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Research report

Two qualitatively different impairments in making rotation operations

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ARTICLE INFO

Article history:
Received 13 May 2009
Reviewed 26 June 2009
Revised 9 September 2009
Accepted 14 October 2009
Action editor Jane Riddoch
Published online xxx

Keywords:
Mental rotation
Parietal cortex
Prefrontal cortex
Categorical spatial representation
Metric spatial representation

ABSTRACT

It is widely recognized that mental rotation is a cognitive process which engages a distributed cortical network including the frontal, premotor and parietal regions. Like other visual-spatial transformations it could require operations on both metric and categorical spatial representations. Previous reports have implicated respectively the right hemisphere being involved in the metric processing and the left hemisphere in the categorical processing. By using a modified version of the Bricolo et al.'s task (2000), we attempted to establish the cortical regions relevant for the categorical and metric aspects of mental rotation transformations. Two groups of patients were found to be impaired in our study, namely the left prefrontal and the right parietal. In particular, whereas the right parietal group made poor use of categorical information, the left prefrontal patients showed a broader mental rotation impairment with a significant number of metric errors. The results are discussed in terms of the model of Kosslyn et al. (1989) about the possible mental transformation impairments following brain lesions.

1. Introduction

The ability to imagine the rotation of an object in space has been studied most intensively by using the Shepard and Metzler task in which subjects are required to decide whether two figures are the same or mirror images (Shepard and Metzler, 1971; Cooper and Shepard, 1973). In these pioneering studies reaction times increased proportionally to the angular distance between the two stimuli, which fitted with what would be expected if subjects rotate the objects linearly before making the decision. This mental rotation, they claimed, is an analogue process. Although certain subsequent studies have provided further support for the linearity of the angular distance effect (Shepard and Cooper, 1982; Corballis and Sergent, 1989; Carpenter et al., 1999; Keehner et al., 2006), other researchers have suggested that the mental transformations involved are not always smooth and analogue, but can occur in a more categorical step-like manner, that is by moving from

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0010-9452/$ – see front matter © 2009 Published by Elsevier Srl.
doi:10.1016/j.cortex.2009.10.006

an object's position to another without passing through the space between them (Kosslyn, 1980; Franklin and Tversky, 1990; Hegarty, 1992).

Consider for instance the simple situation in which a subject is working with objects which have then to be acted on from a different viewpoint, like the situation in which yours is one of a number of identical cups of tea on a table. You walk round to another side of the table but then need to pick up the appropriate cup. One needs to know which is one's own. Introspectively one does not do this by rotating the table in one's head. It is possible to localize and infer spatial relations between and within objects despite changes of the direction from which they are viewed (Corballis, 1988; Marr, 1980), and not necessarily by using continuous transformations through intermediate positions. In these situations other cognitive strategies can be used, such as using categorical representations of the objects in relation to stored spatial frames. From this perspective, as suggested by Pylyshyn (2002), the evidence favouring the linearity of the angular distance effect may be specific to the task used. It remains possible that linearity and the use of analogue transformation are not principles which govern mental rotation in all situations.

A related project is the attempt to isolate the subsystems and their neural basis involved in mental rotation. A pioneering study by Ratcliff (1979) in brain-damaged patients demonstrated that lesions to the right parietal cortex selectively impair the mental rotation process. In this experiment patients were presented with a schematic drawing of a man with one marked hand. On each trial this figure was presented in an upright or an inverted position and participants were required to say which of the two hands was marked – the left or the right hand. The authors found that patients with right parietal lesions made more errors in the inverted condition, which required a mental re-orientation of the stimulus, in comparison to patients with left hemisphere and bilateral lesions.

The involvement of the right parietal cortex in the mental rotation processing has been further supported using different experimental methodologies including neuropsychological (Ditunno and Mann, 1990), brain imaging (Deutsch et al., 1988; Carpenter et al., 1999; Harris et al., 2000), topographical ERPs (Yoshino et al., 2000) and TMS (Harris and Miniussi, 2003) studies. However, other research has provided evidence that rotation may also involve left hemisphere neural activation depending on the stimuli and the tasks used (Kosslyn et al., 1998; Vingerhoets et al., 2001; Jordan et al., 2001; Tomasino et al., 2003). In addition, some functional imaging studies have also obtained activations in the premotor and supplementary motor areas while performing mental rotation tasks (Cohen and Bookheimer, 1994; Richter et al., 2000; Lamm et al., 2007; de Lange et al., 2005). These results led researchers to claim that motor simulation could be used to solve mental rotation tasks. Moreover, a recent meta-analysis (Zacks, 2008) showed that brain regions that were mainly activated during mental spatial transformations included frontal and inferotemporal areas. More specifically, although the brain was bilaterally activated in most regions, these studies stressed a major involvement of the right parietal cortex (Harris et al., 2000; Halari et al., 2006) and an involvement of the left prefrontal cortex (Johnston et al., 2004; Kosslyn et al., 2001; Zacks et al., 1999).

Another important issue related to mental rotation and its neural substrates concerns the model put forward by Kosslyn et al. (1989). They argued that creating the representation of the spatial context in which objects lie involves at least two distinct processes. The first involves a *categorical* analysis in which the spatial relations among objects in scenes are represented in qualitative terms (as is captured by an expression such as 'the pen is near the big cup on the desk'). The second involves a *metric* analysis of the vector spatial relationships in terms of quantitative distances and angles, which they called *coordinate* representations. Kosslyn et al. (1989) argued that while metric spatial processing engages the right hemisphere, categorical processing involves the left. The latter would follow if categorical processing relates to language processes. On this approach, mental rotation transformations, like many other visuo-spatial processing could require operations on both categorical and coordinate representations of objects. Following the ideas of Kosslyn, it is possible that these two processes might be selectively impaired and so cause different types of mental rotation deficits according to the side of the lesion: a lesion of the left hemisphere would impair categorical representations, whereas the metric operations would be disrupted by a lesion of the right hemisphere.

The anatomical basis of the theoretical framework of Kosslyn et al. (1989) was questioned in the work of Bricolo et al. (2000). They described a patient (PAO) who had sustained a right parietal lesion, but despite that, had relatively good performance in object recognition and in several visuo-spatial tasks. However, he was grossly impaired in any task involving rotation such as Kohs's Blocks. A specific rotation task was investigated in more detail. PAO was presented with a dot inside a tilted square frame of reference and had to reproduce its position, relative to the square, after the square had been rotated to the vertical. If his attempt was in the vicinity of the correct response, then his psychophysical accuracy curve was as good as that of normal controls. However, a high proportion of his attempts were in completely inappropriate parts of the square. His performance was interpreted as preserving metric operations, but with ones based on categorical representation impaired. Thus in his case a specific disorder of operations based on categorical representation appeared to follow a right hemisphere lesion. This idea has subsequently been supported by the work of Toraldo and Shallice (2004) who found similar impairments of operations on categorical spatial representations in another right hemisphere patient (VQ). However, both these studies used single-case methodology, which is not sufficient for proper localization of relevant lesion sites.

In the categorical-metric (or coordinate) coding debate, a different hypothesis has been recently proposed by Martin et al. (2008) on the basis of their fMRI study. The authors claimed that both the right and the left hemispheres are activated in coding categorical as well as coordinate positions. Indeed, when using working-memory tasks in which the coding of categorical or coordinate spatial relations was required, the authors failed to find a strong hemispheric specialization. Task involving both categorical and coordinate representations evoked activity in a similar fronto-parieto-occipital neural network and the differences were more of a quantitative than of a qualitative nature. Moreover, a significant activation was found in the dorsolateral prefrontal cortex when no visible space

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categorization was given (coordinate task) or when more than three elements had to be coded. Martin et al. interpreted their data as supporting the '*Continuous Spatial Coding*' (CSC) hypothesis, according to which there might be "continuity between categorical and coordinate spatial relations along a complexity dimension" and both hemispheres might be implicated in both types of spatial relation coding.

