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Hemispatial neglect and serial order in verbal working memory

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Working memory refers to our ability to actively maintain and process a limited amount of information during a brief period of time. Often, not only the information itself but also its serial order is crucial for good task performance. It was recently proposed that serial order is grounded in spatial cognition. Here, we compared performance of a group of right hemisphere-damaged patients with hemispatial neglect to healthy controls in verbal working memory tasks. Participants memorized sequences of consonants at span level and had to judge whether a target consonant belonged to the memorized sequence (item task) or whether a pair of consonants were presented in the same order as in the memorized sequence (order task). In line with this idea that serial order is grounded in spatial cognition, we found that neglect patients made significantly more errors in the order task than in the item task compared to healthy controls. Furthermore, this deficit seemed functionally related to neglect severity and was more frequently observed following right posterior brain damage. Interestingly, this specific impairment for serial order in verbal working memory was not lateralized. We advance the hypotheses of a potential contribution to the deficit of serial order in neglect patients of either or both (1) reduced spatial working memory capacity that enables to keep track of the spatial codes that provide memorized items with a positional context, (2) a spatial compression of these codes in the intact representational space.

Hemispatial neglect is a neuropsychological syndrome observed after brain lesion and consisting in the failure to report, respond or orient to novel and meaningful stimuli presented in the contralesional space when this failure cannot be attributed to either sensory or motor defects (Heilman, 1979). Hemispatial neglect is more frequent, severe and durable after lesion to the right than the left hemisphere (Stone, Patel, Greenwood, & Halligan, 1992). When asked to indicate the centre of horizontal lines (line bisection task),

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patients with left neglect deviate the subjective mid-point to the right of the objective mid-point of the line. Similarly, when asked to cross out items distributed on a sheet of paper (cancellation task), they typically omit items located on the left of the sheet. Hemispatial neglect is a complex and heterogeneous syndrome, both at the functional and the anatomical level (Halligan & Marshall, 1992; Marshall & Halligan, 1995; Molenberghs, Sale, & Mattingley, 2012). Among the more frequent damaged regions associated with hemispatial neglect, the critical role of the parietal lobe (e.g., the inferior parietal lobule, Mort *et al.*, 2003) and the temporal lobe (e.g., the superior temporal gyrus, Karnath, Ferber, & Himmelbach, 2001) has been lively debated. Other researchers have argued that hemispatial neglect can be considered as a disconnection syndrome (e.g., Lunven *et al.*, 2015; for a review, see Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007), with an emphasis on frontoparietal disconnection. Damage to selective cortical region(s) and/or sector(s) of the white matter tract of the frontoparietal network could then account for the behavioural and anatomical heterogeneity of hemispatial neglect.

Hemispatial neglect is also heterogeneous in the sense that it can be associated with deficits that extend to higher cognitive functions, such as spatial working memory (e.g., Malhotra *et al.*, 2005) and numerical cognition (e.g., Zorzi, Priftis, Meneghello, Marenzi, & Umiltà, 2006; Vuilleumier, Ortigue, & Brugger, 2004). By contrast, verbal working memory is considered to be spared in hemispatial neglect (e.g., Doricchi, Guariglia, Gasparini, & Tomaiuolo, 2005; Malhotra *et al.*, 2005). In what follows, we will hypothesize that a more fine-grained assessment of verbal working memory in patients with neglect may unveil specific yet hidden impairments. The rationale for this prediction comes from two complementary lines of evidence. On the one hand, item information processing and order information processing in verbal working memory are thought to rely on different mechanisms (Majerus *et al.*, 2006; Attout, Van der Kaa, George, & Majerus, 2012). On the other hand, there is a close link between order information in verbal working memory and space processing. van Dijck, Abrahamse, Majerus, and Fias (2013); van Dijck, Abrahamse, Acar, Ketels, and Fias (2014) used a variant of the Posner detection task (Posner, 1980). In this task, a dot appears either on the left or on the right side of the computer screen. When its appearance is detected, a central button press has to be given. In the original Posner task, dot detection time is modulated by the presentation of a centrally presented directional cue, that is, a leftwards or rightwards arrow. Dot detection is facilitated when the arrow correctly indicates the upcoming target location and is impaired when the arrow points to the side opposite of the upcoming target. van Dijck *et al.* (2013, 2014) administered this Posner task to participants who were maintaining a sequence of items in working memory and replaced the arrow with an item that was (or was not) part of the memorized sequence. To ensure working memory access, participants had to execute the detection of the lateral target only when the item cue belonged to the memorized sequence. The retrieval of these items modulated dot detection times such that the further the serial position of the item in the memorized sequence, the faster the dots appearing on the right side of the screen were detected. In a follow-up study, it was shown that the retrieval of working memory items occupying beginning positions goes faster after having seen a left-sided compared to a right-sided visuo-spatial prime and the opposite for items from the end of the sequence (De Belder, Abrahamse, Kerckhof, Fias, & van Dijck, 2015). A similar observation was made with the line bisection task: the further the serial position of the number in the memorized sequence, the more the subjective mid-point of horizontal lines was shifted to the right (Antoine, Ranzini, Gebuis, van Dijck, & Gevers, 2016). On top of that, it was observed that during verbal recall of memorized sequences of numbers, eye position is shifted from left to right as a function of the serial position of the numbers (Rinaldi, Brugger, Bockisch, Bertolini, & Girelli, 2015). Finally, a correlation was observed between visuo-spatial breadth of attention (i.e., the extent of space that can be covered by attention; Hüttermann, Bock, & Memmert, 2012) and verbal working memory: wider (narrower) attentional breadth was associated with higher (smaller) verbal working memory capacity (Kreitz, Furley, Memmert, & Simons, 2015). On the basis of the interactions between order in working memory and space processing (e.g., van Dijck *et al.*, 2013, 2014; De Belder *et al.*, 2015; Antoine *et al.*, 2016), it is possible that broader attentional breadth allows a larger mental distance between the spatial codes associated with memorized items, making them more distinct and thus improving verbal working memory capacity (Guida, van Dijck, & Abrahamse, 2016).

