

Spatial bias in symbolic and non-symbolic numerical comparison in neglect

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ABSTRACT

When asked to bisect mentally numerical intervals, neglect patients show a displacement of the numerical midpoint similar to the one observed in physical line bisection. This spatial-numerical bias has been taken as evidence of the spatial nature of numerical magnitude representations. However, to date, neuropsychological studies in neglect patients have only used symbolic numerical material. Here, we compare the results of patients with right-hemisphere damage with and without unilateral left neglect and age-matched healthy control participants in two numerical comparison tasks using symbolic and non-symbolic materials, in order to determine whether the representation of non-symbolic numerosities was altered or not by the presence of neglect. When asked to judge if an Arabic digit or a sequence of flashed dots was smaller or larger than a reference value (i.e., 5), the responses of neglect patients to smaller magnitudes (i.e., 4) were impaired. Moreover, only neglect patients presented an asymmetrical distance effect (i.e., an enhanced effect only for stimuli of smaller numerical magnitude than the reference). These results provide the first direct evidence of a spatial bias in non-symbolic numerosity in neglect patients, and support the existence of common processing mechanisms and/or a representational system for symbolic and non-symbolic inputs.

Keywords: Spatial Neglect; Numbers; Symbolic and Non-symbolic inputs

1. Introduction

Interactions between number and space processing have been reported in many studies (for a review, see Hubbard, Piazza, Pinel, & Dehaene, 2005), which has led to the suggestion that numerical magnitudes may be represented spatially with small numbers on the left and large numbers on the right side of a mental number line (Dehaene, 1992). To test the spatial nature of this numerical representation, recent neuropsychological research has investigated numerical abilities in neglect patients. Unilateral spatial neglect is defined as a failure to report, respond to or orient towards stimuli in contra-lesional space (Heilman, 1979) that often occurs after cerebral lesions involving the posterior-inferior parietal and the premotor cortices (Vallar, 1998), and that could possibly arise from a disruption of fronto-parietal white matter pathways (Doricchi and Tomaiuolo, 2003; Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomé, 2008). When asked to indicate the midpoint of a physical line, neglect patients show a significant rightward deviation (e.g., Binder, Marshall, Lazar, Benjamin, & Morh, 1999; Marshall, & Halligan, 1989; Pizzamiglio, Committeri, Galati, & Patria, 2000). Neglect is not restricted to the perception of physical space and may extend to representational space. Indeed, there is evidence that neglect patients fail to recall the left side of well-known places, depending on their imagined viewpoint (e.g., Bisiach & Luzzatti, 1978). Nevertheless, a double dissociation between perceptual and representational neglect has been observed, suggesting the existence of at least partly independent attentional mechanisms operating in the perceptual and imaginal space (Anderson, 1993; Guariglia, Padovani, Pantano, & Pizzamiglio, 1993).

In numerical interval bisection tasks (i.e., determining the midpoint of a numerical interval), left neglect patients showed a displacement of the midpoint towards large numbers, suggesting a deviation to the right part of the mental number line (Cappelletti, Freeman, & Cipolotti, 2007; Hoeckner et al., 2008; Zorzi, Priftis, & Umiltà, 2002; Zorzi, Priftis, Meneghello, Marenzi, & Umiltà, 2006). A case study of a right unilateral neglect patient showing the opposite bias (i.e., underestimation rather than overestimation of the midpoint; Pia, Corazzini, Folegatti, Gindri, & Cauda, 2009) supports the idea of a distortion of numerical representation caused by a deviation of visuospatial attention (however, see below van Dijck, Gevers, Lafosse, Doricchi, & Fias, 2011 for a rightward bias in a right neglect patient). Moreover, it has recently been demonstrated that neglect patients who present prismatic adaptation as a consequence of having worn shifting prisms (Rossetti et al., 2004) or who have received leftward optokinetic stimulation¹ (Priftis, Pitteri, Meneghello, Umiltà, & Zorzi, 2012), both techniques inducing visuo-spatial shifts of attention to the left, showed a reduction in the overestimation bias. When neglect patients had to judge a given number as smaller or larger than a fixed reference number, they processed numbers just smaller than the reference more slowly than those just larger (Vuilleumier, Ortigue, & Brugger, 2004): when asked to compare numbers to a standard reference of 5, the patients were slower to respond to 4 than to 6, while they were slower to respond to 6 than to 8 when the reference was 7. This asymmetrical distance effect implies that neglect does not alter the representation of numbers *per se*, but induces a failure to access the left side of the mental number line relative to the standard. Random dot kinetograms (RDK, a technique that induces a perception of movement

¹ Optokinetic stimulation is a technique inducing visuospatial shifts of attention by means of activation of the optokinetic nystagmus (for a review, see Kerkhoff, 2003).

without eye movements) to the left also reduced this spatial bias in symbolic comparison tasks (Salillas, Granà, Juncadella, Rico, & Semenza, 2009). Taken together, these findings suggest that numerical judgements are biased by impaired spatial processing, which provides strong evidence of a numerical representation with spatial properties.

