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Cingulate neglect in humans: Disruption of contralesional reward learning in right brain damage

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ABSTRACT

Motivational valence plays a key role in orienting spatial attention. Nonetheless, clinical documentation and understanding of motivationally based deficits of spatial orienting in the human is limited. Here in a series of one group-study and two single-case studies, we have examined right brain damaged patients (RBD) with and without left spatial neglect in a spatial reward-learning task, in which the motivational valence of the left contralesional and the right ipsilesional space was contrasted. In each trial two visual boxes were presented, one to the left and one to the right of central fixation. In one session monetary rewards were released more frequently in the box on the left side (75% of trials) whereas in another session they were released more frequently on the right side. In each trial patients were required to: 1) point to each one of the two boxes; 2) choose one of the boxes for obtaining monetary reward; 3) report explicitly the position of reward and whether this position matched or not the original choice. Despite defective spontaneous allocation of attention toward the contralesional space, RBD patients with left spatial neglect showed preserved contralesional reward learning, i.e., comparable to ipsilesional learning and to reward learning displayed by patients without neglect. A notable exception in the group of neglect patients was L.R., who showed no sign of contralesional reward learning in a series of 120 consecutive trials despite being able of reaching learning criterion in only 20 trials in the ipsilesional space. L.R. suffered a cortical-subcortical brain damage affecting the

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anterior components of the parietal-frontal attentional network and, compared with all other neglect and non-neglect patients, had additional lesion involvement of the medial anterior cingulate cortex (ACC) and of the adjacent sectors of the corpus callosum. In contrast to his lateralized motivational learning deficit, L.R. had no lateral bias in the early phases of attentional processing as he suffered no contralesional visual or auditory extinction on double simultaneous tachistoscopic and dichotic stimulation and detected, with no exception, single contralesional visual and auditory stimuli. In a separate study, we were able to compare L.R. with another RBD patient, G.P., who had a selective lesion in the right ACC, in the adjacent callosal connections and the medial-basal prefrontal cortex. G.P. had no contralesional neglect and displayed normal reward learning both in the left and right side of space. These findings show that contralesional reward learning is generally preserved in RBD patients with left spatial neglect and that this can be exploited in rehabilitation protocols. Contralesional reward learning is severely disrupted in neglect patients when an additional lesion of the ACC is present: however, as demonstrated by the comparison between L.R. and G.P. cases, selective unilateral lesion of the right ACC does not produce motivational neglect for the contralesional space.

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1. Introduction

Assigning motivational valence to sensory stimuli and to their spatial location in the environment has a key-role in guiding the distribution of attentional resources. As originally emphasised by Mesulam (1981; 1999), a major function of any attentional system is in fact that of focussing attention on locations that "harbour expected events of motivational salience". The ability to process motivational-reward signals and to associate these signals to sensory stimuli and motor actions is based on a network of cortical and subcortical structures. Dopaminergic neurons in the ventral tegmental area (VTA), in the ventral striatum (i.e., nucleus accumbens) and neurons in the ventral medial prefrontal cortex show typical patterns of discharge in response to rewards (Bromberg-Martin, Matsumoto, & Hikosaka, 2010; Matsumoto & Hikosaka, 2009; Montague, Dayan, & Sejnowski, 1996; Platt & Huettel, 2008; Satoh, Nakai, Sato, & Kimura, 2003; Schultz, Dayan, & Montague, 1997). These neurons increase their discharge in response to unpredicted rewards, hold their rate of discharge steady in response to expected rewards and show reduced discharge when no reward occurs. Through their efferent connections, these neuronal populations modulate the activity of neurons with spatially selective responses in sensory (Superior Colliculus; Ikeda & Hikosaka, 2003; V1: Shuler & Bear, 2006), attentional (Parietal cortex: Platt & Glimcher, 1999), pre-motor and motor structures (Frontal eye field, Prefrontal Cortex and Caudate Nuclei: Ding & Hikosaka, 2006; Kobayashi, Lauwereyns, Koizumi, Sakagami, & Hikosaka, 2002, Kobayashi et al.,2007; Roesch & Olson, 2003) and send reward signals to higher-order structures implicated in action-planning and executive control (Rushworth & Behrens, 2008; Silvetti, Alexander, Verguts, & Brown, 2013; Silvetti, Seurinck, & Verguts, 2011). This allows a large-scale integration between motivational inputs and the neural representation of space and action. Motivational signals can have both a direct impact on sensory processing and provide the information that is necessary to keep track of reward history and to establish appropriate strategies in the exploitation of rewards as a function of their value and probability of occurrence in space and time (Della Libera & Chelazzi, 2006; 2009; Hickey, Chelazzi, & Theeuwes, 2010). These two different modalities of "sensory based" and "strategically biased" reward processing might correspond, respectively, to early and late phylogenetically developed mechanisms of cognitive control operating in parallel (Hickey et al., 2010).

Several lines of evidence point out that the medial Anterior Cingulate Cortex (ACC) has a pivotal role in reinforcement learning (Rushworth & Behrens, 2008; Silvetti, Alexander, Verguts & Brown, 2013; Silvetti, Seurinck, et al., 2011). Neurons in the ACC are sensitive to the association between expected rewards and sensory cues or motor actions. Importantly, the ACC is also endowed with populations of neurons that respond to mismatches between expected and actual rewards, thus encoding errors in reward prediction. Altogether, the functional and computational activity of the ACC has a key role in the discovery, exploitation and updating of rewards distribution in the environment (Jessup, Busemeyer, & Brown, 2010; Silvetti, Seurinck, et al., 2011). Thanks to its anatomical connectivity, the ACC is ideally suited to play this function. The ACC receives dopaminergic reward-related inputs from the midbrain and has direct cortico-cortical connections with prefrontal, parietal and temporal areas participating in the control of spatial attention (Morecraft, Geula, & Mesulam, 1993; Morecraft et al., 2012). The ACC also conveys important efferent signals to the noradrenergic Locus Coeruleus (LC) complex in the midbrain (Aston-Jones & Cohen, 2005). The LC, in turn, has efferent projections to the inferior parietal and the caudal superior temporal area, thus providing a supplemental indirect pathway for the transmission of ACC signals to cortical sites involved in attentional control (Aston-Jones & Cohen, 2005). Noradrenergic signals from the LC help resetting attentional priorities when an established associative rule between

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Table 1 – Study 1. Clinical and demographic data of patients with (N +: cases 1–8) and without (N–: cases 9–14) left spatial neglect.