In the present research we attempted to establish the critical regions of the prefrontal, premotor and parietal cortex involved in mental rotation transformations. For this purpose, we used the experimental paradigm based on the previous work by Bricolo et al. (2000), which required patients to remember the position of a dot inside an upright or a tilted frame of reference and to reproduce it inside a subsequent identical upright reference frame after the frame was re-oriented vertically.

Different methods of analysis were used. The first traditional methodology used was an anatomically-based group study approach. In the initial comparisons, following the procedure of Stuss et al. (2005), the relative performance of patients with tumours in six different regions of cortex was contrasted. This analysis allowed us to investigate the contaminating effects of variables such as lesion size and age. This procedure was then followed by an examination of the lesion sites of poorly as opposed to satisfactorily behaving patients. Here the procedure adopted was the *Voxel-Based Lesion-Symptom Mapping* (VLSM) analysis (Bates et al., 2003; Rorden and Karnath, 2004; Rorden et al., 2007). Finally, in order to validate the main findings of the group analysis and to exclude any possibility that the pattern of responding observed was achieved by chance, we also contrasted our empirical findings with a Monte–Carlo simulation study.

As the patients were all tested 2–6 days after surgery (so that the errors could involve general post-operative effects), we used comparisons between subgroups rather than comparing the patient groups with normal controls. This procedure was also motivated by the fact that the six control patients we tested (patients with lumbar disc disease, mean age: 50.17; mean education: 11.17) were virtually at ceiling, producing on average 1.89 errors each (5.7% of the total number of trials).

2. Methods

2.1. *Patients*

A total of 95 patients with a single circumscribed brain tumour confined in the left or right prefrontal, premotor and parietal cortex were selected and tested in the Neurosurgery Department (Santa Maria della Misericordia Hospital, Udine) within a time period of about three years. Of these 95 patients, 40 were excluded by means of the following criteria: (i) multiple or bilateral lesions; (ii) recurrence of the tumour; (iii) hemianopia, severe neglect or right hand motor impairment, (iv) diagnosed stroke, head injury or other neurological and psychiatric diseases. We performed the experimental test on the remaining 55 patients (Table 1). All the 55 patients underwent the experimental assessment within one week from their operation. Within this patient group, 26 patients had a predominant prefrontal lesion (12 right prefrontal, 14 left prefrontal), 13 a predominant premotor lesion (5 right premotor, 8 left premotor) and 16 a predominant parietal lesion (9 right parietal, 7 left parietal). A display of the overlapping regions is shown in Fig. 1. Patients were between 20 and 70 years of age (mean age, 45.35 years; SD, 12.79 years). The mean educational level was 11.27 years, SD 4.02 years. With respect to the aetiology, 43 patients with glioma (17 high grade; 26 low grade), 8 with meningioma, 3 with metastases and 1 with an arteriovenous malformation (AVM) were tested. Lesion volume mean was 46.76 ml, SD 35.83 ml. A significant difference between groups was found for lesion size [Kruskal–Wallis $\chi^2 = 11.88$, $p = .04$]. Premotor patients tended to have smaller lesions than parietal and prefrontal patients. No significant differences were found among the six groups for educational level [$F(5, 48) = 1.6$, $p = .18$] and age [$F(5, 48) = .77$, $p = .57$].

The rotation test was one of 17 given to the patients. We show in Table 1 the results for the most directly relevant tests, a test for neglect – Star cancellation (Wilson et al., 1987), and two non-spatial attentional tests – the Elevator Counting test (Test of Everyday Attention, Robertson et al., 1994) and the Phonemic Verbal Fluency test (Multilingual aphasia examination, Benton and Hamsher, 1978).

The study was approved by the Ethics Committee of the International School for Advanced Studies (SISSA).

2.2. *Stimuli*

A 15-inch resistive high resolution touch screen (3M) and a personal computer (Pentium 4, 3 GHz) were used for the presentation of the stimuli and to record the responses of participants. All patients sat in a normally lit room with a viewing distance of 60 cm from the display. The starting hand position was aligned to the display's centre and located 40 cm away from it. As far as the mental rotation task was

Table 1 – Age, education, lesion size (mean, SD) and gender distribution of the six patient groups.

Group	Gender (M/F)	Age	Years of education	Lesion size (ml)	Star cancellation (left side)	Elevator counting	Phonemic fluency
LPreF	6/8	44.14 (12.81)	10.21 (4.26)	71.14 (43.22)	26.91 (.30)	5.00 (2.17)	21.79 (15.66)
RPreF	10/2	43.33 (10.87)	13.58 (3.61)	50.50 (26.61)	26.50 (.52)	6.25 (.87)	40.20 (9.90)
LPreM	5/3	41.38 (12.54)	11.50 (3.07)	22.88 (17.83)	27.00 (.00)	5.71 (1.50)	26.33 (13.06)
RPreM	4/1	40.00 (15.38)	13.20 (3.35)	13.80 (14.45)	27.00 (.00)	6.20 (1.30)	45.00 (17.48)
LeftPar	5/2	52.57 (13.97)	8.57 (2.64)	51.71 (29.57)	26.71 (.76)	6.00 (2.24)	25.29 (10.50)
RightPar	6/3	50.78 (12.79)	10.67 (4.87)	39.56 (35.08)	25.11 (2.93)	6.00 (1.58)	29.67 (10.49)

L = left, R = right, PreF = prefrontal, PreM = premotor, Par = parietal.

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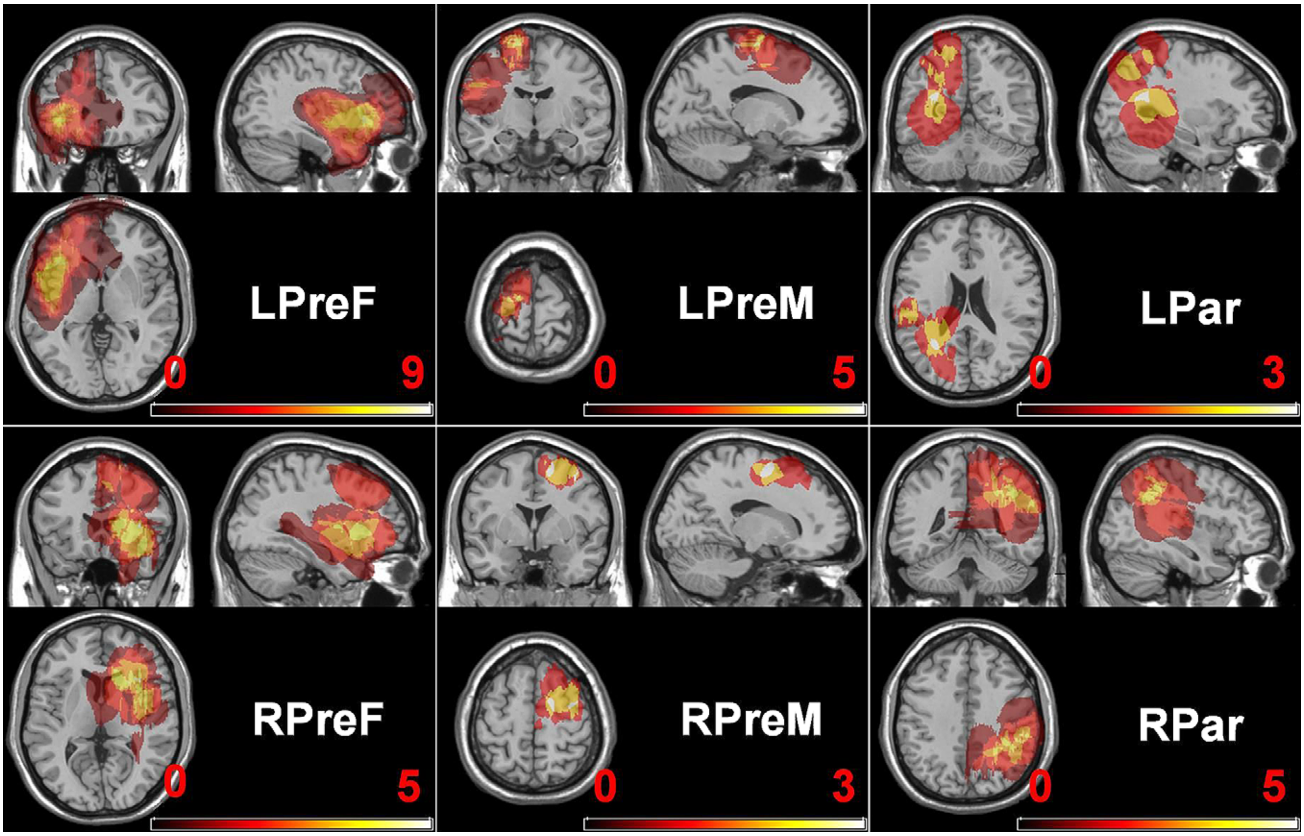