Taken together, these findings indicate that serial order in verbal working memory and space are in bidirectional relationship, suggesting that serial order in verbal working memory is grounded in spatial cognition (Abrahamse, van Dijck, Majerus, & Fias, 2014). In addition, these demonstrations were made with hallmark tasks used to detect hemispatial neglect (Posner detection task, line bisection task). It is thus possible that the impairments in spatial processing characterizing hemispatial neglect also extend to a deficit for serial order in verbal working memory. Support for this hypothesis comes from a recent study (Bonato, Saj, & Vuilleumier, 2016) in which patients with left neglect showed performance selective slowing when categorizing events of a story as occurring before rather than after a central event. Despite the verbal nature of the material, patients responded by pressing a left- or right-sided button, which might have triggered the spatial coding of events as left or right. In addition, performance in this task also relies on semantic and episodic knowledge. Here, we aimed to go one step further and thoroughly assessed in a pure manner whether patients with neglect have deficits for serial order using prototypical verbal working memory tasks without any spatial input/output. Item information and order information in verbal working memory were assessed in a group of right brain-damaged patients with left neglect using tasks in which items were centrally presented, and responses were verbal (yes–no tasks). In the item task, retrieving item information was sufficient for a correct response, as participants simply had to judge whether an item belonged to the memorized sequence. It has been argued that maintenance of verbal information in working memory can be accomplished through articulatory rehearsal mechanisms (Baddeley, Lewis, & Vallar, 1984; Camos, 2015). Also, patients with neglect typically show intact performance in forward digit span tasks (e.g., Doricchi *et al.*, 2005; Malhotra *et al.*, 2005). For these reasons, we did not anticipate impaired performance in item processing. In the order task, ordinal processing was necessary, as participants had to judge whether pairs of consecutive items were presented in the same order as in the memorized sequence. Assuming a close link between order information in verbal working memory and space processing, we expected that patients with neglect would present a specific deficit for order information processing. If such an impairment could be demonstrated, a secondary interest is to describe the nature of this impairment. A first possibility is that the impairment is lateralized (e.g., more difficulties when judging the ordinal relation of items at begin positions in the memorized sequence compared to items at end positions in the memorized sequence). This would suggest that positional codes are spatially represented across the entire mental workspace, with the left part of this representation being neglected. Another possibility is that the impairment is not lateralized (i.e., difficulties in judging the ordinal relation between memorized items regardless of the position of these items in the memorized sequence). This might suggest that the positional codes of all memorized items are spatially represented in the intact (right) side of mental workspace, but in a strongly compressed manner.

Methods

Participants

All participants gave their written consent according to the Declaration of Helsinki. The study was approved by the Hospital Ethics Committee. A group of 10 patients (four females, six males, mean age: 51.5 years, *SD*: 14.8 years, see Table 1) with right hemisphere brain lesion and presenting clinical neglect (as assessed by standardized paper-and-pencil tests, that is in at least one of the subtests of the Conventional Behavioural Inattention Test, BIT; Wilson, Cockburn, & Halligan, 1987) or subclinical neglect (as assessed by the computer-based detection task with increasing cognitive load; Bonato, Priftis, Umiltà, & Zorzi, 2013) was tested (see Table 1 below for details). A group of 37 healthy participants matched for gender (17 females, 20 males) and age (mean age: 51.5 years, *SD*: 13 years), without neurologic antecedents and above cut-off score of 25 in the Montreal Cognitive Assessment (MoCA, Nasreddine *et al.*, 2005) was tested as control group. Education level was calculated in years of study and corresponded to 13.9 (*SD*: 3.2) in patients and 15.7 (*SD*: 2.2) in controls. Statistical comparisons between patients and controls revealed no significant difference neither in the proportion of male and female individuals, $\chi^2(1) = .11, p = .74$, nor in age, $t(45) = .003, p = .998$, nor in the education level, $t(11.4) = -1.65, p = .13$.

Materials and data analyses

Digit span task

The task was a computerized version of the digit span task, adapted from the version by Mondini, Mapelli, Vestri, and Bisiacchi (2011). Participants were presented with random sequences of digits of increasing length. Digits were presented sequentially in the centre of the screen. Each digit was presented for 800 ms with an interstimulus interval of 200 ms. After the last digit was presented, a 450-ms interval was followed by a question mark, indicating to the participant to verbally recall the sequence. In case of incorrect recall, a sequence of the same length was presented; otherwise, a sequence of increasing length (by one item) was presented. The task started with a training (sequence of two items) for which feedback was provided. The task ended when two consecutive sequences of the same length were incorrectly recalled. The span corresponded to the longest correctly recalled sequence.