However, the double dissociation between physical line and numerical interval bisection impairments found in some neglect and non-neglect patients (Aiello, Merola, & Doricchi, 2013; Aiello et al., 2012; Doricchi, Guarglia, Gasparini, & Tomaiuolo, 2005; for a review, see Rossetti et al., 2013) questions the idea of a simple functional equivalence between the mental number line and the representation of physical space. Indeed, not all neglect patients show a numerical impairment and, conversely, some right brain-lesioned non-neglect patients show a spatial-numerical bias during mental bisection of number intervals. In the sample tested by Doricchi and collaborators (2005), only patients with lesions in the prefrontal cortex, a region known to support some working memory processes, showed a rightward numerical bias, suggesting that this region contributes to activating a numerical continuum in visuo-spatial working memory. An additional argument in favour of a working memory account comes from a case study of a patient with an extended left hemispheric lesion who presented spatial neglect for the right visual hemispace but left neglect for numbers (i.e., overestimation of the midpoint of number interval bisection; van Dijck et al., 2011). This patient had difficulty retrieving the first items of verbal sequences, suggesting that the overestimation in number interval bisection observed in neglect patients could originate in verbal working memory impairment for the initial items. Moreover, the role of working memory in spatial-numerical associations has been supported by several

behavioural studies showing that the ordinal information stored in verbal working memory can overcome the spatial-numerical interaction based on magnitude (Fias, van Dijck, & Gevers, 2011; van Dijck & Fias, 2011; van Dijck, Ginsburg, Girelli, & Gevers, in press).

The actual meaning of the spatial-numerical bias observed in neglect patients is thus unclear, as it could be due either to the spatial properties of a long-term representation or to order-related processes in short-term working memory. In this context, using non-symbolic stimuli may provide a significant way of disentangling these two possibilities. On the one hand, computational modelling suggests that symbolic and non-symbolic numerical inputs are coded by specific mechanisms, but are represented within a common numerical magnitude system (Verguts & Fias, 2004), possibly implemented in the left and right parietal cortices (Dormal, Andres, Dormal, & Pesenti, 2010; Holloway, Price, & Ansari, 2010; Piazza, Pinel, Le Bihan, & Dehaene, 2007; Santens, Roggeman, Fias, & Verguts, 2010; Venkatraman, Ansari, & Chee, 2005). Furthermore, various magnitudes (e.g., numerosity, length, duration, etc.) may be represented, irrespective of their mode of presentation, within a common magnitude processing system, possibly located in the parietal cortex (Bonato, Zorzi, & Umiltà, 2012; Walsh, 2003). Accordingly, the spatial-numerical bias should occur when processing symbolic but also non-symbolic stimuli. Yet, despite a growing interest in the neuropsychological investigation of unilateral neglect in the numerical domain, the studies so far have only tested spatial-numerical biases with symbolic notations. To the best of our knowledge, only one study to date has attempted to demonstrate the existence of a spatial bias in the perception of non-symbolic numerosities in healthy participants (de Hevia & Spelke, 2009). In a line bisection task flanked with a 2-dot and a 9-dot array, a shift of the subjective midpoint

of the line in the direction of the numerically larger set of dots was observed. However, this experiment has been criticised because some non-numerical parameters were not controlled (e.g., area; Gebuis & Gevers, 2011). The assumption that processing non-symbolic magnitudes involves spatial representations is thus still an open question. On the other hand, non-symbolic sequential comparison requires more working memory resources than symbolic comparison, as the traces of each single presented dot must be somehow kept active to compare the target sequence to the standard. Therefore, patients with lower verbal working memory capacities should perform globally worse in this demanding task than controls with preserved working memory abilities. Finally, according to a working memory account, a bias for processing numerical magnitudes smaller than a reference in neglect patients should occur concomitantly with verbal working memory impairment (Doricchi et al., 2005).

The present study thus aims to determine whether or not the spatial bias observed in neglect patients when comparing symbolic numbers extends to non-symbolic materials which would (i) support the idea of a common system for processing/representing symbolic and non-symbolic numerical magnitudes and its spatial nature, and (ii) assess the extent to which a working memory interpretation better accounts for the data. Patients with and without left neglect and healthy controls were tested in two numerical comparison tasks, using Arabic digits or sequences of flashed dots. Given prior studies using numerical comparison, a distance effect (i.e., an increase in the response latencies and/or the error rates as the numerical distance between the numbers being compared decreases; Moyer & Landauer, 1967) is expected for both symbolic and non-symbolic inputs in control groups. Neglect patients are expected to be slower in symbolic number comparison task when responding to digits that are just smaller than the standard (i.e., in the

number range from 1 to 9 and for a given reference of 5, digit 4 should be more difficult to process for the neglect group). Thus, particular attention will be devoted to performance on numerical magnitudes close to the standard on both sides of the standard. If this difficulty is attributed to an impaired access to the numerical representation on the relative left of the standard value on an input-independent spatial magnitude representation system, a similar pattern should arise both in symbolic and non-symbolic numerical comparison tasks. An absence of spatial-numerical bias in the non-symbolic task in neglect patients would challenge the hypothesis of a common spatial representation of symbolic and non-symbolic numerical magnitude. Working memory capacities of each group will be compared to evaluate if verbal working memory deficit accounts for the spatial-numerical bias in the neglect group.