Case	Age (y)	Sex	Stroke onset (days)	Line bisection (length: 200 mm)	Line cancellation		Letter cancellation		Wundt–Jastrow illusion	
					Left	Right	Left	Right	Left	Right
1 (L.R.)	60	M	45	15.8	0	8	0	10	19	0
2	66	M	90	20.6	0	7	0	29	6	0
3	51	F	75	11.6	11	10	28	48	3	0
4	55	M	60	0	11	10	0	31	10	18
5	70	M	52	0	11	10	17	49	10	1
6	71	M	76	16	11	10	23	41	0	0
7	60	M	59	7.6	10	10	52	51	2	0
8	40	F	90	n.a.	1	10	23	42	n.a.	n.a.
9	64	M	64	–4	11	9	53	51	0	0
10	57	M	88	–5	11	10	53	51	0	0
11	67	F	60	–5	11	10	52	51	0	0
12	67	M	99	1	11	10	41	51	1	0
13	54	M	88	–2	11	10	49	49	2	0
14	50	F	70	–5	11	10	53	51	0	0

reward and sensory stimuli or motor actions is no longer valuable and new associations must be explored (Aston-Jones & Cohen, 2005; Bouret & Sara, 2005). In summary, the ACC constitutes a limbic–cortical interface allowing the modulation of attentional and motor behaviour by motivational-hedonistic inputs.

A few evidences have recently suggested that improved motivation can ameliorate spatial search in right brain damaged patients affected by attentional neglect for the contralesional left side of space. Mesulam (1985) first reported the observation of one patient with severe left side neglect who showed a marked improvement in detecting targets on the left side of a letter cancellation task when he was promised with a reward of one penny for the detection of each target. Some years later, Ishiai et al. (1990) showed that neglect patient engaged in a line cancellation task improved their performance when they were requested to number rather than crossing-out lines, just as if the need to use consecutive and increasing numbers motivated patients to look for additional lines in the contralesional space. More recently, Malhotra, Soto, Li, and Russell (2013) first formally tested the original anecdotal observation reported by Mesulam (1985). Studying a group of ten neglect patients, these authors showed that promising a small monetary reward for each target found, improved the performance in a multiple item cancellation task as compared with an equivalent no-reward condition. Patients showing the lowest effects of monetary incentive had lesion centred in the right striatum.

Notwithstanding these encouraging clinical reports and the well-established knowledge on ACC functions, no study has systematically investigated whether RBD patients with spatial neglect can explicitly learn and exploit the release of rewards in the contralesional left hemispace and, eventually, to which degree contralesional reward learning is resistant to the competitive release of rewards in the ipsilesional right hemispace. Most important, it entirely remains to be established whether in humans, selective unilateral lesions of the ACC engender contralesional reward-learning deficits, i.e., motivational neglect, or whether such a disturbance arises from the combined unilateral lesion of the ACC and the adjacent parietal-frontal attentional areas that are most frequently damaged in neglect patients. Adding these pieces of knowledge to the rich literature on the neglect syndrome seems important, because ascertaining spared contralesional reward learning in neglect patients might lead to the adoption of reward-learning based rehabilitation strategies and the improvement of currently adopted rehabilitation protocols.

Here, in a series of one group- and two single-case studies, we addressed these issues using a simple reward-learning task that allows manipulating and contrasting the motivational valence of the left and the right hemispace. More specifically, in separate blocks of trials the higher motivational valence of the left hemispace was contrasted with the lower

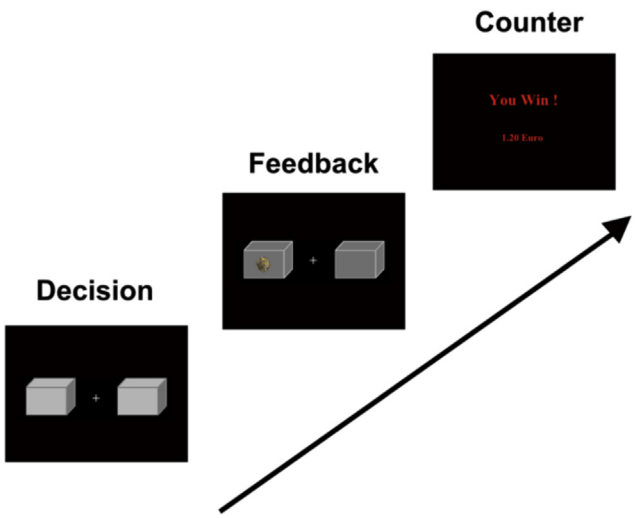

Fig. 1 – Study 1. Time course of events during trials of the Reward Learning task. On each trial patients were asked to make a choice between two horizontally arranged boxes to guess which one contained 5 Euro cents. A feedback was displayed indicating whether their choice was successful. Finally, a counter showed the amount of money won. These feedbacks were also provided verbally by the examiner.

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motivational valence of the right hemispace and vice versa. The results of our investigations demonstrate that RBD patients with spatial neglect can adequately appreciate and exploit the prevalent release of rewards in the contralesional space: this, however, with the notable exception of one patient who, compared to all other patients, suffered an additional lesion in the ACC and in the adjacent callosal connections.