Fig. 1 – Overlapping lesion reconstructions for each of the six patient groups. The lighter the colour the higher the number of patients within that group who have that voxel damaged. LPreF = left prefrontal (*n* = 14); RPreF = right prefrontal (*n* = 12); LPreM = left premotor (*n* = 8); RPreM = right premotor (*n* = 5); LPar = left parietal (*n* = 7); RPar = right parietal (*n* = 9).

concerned we used an adapted version of Bricolo et al.'s paradigm (2000). The stimulus was a 12 × 12 cm square which had a thick top. A small black dot (diameter: 3 mm) was located inside the square following some procedural constraints: it could appear in a 0–3 mm radius circle around one of the six crossing grids which were obtained by dividing the 12 × 12 cm square into 16 invisible smaller equal squares. The probe square was presented in pseudorandomly selected positions within the display. The square was presented in one of three possible orientations: upright (0° *rotation*), tilted rightwards (the patients had to mentally rotate the square *anticlockwise*, AC45° *rotation*) or tilted leftwards (the patients had to mentally rotate the square *clockwise*, CL45° *rotation*). Twelve practice trials and 33 experimental trials were given to each patient. The same number of experimental trials (11) was used for the three probe orientations with a fixed random sequence for all patients. Examples of the stimuli used in the experiment are shown in Fig. 2.

2.3. *Procedure*

As illustrated in Fig. 2, each trial began with the presentation of the probe square which could be rotated by 0°, −45° (CL45° condition) or +45° (AC45° condition) from an upright position. After 500 msec, the small black dot appeared inside the reference frame and remained visible for 300 msec. Patients were instructed to identify and remember the position of the dot with respect to the reference frame and 1 sec after its disappearance, they were asked to reproduce its position inside the now upright frame of reference. The exact instructions were: "Look at this (first) square – it can be upright, or tilted towards one side, but you can easily recognize it because its top edge is thicker. A dot will appear shortly inside the square – remember its exact position within it. After a while you will be presented with an empty upright square. Your task will then be to touch where you remember that the dot was in the previous square". While the response frame was always presented at the geometric centre of the computer screen, the probe square appeared at random positions on the screen. This was done in order to prevent reaching movements towards untransformed positions of the screen. All of the patients responded with a pen using their right (dominant) hand. The upright response frame remained visible until the participants responded. When they pointed to the touch screen, the stimulus disappeared and the experimenter started the next trial by pressing the spacebar. Patients were given four practice trials for each orientation condition. Each session lasts about 10 min.

2.4. *Data analyses*

2.4.1. *Behavioural data*

For the data analyses we employed an anatomically-based group study approach that was based on the Stuss et al.'s

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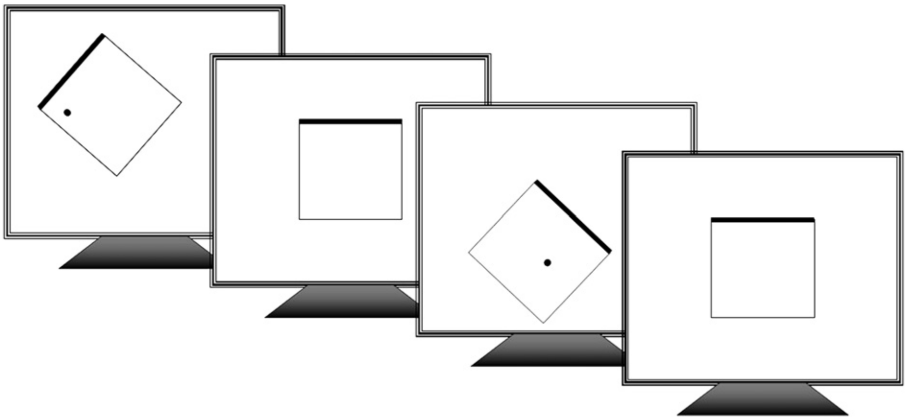

Fig. 2 – Examples of stimuli and procedure used for the Bricolo et al. mental rotation paradigm. The probe square was presented in one of three possible orientations: 0°, −45° (square tilted leftwards, clockwise rotation is required, CL45°), +45° (square tilted rightwards, anticlockwise rotation is required, AC45°). The black dot remained visible for 300 msec; afterwards, the patient was required to reproduce its position by touching in the subsequent upright reference frame. After the patient's response a new trial began.

(2005) procedure. The methodology used to infer brain–behaviour relations involved three levels of analysis:

(i) We selected and divided patients into six groups according to the side and the predominant location of the brain tumour (right prefrontal, *RPreF*; left prefrontal, *LPreF*; right premotor, *RPreM*; left premotor, *LPreM*; right parietal, *RPar*; left parietal, *LPar*) and we first compared the performance among these groups.
(ii) If a significant overall effect was obtained, we compared the performance of each group of patients with those of the other groups combined (e.g., RPar *vs* RPreF, LPreF, RPreM, LPreM, and LPar combined). In this way we were able to be more specific about the location of any impairment with respect to our patient population.
(iii) If we found a significant effect at this level, we performed more detailed analyses.

We applied the following procedure of error classification to the data set of each individual patient (Toraldo and Shallice, in preparation):

1. *Errors*. An error was assigned when the patient reached out to a point more than 1.5 cm away from the correct position. The 1.5 cm criterion corresponds to the 25% of the width of one of the four quadrants into which the 12 × 12 square was divided for the qualitative analyses (see below).
2. *Classification of errors in spatial categories*. The reference frame was considered as a square divided into four quadrants (top–left, top–right, bottom–left, bottom–right) and we determined whether the target's position and the wrong response of the patients were in the same or in a different quadrant. In this way, each response was broadly classified as "*Correct Quadrant*" (CQ, response in the correct quadrant but more than 1.5 cm away from target position) or as "*Quadrant*" error (Q, response in an incorrect quadrant). A subsequent analysis was carried out on the direction of *Quadrant* errors. Thus, we evaluated whether the Q errors were in the same (Q+) or in the opposite direction (Q−) with respect to the required rotation (Fig. 3).

