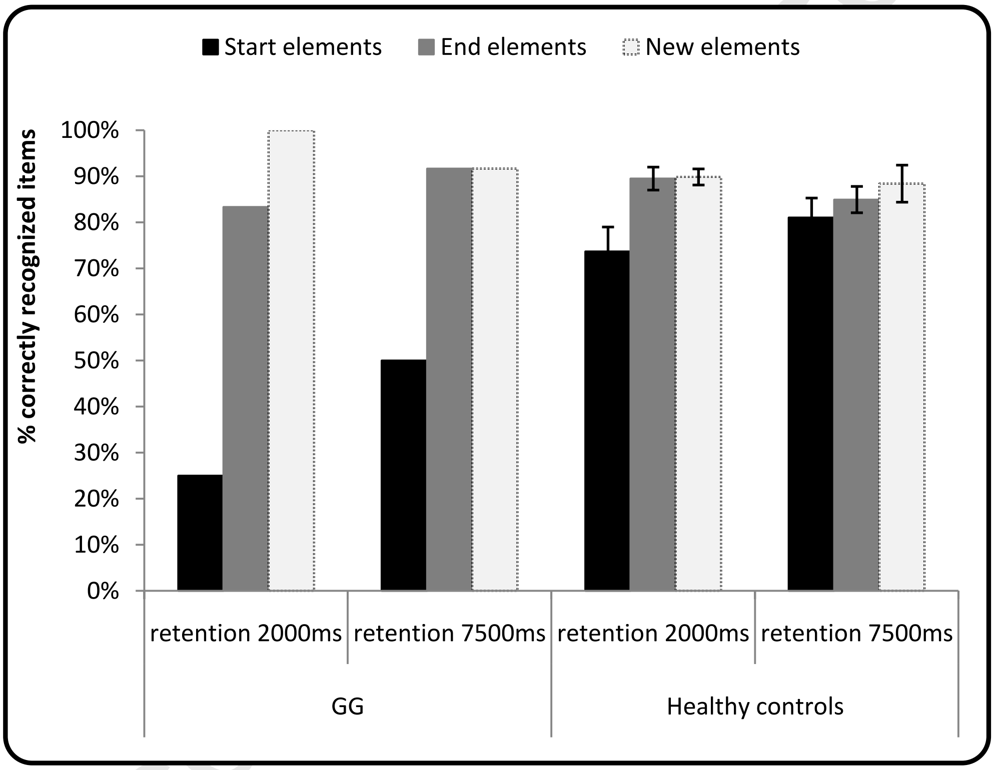
Start elements
End elements
New elements
% correctly recognized items
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
retention 2000ms
retention 7500ms
retention 2000ms
retention 7500ms
GG
Healthy controls

Figure 5

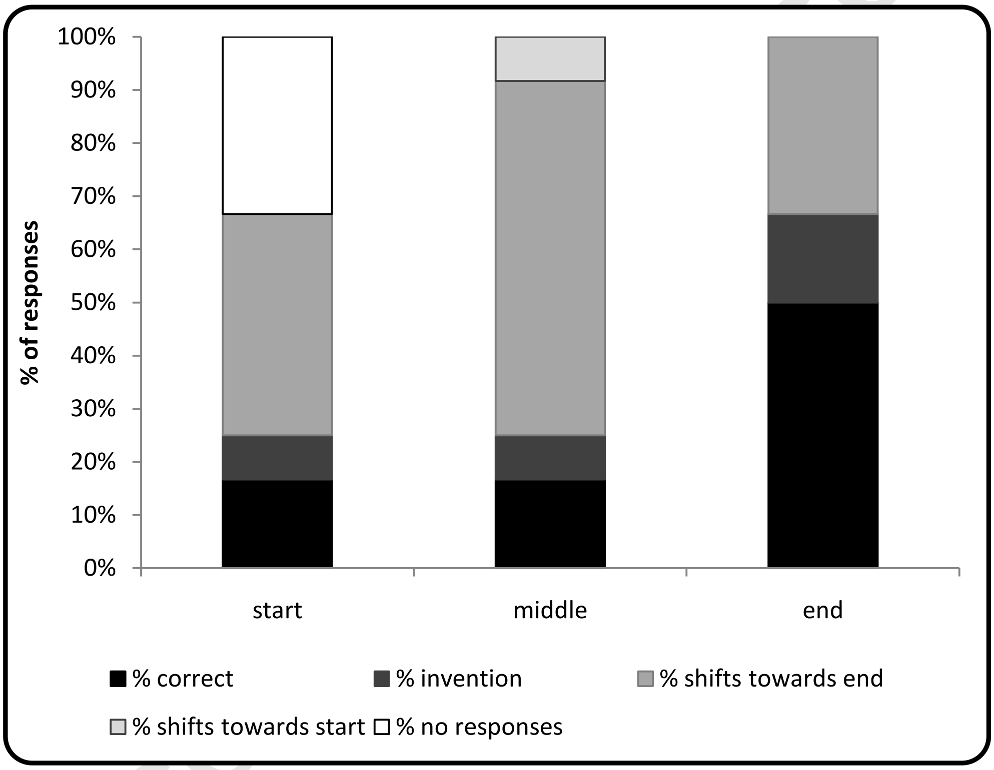
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
% of responses
start
middle
end
■ % correct
■ % invention
■ % shifts towards end
□ % shifts towards start
□ % no responses