2. Study 1: Reward learning in RBD with and without left spatial neglect

2.1. Material and methods

2.1.1. Participants

We tested a sample of 14 patients with right brain damage (3 females and 11 males; mean age 60.8 SD 7.1, range 51–71 years). They were admitted for physical and neuropsychological rehabilitation at the Santa Lucia Foundation IRCCS in Rome. At the time of clinical and experimental evaluation all patients were free from confusion and from temporal and spatial disorientation. They gave written informed consent to participate in the study, which was previously approved by the local ethical committee. Clinical and demographic data of patients are detailed in Table 1.

Left unilateral neglect was assessed with the line bisection task (5 trials, line length 200 mm) and with two tests of visual-motor exploration: the letter cancellation task (Diller et al., 1974) and the line cancellation task (Albert et al., 1973). For the line bisection task, the cut-off was taken from normative data collected in a sample of 206 patients with right brain damage (Azouvi et al. 2002); cut-off = 6.5 mm deviation from the actual midpoint. The cut-off for neglect in the line cancellation task is 2 or more omissions on the left and in the letter cancellation task a difference of 4 or more omissions between the left and the right side of the sheet (Pizzamiglio, Judica, Razzano, & Zoccolotti, 1989). We also administered the Wundt-Jastrow area illusion test (Massironi, Antonucci, Pizzamiglio, Vitale, & Zoccolotti, 1988), a modified version of the Wundt-Jastrow area illusion that requires a perceptual judgment: a difference ≥ 2 between unexpected responses (i.e., responses in the direction opposite to the illusory effect in normal participants) given for left oriented minus right oriented stimuli is considered the cut-off score for neglect. Pathological performance on two out of four tests was considered indicative of contralesional spatial neglect. Patient 8 only performed the line cancellation task and the letter cancellation task. As can be seen in Table 1, eight patients showed a pathological performance in at least two neglect tests (Group N+: cases 1–8) whereas the remaining six patients had normal performance in all tests (Group N−: cases 9–14).

2.1.2. Reward learning task

Patients performed a simple decision-making task (see Fig. 1). In each trial, they were asked to make a forced choice between two boxes, arranged horizontally one to the left and one to the right of a central reference (i.e., a small cross, size 1.1° × 1.1°). In each trial, patients were asked to "guess" which one of the two boxes contained a 5 cent Euro coin with the aim of collecting as many coins as possible. In two different blocks of trials, the monetary reward was more frequently associated (75%) with the choice of the left box ("reward-left" block) or the right box ("reward-right" block). All participants performed the "reward-left" and "reward-right" blocks of trials in two different experimental sessions separated by a two-day interval. The block order was counterbalanced across participants. In order to counteract any spurious influence on performance due to block order administration or delayed reward learning, in each block patients were allowed to perform a long series of 120 trials.

Stimuli were projected onto a wall-screen by means of a digital projector "BenQ PB6240". Patients were placed at a distance of about 1 m from the wall. Stimulus presentation, response recording and on line control of reward learning rate were performed using "E-Prime programming software" (Psychology Software Tools, Inc., www.pstnet.com). Trial events were as follows. At the beginning of each trial the two boxes were presented. The size of each box was 10.9° × 6.8° and the centre of each box was at 13.1° from the centre of the screen. The examiner first asked the patient to indicate each box with his/her right index. Then, the patient was asked to choose one of them by pointing in order to obtain the monetary reward. Following the choice, the examiner pressed a button to show which one of the two boxes contained the coin. The patient was then asked to point manually and report verbally the spatial position of the box that had been rewarded and state whether this had matched the initial choice or not. Following the response, the examiner pressed a button to display a prompt reminding the patient whether the choice was successful or not (Positive feedback: "You won 5 cents"; Negative feedback: "You didn't win") together with a counter showing the amount of money won so far. The examiner also communicated this information verbally. The software-program calculated on line the percentage of correct choices in a sliding window of 12 trials (i.e., percentage within trials 1–12, 2–13, 3–14 etc.). The patient was considered having reached the learning-criterion when his/her choices were correct on 75% of trials (9 times out of 12). At this point, the program automatically interrupted the administration of trials and patients were given the amount of money gained through task performance.

2.1.3. Anatomical correlates

Patients underwent radiological 1.5-T MRI examination, including T1, T2 and fluid attenuated inversion recovery. Radiological examination was run within 10 days from the time of neuropsychological testing. The standard MRI axial slice thickness was 6 mm (inter-slice gap: 1 mm). For optimal identification of damaged areas, we used T1-weighted images. Inter-slice registration was performed according to slice thickness and inter-slices gap measures. Each of the reconstructed MRI brain volumes was registered into the normalised stereotaxic space, using a nine-parameters linear brain volume registration (Collins et al., 1994) based on 27 T1 weighted MRI scans of the same healthy subject (Colin_brain; guaranteed by BIC, MNI, Quebec, Canada). T1 weighted images magnetisation prepared rapid gradient echo (Erlangen, Germany; 1 mm isotropic voxel, repetition time 11.4 msec, echo

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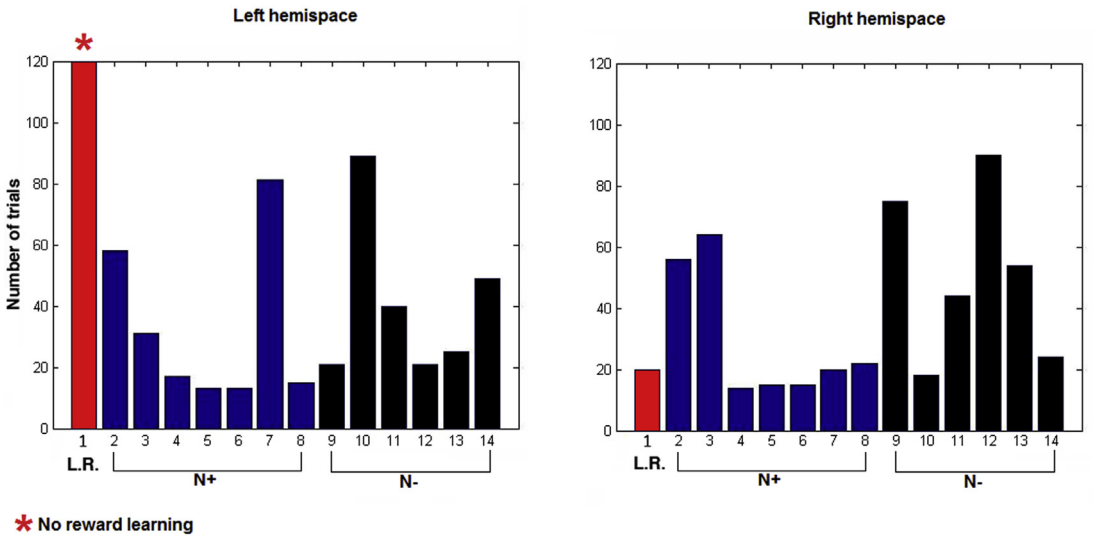