In order to address the model put forward by Kosslyn et al. (1989), all responses were further classified into a number of *spatial subcategories*, according to whether or not the patient's response was close to (i.e., less than 1.5 cm from) theoretically important positions within the frame of reference (see Fig. 3 for details).[1] These positions were:

(i) *OR* (*Omitted Rotation*). The *OR* position is where a patient would point to, when no mental rotation at all has been applied to the square. In other words, the position of the stimulus dot with respect to the square centre has been reproduced, with no regard for the orientation of the frame.
(ii) *Cat* (*Pure Categorical*): *Qr* (*Reflection error*), *Qd* and *d* (*Dimension errors*). We defined the response of the patient as *Qr* error, when the placed mark was in a reflection of the correct position with respect to the horizontal, the vertical, or both axes of the square. A *d* error was diagnosed when the mark was within the correct quadrant, but in the position obtained by swapping the two vectors from the two closest edges of the square; e.g., if correct position was 1 cm from the left edge and 3 cm from the top edge, the *d* point was 3 cm from the left, and 1 cm from the top edge. *Qd* positions were axes-reflections of the *d* position in other quadrants. Interestingly, the $Q + d$ and the $Q - d$ points are exactly 90° away from the correct position in either direction with respect to the reference frame. All these categories were collectively called "*Pure Categorical*" errors because they both

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[1] *Disambiguation procedure*. When more than one error category could be applied to a given response, we chose the closest theoretical point to classify it. For instance, if a patient responded 1.1 cm from the *OR* point and 1.3 cm from the $Q - r$ point, we classified the error as *OR* because the *OR* point was the closer.

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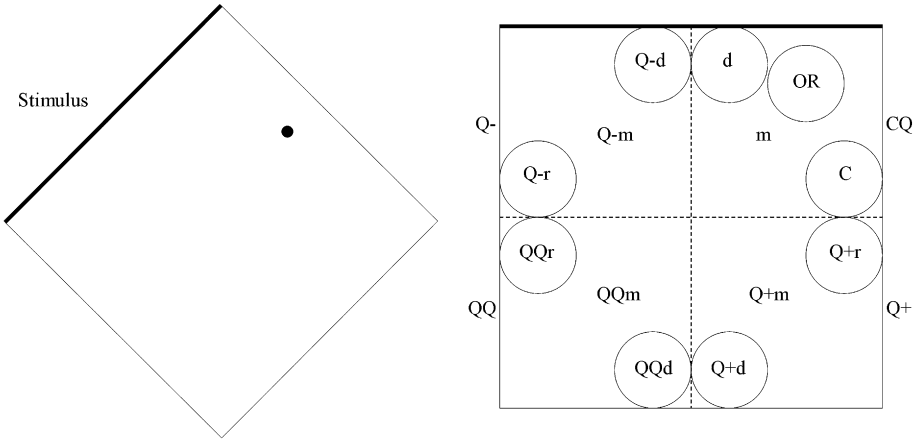

Categories	Type of Error	Description
CQ		
C	Correct Response	response within the 1.5 cm criterion
	Correct quadrant, incorrect position	
OR*	Omitted Rotation	not mentally rotated
d	Dimension	reflection in square diagonal of correct response (C)
m	Pure Metric	outside the theoretically important categories
Q+	*Quadrant error, same rotation direction*	
Q+r	Reflection	reflection in axes of the correct response (C)
Q+d	Dimension	reflection in axes of “d” point = 90° out the correct position
Q+m	Metric	outside the theoretically important categories
Q+cat	Pure Categorical	Sum of reflection and Dimension errors
Q-	*Quadrant error, opposite rotation direction*	
Q-r	Reflection	reflection in axes of the correct response (C)
Q-d	Dimension	reflection in axes of “d” point = 90° out the correct position
Q-m	Metric	outside the theoretically important categories
Q-cat	Pure Categorical	sum of Reflection and Dimension errors
QQ	*Opposite Quadrant error*	
QQr	Reflection	reflection in axes of the correct response (C)
QQd	Dimension	reflection in axes of “d” point
QQm	Metric	outside the theoretically important categories
QQcat	Pure Categorical	sum of Reflection and Dimension errors

Fig. 3 – Spatial subcategories of errors. The errors were classified according to the spatial position of the patient's response within the frame.

preserve the metrics – the touched position is at correct distances from the closest sides of the square – but do not respect the categorical aspects of the representation. We first analysed the general category – *Pure Categorical* errors – and on a following step we analysed "*Reflection*" and "*Dimension*" errors separately.

(iii) *m* (*Pure Metric*). We called "*Pure Metric*" errors those responses that were located in the correct quadrant – thus indicating preserved categorical processing – but well away (more than 1.5 cm) from all theoretically relevant positions, i.e., the correct position (*C*), the *d* and the *OR* points. This indicates selective damage to the metric component of the processing (we use the term 'metric' as we restrict the term 'coordinate' to representations as opposed to, for instance, operations).

(iv) *Qm* (*Quadrant and Metric error*). We called *Qm* errors those responses located in an incorrect quadrant and outside all of the theoretically important areas (*d* and *r*).

Kosslyn et al.'s (1989) distinction between categorical and metric processing is best characterized, in this error classification procedure, by classes (ii) and (iii) above, i.e., "*Pure Categorical*" and "*Pure Metric*" errors.

The raw data were first checked for normality using the Kolmogorov–Smirnov test and for homogeneity of variance by the Levene test. As the data were not normally distributed, non-parametric tests were used. The results were considered significant if the p value was $<.05$. All the significant tests were two-tailed unless otherwise specified.

2.4.2. *Anatomical data*

The pre-operative location of the tumour was carried out using a digital format contrast-enhanced T1-weighted Magnetic Resonance Imaging (MRI) scan obtained 1–2 days before operation, using a 1.5 T machine and a GRE-3D T1-weighted scan [Inversion Time (TI) 600 msec, Repetition Time (TR) 1400 msec, Echo Time (TE) 31 msec, Thickness (TH) 1 mm, Distance Factor (DF) 1 mm]; this image was selected as it is the

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scan generally used by the neurosurgeon during the operation with the Neuronavigator as the best indicator of macroscopic tumour extent. MRicro reconstructional software was used to extrapolate a 3D representation of the lesion from digital MR scans (Rorden and Brett, 2000). The boundary of a lesion was drawn as a region of interest (ROI) on each sagittal slide in collaboration with the neurosurgeon and a neuroradiologist, who did not know the behavioural results, so as to limit the lesion's boundary to the brain tissue removed during the surgical approach. The scans and ROIs were normalized using SPM05b with 12 affine transformations and 7 × 9 × 7 basis functions. Each patient's lesion was referred to an anatomical template image *Automated Anatomical Labelling* (AAL) (Tzourio-Mazoyer et al., 2002), a macroscopic anatomical parcellation of Montreal Neurological Institute (MNI) volume (Collins et al., 1998). Afterwards, the VLSM analyses were run. The procedure allows one to use the statistical relation between behavioural data and the specific voxels affected by the lesion without grouping patients for lesion location or relying on behavioural cut-offs (Bates et al., 2003; Rorden and Karnath, 2004). The Non-Parametric Mapping (NPM) software (Holmes et al., 1996) was used to run the Brunnel–Munzel test (Brunner and Munzel, 2000) and compute a statistical map for continuous variable results (Rorden et al., 2007). The results are shown using Bonferonni corrected significance values, requiring a minimum of three patients affected for a voxel for it to be included.