2. Methods

2.1 Participants

Fourteen patients with left-unilateral spatial neglect following right posterior hemispheric damage (hereafter N+; mean age: 58 ± 11 years, 4 females, 13 right-handed) and eleven patients showing no sign of neglect (hereafter N-; mean age: 60 ± 11 years, 3 females, all right-handed)² participated in this study after giving written informed consent. All the patients had suffered from a right cerebral lesion at least three months previously; demographical and clinical details are listed in Tables 1 and 2. The presence of neglect was assessed by neurologists and neuropsychologists

² Two participants of the N- group had right brain lesions consecutive to a traumatic brain injury whereas all the other patients suffered from vascular lesions. It is however worth noting that withdrawing the data of these two patients from the analyses did not modify any of the results.

using standard clinical tests including cancellation (Gauthier, Dehaut, & Joanette, 1989), line bisection (Azouvi et al., 2006) and the computerized neglect subtask of the Test for Attentional Performance (TAP; Zimmermann & Fimm, 2002; see below for more methodological details). A patient was included in the N+ group if she/he showed evidence of neglect (i.e., significant right deviation in line bisection or left omissions in cancellation or neglect TAP task) in at least one of the three tasks (see Table 2 for score details). Fourteen healthy control adults (hereafter HC; mean age: 58 ± 11 years, 4 females, all right-handed) with no history of neurological or psychiatric disease also performed the working memory span and numerical comparison tasks. The mean age of N+ patients did not significantly differ from the N- patients ($t(23)=0.396$, *ns*) or the HC participants ($t(26)=0.17$, *ns*). Finally, no difference was found between N- and HC ($t(23)=0.415$, *ns*).

Insert Table 1 about here

2.2 Neglect assessment

2.2.1 The Bells Test (Gauthier et al., 1989).

The Bells Test requires the patient to search and cross out all the targets (i.e., bells) among various distractors on an A4 sheet. The scores correspond to the numbers of targets that the patient fails to cross for the left and the right parts of the sheet, respectively; six omissions out of 15 targets in the left part of the sheet indicate a left visual neglect (Gauthier et al., 1989).

2.2.2 Line Bisection Task (GEREN, Azouvi et al., 2006)

The patient has to mark with a pencil the midpoint of a 20-cm line centred on an A4 sheet aligned with the body midline. A deviation larger than 6.5 mm to the right side of the line indicates the presence of a left visual neglect.

2.2.3 Neglect subtest of Test for Attention Performance (TAP; Zimmermann & Fimm, 2002)

In this computerized task, the patient has to detect peripheral flickering targets (i.e., digit numbers) appearing at random positions among steady distractors, while keeping central fixation. The score corresponds to the number of left and right omissions. An asymmetric number of omissions towards the left is interpreted as a sign of left spatial neglect.

2.3 Working memory assessment

Working memory was assessed using the digit span tasks from the Weschler Adult Intelligence Scale (WAIS-III; Wechsler, 1997). The patients were given orally sets of digits that they had to repeat forwards or backwards.

Insert Table 2 about here

2.4 Numerical tasks

2.4.1 Tasks and stimuli

Two comparison tasks were used: the comparison of (1) Arabic digits (hereafter, AC for Arabic comparison), and (2) sequences of dots (hereafter, DC for dot comparison) to the standard “5”.

Insert Figure 1 about here

In the AC task, the stimuli were 20 mm-high Arabic digits from 1 to 9 (except the standard 5), centrally presented for 400 ms in white on a black background (Fig. 1A). In the DC task, the stimuli were composed of a central black dot (25 mm-diameter) flashed rapidly inside a white rectangle (95 mm x 160 mm). This sequential mode combined with a central presentation was chosen to ensure that N+ perceived the stimuli correctly. The sequences contained 1 to 9 dots (except the standard 5); four different sequences were composed for each numerosity. Numerical and temporal features of the sequences were unconfounded by creating non-periodic signals (for details, see Breukelaar & Dalrymple-Alford, 1998; Dormal, Seron, & Pesenti, 2006; Dormal et al., 2010; Dormal, Grade, Mormont & Pesenti, 2012), that is sequences of dots and intervals, the duration of which was pseudorandomly varied by applying the following rules. Firstly, the mean total duration of presentation of the dots and the mean total duration of the interdot intervals were kept roughly equivalent (mean duration: 750 ± 30 ms each, for a total duration of 1500 ms) within and across numerosities, such that numerosity did not correlate with the total duration of the dots ($r=-0.16$, $p>0.6$) or the total duration of the intervals ($r=0.16$, $p>0.4$). Critically, there was no difference in the range of durations used for numerosities 4 and 6 ($t(6)=0.118$, *ns*). Secondly, the duration of each dot and each interdot interval varied

separately between 50 ms and 410 ms (Fig. 1B). To avoid pattern recognition, each sequence involved at least one dot and one interval of 50 ms and one dot and one interval longer than 200 ms, and each sequence finished with an interval of 50 ms. To ensure that the temporal ratio did not constitute a potential confounding variable, ratio deviation scores (DS ratio; i.e., a measure of the deviation from the corresponding periodic signal with constant dot and interval durations; the more distant the ratio from 0, the less numerosity and duration are confounded) were kept equivalent across numerosities (mean DS ratio for numerosities 3 to 9: $246 \pm 0,5$). This later constraint could not be applied to numerosity 2 (DS ratio: 945 ± 277) due to fewer variation possibilities once one dot and one interval of 50 ms are imposed, and to numerosity 1 (DS ratio: 1299 whatever the dot and interval duration); this resulted in sequences with higher DS ratios, thus with numerosity and duration even less confounded.

2.4.2 Procedure

Stimulus presentation and data collection were controlled by a Toshiba laptop using E-Prime program (Schneider, Eschman, & Zuccolotto, 2002). The participants were installed at a distance of approximately 60 cm from the screen. At the beginning of each trial, a central white fixation cross appeared for 1000 ms. The stimuli described above were then presented, followed by a white centred question mark (i.e., "?") on a black screen which remained until a response was made. The participants were asked to wait for the disappearance of the digit (for AC) or of the last dot of the sequences (for DC) before answering. As soon as the answer was given, the next trial started.