Fig. 2 – Study 1. Number of trials needed to reach the criterion (75%) showed by each patient in the left and the right hemispace. L.R. (Case 1 in Table 1) showed no reward-learning on the left side and a normal reward-learning on the right side.

time 4.4 msec, flip angle = 15°) were also obtained for case L.R. and M.C. (see below section 5, Study 3) using a Siemens 1.5 Tesla Vision Magnetom MR system. Mapping of lesions was performed manually on the re-oriented brain volume MRI transformed into MNI standardized stereotaxic coordinate system using DISPLAY (http://packages.bic.mni.mcgill.ca).

Average lesion probability maps were computed for the N+ and N− groups separately. The probability map of the N− group was subtracted from the probability map of the N+ group. Only areas that after subtraction were damaged at least 50% more often in N+ than N− were considered for descriptive purposes. Areas showing the highest percentage of lesion overlap after subtraction were also individuated and the statistical significance of their higher involvement in N+ patients was assessed using Fisher exact test.

3. Results

3.1. *Reward learning*

On average, N+ patients took 44 trials (SD 39.6) to reach learning criterion when the left box was more frequently rewarded (reward-left) and 28 trials (SD: 19.9) when the right box was more frequently rewarded (reward-right). These learning rates were equivalent [$F(1,7) = 1$, $p = .35$; $\eta^2 = .13$]. N− patients took 40.8 trials (SD: 26.1) to reach criterion in the reward-left block and 55.1 trials in the reward-right block (SD 36.2). These learning rates were equivalent [$F(1,5) = .35$, $p = .57$; $\eta^2 = .06$]. A group (N+, N−) × Side of reward (left box, right box) Anova, showed no significant main effect [Group: $F(1,12) = 1.3$, $p = .26$, $\eta^2 = .10$; Side: $F(1,12) = .001$, $p = .97$] or Group × Side of reward interaction [$F(1,12) = 1.1$, $p = .3$; $\eta^2 = .10$]. No difference in the number of trials performed to reach criterion in the reward-left and reward-right conditions was found when data from the two groups of patients were combined in a single group [$F(1,13) = .2$, $p = .78$]. Finally, in order to check whether the order of block administration, i.e., reward-left first versus reward-right first, had an influence on performance, we run a Group (N+, N−) × Block-Side Order (First Left, First Right) × Block (First, Second) ANOVA: no main effect or interaction was significant (all $F < 1$).

It is important to note that all these results were replicated when the reciprocal transformation of data (Sheskin, 2003) was used to correct for the non-normal distribution of data in the N+ group for the reward-right condition (*Kolmogorov–Smirnov test* (8) = .373, $p = .002$). In summary, these results suggest that reward learning was comparable between N+ and N− and between the two sides of space (see Fig. 2).

Inspection of individual data revealed the presence of one patient (case L.R., see Fig. 2) who showed no contralesional reward learning in the entire series of 120 trials while showing very good ipsilesional reward learning, where criterion was attained in only 20 trials.

3.2. *Anatomical correlates*

Subtraction of the lesion probability map of N− patients from the lesion probability map of N+ patients (see Fig. 3) revealed two peaks of lesion overlap in the group of N+ patients. One was located subcortically in the sector of the Superior Longitudinal Fasciculus (SLF) in the white matter underlying the middle frontal and the post-central gyrus (MNI-Talairach coordinates: 27, −7, 36; Catani and Thiebaut de Schotten, 2012). The other involved the rolandic operculum (MNI-Talairach coordinates: 54, −13, 11) and the inferior sectors of the post-central gyrus adjacent to the supramarginal gyrus (MNI-Talairach coordinates: 66, −8, 20). All these areas resulted to be involved by the lesion 86% more frequently in N+ than in N− patients. This higher involvement was statistically significant on Fischer exact test (Chi-Square = 7, $p < .01$; Fischer exact test, two tails, $p = .025$).

Inspection of individual data revealed that, compared to all other patients, the patient showing no contralesional reward

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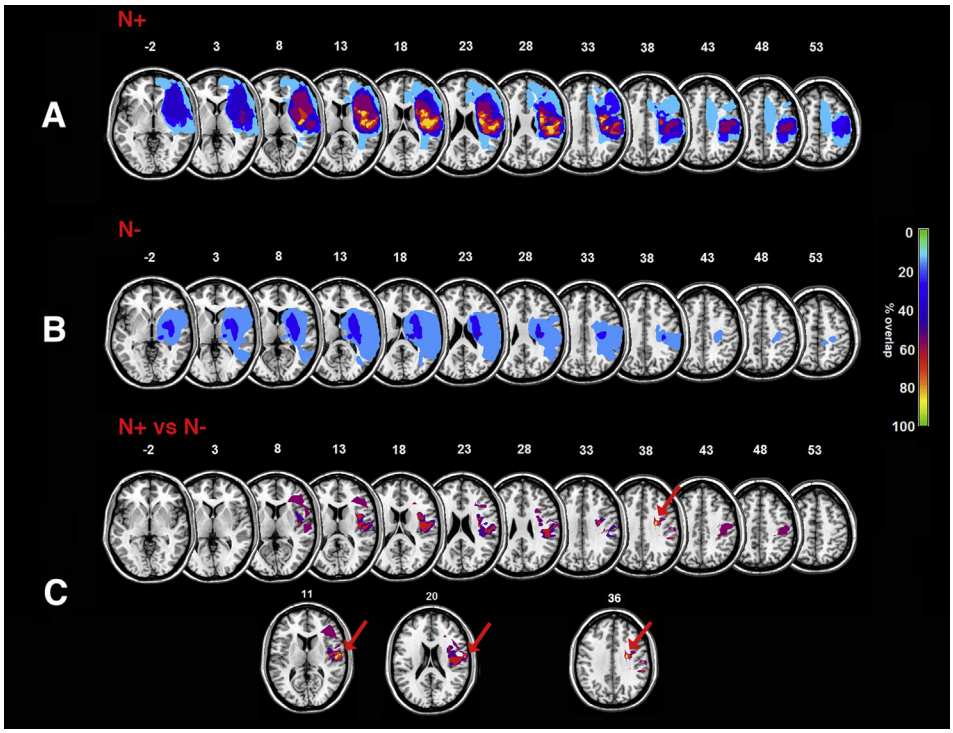