Figure 6

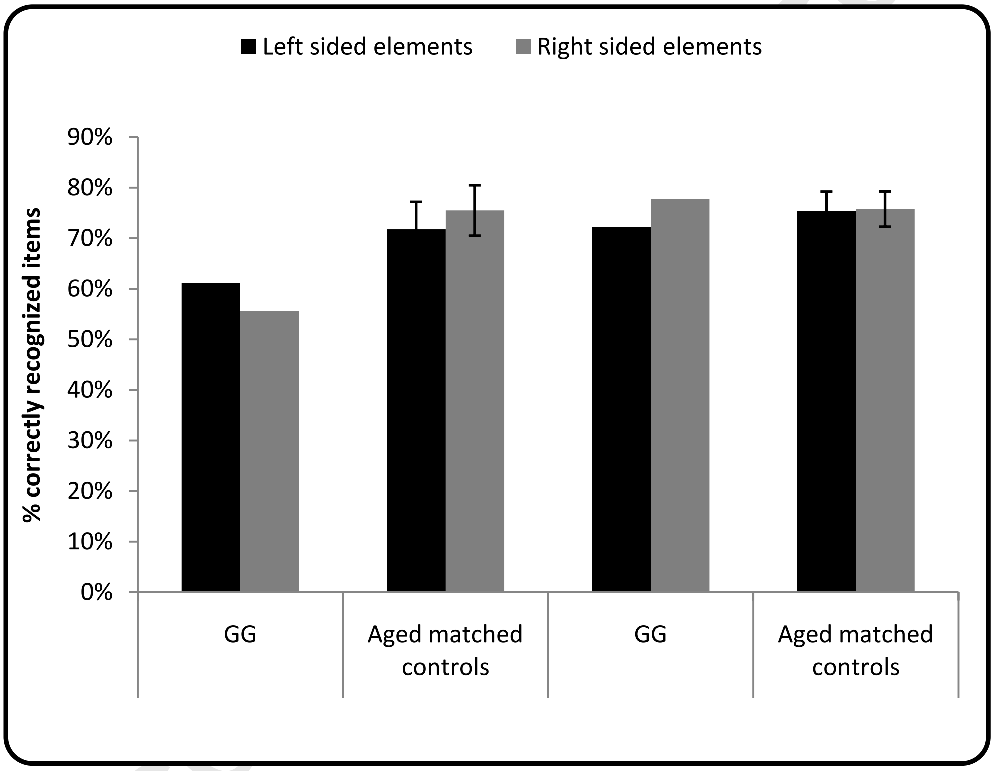
Left sided elements
Right sided elements
% correctly recognized items
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
GG
Aged matched controls
GG
Aged matched controls

Table 1

		Administered tasks	Raw score	Interpretation
Perception	Auditory perception			
		Seashore Rhythm test [1]	12/12	normal
	Visual object recognition			
		Effron-figures for visual form perception	No inaccurate responses	normal
		Visual Object and Space Perception Battery (VOSP) [2]	No inaccurate responses	normal
		Birmingham Object Recognition Battery (BORB) [3]	No inaccurate responses	normal
	Visuo-spatial perception			
		Dot Counting (VOSP)	No inaccurate responses	Normal
Memory	Verbal			
		Letter span (forward)[20]	Sequence length= 3	impaired
		Buschke Selective Reminding test [4]	Total recall= 89; z=-3.4	impaired
	Visuo-spatial			
		Visual Patterns Test [5]	Score=2; <pc.05	impaired
		Corsi block span [20]	Sequence length= 5	normal
Attention	Focused attention	*Bourdon-Vos Cancellation* [6]	4 omissions; z=-1	borderline
		Symbol Digit Modalities test (SDMT) [7]	n=40; z=-1.2	borderline
		Computerised Visual Search Task (FEPSY) [8]	Mean time= 3.86; <dc.1	impaired
	Sustained attention	*Continuous Performance task (FEPSY)*	Hit rate= 0.87; pc.50	Normal
	Spatial attention	*Schenckenberg Line Bisection* [9]	Left= 2%dev; Centre= -4%dev; Right=-7%dev	impaired
		Albert Line Cancellation [10]	Omissions left=0; right=3	borderline
		Star Cancellation [11]	Omissions left=0; right=4	borderline
		Bell Cancellation [12*]	Omissions Left=1; Right= 5	impaired
		Benton Line Orientation test [13]	Nr. correct=13	borderline
Language		*Aachen Aphasia Test* [14]	Normal score on all subtests	normal
		Boston Naming task [15]	No inaccurate responses	Normal
Executive functions		*Behavioural assessment of Dysexecutive syndrome (BADS)* [16]	Total profile score=15; z=-1	Borderline
		Stroop Color-Word Test [17]	Interference score=66; pc. 1	Impaired
		Wisconsin Card Sorting test [18]	Number of perseverations :6	borderline
		Tower of London [19]	Total scaled score=15	normal