In each task, the participants had to judge whether the stimulus was smaller or larger than the standard, by pressing a left or right response key respectively on a keyboard placed in front of them such that the answer keys were on the right side of external space compared to their body. As many of the right brain-lesioned patients showed left-sided paresis, all the participants were asked to respond with their right index for the left response button (i.e., response key “k” on the keyboard) and with their right middle finger for the right response button (i.e., response key “m” on the keyboard). Note that the methodological choice not to reverse the response mapping was motivated by previous studies employing comparison paradigms in neglect patients that showed no effect of response mapping (see Vuilleumier et al., 2004; van Dijck et al., 2012) or difficulty switching from a learned response mapping to another for brain-lesioned patients (Vuilleumier et al., 2004).

Each task contained 3 blocks of 32 trials (for a total of 96 trials, corresponding to 12 repetitions of each item) and was preceded by 8 training trials not included in the analyses, to ensure that the participants understood the instructions. The participants were asked to respond as fast and accurately as possible. They were also instructed to adopt an approximate judgement strategy and to avoid explicit counting strategies in the DC task. The testing session always began with the digit span tasks followed by the numerical comparison tasks. The order of the two comparison tasks was counterbalanced across participants; they were tested in one or two sessions depending on the availability of the participants.

3. Results

Trials for which the participants could give no response (50/3744 data points) were excluded from further analyses. The median response latencies (RLs) of correct

answers and the mean error rate (ER) for each digit or dot sequence were computed for all the participants. Hereafter, the variable Response will be used to categorise the stimuli as being smaller or larger than the fixed standard. The variable Distance (from 1 to 4) corresponds to the numerical distance between the stimuli and the standard. These variables were used in analyses of variance (ANOVAs) for each numerical task (i.e., AC and DC tasks). Because our hypothesis predicts a more pronounced distance effect for small responses in N+, interactions involving these variables were further investigated by means of (i) planned comparisons (pairs of numbers/numerocities at the same distance for each group; N+ vs. N- and N+ vs. HC for distance close to the standard) and (ii) comparisons of asymmetry indexes of the distance effect (see below for further details) in each group. Finally, we compared the working memory performances in forward and backward digit spans for the three groups of participants.

3.1 AC task

3.1.1 Response latencies

An ANOVA on the RLs with Response (Smaller vs. Larger) and Distance (d1, d2, d3 vs. d4) as within-subject variables, and Group (N+, N- vs. HC) as a between-subject variable was carried out. The analysis revealed a significant main effect of Group ($F(2,36)=13.697$, $p<0.001$) indicating that N+ ($1062\pm334\text{ms}$) were slower than N- ($762\pm165\text{ms}$, $t(23)=2.724$, $p<0.05$) and HC ($601\pm149\text{ms}$, $t(26)=4.722$, $p<0.001$); HC were also globally faster than N- ($t(23)=2.567$, $p<0.05$). A main effect of Distance was also observed ($F(3,108)=20.112$, $p<0.001$): all the distances differed significantly from each other, RLs decreasing with the distance (mean RLs for d1: $855\pm331\text{ms}$; d2: $821\pm296\text{ms}$; d3: $793\pm302\text{ms}$; d4: $777\pm301\text{ms}$; all $p\text{-values}<0.05$). Moreover, a

significant three-way interaction between Response, Distance and Group was observed ($F(6,108)=3.114$, $p<0.01$). Separate ANOVAs for each group with Response and Distance as within-subject variables were carried out. A classical main effect of Distance was present in each group (all p -values <0.001) whereas a Response effect was only observed in N+ ($F(1,13)=6.761$, $p<0.05$) and in N- ($F(1,10)=18.189$, $p<0.005$). The N+ patients were slower for "smaller" (1096 ± 343 ms) than for "larger" (1027 ± 332 ms) responses, while the reverse was found for the N- patients (mean RLs for Smaller: 740 ± 158 ms; for Larger: 784 ± 172 ms). Finally, these main effects were qualified by a significant Response by Distance interaction in the N+ group ($F(3,39)=3.769$, $p<0.05$) and in the HC group ($F(3,39)=3.333$, $p<0.05$), but not in the N- group ($F(3,30)=1.641$, $p>0.2$).

In N+, median RLs were compared for all pairs of numbers at the same distance from the standard. N+ were significantly slower to respond to 4 (1191 ± 405 ms) than to 6 (1059 ± 330 ms; $t(13)=3.435$, $p<0.005$; Fig. 2). Other pairwise comparisons showed no difference between items at the same distance (p -values >0.05 for all t -tests). In HC, no such difference for pairs of numbers at the same distance was observed ($p>0.1$ for all t -tests; Fig. 2). A significant difference was only found between d1 and d2 for "smaller" (mean RLs for d1: 631 ± 136 ms; for d2: 598 ± 132 ms; $t(13)=2.559$, $p<0.05$; Fig.2) but not for "larger" (mean RLs for d1: 611 ± 162 ms; for d2: 621 ± 154 ms; $t(13)=0.861$, ns) responses. Moreover, close to the standard, N+ differed from N- for "smaller" ($t(21)=2.698$, $p<0.05$) but not for "larger" responses ($t(21)=1.412$, $p>0.1$). HC were more accurate than N+ both for "smaller" ($t(26)=4.587$, $p<0.001$) and "larger" ($t(26)=4.555$, $p<0.001$) responses.