3. Results

3.1. *Overall error analysis*

An exploratory analysis was performed by comparing the overall number of errors in the rotation conditions (CL45° and AC45° combined) and in the non-rotation condition (0°). The average number of errors was greater for the CL45°/AC45° conditions combined than for the 0° condition. This result was significant for almost all patient groups [LPreF: $z = -2.94$, $p = .002$; RPreF: $z = -2.49$, $p = .007$; LPreM: $z = -1.81$, $p = .036$; RPreM: $z = -1.00$, $p = .159$; LPar: $z = -1.63$, $p = .051$; RPar: $z = -2.67$, $p = .004$; one-tailed Wilcoxon Signed Rank tests]. No significant differences were observed by comparing the number of error responses in the CL45° and the AC45° rotation conditions within each patient group (for all groups: $p > .05$, Wilcoxon Signed Rank test) (Fig. 4).

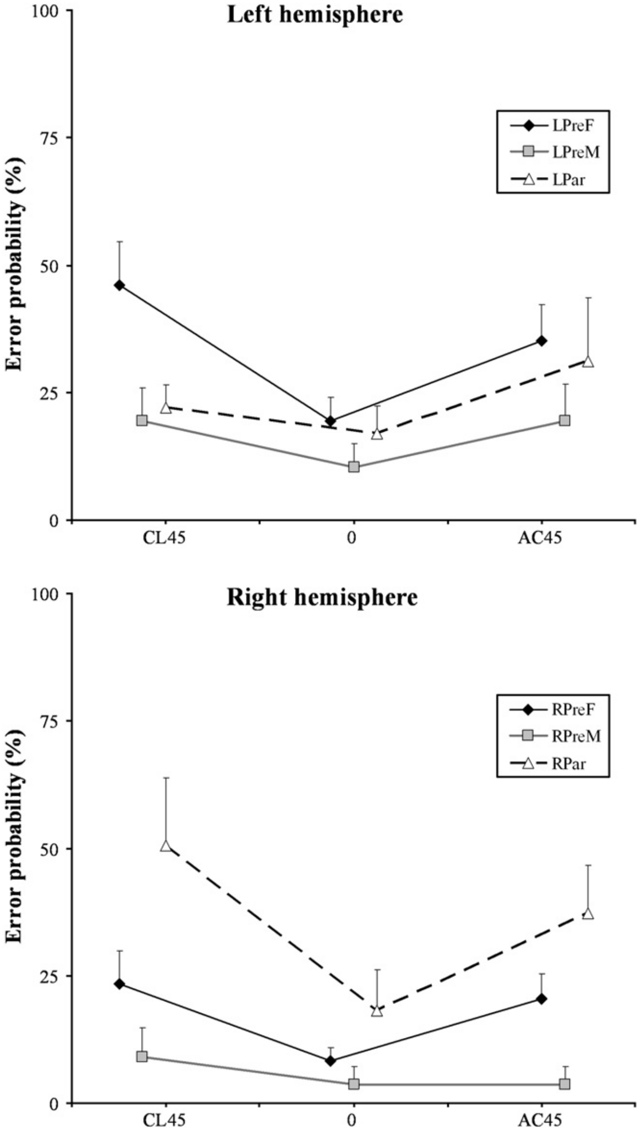

Fig. 4 – Relative error frequency (mean and standard error) as a function of condition and patient group.

A one-way non-parametric ANOVA across all six groups on the number of errors occurring in the rotation conditions (CL45°/AC45°) showed that the groups differed significantly [Kruskal–Wallis; $\chi^2(5) = 13.18$, $p = .02$]. In order to determine whether the effect observed was related to differences in lesion size, we correlated the patients' performance in the CL45°/AC45° conditions combined with lesion size. Overall the correlation of the total number of errors with lesion size was completely insignificant [$F(1, 46) = .83$, $p = .37$].

The main aim of this study was to examine whether or not the more impaired groups behave qualitatively differently in the nature of their errors from other impaired groups and from less impaired patients. However this aim is faced by the methodological problem that controls are virtually at ceiling, so we cannot use the nature of their errors to contrast with the pattern of errors made by impaired groups. So a modification of the approach developed by Stuss and colleagues was adopted to putatively identify the more impaired groups and potential control groups. First, we compared the performance among all the six groups to determine whether there was a significant difference between them. Given that it was found (see above), we then contrasted the performance of each group of patients with the other five groups combined. At this stage the left prefrontal group differed significantly from the other five (CL45°/AC45° errors combined, Mann–Whitney $U = 178$, $p = .035$), but the right parietal did not. In order to investigate whether there were differences among the other five groups, we removed the left prefrontal group and repeated the analogous procedure. On this second round only the right parietal group performed statistically worse than the other groups combined (RPar: $U = 77$, $p = .03$; Mann–Whitney). Repeating the procedure a third time did not lead to any new significant

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effects ($p > .35$). We will therefore putatively take the right parietal and left prefrontal groups as impaired groups and treat the other groups combined as a control group.

3.2. *Direction of* Quadrant (Q) *errors*

Restricting attention to grosser *Quadrant* errors, statistical analyses revealed that both the right parietal and the left prefrontal groups made a significantly greater number of such errors compared to the other four groups combined [RPar *vs* Others: Mann–Whitney $U = 75$, $p = .03$; LPreF *vs* Others: Mann–Whitney $U = 130$, $p = .02$]. We used such errors to examine the direction of rotation. For the *negative* Quadrant errors (Q−) – moving in the direction *opposite* to that of the rotation required – the right parietal patients made a significantly greater number than the other groups combined [RPar *vs* Others: Mann–Whitney $U = 62$, $p = .01$]. However, for the *positive* Quadrant errors (Q+) – moving too far in the same direction as that of the required rotation, the left prefrontal patients made a larger number than the other groups combined [LPreF *vs* Others: Mann–Whitney $U = 153.5$, $p = .04$] (Table 2).

When a direct comparison of the number of Q− and Q+ errors within each group was carried out, a significant effect was found for the right parietal patients with the Q− errors being the more frequent (Wilcoxon Signed Rank test $z = -2.54$, $p = .01$). The four patient control groups combined also showed significantly more Q− than Q+ errors ($z = -2.52$, $p = .01$). However, in the left prefrontal group, the difference was far from significant ($p = .51$). If we consider the direction in which the square has to be rotated, clockwise (CL45°) versus anticlockwise (AC45°), the right parietal patients showed a similar rate of Q− errors in both conditions – no significant difference could be detected. In other words, the right parietal patients tended to rotate in an incorrect direction more than the other lesion control groups irrespective of the direction required, clockwise or anticlockwise.

3.3. *Qualitative differences in error types: metric and categorical errors*

The analysis of *Quadrant* errors showed us that gross group differences emerged with respect to the *direction* of the error. We then investigated whether the errors could arise from the malfunction of a purely *metric* or *categorical* process. For this reason we considered the number of errors that fell into three qualitative error categories. One type is the error that would arise if the patient did not perform a rotation operation and responded on the basis of the initial position of the target point (*Omitted Rotation*).[2] A second is if the patient produced a response in the reflection of the correct response point with respect to the horizontal, the vertical, or both axes of the square (*Reflection error*). The third is if the patient made the correct metric operation on the target point but used an incorrect neighbouring side or corner as the starting point for the metric operation (*Dimension error*); these were the type of categorical errors described by Bricolo et al. (2000) and Toraldo and Shallice (in preparation) in individual right hemisphere patients. These last two types were collectively considered as "*Pure Categorical*" errors. Symmetrically, we identified another category as "*Pure Metric*" errors, i.e., locations of the response mark that unambiguously suggest a specific impairment of metric information processing, with spared categorical information: this area is the part of the correct quadrant which is outside of all the theoretically relevant areas (*OR*, *d*, correct target position). A final error type, which is not purely categorical is the "*Quadrant and Metric*" error, which occurs when the patients place the mark in an incorrect quadrant and outside all the theoretically important areas listed above.

Table 2 – Mann–Whitney *p*-values for comparing the left prefrontal and the other four patient groups, the right parietal and other four patient groups, on several spatial subcategories of errors. Significant *p*-values are reported in bold.