Item and order tasks

Each trial started with the presentation of a fixation cross for 500 ms. Then, consonants printed in black were presented sequentially at the centre of the screen for 1,000 ms, and interstimulus interval was set at 250 ms. After the last consonant was presented, a rehearsal period of 2,250 ms elapsed, followed by the target(s) printed in green. In the item task (Figure 1a), the target was a consonant that could either belong or not to the memorized sequence, presented in the centre of the screen for a duration of 1,000 ms. The task was to indicate, by saying ‘yes’ or ‘no’ whether the target belonged to the memorized sequence. In the order task (Figure 1b), two consonants were sequentially

Table 1. Neglect patients

	Gender	Lesion type	Age	Time since lesion onset (days)	Lesion volume (cm^3)	MoCA	BIT				Detection task % omissions left < right	
							Total	Star cancellation	Figure and shape copying	Line bisection	Single	Double
1	F	Haem. stroke	47	60	63.8	**21**	**104**	0.362	**2**	**3**	n.a.	n.a.
2	M	Isch. stroke	39	20	63.2	**17**	129	0.022	**2**	7	−6.25	0
3	M	Isch. stroke	55	27	3.7	29	130	0.037	3	**2**	6.25	6.45
4	M	Haem. stroke	65	33	40.3	26	135	−0.034	**2**	8	0	0
5	F	Isch. stroke	66	31	51.4	**24**	**125**	0.179	**1**	9	*93.75*	n.a.
6	M	Haem. stroke	50	25	73.1	**20**	**126**	0.017	**1**	**5**	*87.5*	*56.92*
7	F	Haem. stroke	20	17	40.9	29	146	0	4	9	0	*21.88*
8	M	Haem. stroke	70	51	18.9	n.a.	**122**	0.121	**2**	9	*43.75*	n.a.
9	M	Cerebral abscess	47	29	17.3	n.a.	145	0	3	9	*37.5*	*62.07*
10	F	Isch. stroke	56	105	n.a.	**23**	140	0	**2**	7	*56.25*	*46.88*
Mean			51.5	39.8	43.1	23.6	130.2	0.07	2.2	6.8	35.40%	27.70%
SD			14.8	26.5	23.2	4.3	12.4	0.12	0.9	2.6	38.30%	27.20%

Gender: M = male; F = female; n.a. = not administered; MoCA = Montreal Cognitive Assessment, maximum score = 30; BIT = Behavioural Inattention Test (conventional), maximum score = 146; Figure and shape copying (subtest of the BIT) = maximum score = 4. Line bisection task (subtest of the BIT) = maximum score = 9; Scores under cut-off are printed in bold. Star cancellation = centre of cancellation (CoC, Rorden & Karnath, 2010); Detection task = detection of a right- or left-sided target in a single task design or under cognitive load (two blocks: during a concurrent visual and auditory task, see Bonato *et al.*, 2013). Patient 6 was only assessed under auditory load. The percentage of omissions for left- minus right-sided targets when the concurrent task was accurate are reported. Italized values indicate that there was a significant difference in omission rates between left-sided and right-sided targets (chi-squared test).

presented in the centre of the screen (for a duration of 1,000 ms each and an interval of 250 ms). Participants were informed that these consonants always belonged to the memorized sequence and had to indicate by saying 'yes' or 'no' whether they were presented in the same order or not as in the memorized sequence. Sequence length was adapted for each individual, at span level. For each sequence length, two different lists of sequences were created. Each participant was tested with the same list of sequences in the item and the order tasks, but the order of sequences was different in each task. The two lists of sequences were counterbalanced across participants. In each list, half of the sequences were generated from the set of consonants B,D,G,J,L,N,Q,S,V, while the other half of sequences were generated from the set of consonants C,F,H,K,M,P,R,T,X. In this way, consecutive letters of the alphabet (e.g., B and C) were never presented at consecutive positions in the sequences. All sequences can be found in the Table S1. Each task consisted of 48 trials, with half of the trials corresponding to positive trials ('yes' responses were awaited) and the other half to negative trials ('no' responses were awaited). Prior to each task, three training trials (on sequences of three items) with feedback were given to ensure that the task instructions were understood. The order of the item and order tasks was counterbalanced across participants.

Because assumptions for parametric tests (homogeneity of variances and normal distribution) were not satisfied, nonparametric tests were used (Mann–Whitney *U* test for