Table 2

		GG	HC	
Neglect			average	stdev
Physical line bisection	RNS-LNS misplacements	*14*	0,08	5,53
Map of Flanders	Lq	*100*	-30	25
Desciption picture	Lq	*26,34*	-0,94	9,18
o'clock	Lq	*22,22*	-1,84	5,75
Verbal Screening				
Reading	Words (40items)	*38*	39,9	0,35
	Non-Words (40items)	*25*	37,37	1,41
Writing				
Spelling	Visual (26items)	26	25,5	0,53
	Oral (9items)	8	8,75	0,46
Numerical screening				
Counting	Forward (1-20)	20	20	0
	Backward (20-1)	20	20	0
Simple calculation	Addition (24items)	24	23,88	0,35
	Subtraction (24items)	23	23,75	0,46
	Multiplication (24items)	24	22,25	2,25
	Division (24items)	23	23,63	0,52
Complex calculation	Addition (24items)	23	23,63	0,52
	Subtraction (24items)	21	23,13	1,36
Computing average	48 items	44	45,34	1,83

Appendix 1

Stimuli used in the number interval bisection task

Interval length	First number	Second number	Interval length	First number	Second number
3	1	3	5	4	8
3	2	4	5	5	9
3	3	5	5	11	15
3	4	6	5	12	16
3	5	7	5	13	17
3	6	8	5	14	18
3	7	9	5	15	19
3	11	13	5	21	25
3	12	14	5	22	26
3	13	15	5	23	27
3	14	16	5	24	28
3	15	17	5	25	29
3	16	18	7	1	7
3	17	19	7	2	8
3	21	23	7	3	9
3	22	24	7	11	17
3	23	25	7	12	18
3	24	26	7	13	19
3	25	27	7	21	27
3	26	28	7	22	28
3	27	29	7	23	29
5	1	5	9	1	9
5	2	6	9	11	19
5	3	7	9	21	29

Appendix 2

Stimuli used in the word bisection task

Length	Word	Length	Word
3	Mus	7	Bezopen
3	Kat	7	Tilburg
3	Gil	7	Zwalpen
3	Rog	7	Traject
3	Zeg	7	Volgens
3	Wis	7	Brigade
3	Kip	7	Syncope
3	Puf	7	Plonzen
3	Kot	7	Narcose
3	Dus	7	Replica
3	Vos	7	Viaduct
3	Mes	7	Voltage
5	Pater	9	marmelade
5	Gunst	9	Lamineren
5	Hemel	9	Gesternte
5	Kelen	9	Verstoten
5	Jagen	9	Extravert
5	Zaken	9	Verlating
5	Clown	9	Klisteren
5	Tegel	9	Halvering
5	Spion	9	Vertolken
5	Flink	9	Hospitant
5	Wonen	9	Induceren
5	Forel	9	Magnetron

Appendix 3

Stimuli used in the letter interval bisection task

Distance	Order	Letter1	Letter2	Distance	Order	Letter1	Letter2
3	ascending	r	t	7	ascending	m	s
3	ascending	v	x	7	ascending	f	l
3	ascending	o	q	7	ascending	h	n
3	ascending	e	g	7	ascending	s	y
3	ascending	f	h	7	ascending	a	g
3	ascending	w	y	7	ascending	e	k
3	descending	h	f	7	descending	i	c
3	descending	l	j	7	descending	m	g
3	descending	z	x	7	descending	r	l
3	descending	g	e	7	descending	l	f
3	descending	u	s	7	descending	u	o
3	descending	w	u	7	descending	v	p
5	ascending	d	h	9	ascending	e	m
5	ascending	t	x	9	ascending	j	r
5	ascending	k	o	9	ascending	l	t
5	ascending	v	z	9	ascending	r	z
5	ascending	o	s	9	ascending	m	u
5	ascending	g	k	9	ascending	b	j
5	descending	m	i	9	descending	z	s
5	descending	l	h	9	descending	x	p
5	descending	w	s	9	descending	p	h
5	descending	k	g	9	descending	l	d
5	descending	o	k	9	descending	q	i
5	descending	y	u	9	descending	n	f