Spatial Subcategories	LPreF versus Others	RPar versus Others
Quadrant errors: Q	**.02**	**.02**
Negative: Q−	.19	**.01**
Positive: Q+	**.04**	.57
Omitted rotation: *OR*	.20	.25
Pure metric: *m*	**.02**	.77
Dimension: $Q+d$, $Q-d$, QQd, d	.39	**.05**
Reflection: $Q+r$, $Q-r$, QQr	.77	**.01**
Pure Categorical: $Q+d$, $Q-d$, QQd, d, $Q+r$, $Q-r$, QQr	.67	**.04**
Quadrant and metric: $Q+m$, $Q-m$, QQm	**.002**	.26

There were theoretically important effects involving the two relevant groups, namely the right parietal and the left prefrontal (Table 2). *First*, for both groups no significant difference was found in the number of *Omitted Rotation* (*OR*) [RPar *vs* Others: Mann–Whitney $U = 111$, $p = .25$; LPreF *vs* Others: Mann–Whitney $U = 174$, $p = .20$]. *Second*, a Mann–Whitney analysis revealed that only the left prefrontal patients were impaired in the processing of metrics, showing a larger number of *Pure Metric* (*m*) errors [LPreF *vs* Others: Mann–Whitney $U = 127$, $p = .02$]. Conversely, with respect to the *Pure Categorical* errors (d, $Q+d$, QQd, $Q+r$, QQr), we found that only the right parietal patients made a significantly larger number of such errors [RPar *vs* Others: Mann–Whitney $U = 82.5$, $p = .04$]. In more detail, by looking separately at the two spatial subcategories, we observed that the right parietal group made a significantly greater number of both *Dimension* (d, $Q+d$, $Q-d$, QQd) [RPar *vs* Others: Mann–Whitney $U = 87$, $p = .05$] and *Reflection* errors ($Q+r$, $Q-r$, QQr) [RPar *vs* Others: Mann–Whitney $U = 78$, $p = .02$]. No significant effects were observed with these measures for the left prefrontal group. *Third*, with respect to the *Quadrant and Metric* ($Q+m$, $Q-m$, QQm) errors a significant result was again observed only for the left prefrontal group [LPreF *vs* Others: Mann–Whitney $U = 102$, $p = .002$].

3.3.1. *Voxel lesion-symptom mapping*

With VLSM analyses we were able to anatomically localize the brain areas responsible for the mental rotation deficits without any a priori grouping method. For the *Pure Categorical*

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[2] The omitted rotation point (*OR*) falls in the correct quadrant in some trials, and in the Q− quadrant in some others, according to where the target is located within its quadrant.

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errors patients with lesions in the right inferior parietal cortex showed a significant involvement. On the other hand, the common area for the *Pure Metric* and *Quadrant and Metric* errors was the left insula verging on the putamen. All these anatomical loci survived Bonferroni corrections.

3.3.2. *Monte–Carlo simulation*

In order to test whether the qualitative impairments observed in the right parietal and in the left prefrontal groups truly reflected a mental transformation deficit and were not just the effect of random selection of locations within the square, we additionally performed a Monte–Carlo simulation study to obtain chance levels. We generated random positions within the square as responses to each of the 33 stimuli that had actually been administered, and repeated this procedure 10,000 times. On each of the 10,000 samples, we applied the same error classification procedure as was applied to real data from patients. For each spatial subcategory we compared the probability of an error occurring by chance (*expected* probability) with the *observed* probability. Binomial tests revealed that the error proportions in the *Pure Metric* subcategory were above chance in both prefrontal and premotor groups ($p < .0001$ for all the groups) and below chance in the *Quadrant and Metric* subcategory for all groups ($p < .0001$). Moreover, the observed proportions of *Pure Categorical* errors were more frequent than expected by chance in the right parietal group ($p < .0001$). These findings clearly indicate that the incorrect responses of patients in theoretically important regions did not occur by random selection of points in the square (Fig. 5).

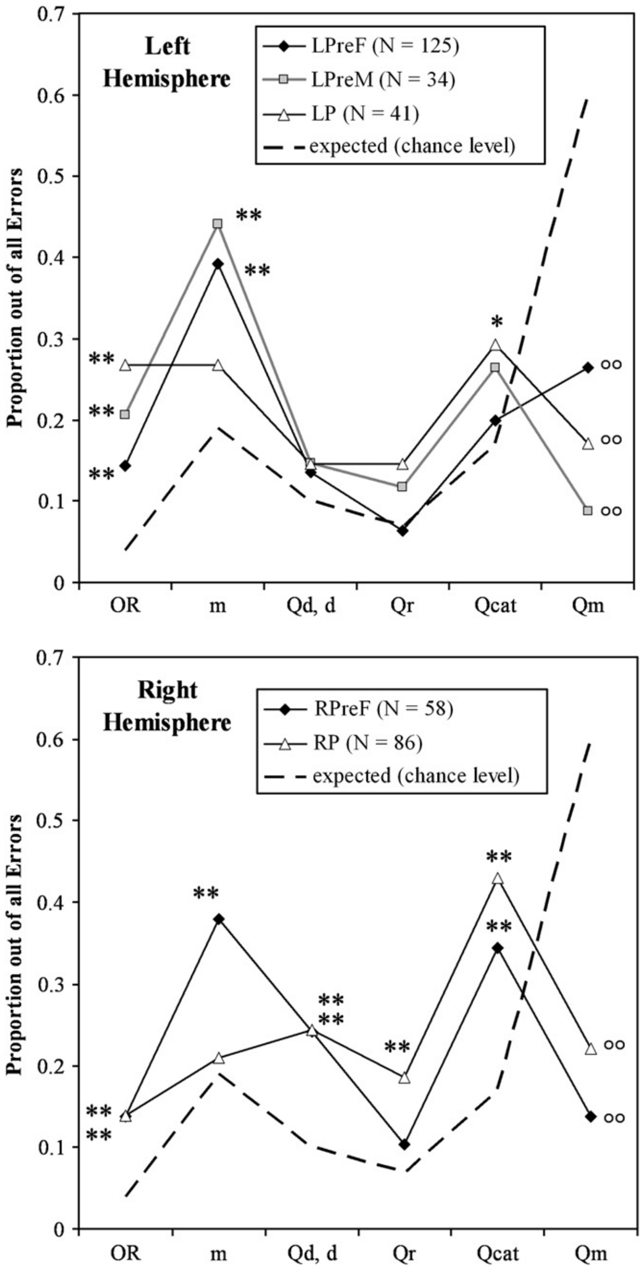

Fig. 5 – Proportion of errors of a given category out of all *errors* (vertical axis) is reported as a function of error category (horizontal axis) and patient group. Dashed plot: chance levels, i.e., proportions obtained from random selection of locations in the square (Monte–Carlo simulation study). Asterisks indicate above-chance empirical error frequencies (two-tailed binomial test: $^{*}p < .05$; $^{**}p < .01$); circles indicate below-chance error rates (two-tailed binomial test: $^{\circ\circ}p < .01$). *OR*: omitted rotation, *Cat*: Pure Categorical, Q*r*: Reflection, Q*d*, *d*: Dimension, Q*m*: Quadrant And Metric, *m*: Pure Metric. *N* values: overall number of errors by all patients in a group. Since the RPreM patients made only 7 errors in total, data from this group are not reported. Below-chance rates (°°) are of little importance as they just reflect the increased error frequency in other categories.