Insert Figure 2 about here

In order to decompose these interactions in terms of asymmetry of distance effects, RLs for "smaller" and "larger" responses of each participant were entered into separate regressions with the Distance as a predictor (Lorch & Myers, 1990). First, the slopes for each response were compared to zero with one-sample *t*-tests to assess the presence of significant distance effects. Both slopes differed significantly from zero (mean β for smaller: -33 ± 34 ms; $t(38)=6.111$, $p<0.001$; for larger: -19 ± 29 ms, $t(38)=4.113$, $p<0.001$). The regression weights for "smaller" responses were then subtracted from the weights for "larger" responses to obtain an asymmetry index of the distance effect (van Dijck, Gevers, Lafosse, & Fias, 2012; Zorzi et al., 2012). A negative asymmetry index would indicate an enhanced distance effect for "smaller" responses, whereas a positive value would indicate an enhanced distance effect for "larger" responses. The asymmetry index of each group was then compared to zero with one-sample *t*-tests. Only the N+ group had an asymmetry index that differed significantly from zero (mean asymmetry index for N+: -38.2 ± 55 ms; $t(13)=2.598$, $p<0.05$; N-: 10.1 ± 42.5 ms, $t(10)=0.788$, *ns*; HC: -10.4 ± 23 ms, $t(13)=1.704$, *ns*). A one-way ANOVA on the asymmetry index with the Group as an independent variable was significant ($F(2,38)=4.131$, $p<0.05$). Direct comparisons between groups demonstrated that the asymmetry index of N+ group was significantly different from N- ($t(23)=2.4$, $p<0.05$) and that there was no difference between N- and HC ($t(23)=1.551$, *ns*).

3.1.2. Mean error rates

An ANOVA with the same factors was performed on the ER. Only the main effect of Distance was significant (d1: $5.7 \pm 7.9\%$; d2: $3.9 \pm 5.4\%$; d3: $1.4 \pm 2.7\%$; d4: $0.7 \pm 2.4\%$; $F(3,108)=12.902$, $p<0.001$): the percentage of errors increased as the distance decreased. No other significant main effects or interactions were found (all p -values at least >0.7). No other analyses were conducted due to the small overall ER (2.9 %).

3.2 DC task

3.2.1. Response latencies

An ANOVA on RLs with Response (Smaller vs. Larger) and Distance (d1, d2, d3 vs. d4) as within-subject variables and Group (N+, N- vs. HC) as a between-subject variable revealed the main effects of Group ($F(2,36)=16.99$, $p<0.001$) and Response ($F(1,36)=29.505$, $p<0.001$). The HC participants responded faster ($491 \pm 164\text{ms}$) than the N- participants ($799 \pm 258\text{ms}$, $t(23)=3.636$, $p<0.01$) and N+ ($1178 \pm 439\text{ms}$, $t(26)=5.493$, $p<0.001$) that also differed from each other ($t(23)=2.541$, $p<0.05$). Overall, the participants were also globally faster for larger ($713 \pm 362\text{ms}$) than for smaller items ($935 \pm 521\text{ms}$).

A significant interaction between Group and Response was also observed ($F(1,36)=8.133$, $p<0.001$): N+ and N- were significantly slower to respond to smaller ($1394 \pm 526\text{ms}$) than to larger numerosities (mean RLs in N+ for Smaller: $1394 \pm 526\text{ms}$; for Larger: $962 \pm 408\text{ms}$; $t(13)=4.728$, $p<0.001$; mean RLs in N- for Smaller: $880 \pm 312\text{ms}$; for Larger: $717 \pm 253\text{ms}$; $t(10)=2.274$, $p<0.05$) whereas this difference was not significant for HC (mean RLs for Smaller: $522 \pm 172\text{ms}$; for Larger:

460±174ms; $t(13)=2.042$, $p=0.062$). No other interaction was observed (p -values>0.4).

3.2.2 Mean error rates

The same ANOVA on the ER revealed a significant main effect of Group (mean ER for N+: 27.2±12.6%; N-: 15.7±8.7%; HC: 5±5.3%; $F(1,36)=19.355$, $p<0.001$) indicating that N+ made more errors than N- ($t(23)=2.57$, $p<0.05$) and HC ($t(26)=6.051$, $p<0.001$). N- also had a higher ER than HC ($t(23)=3.788$, $p<0.001$). A significant main effect of Distance was observed (mean ER for d1: 27.9±16%; d2: 14.8±16.4%; d3: 10.2±12.4%; d4: 11.4±14.3%; $F(3,108)=45.450$, $p<0.001$). Direct comparisons revealed that d1 differed significantly from d2 ($t(38)=5.81$, $p<0.001$), and d2 from d3 ($t(38)=3.538$, $p<0.001$), but the difference between d3 and d4 was not significant ($t(38)=0.633$, *ns*).

Interestingly, there was a significant three-way interaction between Group, Response and Distance ($F(6,108)=7.243$, $p<0.001$). Separate ANOVAs for each group with Response and Distance as within-subject variables indicated that the main effect of Response was significant in the HC group (mean ER for Smaller: 1.7±2.2%; Larger: 8.4±10.4%; $F(1,13)=5.434$, $p<0.05$) but not in the N+ (mean ER for Smaller: 28.99±18.62%; Larger: 25.31±20.38%; $F(1,13)=0.213$; *ns*) nor in the N- group (mean ER for Smaller: 7.31±7.58%; Larger: 24.06±20.4%; $F(1,10)=4.781$, $p=0.054$). Importantly, a significant main effect of Distance was present for each group (N+: $F(3,39)=11.484$, $p<0.001$; N-: $F(3,30)=28.001$, $p<0.001$; HC: $F(3,39)=10.771$, $p<0.001$), suggesting that all the participants actually processed the numerical dimension. Moreover, there was a significant interaction between Response and Distance in the N+ ($F(3,39)=13.657$, $p<0.001$) and HC ($F(3,39)=5.461$, $p<0.005$)