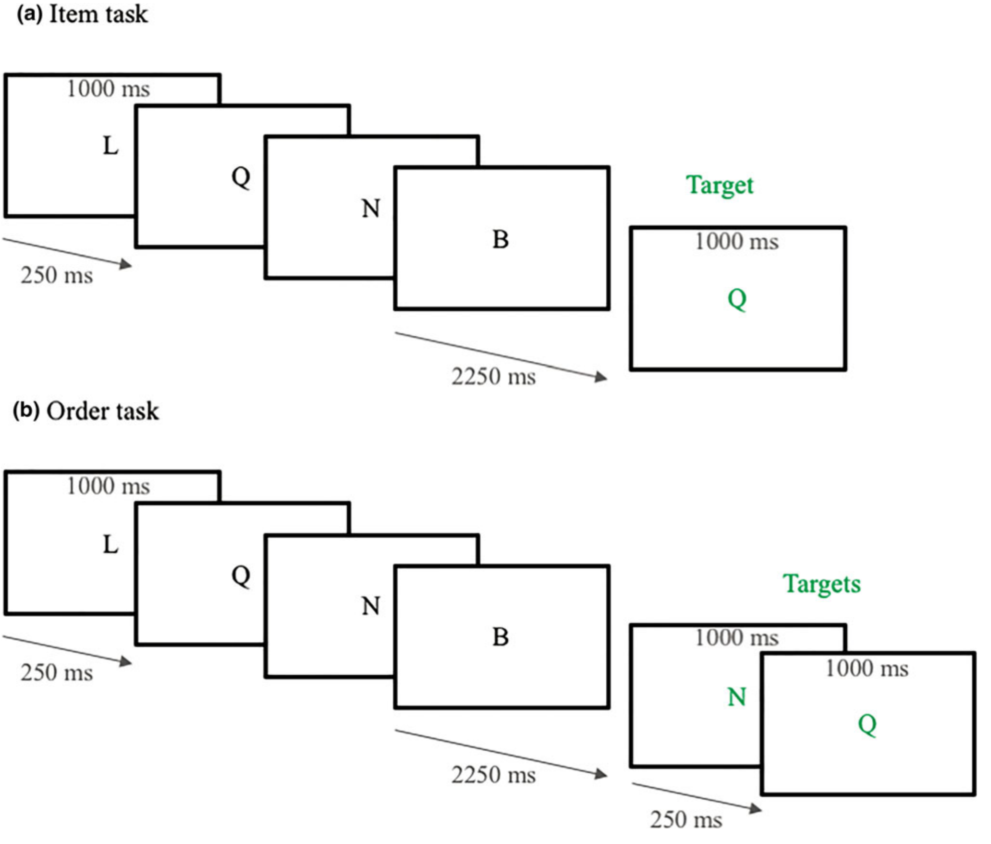


Figure 1. Trial in the item and order tasks. Illustration of (a) a positive trial in the item task, (b) a negative trial in the order task for a participant with a verbal span of 4.

Table 2. Performance of patients with neglect in the experimental tasks

	Digit span	Slopes of deviation in the computerized line bisection task (mm)	% errors item task	% errors order task
1	6	13.2	8.3	***47.9***
2	6	6.4	6.3	***37.5***
3	4	12.4	8.3	***39.6***
4	5	4.8	2.1	**27.1**
5	8	1.6	***22.9***	***47.9***
6	3	10.6	10.4	***29.2***
7	6	−0.5	**14.6**	***31.3***
8	5	0.2	***18.8***	***31.9***
9	5	0.2	2.1	14.6
10	4	4.4	2.1	10.4

Individual scores of patients with neglect in the digit span task, the computerized line bisection task and the item and order tasks. For completeness, percentages of errors that are significantly higher than healthy controls are printed in bold italized, and percentages of errors that are marginally (*p*s $< .066$) higher than healthy controls are printed in bold (using tests to compare individual scores to a normative sample, Crawford & Garthwaite, 2005).

independent samples and Wilcoxon test for related samples, one-sided tests were applied where appropriate). We performed inter- and intragroup analyses on the percentage of errors to investigate whether patients with neglect differed from healthy controls in the item and order tasks and whether performance in the item task differed from performance in the order task in patients with neglect and healthy controls. Because the raw percentage of errors in the order task could still be contaminated by item information, we additionally computed the percentage of order-specific errors in verbal working memory by subtracting the percentage of errors in the item task from the percentage of errors in the order task for each participant. This approach allowed to control for individual differences in maintaining item information (see Table 2 and Table S2 for individual percentage of errors in the item task for patients and healthy controls, respectively) and to demonstrate potential impairment of patients with neglect that are specific to order processing in working memory.

To assess whether the distribution of errors was lateralized in the order task, each pair was categorized corresponding as begin or end positions in the memorized sequence (for sequences with an even number of items, pairs of targets crossing the middle were discarded from this specific analysis, like position two and three in four items sequences). We performed inter- and intragroup analyses on the percentage of errors for begin and end positions.

Line bisection task

The task was a computerized version of the classic paper-and-pencil line bisection task. Black horizontal lines of three different lengths (1.8, 9 and 18 cm) were presented one by one on a white background in random order in the centre of a 17” touch screen monitor arranged almost horizontally (18°). Participants used a touch pen to draw a black mark on the mid-point of the line. There were 10 repetitions for of each line length, except for one patient and nine controls who were tested with a shorter version with six repetitions. There was no time limit. For each trial, the deviation (in millimetres) of bisection was computed by subtracting the objective mid-point from the subjective mid-point. For each participant, we excluded deviations higher or lower than 3 *SD* from his/her own mean deviation (this resulted in the exclusion of 1% of trials in the whole sample). As we were interested in correlating the percentage of order-specific errors with neglect severity, we focused on the effect of line length on bisection deviations. For this, we computed the slope of bisection deviation as a function of line length, with the logic that the more severe neglect was, the greater the slope relating line length to bisection deviation (Halligan & Marshall, 1989; Marshall, 1998). It is typically observed that rightward bisection deviation increases with longer lines in patients with neglect. We used nonparametric tests for independent samples to confirm that the slopes of bisection deviation as a function of line length were significantly different between patients with neglect and healthy participants.