4. Discussion

The initial aim of this study was to provide further evidence on what cortical regions are responsible for mental rotation transformations. We employed the mental rotation task developed by Bricolo et al. (2000), but we used an anatomically-based group study approach rather than a single-case method. Each patient was assigned to one of six groups, namely left prefrontal, right prefrontal, left premotor, right premotor, left parietal, right parietal. A broad analysis on the number of error responses in the rotation conditions revealed that the six groups performed in a significantly different way. We used a modification of the procedure adopted by Stuss et al. (2005) to determine candidate impaired groups. This procedure selected the left prefrontal and right parietal groups, which did not differ significantly from each other for the overall number of errors, as candidate impaired groups; the other four groups were treated collectively as a patient control group. The appropriateness of this candidate categorization was supported by the analyses carried out on the qualitative nature of the errors, which revealed that the impairments in the left prefrontal and right parietal groups were significantly different in a number of ways from the other patient groups combined. These include findings on the direction of errors, namely the *positive* Quadrant errors for the left prefrontal group and the *negative* Quadrant errors for the right parietal group. In addition if one considers the qualitative error classification, there were again significant effects for the left prefrontal group with respect to *Pure*

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Metric and *Quadrant and Metric* and for the right parietal group with respect to *Dimension* and *Reflection* errors.

4.1. *Right parietal group*

The analysis of the overall error rate indicated that patients with a lesion centred on the right parietal cortex made a significantly larger number of errors with respect to the other four patient groups combined. Particularly, in the two rotation conditions about 44% of their responses were errors, which is a major effect. This result supports the widely accepted claim that the right parietal cortex is specifically involved in mental rotation transformations, which is consistent with previous neuropsychological, EEG, TMS and neuroimaging researches (Ratcliff, 1979; Inoue et al., 1998; Harris et al., 2000; Harris and Miniussi, 2003). In detail, by looking at the qualitative nature of these errors we observed that the right parietal patients were specifically impaired in the processing of categorical spatial information. Indeed, they produced a significant number of *Pure Categorical* errors, which occur when one makes an error in the qualitative organization of space without any metric impairment. If a patient operates correctly metrically with respect to a landmark, say a corner, but chooses an incorrect neighbouring corner for the operation, this produces a *Dimension* error. The patient's performance is metrically correct, but categorically incorrect. One subset of such errors ($Q - d$) corresponds to rotating the square in the incorrect direction. The right parietal group made significantly more *Dimension* errors than the other four control patient groups combined. If a patient takes a reflection of the position of the target with respect to the horizontal, the vertical, or both axes of the square, this is a *Reflection* error. S/he places the mark in a complementary horizontal or vertical position in an incorrect quadrant, failing to take into account the categorical representation of the target. Right parietal patients also produced significantly more such errors than the other four patient groups combined. These results were confirmed by a subsequent simulation study, which showed that the proportion of categorical error responses were significantly greater than would be expected by random selection of locations in the square.

Moreover, we observed that unlike the patient control groups the right parietal patients showed a greater tendency to rotate the square in the wrong direction ($Q-$ errors). We believe that this behaviour reflects a deficit which is specifically qualitative in nature. One could argue that this significant frequency of $Q-$ errors might instead reflect lack of precision in applying the appropriate spatial transformations (angles). However, if this hypothesis holds true, then it would remain unexplained why in the right parietal group both the *Pure Metric* and the *Quadrant and Metric* error rates were not statistically different from those in patient control groups, or even from chance (Monte–Carlo simulation). In fact errors clustered in *categorically* important positions of the square.

One possible hypothesis is that the findings observed in the right parietal group might be explained in terms of neglect. In a study performed by Kerkhoff and Zoelch in 1998, it has been observed that when asked to orient an oblique line (‘‘target’’) to match a horizontal, vertical or 45° reference line, neglect patients with a right hemisphere lesion showed a significant anticlockwise tilt of the target. In the present study, signs of neglect on the Star Cancellation task (Wilson et al., 1987) were observed in three out of nine right parietal patients. All three were in the subset of five patients making the larger number of categorical errors. Of the other two patients in this subset, one obtained a perfect score on Star Cancellation and the other had a poor but not lateralized performance. However, with respect to our rotation task, it is not likely that the pattern of results shown by right parietal patients can be explained just in terms of an indirect effect of neglect. If neglect had had a major role, one would have predicted a sizable difference in performance according to the direction – clockwise (CL45°) versus anticlockwise (AC45°), of the required rotation. Following Kerkhoff and Zoelch (1998), neglect should induce a bias towards performing anticlockwise rotations, resulting in more frequent errors in those trials where the opposite rotation is required, i.e., the CL45° condition. The same prediction is derived by another possible scenario related to neglect: in the CL45° condition the thick side is in the left half of the tilted stimulus; failure to detect the thick side would induce random selection of rotation direction, with consequent $Q-$ errors being more frequent in this CL45° than in the AC45° condition. However, no such effect was found, with right parietal patients who make roughly comparable numbers of errors in the two conditions. Indeed, they made more errors than patient controls in rotating leftwards when presented with a CL45° stimulus, and rightwards when an AC45° stimulus was displayed. In other words, they had an increased tendency to rotate in the wrong direction, whichever direction was required on a trial. A possible partial role of neglect in the categorical errors remains a possibility.

Martin et al. (2008) have argued that both hemispheres are involved in coding both coordinate and categorical representations. In their CSC hypothesis both hemispheres are implicated in both types of spatial relation coding. They found some degree of hemispheric specialization, not related to the categorical/metric nature of the task, but to the processing load involved. Thus for instance, they found a right hemisphere advantage in the inferior parietal lobule and the angular gyrus. In many respects our evidence fits well with their findings: we also obtained greater involvement of the right parietal than the left parietal cortex in the task. However unlike in the work of Martin et al., we did not find any deficits in right parietal patients in carrying out metric operations *per se*. This dissociation – a categorical deficit without a metric deficit – is rather difficult to reconcile with the CSC hypothesis, which had explained Martin et al.'s findings well. This model assumes that categorical and metric relations differ on a complexity continuum, with metric encoding being generally more complex than categorical encoding. In this case, however, one would expect that a lesion would produce the complementary dissociation, with categorical relations being relatively spared. It is plausible that the difference between the results of the present study and those of Martin et al. arises from the different type of task used. Martin et al. used a working-memory task, in which rotation was not involved. In such a task, metric accuracy is likely to be more stressed than categorical accuracy, as no transformation is required. By

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contrast, our rotation task is more heavily loaded on categorical operations than on metric accuracy, both because of the need to rotate, and because the absolute metric error allowed was quite large (1.5 cm).

In summary, we agree with Martin et al. on the likely involvement of both hemispheres in both metric and categorical operations. However, the existence of an above-chance rate of error types such as *Reflection* and *Dimension* strongly suggests that the two types of operation can be separately impaired. Indeed in *Reflection* and *Dimension* errors, responses are very close to simple geometrical transformations of the correct position. Thus a gross categorical mistake and a fine metric analysis are *simultaneously* observed. Such a dissociation is even more convincing if other error types involving metric-based inaccuracies do *not* occur at above-chance levels. This profile was previously reported in an individual case study of Bricolo et al. (2000) and is also the case for the right parietal group in the current study.

How might such errors be explained? A typical analogue rotation process (à la Shepard & Meltzer) would predict very different error patterns from the ones we observed. It should be noted that our task, while corresponding to operations often made in the daily life, is very different from the tasks standardly used in ''mental rotation'' experiments. Indeed, it allows another strategy in addition to the analogue rotation procedure. Suppose that the spatial analysis of the figure is carried out in two main steps, (i) *categorical* operations are carried out to relate parts of the figure to an object-centred reference frame – known to be important, for instance, in neglect (Behrmann and Moscovitch, 1994; Driver, 1998; Humphreys et al., 1996; Humphreys and Riddoch, 1995), and subsequently (ii) *metric* operations are carried out with respect to crucial parts of the figure. It would then follow that our task allows subjects the much easier possibility of *not* actually carrying out an analogue rotation operation. Instead, the subject might store the categorical and metric encodings from the first square, and reproduce them on the second square. This would only be possible if subjects could categorically organize the figure in terms of an object-centred reference frame. The gross spatial agnosia shown clinically by many right parietal patients (e.g., Warrington, 1969) suggests that this may not be possible in some patients of this group. In this case *Reflection* and *Dimension* errors would correspond to a failure of one of the categorical operations stages of the process.