groups. In N+, ERs were significantly higher for close distances (d1 and d2) than far distances (d3 and d4) for "smaller" (mean ERs for close: $37.79 \pm 19.68\%$; for far: $20.24 \pm 19.81\%$; $t(13)=4.989$, $p<0.001$) and "larger" (mean ERs for close: $28.35 \pm 23.29\%$; far: $22.27 \pm 18.46\%$; $t(13)=2.229$, $p<0.05$) responses. In HC, ERs also differed for "smaller" (mean ERs for close: $3.09 \pm 4.55\%$; for far: $0.3 \pm 1.11\%$; $t(13)=2.137$, $p<0.05$) and "larger" (mean ERs for close: $14.19 \pm 17.18\%$; for far: $2.57 \pm 4.8\%$; $t(13)=3.069$, $p<0.01$) responses. Then, the mean ERs for trials of similar distance but different responses were compared. In the N+ group, the patients made more errors for 4 than for 6 dots (mean ER for 4 dots: $53 \pm 22.2\%$; 6 dots: $26 \pm 22.6\%$; $t(13)=2.46$, $p<0.05$; Fig. 3). In HC, a significant difference was observed between sequences of d1 (mean ER for 4 dots: $4.9 \pm 7.9\%$; 6 dots: $20.3 \pm 22.7\%$; $t(13)=2.582$, $p<0.05$; Fig. 3). Moreover, close to the standard, N+ differed from N- and HC for "smaller" (N+ vs. N-: $t(21)=2.645$, $p<0.02$; N+ vs. HC: $t(26)=7.632$, $p<0.001$) but not for "larger" responses (N+ vs. N-: $t(21)=1.657$, $p>0.1$; N+ vs. HC: $t(26)=0.659$, $p>0.5$).

 Insert Figure 3 about here

In order to examine the asymmetry of the distance effects, ERs were entered into similar regression analyses as in the AC task. Both slopes differed significantly from zero (mean β for smaller: $-5.77 \pm 7\%$; $t(38)=5.141$, $p<0.001$; for larger: $-5.3 \pm 6.6\%$, $t(38)=4.903$, $p<0.001$). Only the N+ group had a negative asymmetry index that differed significantly from zero (mean asymmetry index for N+: $-7.49 \pm 8.2\%$; $t(13)=3.417$, $p<0.005$; N-: $2.4 \pm 4.115\%$, $t(10)=0.586$, *ns*). The HC group

had a significant positive asymmetry index, suggesting a stronger distance effect for larger responses (HC: $4.3 \pm 6.47\%$, $t(13)=2.488$, $p<0.05$). A one-way ANOVA on the asymmetry index with the Group as an independent variable was significant ($F(2,38)=6.046$, $p<0.005$). Direct comparisons between groups demonstrated that the asymmetry index of N+ was significantly different from N- ($t(23)=2.254$, $p<0.05$) and from HC ($t(26)=4.224$, $p<0.001$), and that no difference was observed between N- and HC ($t(23)=0.461$, *ns*).

3.3 Working memory assessment

A one-way ANOVA with the mean span level as dependent variable and Group (N+, N- vs. HC) as independent variable was carried out for forward and backward digit spans separately. The three groups did not differ significantly for the forward digit span (mean span level for N+: 6.2 ± 1.5 ; N-: 5.8 ± 1.2 ; HC: 6.1 ± 0.8 ; $F(1,27)=0.42$, *ns*), or the backward digit span (mean span level for N+: 4.6 ± 1.6 ; N-: 4.1 ± 0.8 ; HC: 5.1 ± 1.7 $F(1,27)=2.021$, $p>0.1$).

4. Discussion

The performance of neglect patients in numerical tasks using symbolic stimuli had previously been interpreted as supporting the idea of a spatial representation of numbers. However, this bias was observed with symbolic inputs only and could be accounted for by serial order-related processes in verbal working memory. In this study, patients with right-hemisphere damage with or without left neglect and healthy control participants were tested in comparison tasks with symbolic and non-symbolic numerical inputs to assess whether the spatial-numerical bias observed in symbolic number comparison extends to non-symbolic number comparison, which would

suggests that the bias is due to the spatial properties of a common processing or representational system for numerical magnitudes rather than to verbal working memory mechanisms.

With symbolic stimuli, N+ patients showed increased RLs when numerical distance decreased. This was particularly true for the Arabic digit just smaller than the standard (i.e., 4) compared to a larger digit at the same numerical distance (i.e., 6). This result was confirmed by the asymmetry index showing that only N+ had a stronger distance effect for numerical magnitudes smaller than the standard. This dependence of the numerical bias on the reference point is similar to the one previously found in symbolic comparison tasks when the standard value was modified (Vuilleumier et al., 2004). Such an effect is consistent with previous studies (Salillas et al., 2009; Vuilleumier et al., 2004; van Dijck et al., 2012; Zorzi et al., 2012), and has been attributed to a difficulty in orienting attention towards the left part of the mental number line relative to the standard.