Fig. 3 – Study 1. Anatomical lesion mapping in the N+ and N− groups and results of N+ minus N− subtraction. Lesion overlap (%) is reported on transversal cuts (Z Talairach-MNI coordinates). (A) Probability map of lesion overlap in the N+ group. (B) Probability map of lesion overlap in the N− group. (C) Results of the subtraction of the probability map of the N− group from the probability map of the N+ group. Only areas that were damaged 50% more frequently in N+ than N− are reported in the figure. Red arrows point at peaks of lesion overlap that were observed after subtraction: 86% of lesion overlap was found in these peaks. One peak was located in the Superior Longitudinal (MNI-Talairach coordinates: 27, −7, 36) and another involved the rolandic operculum (MNI-Talairach coordinates: 54, −13, 11) and the inferior sectors of the post-central gyrus adjacent to the supramarginal gyrus (MNI-Talairach coordinates: 66, −8, 20).

learning, case L.R., had lesion involvement of the medial ACC and the adjacent callosal connections. Detailed anatomical comparison between L.R. and N+ and N− patients is reported below in study 2.

3.3. *Discussion*

The main result of this first study is that reward learning in the contralesional space is generally preserved in patients with left spatial neglect and comparable to that observed in patients without neglect. As it will be considered more in details in the general discussion, this finding might have important implications for strategies and exercises used in neuropsychological rehabilitation. The results of the anatomical group comparison, provided results that are in line with previous findings. Neglect was linked to cortical lesions in the inferior parietal and the adjacent opercular cortex (Doricchi & Tomaiuolo, 2003; Mort et al., 2003) and to lesions of parietal-frontal subcortical connections (SLF; Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007; Thiebaut de Schotten et al., 2005: Thiebaut de Schotten et al., 2014; Doricchi & Tomaiuolo, 2003). However, the most important finding of this first study comes from the detailed inspection of individual behavioural and anatomical data. This revealed the presence of one neglect patient (patient L.R.) who showed no reward-learning when rewards were preferentially released in the box on the left side of space whereas he only required 20 trials to reach the reward-learning criterion when rewards were preferentially released on the right side of space (see Fig. 2). In order to gain a finer insight on this contralesional reward learning deficit we explored in more details the clinical and anatomical profile of this patient in a separate study.

4. Study 2: L.R.: a case of severely impaired contralesional reward learning in spatial neglect

4.1. *Case study*

L.R. is a right-handed 60-year-old retired marshal, who suffered a cerebral ischaemia in August 2010. The investigation we report here took place 45 days after the ischaemic event. By that time, L.R. was well oriented in time and space, cooperative and well motivated despite his left hemiplegia and being easily fatigued. His speech was well organized and he was able to correctly report his clinical history. He also complained about hemiplegia and slowness in finding things. Object naming (score = 20/20; Spinnler & Tognoni, 1987), verbal-phonetic fluency (score = 22; Novelli et al., 1986) and verbal abstract-logical reasoning (score 50/60; Spinnler & Tognoni,

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1987) were normal whereas verbal-categorical fluency was slightly impaired (score 11; Novelli et al., 1986). His short-term verbal (WAIS digit span: raw score 4, corrected score = 3.75) and visual spatial memory abilities (Corsi span: raw score = 4, corrected score 3.75) were normal. His episodic memory abilities were also within the normal range (score: 12/28; Spinnler & Tognoni, 1987). L.R. suffered severe peripersonal left hemispatial neglect (Case 1, Table 1). In the line bisection task (line length 20 cm, 5 trials), he showed an average ipsilesional deviation of 15.8 mm from the objective line midpoint. In the letter cancellation task he marked only 10 targets placed on the rightmost side of the sheet and in the line cancellation task, he only marked 8 lines out of 10 on the right side of the sheet. In the Wundt-Jastrow Area Illusion test, when the elements were oriented leftward L.R. was sensitive to the illusion only on 4 over 20 trials whereas he was always influenced by the illusion when the elements were oriented rightward. Goldman's perimetry showed no visual field defects.

We compared L.R.'s demographic data and neglect scores with those of the N+ and N− groups using the program SINGLIMS.EXE (Crawford & Garthwaite, 2002; Crawford, Howell, & Garthwaite, 1998), which allows investigating whether an individual score is significantly different from the average score of a reference sample. This method uses a *"t-distribution"* rather than a standard normal distribution and it is reliable and particularly useful in case of small reference control samples. In all neglect tasks, the scores obtained by L.R. were not different from the average scores observed in the group of N+: line bisection task [t (1,6) = .71, $p > .05$], line cancellation task [t (1,6) = 1.37, $p > .05$], letter cancellation task [t (1,6) = −1.77, $p > .05$] and Wundt-Jastrow area illusion test [t (1,6) = .09 $p > .05$]. These findings show that neglect severity in L.R. was comparable to the average neglect severity in the group of N+ patients. L.R. (60 years) did not differ in age from both N+ [t (1,6) = .08, $p > .05$; mean = 59; SD = 11.22] and N− patients [t (1,5) = .04, $p > .05$; mean = 59.6; SD = 7.09]. Finally, time from stroke onset in P.G. was equivalent to that of N+ [t (1,6) = −1.57, $p > .05$; mean = 71.71; SD = 15.2] or N− patients [t (1,5) = −1.96, $p > .05$; mean = 78.17; SD = 15.65].