More specifically, we suggest that poor performance in our mental rotation task could be explained by an impairment of one or more steps of the following procedure:

1. Implement a correct object-centred reference frame on the first (tilted) square.
2. Carry out a categorical encoding of the position of the dot.
3. Carry out a metric encoding of the position of the dot.
4. (Following presentation of the upright empty square), retrieve the object-centred reference frame.
5. Retrieve the appropriate categorical representation.
6. Retrieve the metric representation.

Our proposal is that a lesion of the right parietal cortex may disrupt the object-centred system of reference, the categorical spatial representation of the target, or both. The account is motivated by the need to explain the qualitative impairments we observed in our clinical population. New investigations would be needed to test whether other predictions of the model are correct.

4.2. *Left prefrontal group*

A second group of patients was impaired in the performance of our mental rotation task, namely the left prefrontal group. More detailed determination of the anatomical locus involved was limited by characteristics of our patient series, namely a lack of patients with tumours involving the more superior parts of prefrontal cortex.

The left prefrontal group had a different type of mental transformation deficit with respect to right parietal patients. They produced a significant increase in the number of metrically incorrect responses both in the correct and in the incorrect quadrants. This finding is in agreement with the study of Martin et al. (2008), who found a strong recruitment of the attentional and executive processes, especially when metric coding was required. In addition, with respect to the other four groups combined the left prefrontal group was the only one to produce a relatively large number of errors where rotation was too far in the correct direction (Q+). They also made a similar number of errors of rotation in the wrong direction (Q−). The specific mental rotation impairment of the left prefrontal patients might be explained in different ways.

One possible explanation is that the deficits found in the left prefrontal patients are due to impairments in the short-term retention of spatial information. Indeed activity in the DLPFC has been often observed in both humans and primates in tasks which require the retention of spatial information for a limited period of time (Wilson et al., 1993; Courtney et al., 1996, 1998; Owen et al., 1996; Levy and Goldman-Rakic, 2000; Wager and Smith, 2003). However, lesions to the right prefrontal cortex impair spatial working memory more than ones to the left (Bor et al., 2006), so this makes this account less plausible for a specifically left prefrontal deficit.

A second account would be in terms of a difficulty in producing the appropriate amplitude for the motion response. Desmurget et al. (2004) presented results that are clearly supportive of a role of the basal ganglia in advance planning of movement extent. Patients with Parkinson disease were found to be selectively impaired in using advance information about movement amplitude. Moreover, in a subsequent PET experiment increased neural activation in the rostral and caudal portions of the bilateral putamen was specifically observed in a task requiring amplitude planning. The results found for some of the patients placed in our left prefrontal group would fit well with damage or a disconnection of the putamen (three patients), but this would be a less satisfactory account for patients with a more specifically prefrontal damage. Moreover, a hypothetical amplitude planning deficit could well affect the baseline condition too (0°, no rotation); however our left prefrontal group was not specifically impaired in such a condition.

One related question is why no sign of any such impairment was found in the *right* prefrontal group. As reported in the overall error analysis, the performance of the right

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prefrontal patients was not statistically different from that observed for the other groups combined. The absence of effects cannot be a problem of lack of statistical power. Indeed the sample size was similar for right prefrontal ($N = 12$) and left prefrontal ($N = 14$) groups and the difference in the overall number of errors was sizeable and significant (averaging at, respectively, 5.7 and 11 out of 33; Mann–Whitney $p = .041$).

It might be suggested that the greater impairment observed in the left as compared to the right prefrontal patients simply reflects their using of the right hand. This possibility cannot be ruled out. However, if a lateralized hand effect was contributing to the results, then one would expect greater impairments in the left premotor group, which was not found.

As a third possible explanation, we suggest that the pattern of performance found in the left prefrontal group arises from a set of processes related to acquiring action operations. This are the so called *task-setting* operations (Stuss et al., 1995; Alexander et al., 2005; Shallice et al., 2008a, 2008b) specifically impaired in left prefrontal lesions. Task setting is the collective name for the processes involved in going from a novel set of operations when the subject is initially faced by a new task to their smooth well-learned execution after repeated practice. A left prefrontal lesion would be expected to increase error rates early in task performance because of impairments in task setting. In our study the task was very short requiring only 5 min to be completed. Thus the errors occurred before the task was over-learned. We propose that the failure on the task of the left prefrontal patients arises because they do not acquire the specific categorical and metric operations listed in the section above [“Right Parietal group” (the six-step procedure)]; instead they would fall back on a rough rotation operation, with little control over its correct angular size, failing to carry out a proper metric or a categorical encoding. This hypothesis would explain the specific pattern of performance of the left prefrontal patients and in particular the relatively large number of *Quadrant* errors in the same direction as that of the rotation required (Q+ errors), and the high incidence of metric errors.

5. Conclusions

Although several studies suggest a hemispherical lateralization of the categorical representations to the left hemisphere, our study does not support this hypothesis. In accordance with previous single-case neuropsychological investigations (Bricolo et al., 2000; Toraldo and Shallice, 2004), we found that patients with right and not left parietal cortex lesions had problems which we interpreted as involving categorical spatial processing. In our task we required patients to remember the position of a dot with respect to an upright or a tilted frame of reference and physically to reproduce it inside a subsequent identical upright reference frame. It is likely that the patients did not use a matching strategy (mentally rotate the image until it is aligned, as used in the classical mental rotation task of Shepard and Metzler, 1971). Moreover, the use of an analogue process to mentally rotate the frame would not completely explain our results. If an analogue process had been used to solve the task, one could not explain why in the right parietal group the errors were mainly clustered in some categories (*Reflections* and *Dimension* errors) and not broadly distributed. Conversely, we propose that participants could simply use object-centred and categorical spatial representations of the dot in relation to the spatial reference frame and could perform the rotation in a step-like manner. A failure to implement the object-centred representation or to encode the categorical features could therefore have been responsible for the deficits we observed in the right parietal group.

On the other hand, with respect to the left prefrontal group, we found a broader mental transformation deficit, which resulted in a significant number of metrically incorrect responses in both the correct and the incorrect quadrants. This finding is in agreement with the study of Martin et al. (2008), who observed a strong recruitment of the attentional and executive process, especially when a coordinate coding was required. We currently favour the task setting hypothesis according to which left prefrontal patients would have a difficulty in acquiring the specific program necessary to organize the sequence of operations required to carry out the task. However, we consider such an interpretation as provisional and further investigation is needed in this respect. The critical point however is that lesions to the right parietal and the left prefrontal cortex both impair the carrying out of rotation operations in this situation, but they do so in qualitatively very different ways.

Acknowledgements

We are grateful to the medical and nursing staff of the Neurosurgery Department (Azienda Ospedaliera Universitaria, Udine) and to Alessio Isaja for their help. This research was supported by a grant from MIUR (Ministero dell’Istruzione, dell’Universita’ e della Ricerca) to TS.

We would like to thank the two referees for their helpful comments on an earlier version of the paper.

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Please cite this article in press as: Buiatti T, et al., Two qualitatively different impairments in making rotation operations, Cortex (2009), doi:10.1016/j.cortex.2009.10.006