Finally, we correlated the percentage of errors in the item and order tasks, as well as the percentage of order-specific errors, to independent measures of neglect severity (BIT scores, star cancellation task, detection task, see Table 1, and line bisection slopes, see Table 2) in neglect patients with nonparametric correlations (Spearman correlation tests with Bonferroni corrections for multiple comparisons, one-sided tests were applied where appropriate). In the star cancellation task, the centre of cancellation (CoC, Rorden & Karnath, 2010) was used as a measure of neglect severity. In the detection task, the percentage of omissions for left- minus right-sided targets was used as a measure of neglect severity (Bonato *et al.*, 2013).

Results

There was no significant difference between the span of patients with neglect (median: 5, see individual spans in Table 2) and the span of healthy participants (median: 5) in the digit span task ($U = 150, p = .38, r = -.14$). The slope of bisection deviation as a function of line length significantly differed between patients and controls ($U = 59$, $p < .001$, $r = -.48$): the slope of patients with neglect was higher (median: 4.6, see individual slopes in Table 2) than one of the healthy participants (median: −0.03), indicating that patients with neglect were strongly influenced by line length and increasingly deviated their bisection to the right with longer lines.

Both patients ($Z = -2.8$, $p < .01$, $r = -.63$, see individual percentages of errors in Table 2) and healthy controls ($Z = -4.8, p < .001, r = -.56$, see individual percentages of errors in Table S2) made more errors in the order task (medians: 31.6 and 12.5%, respectively) than in the item task (medians: 8.3 and 6.3%, respectively). Importantly, patients with neglect made significantly more errors than healthy controls in the order task ($U = 44.5, p < .001, r = -.53$), while there was no significant difference in the item task ($U = 148.5, p = .35, r = -.14$). This was corroborated by the fact that patients with neglect made significantly more order-specific errors (i.e., percentage of errors in the order task minus percentage of errors in the item task, median: 21.9%) compared to healthy participants (median: 6.3%, $U = 39.5$, $p < .001$, $r = -.55$, see Figure 2). To ensure that the difficulties of patients with neglect reflected difficulties with order processing rather than mere difficulties in processing two targets (order task) compared to one target (item task), we computed for each subject the joint probability for correctly processing two items on the basis of the probability to correctly process one item (i.e., squared percentage of accuracy in the item task, for a similar analysis on the extinction

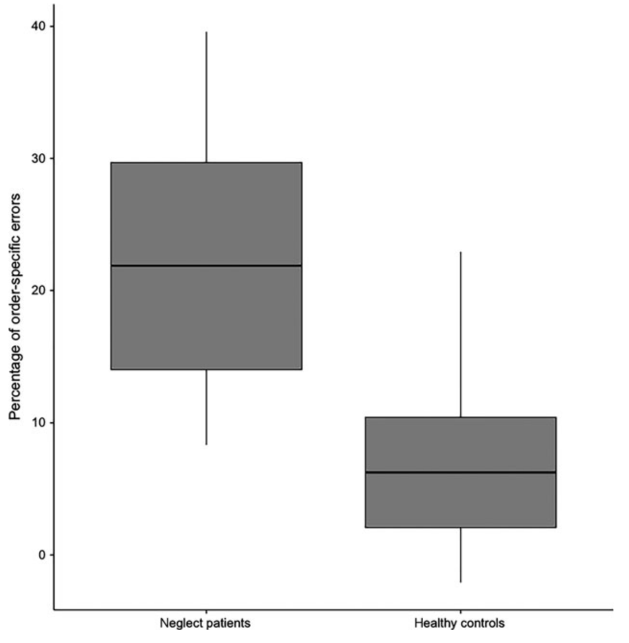


Figure 2. Box plots of order-specific errors in patients with neglect and healthy controls. Patients with neglect make significantly more order-specific errors compared to healthy controls. Lower segment of the box = first quartile, middle segment of the box = median, upper segment of the box = third quartile. Lower whisker = first quartile – 1.5 interquartile range, upper whisker = third quartile + 1.5 × interquartile range.

phenomenon, see Farnè, Brozzoli, Làdavas, & Ro, 2008). This analysis confirmed that the difficulties of patients with neglect genuinely related to order processing, as the joint probability was significantly higher (median = 84.03%) than the percentage of accuracy in the order task (median = 68.42%, $Z = -2.7$, $p < .01$, $r = -0.60$). For both patients with neglect ($Z = -0.35$, $p = .36$, $r = -.08$) and healthy controls ($Z = -1.16$, $p = .25$, $r = -.13$), there was no significant difference between the percentage of errors for begin (medians: 34.06 and 12.5%, respectively) and end position (medians: 29.17 and 12.5%, respectively). Patients with neglect made significantly more errors than healthy controls for both begin ($U = 70$, $p < .005$, $r = -.44$) and end position ($U = 37$, $p < .001$, $r = -.56$), indicating that the difficulties of patients with neglect for ordinal information were not lateralized (see individual percentage of errors for begin and end positions in both tasks in Table S3).