Notwithstanding left spatial neglect, on clinical examination L.R. showed no contralesional visual or auditory extinction on double simultaneous stimulation and perceived, with no exception, single contralesional stimuli. These findings suggested no lateral bias in the early phase of attentional processing. This was investigated in more depth using controlled tachistoscopic and dichotic stimulations.

4.1.1. *Visual extinction*

In each trial one or two small black squares (square size: 1° × 1°) were presented on a light grey background. Squares appeared at 6° from a central fixation cross (size: .5° × .5°). L.R. was placed 57.7 cm from the computer screen with the head on a chin rest and was asked to keep his eyes on central fixation. The examiner started each trial after controlling maintenance of central fixation by L.R. Sixty trials were administered: twenty with a single stimulus on the left of the fixation, twenty with a single stimulus on the right of the fixation and 20 bilateral stimuli. All stimuli lasted 200 msec. L.R. was asked to report the number and position of stimuli. L.R. reported with no error all single and double stimuli.

4.1.2. *Auditory extinction*

L.R. was asked to keep his eyes on a black fixation cross (size: .5 × .5 cm) against a white background. Shortly after, a brief

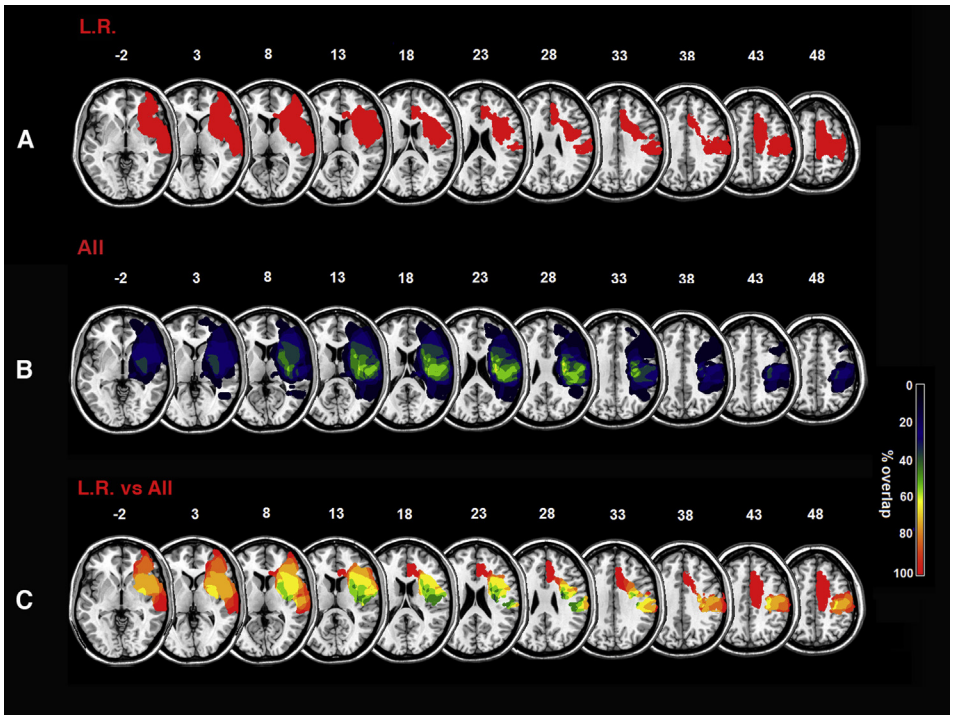

Fig. 4 − Study 2. (A) Lesion reconstruction in L.R. (B) Lesion overlay in N+ and N− (All) (C) Lesion subtraction between L.R. and the group of N+ and N− patients (All).

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beep (200 msec) was delivered through headphones (Sony Headphones, MDR-XD200). We administered a total of 60 trials: 20 to the right ear, 20 to the left ear and 20 bilaterally. As for the visual version of the task, the patient was asked to state the position and number of stimuli. L.R. reported with no error both single and double stimuli.

4.2. *Reward learning in L.R.: comparison with N+ and N− groups and reward learning between alternative positions presented within the contralesional or the ipsilesional space*

In order to get a quantitative analysis of L.R.'s reward learning abilities, we compared the number of trials required by L.R. to reach the learning criterion when the release of rewards was prevalent (i.e., 75% of trials) in the left or in the right side of space, to the number of trials required by the groups of N+ and N− RBD patients. These comparisons were run with the same methods used in the analyses of L.R.'s clinical-demographic data (Crawford & Garthwaite, 2002; Crawford et al., 1998). In the experimental design L.R. was originally assigned to the group of patients performing the reward-right block in the first session and the reward-left block in the second one. In the left side of space, L.R.'s performance, that was equivalent to the maximum number of trials allowed in the task, was significantly worse than that of N+ [t (1,6) = 2.38, p = .02] and N− [t (1,5) = 2.8, p = .018] patients. In the right side of space, L.R.'s performance was comparable to that of N+ [t (1,6) = −.43, p > .05; t (1,6) = .12, p > .05 using the reciprocal transform of data to normalize data distribution of N+ for the reward-right condition] and N− patients [t (1,6) = −.95, p > .05].