With non-symbolic stimuli, N+ patients presented a bias similar to the one observed with symbolic inputs. Indeed, the ER showed an asymmetry of the distance effect comparable to the pattern observed for latencies in the symbolic task, with more errors when comparing a small numerosity close to the standard than when comparing a large one. It is worth noting that the two tasks, though similar, have different properties. Standard comparison to 5 in symbolic notation is a very easy task that usually leads to very few errors (e.g., less than 3% errors; Buckley & Gilman, 1974; Duncan & McFarland, 1980; Foltz, Poltrock, & Potts, 1984), hence the analyses usually focus on latencies only; DC being less easy, it usually leads to more errors. The critical point here is that the latency pattern in AC is similar to the ER

pattern in DC, which legitimates the parallel we draw. Could this pattern of impairment limited to the numerosity close to and smaller than the standard be accounted for by undesirable counting strategies or some response biases? As suggested by an anonymous reviewer, the participants could indeed simply stop processing the dots after the fifth one and, as there was no reverse mapping of the response keys, N+ patients could have a tendency to respond with the right key when the task becomes more difficult (i.e., for sequences containing more dots) resulting in correct responses for sequences of large numerosities and wrong answers for small ones. Although we cannot exclude that some participants used counting for very small numerosities (e.g., 1 or 2 dots), this seems less plausible for sequences of large numerosities given the short total duration which has been shown to make a counting strategy little efficient (Grondin, Meilleur-Wells & Lachance, 1999). Moreover, if participants were using a "counting–stop" strategy, it is sensible to expect at least HC participants to be very accurate for all numerosities larger than 5, which was not the case. The presence of a significant distance effect for large numerosities also indicates that the participants were really processing all numerosities even those with more than five dots. We thus believe "counting–stop" can reasonably be excluded as an effective strategy. A specific response bias for the right key in N+ can also be excluded. Besides the fact that previous studies disproved such a possible bias in N+ (e.g., van Dijck et al., 2012; Vuilleumier et al., 2004), N+ made globally no fewer errors for "larger" than for "smaller" trials, while they should be better if not virtually perfect for the former if they had a right response bias, whereas in fact they did not differ from N- and HC for the "larger" trials: this clearly runs against the suggestion of a specific right-response bias associated with difficulty in N+.

The spatial-numerical bias occurring irrespective of the numerical input is in line with the observation of a spatial bias induced by non-symbolic flankers on a line bisection task (de Hevia & Spelke, 2009), and supports the hypothesis of an input-independent representation system of numerical magnitude. Despite specific coding mechanisms for symbolic numbers and non-symbolic numerosities, neglect patients may be unable to distribute their attentional resources to the left part of their mental representation relative to the standard. This is consistent with observations of spatial representational neglect that depend on the imagined point of view (Bisiach & Luzzatti, 1978). For attentional theories, each hemisphere tends to orient attention to the contro-lateral external or imaginal hemi-space (Kinsbourne, 1993). A lesion to the right hemisphere that is supposed to be dominant for attention leads to attention being oriented only towards the ipsi-lesional side of space (Kinsbourne, 1987). Caution is however required here as the brain lesions of the patients in this study were too extended to properly address the issue of whether common or distinct regions of the parietal cortex are responsible for the processing of numerical magnitude and visuospatial functions.

Recently, the hypothesis of spatial attention mechanisms operating on a mental number line has been challenged by several neuropsychological studies suggesting that an impairment of verbal working memory could be the source of the spatial-numerical bisection bias in neglect patients (Doricchi et al., 2005; van Dijck et al., 2011). The study of a right unilateral neglect patient revealed difficulties in retrieving initial items of verbal sequences (van Dijck et al., 2011), and a correlation between numerical bisection bias and working memory span has been observed in neglect but also in non-neglect right brain-lesioned patients (Aiello et al., 2013; Doricchi et al., 2005). Thus, the overestimation of the midpoint of numerical intervals

may be the consequence of the cerebral damage causing an inability to maintain ordinal information from the earlier items (i.e., small quantities) in working memory. However, this working memory explanation does not properly account for the numerical biases observed in comparison tasks in our and previous studies (Salillas et al., 2009; van Dijck et al., 2012; Vuilleumier et al., 2004; Zorzi et al., 2012). Indeed, this assumption predicts that, in a numerical comparison task with a reference value of 5, neglect patients would have difficulty processing the earliest numbers of the verbal numerical sequences (i.e., 1 and 2 for sequences of numbers smaller than the reference, and 6 and 7 for sequences of numbers larger than the reference), whereas in fact a numerical impairment has only been consistently demonstrated for small values close to the standard (e.g., 4 in comparison to 5). Moreover, our results do not support Aiello et al. (2013)'s proposal since our N- patients did not show this spatial-numerical bias despite a right lesion, and since no differences were observed between N+ and the N- and HC groups in the forward and backward digit span tasks. Additionally, none of our N+ patients was affected by frontal lesions and many neglect patients included in previous studies showed a number-bisection bias without any prefrontal damage (Umiltà, Priftis, & Zorzi, 2009). In contrast, 7 out of our 11 non-neglect patients suffered from frontal lesions without spatial-numerical biases. This suggests that this cerebral region associated with working memory impairment is not crucially involved in the numerical rightward bias. Finally, rightward-shifting prisms (Rossetti et al., 2004), optokinetic stimulation (Priftis et al., 2012) and random dot kinetograms (Salillas et al., 2009) influence the performance of neglect patients in numerical tasks, which constitutes strong evidence that visuospatial attention modification underlies spatial-numerical biases. Hence, our data and those of studies

using numerical comparison rather than bisection tasks are better accounted for by impaired spatial-attentional orientation than by working-memory impairments.