Next, we investigated whether a relation exists between neglect severity and order processing deficits. To this aim, we correlated the percentage of errors in the order tasks and the percentage of order-specific errors, to independent measures of neglect severity (BIT scores, CoC in the star cancellation task, group membership in the detection task and line bisection slopes) in patients with neglect. While the percentage of errors in the order task and the percentage of order-specific errors did not correlate with the BIT scores or with neglect severity in the detection task (all ps $> .1$), we found that the percentage of errors in the order task correlated with the CoC in the star cancellation task, $r\,(9) = .87$, $p < .005$: the more the CoC was located to the right, the more patients made errors in the order task. In addition, the percentage of order-specific errors marginally correlated with the slope of bisection deviation as a function of line length in the line bisection task, r (9) = .73, p = .06: the more patients made order-specific errors, the more they deviated their bisections to the right with lines of increasing length. Importantly, neither the percentage of errors in the order task, r (7) < .001, p = 7, nor the percentage of order-specific errors, r (7) = −0.2, p = 4.44, correlated with overall cognitive impairment (MoCA scores). In addition, no measure of neglect severity correlated with the percentage of errors in the item task (all ps > .27).

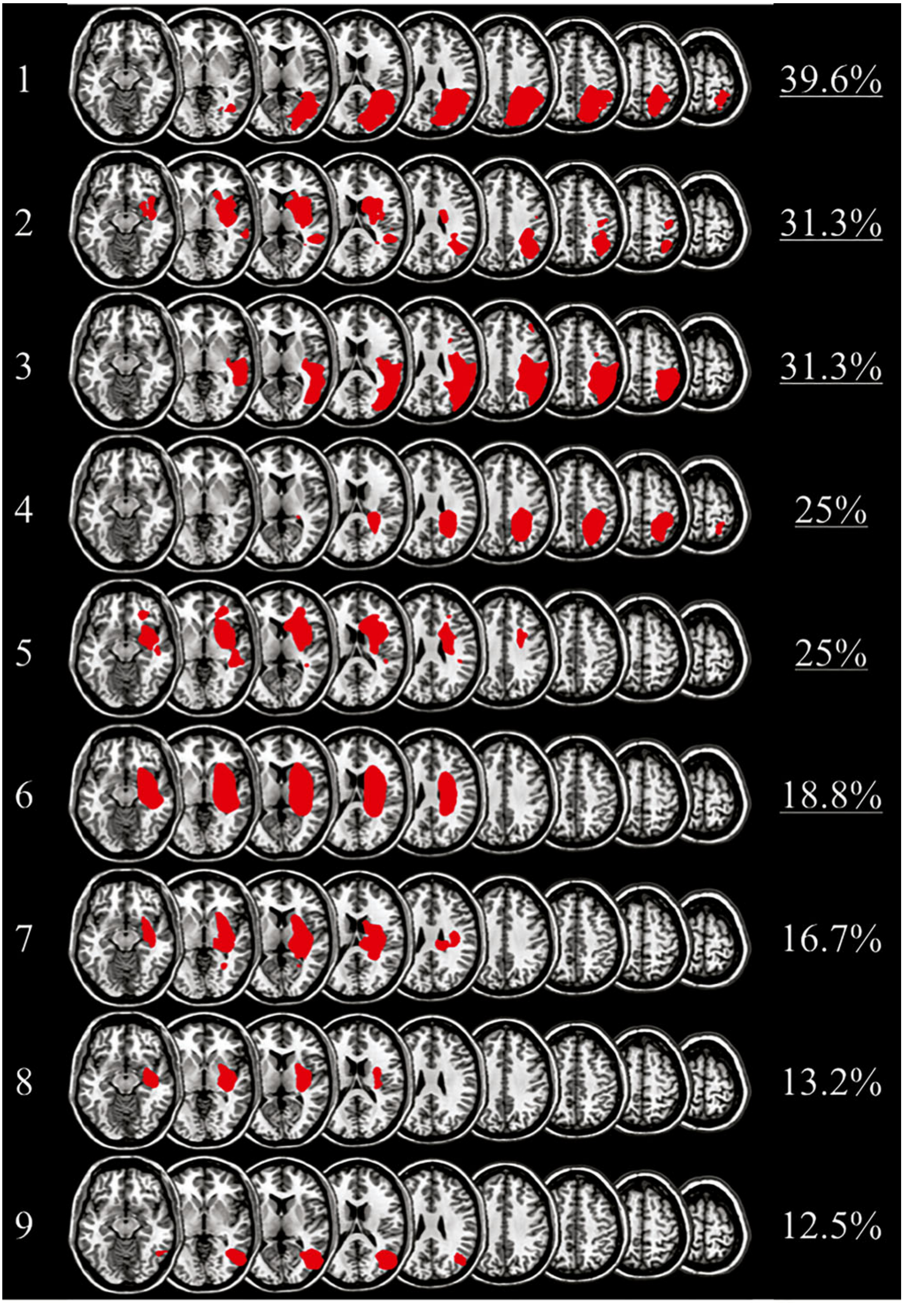
Thus far, we observed that, as a group, patients with neglect have a deficit for order processing. Because group effects, especially on small samples, can sometimes be misleading (for the importance to describe individual tests upon significant group effects, see for instance Majerus, Attout, Artielle, & Van der Kaa, 2015), we combined it with a *post hoc* assessment of individual profiles (tests to compare individual scores to a normative sample, Crawford & Garthwaite, 2005). This indicated that not all patients with neglect had a deficit of serial order. Six patients had a percentage of order-specific errors that were significantly higher than healthy controls, whereas the four remaining patients had a performance similar to healthy controls (scores outside the normal range are underlined in Figure 3). To explore whether lesion location distinguished between patients with neglect who had a deficit of serial order versus patients with neglect who had a performance similar to healthy controls, brain lesions for all patients were manually reconstructed using MRIcron (Rorden & Brett, 2000). Individual scans (MRI or CT) were reoriented using SPM (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007) and then normalized to an age-appropriate template brain by means of the SPM Clinical Toolbox (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012) using enantiomorphic normalization (Nachev, Coulthard, Jäger, Kennard, & Husain, 2008). Individual lesions organized as a function of the percentage of order-specific errors are provided in Figure 3. Lesion volume (see details in Table 1) did not correlate with the percentage of order-specific errors, r (8) = .35, p = 2.46,[1] Visual inspection of individual lesions suggests that the patients with a deficit of serial order had more frequently damaged the posterior parietal cortex than patients with a similar performance than controls, an observation that is in line with results of fMRI studies that contrasted performance of healthy participants in similar item and order tasks (e.g., Majerus *et al.*, 2006).