To investigate whether the contralesional reward learning deficit observed in L.R. was related to the processing of reward related information coming from the contralesional space or by the interfering-competitive release of infrequent rewards in the ipsilesional right side of space, we investigated reward-learning when rewards were released at two different positions that were both located within the left or the right side of space. Boxes were vertically arranged so that the centre of each box was positioned 13.1° above or below the horizontal line passing through the central fixation point. As in the reward task with "left versus right" choices, the horizontal distance between each box and central fixation was 13.1°. In each trial L.R. had to make an "upper versus lower" choice to get monetary reward. The task was administered in two sessions separated by a two-day interval. In the first session the two boxes were placed in the left side of space whereas in the second session they were placed in the right side of space. In each session, based on random choice, one of the two boxes was most frequently rewarded. L.R. was able to perform correctly both blocks of trials: he took on average 59 trials to reach learning criterion in the left side of space and 66 on the right side. Importantly his performance in the left side and right side of space was comparable to that observed in N+ [left side: t (1,6) = .66, p > .05; right side: t (1,6) = 1.63, p > .05 or t (1,6) = −1.17; p > .05 with reciprocal transform] and N− groups in the task with "left versus right" choices [left side: t (1,5) = .64, p > .05; right side: t (1,5) = .27, p > .05].

4.3. *Lesion analysis: comparisons with N+ and N− groups*

L.R.'s brain lesion was located in the areas irrigated by the right middle cerebral (MCA) and the right pericallosal (PeriCallA) artery areas. Damage in the MCA area involved the anterior temporal lobe with sparing of its ventral and posterior sectors, the inferior frontal gyrus and the most posterior part of the superior frontal gyrus. In the parietal lobe, the lesion affected the rostral part of the gyrus supramarginalis. The insula, capsula estrema, claustrum, capsula externa, caudate nucleus, putamen, globus pallidus, capsula interna were all partially affected by the lesion, while the nucleus accumbens was spared. Lesion in the PeriCallA area affected the anterior cingulum, the paracentral lobule up to the precentral gyrus and the anterior part of the corpus callosum. Subtractive comparisons with the entire group of N+ and N− patients considered in the study demonstrated that L.R. suffered selective additional lesion of the ACC and the adjacent callosal connections. Another small additional lesion was present in the anterior part of superior temporal sulcus (Fig. 4).

4.4. *White matter pathways in L.R.*

4.4.1. *Standard diffusion tensor tractography based reconstruction*

We further investigated lesion involvement of white matter pathways in L.R. We used a 3-T whole-body system (Siemens Allegra) to acquire 60 diffusion-weighted volume directions and height volumes with no diffusion gradient applied covering the whole head of the patient with an isotropic resolution of 2 mm^3. We employed a damped Richardson Lucy algorithm for spherical deconvolution (Dell'Acqua et al. 2010) to estimate multiple orientations in voxels containing different populations of crossing fibres (Alexander, 2006). Algorithm parameters were chosen as described before (Dell'Acqua et al., 2012). A fixed fibre response corresponding to a shape factor of $\alpha = 2 \times 10{-}3$ mm^2/s was chosen (Dell'Acqua et al., 2009). Tractography dissection of the SLF I, II and III was performed using a multiple ROIs approach as previously described in Thiebaut de Schotten et al. (2011).

4.4.2. *Tractography results*

Dissection of white matter tracts (Fig. 5) showed that within the SLF, the second (SLF II) and third (SLF III) branch were both relatively spared. In contrast, the dorsal-medial first branch of the SLF (SLF I), which allows connections among the SMA, the PreSMA, the ACC and the superior parietal lobule, was largely damaged. Relative sparing of SLF II and III, which are most frequently damaged in spatial neglect (Bartolomeo et al., 2007; Thiebaut de Schotten et al., 2005, 2014; Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008; Doricchi & Tomaiuolo, 2003), is compatible with absence of lateral biases in the early phases of attentional processing documented by testing with single and double visual (see 4.1.1.) and acoustic (4.1.2.) stimulation.

4.4.3. *Discussion*

The results obtained in study 2, demonstrate that L.R. is able to assign and exploit motivational value to stimuli in the

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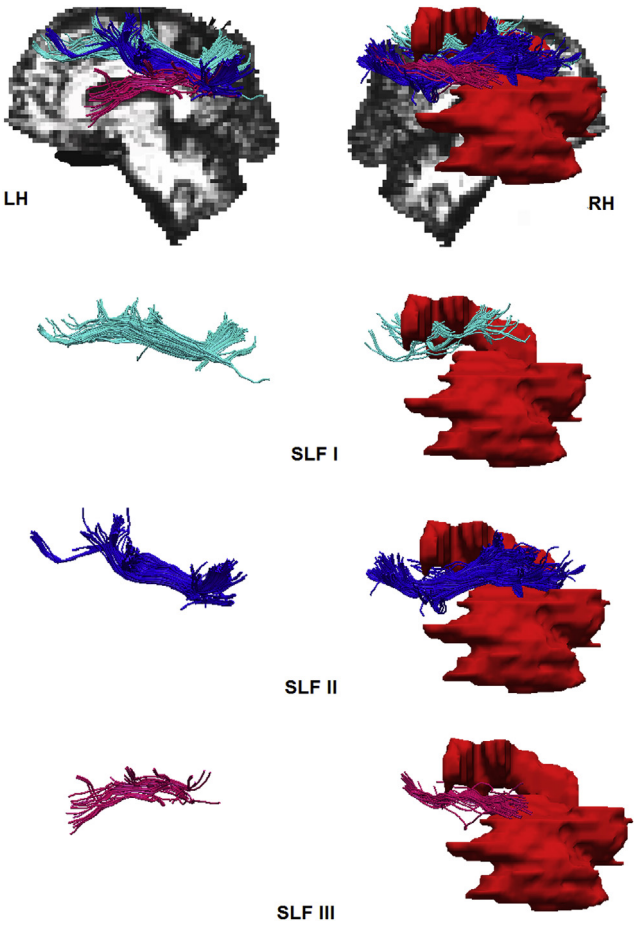

Fig. 5 – Study 2. DTI reconstruction of the three branches of the Superior Longitudinal Fasciculus (SLF) in the left and right hemisphere in L.R. The reconstructed lesion volume in the right hemisphere is depicted in red.

contralesional space as long as competitive rewards are not released in the ipsilesional space. These findings seem to point out that the contralesional reward learning deficit encountered by L.R., is related to a specific impairment in creating a motivational map for contralesional space when competing, though infrequent, rewards are released in the ipsilesional space. These findings together with the absence of contralesional extinction on double simultaneous stimulation and the perfect ability of detecting single visual and acoustic stimuli in the contralesional space point out that impaired contralesional reward learning cannot be attributed to a pathological ipsilesional bias in attentional processing. This point will be further considered in the general discussion section.