Finally, the DC task in HC revealed a substantial ER for sequences of 6 dots. It is worth noting that patients without neglect had also a higher error rate for larger responses (see Fig. 3). One explanation of this high error rate could arise from the combination of two well-known behavioural effects classically observed in numerical comparison (Moyer & Landauer, 1967): the distance (i.e., comparing two numbers that are far apart is easier than numbers that are numerically close) and the size (i.e., comparing small numerical magnitude is easier than comparing larger) effects. As the use of a sequential numerical material should amplify the importance of the size effect (Camos & Tillmann, 2008), sequences of 6 dots (i.e., close distance but large size) were processed worse than sequences of 4 dots (i.e., close distance but small size). Another possibility is that this pattern of higher error rate for larger sequences could reflect a natural tendency to underestimate, which is consistent with the literature in numerical perception tasks (e.g., Bevan & Turner, 1964; Castronovo & Seron, 2007; Kaufman, Lord, Reese, & Volkmann, 1949; Krueger, 1972; Mandler & Shebo, 1982). Although underestimation of sequentially presented stimuli has been reported in a few studies in visual modality (Camos & Tillmann, 2008; Philippi, van Erp, & Werkhoven, 2008), the reason why participants underestimate the perceived non-symbolic quantities is still unclear. Future work should investigate this question.

5. Conclusion

The observed impairment in processing non-symbolic numerosities smaller than a standard extends previous observations on symbolic material. Our findings indicate an impairment of both symbolic and non-symbolic numerical processes

caused by spatial neglect, suggesting that neglect affects a process common to both types of input. Hence, our results support recent models that propose a common numerical magnitude system for symbolic numbers and non-symbolic numerosities and, moreover, the hypothesis that the numerical bias observed in magnitude comparison tasks to a fixed reference are mediated by a visuospatial deficit rather than verbal working memory impairments.

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Figure Captions

Figure 1: Temporal attributes of a stimulus from (A) the AC and (B) the DC tasks. In the DC task, the total duration of a sequence was set to 1500 ms. Note that the duration of each dot and interval dot varied between 50 and 1450 ms.

Figure 2: Mean response latencies ($\pm$ S.E.) for the AC task for the group of patients with (N+) or without left unilateral neglect (N-) and healthy controls (HC) as a function of Response (Smaller vs. Larger) and Distance (d1 to d4).

Figure 3: Mean error rates ($\pm$ S.E.) for the DC task for the group of patients with (N+) or without left unilateral neglect (N-) and healthy controls (HC) as a function of Response (Smaller vs. Larger) and Distance (d1 to d4).

Table1: Clinical and demographical characteristics of patients groups (N+ and N-).

Patients	Age (years)	Gender	Handedness	Aetiology	Time from lesion (months)	Lesion site
<i>With neglect</i>						
1	74	M	R	Hemorrhagic	5	T-P
2	49	F	L	Ischemic	45	T-P
3	52	F	R	Ischemic	11	T-P
4	48	M	R	Hemorrhagic	6	I-C
5	46	M	R	Hemorrhagic	6	P-O
6	80	M	R	Ischemic	4	T-P
7	61	M	R	Hemorrhagic	4	T-P
8	57	M	R	Ischemic	15	T-P
9	40	M	R	Ischemic	6	P-O
10	54	M	R	Ischemic	10	T-P
11	68	M	R	Ischemic	3	T-P
12	62	M	R	Ischemic	18	T-P-O
13	68	M	R	Ischemic	5	T-P
14	55	F	R	Hemorrhagic	25	T-P
<i>Without</i>						
1	75	F	R	Ischemic	109	F-P
2	65	M	R	Ischemic	51	P
3	35	F	R	Traumatic	239	P
4	56	M	R	Ischemic	24	F-P
5	71	F	R	Ischemic	36	F-P
6	68	M	R	Ischemic	7	T-P
7	62	M	R	Ischemic	132	F-P
8	53	M	R	Ischemic	5	F
9	58	M	R	Ischemic	4	F-P
10	56	M	R	Ischemic	3	T-P
11	60	M	R	Traumatic	4	F

M=Male, F=Female; L=Left-handed, R=Right-handed; T-P=Temporo-parietal, P-O=Parieto-occipital, T-P-O=Temporo-parieto-occipital, F-P=Fronto-parietal, P=Parietal, F=Frontal, I-C= Internal Capsule.

Table2: Summary of score of neglect assessment for patients groups (N+ and N-).

Patients	Line Bisection	Cancellation Task		TAP: Neglect subtest	
		Left omissions	Right omissions	Left omissions	Right omissions
<i>With neglect (N+)</i>					
1	NA	7*	0	20*	8
2	NA	6*	4	15*	0
3	+60*	15*	1	22*	7
4	+22*	1	0	4	1
5	NA	8*	0	11*	3
6	NA	7*	0	22*	0
7	NA	5	3	15*	4
8	+30*	6*	5	20*	5
9	+12*	0	0	NA	NA
10	NA	11*	0	NA	NA
11	+18*	2	3	12*	2
12	+12*	2	0	7*	1
13	NA	7*	0	NA	NA
14	+57*	15*	2	22*	4
<i>Without neglect</i>					
1	-2	0	0	0	0
2	+4	1	0	3	5
3	+2	0	0	0	0
4	+5	1	1	3	3
5	-3	2	0	4	5
6	+3	1	0	3	3
7	+1	0	0	1	1
8	+2	1	0	1	0
9	-14	1	0	3	5
10	-4	0	1	4	5
11	-6	0	0	4	4

TAP: Test for Attention Performance (Zimmermann & Fimm, 2002); *=Below cut-off; NA: Test non achievable.