Discussion

Following the observations of a tight link between serial order in verbal working memory and space processing (e.g., van Dijck *et al.*, 2013, 2014; De Belder *et al.*, 2015;

Figure 3. Individual lesions. Individual lesions of patients with neglect, organized as a function of the percentage of order-specific errors. Percentages of order-specific errors that are significantly higher than healthy controls are underlined (using tests to compare individual scores to a normative sample, Crawford & Garthwaite, 2005). Please note that this difference was marginal for patient 6 (p = .06). The order of patients is the same as in Table 1, with the exception of patient 10 whose lesion is not shown in the figure because the delineation of the lesion was not reliable due to movement artefacts. However, it is important to note that this patient had a score within the normal range (8.3% of order-specific errors) but that her lesion included the posterior parietal cortex.

1 *Lesion volume did not correlate with the percentage of errors in the order task either,* r *(8)* = *.25,* p = *3.6.*



Rinaldi *et al.*, 2015; Antoine *et al.*, 2016), it was recently suggested that the ordinal positions of items in verbal working memory are spatially represented (Abrahamse *et al.*, 2014). We therefore hypothesized that a deficit of space processing should be accompanied with a deficit of serial order. To test this, we thoroughly assessed serial order processing with prototypical verbal working memory tasks in right brain-damaged patients with hemispatial neglect. In agreement with our predictions, we observed that, as a group, patients with neglect were spared when processing item information while they had difficulties when judging order information in verbal working memory, as compared to healthy controls. Differences in difficulty level across tasks, such as the higher number of targets and the associated longer retention period in the order task compared to the item task, cannot be entirely ruled out with the present data (for a discussion of the contribution of task difficulty on item–order dissociation, see Majerus *et al.*, 2006). Indeed, both patients and healthy controls made more errors in the order than in the item task. There are nonetheless several indications that the order processing deficit cannot be merely attributed to the difficulty of patients in processing two targets (order task) compared to one target (item task). Indeed, patients with neglect performed as well as controls in the digit span task, indicating that they were able to maintain multiple items in working memory. In addition, the accuracy of patients with neglect in the order task was significantly lower than what would be expected on the basis of their performance in the item task (joint probability). Furthermore, the deficit of serial order was correlated with neglect severity, suggesting a functional link between them. For instance, the more CoC (Rorden & Karnath, 2010) was located to the right in the star cancellation task, the more patients made errors in the order task. On top of that, the slopes of bisection deviation as a function of line length, an index obtained in a task independent from the tasks used to categorize patients as having neglect, (marginally) correlated with the proportion of order-specific errors, an index that corrected for item information processing. The more severe the neglect, as revealed by the magnitude of the slope relating line length to bisection deviation (Halligan & Marshall, 1989; Marshall, 1998) the more patients committed order-specific errors. On the contrary, the deficit of serial order did not correlate with lesion volume or with overall cognitive impairment (MoCA), further suggesting that patients were impaired for the processing of serial order *per se* rather than showing a higher sensitivity to task difficulty due to brain damage.

Inspection of individual profiles indicated that some patients had order performance within the normal range. This is not surprising when considering the large heterogeneity typically observed in patients with neglect, even in the visuo-spatial domain (e.g., Halligan & Marshall, 1992). Inspection of lesions suggested that order deficits were more frequently observed following damage to the posterior parietal cortex. Although purely descriptive and based on a small sample, this observation is in line with previous fMRI studies which demonstrated an important role of the right posterior parietal cortex during ordinal judgements in verbal working memory in healthy participants (e.g., Majerus *et al.*, 2006; Marshuetz, Reuter-Lorenz, Smith, Jonides, & Noll, 2006) and with deviations of patients with neglect in the line bisection task (e.g., Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2009). Further studies will be however needed to determine whether the impairment for serial order in patients with neglect is due to structural damage to the posterior parietal cortex and/or to dysfunction of intact regions connected to the posterior parietal cortex (Bartolomeo, 2011).

It is worth noting that the processing of order in verbal working memory and spatial attention might correspond to two distinct mechanisms, subtended by distinct yet overlapping networks including the posterior parietal cortex. In other words, patients with damage to the posterior parietal cortex would present both a deficit of space processing and of serial order processing, without these deficits being related to each other. Alternatively, our results could indicate that the posterior parietal cortex might be critically involved in the spatial coding of ordinal information in verbal working memory, an interpretation which is supported by the recent observations of order–space interactions (e.g., van Dijck *et al.*, 2013, 2014; De Belder *et al.*, 2015; Rinaldi *et al.*, 2015; Antoine *et al.*, 2016; for a recent overview see Abrahamse, van Dijck, & Fias, 2017). At the functional level, it could be speculated that the deficit of order processing in patients with neglect is mediated by representational neglect and/or spatial working impairments. Indeed, both representational neglect (e.g., Salvato, Sedda, & Bottini, 2014) and reduced spatial working memory capacity (e.g., Malhotra *et al.*, 2005) have been reported in subgroups of patients with neglect, more frequently after posterior parietal cortex damage. Therefore, a failure to represent and/or to keep track of the spatial codes associated with ordinal information in verbal working memory could explain why only some of our patients demonstrated serial order deficits. As explained below, a representational deficit and/or a spatial working memory impairment could also explain why neglect patients' deficits of serial order were not lateralized.

Indeed, patients with neglect were not specifically impaired when judging the ordinal relation of items positioned at the beginning of the sequence compared to items positioned at the end of the sequence. Such behaviour would have indicated that position codes were spatially represented across the entire mental workspace, with the left part of this representation being neglected (for a similar reasoning in the number domain, see Zorzi, Priftis, & Umiltà, 2002). On the one hand, the general decline in performance in the order task with increasing neglect severity might be, at least in part, accounted for by the idea that the positional codes of all memorized items are represented in a compressed manner in the intact (right) side of mental workspace. The stronger the neglect, the more the compression would be needed to spatially represent all positional codes in this intact workspace. The more the compression, the lower the distinctiveness among the spatial codes that provide memorized items with a positional context (Guida *et al.*, 2016). As a consequence, difficulties in judging the ordinal relations between memorized items can be observed regardless of whether these positions were located at the beginning or at the end of the sequence. On the other hand, spatial working memory impairments in patients with neglect are not spatially lateralized, as they can be observed in patients with neglect even when the memory set is sequentially presented centrally in a vertical array (Malhotra *et al.*, 2005). Therefore, a general impairment of keeping track of the spatial codes associated with ordinal information, irrespective of whether they are represented in the neglected or intact space, could explain why we observed a non-lateralized deficit of serial order in our patients. Finally, Wansard *et al.* (2015) observed that simultaneous and sequential aspects of spatial working memory can be selectively impaired in patients with neglect. Because many similarities exist when memorizing the serial order of verbal and visuo-spatial information in working memory (for a review, see Hurlstone, Hitch, & Baddeley, 2014), it would therefore be interesting to investigate whether impairments of serial order in patients with neglect are systematically observed in both verbal and visuo-spatial working memory.

It remains to be explained how patients with neglect can at the same time have a deficit for serial order processing and still have a verbal working memory span within the normal range (e.g., Doricchi *et al.*, 2005; Malhotra *et al.*, 2005; as well as in the patients of this study). This might seem paradoxical, as verbal working memory span is typically assessed by tasks also loading on order information, such as the digit span task in which sequences of digits must be recalled in the correct order. This suggests that, depending on the task at hand, different codes could be used to represent the ordinal positions of items in working memory. In a recent account, Camos (2015, see also Camos, Lagner, & Barrouillet, 2009) proposed two different systems for maintaining verbal information in working memory: a language-based system dependent on articulatory rehearsal and an attention-based system applicable to different types of information (verbal, visual or spatial). The performance of the patients with neglect fits nicely with the idea of an affected attention but preserved language system. When the task requires the forward recall of a memorized sequence, such as in the digit span, linguistic codes might be preferentially used to represent order information (see also Kalm & Norris, 2014). Our order task, on the other hand, may rely more strongly on the attention (refreshment) system (Majerus *et al.*, 2006), potentially directed to spatial codes. This idea is corroborated by recent findings of articulatory suppression interfering with item recognition performance, while the spatial coding of order information remained unaffected (Ginsburg, Archambeau, van Dijck, Chetail, & Gevers, 2017).

In conclusion, we showed that hemispatial neglect syndrome can be associated with a deficit for serial order processing. This deficit was functionally related to neglect severity and was more frequently observed after posterior parietal damage. While it cannot be excluded that serial order deficit is merely a joint deficit that follows posterior parietal damage, this observation converges with the reported interactions between order and space in healthy participants (see Abrahamse *et al.*, 2014, 2017), suggesting that serial order is grounded in spatial cognition. In addition, the deficit was not lateralized. A first possibility is that the spatial codes that provide memorized items with a positional context might be compressed, and therefore less distinct, in the intact representational space. Alternatively, spatial working memory impairments, known to be non-lateralized even in patients with neglect (e.g., Malhotra *et al.*, 2005), might have led to difficulties in keeping track of the spatial codes associated with ordinal positions in verbal working memory, even when successfully represented in the intact hemispace. These findings are not only of theoretical but also of clinical relevance. Indeed, these findings might lead to fine-grained diagnosis of patients with hemispatial neglect by accounting for serial order deficits in verbal working memory even when they present a normal verbal span. Despite the fact that serial order coding in working memory is a fundamental component of many other cognitive domains (e.g., reading and reasoning), this ability is to the best of our knowledge not typically investigated in these patients.

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Supporting Information

The following supporting information may be found in the online edition of the article:

Table S1. Sequences used in the item and order task.

Table S2. Performance of healthy participants in the experimental tasks.

Table S3. Lateralised scores of neglect patients in the item and order tasks.