5. Study 3: Comparison of L.R. Case with that of a patient, G.P., suffering a selective lesion of the right ACC and the right medial orbitofrontal cortex

After the completion of study 1 and 2, we had the opportunity to compare the case of L.R. with the case of G.P., a patient suffering a selective lesion of the medial ACC and the adjacent callosal connections and no lesion involvement of the lateral cortical-subcortical structures that were damaged in L.R.

5.1. *Case study*

G.P. is a 50-year-old, right-handed woman with high school qualifications, employed in the National Social Security Institute. In October 2011, she suffered an ischemic stroke in the cerebral territory supplied by the right anterior cerebral artery. At that time, she was alert, oriented and cooperative. The neurological examination revealed left limb spastic paresis, which affected her leg, arm and, only mildly, her hand. Visual field and voluntary ocular motility were intact. Visual-object and visual-spatial perception were normal. G.P. did not exhibit disorders of short-term verbal (Digit span raw score = 6) and visual short-term memory (Corsi span raw score = 3.8). Long-term memory abilities were also preserved (Verbal Rey's list: immediate recall score 44.79, delayed recall score 6.08; Rey's complex figure: immediate recall score 31, delayed recall score 19.7). Abstract reasoning was normal (Raven progressive matrices score 26.8). Executive functions and phonological verbal fluency were normal. G.P. showed no omission both in the line (Albert et al., 1973) the letter cancellation task (Diller et al., 1974) for the screening of contralesional neglect. She also had normal performance in the Trail Making test (Reitan, 1958).

5.2. *Reward learning*

G.P. performed the reward learning task with left versus right choices (see section 2.1.2). Blocks were administered in the same order as in L.R. case. G.P. took 18 trials to reach the learning criterion for the "reward-left" block and 27 for the "reward-right" block. Her performance was comparable to that observed in the group of N+ and N− patients examined in Study 1 [G.P. *vs* N+: left side $t(1,6) = -.49$, $p > .05$, right side $t(1,6) = -.49$, $p > .05$ or $t(1,6) = -.4$; $p > .05$ using the reciprocal transform; G.P. *vs* N−: left side $t(1,5) = -.48$, $p > .05$, right side $t(1,5) = -.71$, $p > .05$].

5.3. *Anatomical comparison with L.R. case*

G.P. brain damage is related to a vascular lesion in the area of the right pericallosal cerebral artery. The damage involves the central and anterior sectors of the superior frontal gyrus, the medial cingulate cortex with sparing of the paracentral lobule and the posterior cingulate cortex (PCC). The central and anterior sectors of the corpus callosum are also entirely damaged whereas the splenium and part of the anterior genu are spared. Sub-cortically, the damage includes the nucleus accumbens and the head of the caudate nucleus.

Subtractive comparison between L.R. and G.P. (Fig. 6) shows that the ACC and the adjacent callosal connections were damaged in both patients. Patient G.P. showed a lesion involvement of the medial orbitofrontal cortex whereas in L.R. the lateral sectors of the orbitofrontal cortex were damaged together with the lateral-ventral sectors of the frontal, temporal and parietal lobe irrorated by the MCA. Subcortically, both patients have lesion of the caudate nucleus, although the head of the caudate was preferentially involved in G.P., while

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in L.R. the lesion was more extended. L.R. had lesion in the putamen whereas G.P. had lesion in the nucleus accumbens. Although the putamen plays a role in the processing of reward and in keeping track of reward-history (see Muranishi et al., 2011), the reward learning deficit suffered by L.R. seems not ascribable to his putaminergic lesion, as the anatomical comparisons run in study 2 showed that putaminergic lesions were also present N+ and N− patients with preserved contralesional reward learning.

5.4. *Discussion*

The clinical and anatomical comparison between L.R. and G.P. cases suggests that unilateral selective lesion of the medial ACC and the medial orbitofrontal cortex does not lead to contralesional reward learning deficit. On the contrary, this deficit seem to be present when, as in the case of L.R., a unilateral lesion of the ACC is combined with a lesion of more lateral cortical and subcortical structures involved in space representation and in the orienting of spatial attention.

6. General discussion

In the first study of the present series of investigations, we have administered to one group of RBD patients with contralesional left spatial neglect (N+) and one group of RBD patient without neglect (N−), a simple reward-learning task in which two different behavioural conditions were contrasted. In one condition rewards were prevalently (i.e., 75% of trials) released in the left-contralesional side of space and rarely released (i.e., 25% of trials) in the ipsilesional space, whereas in the remaining condition the spatial distribution of rewards was reversed. We have found that despite their deficit in the spontaneous allocation of attention towards the left side of space, N+ have preserved cued-reward learning when rewards are more frequently released in this side of space. In the N+ group, contralesional reward learning was equivalent to ipsilesional learning and comparable to reward learning rates displayed by N− both in the contralesional and ipsilesional side of space. This clinical finding expands on previous evidence showing that N+ can learn and exploit statistical contingencies governing the distribution of attentional targets in both sides of space (Bartolomeo, Siéroff, Decaix, & Chokron, 2001; Geng & Behrmann, 2002) and on findings showing that cognitive (Ishiai et al., 1990) and, more importantly, monetary incentive (Malhotra et al., 2013; Mesulam, 1985) can ameliorate the defective exploration of the contralesional space in these patients. We think it is worth noticing that in previous studies on the effects of monetary incentive, reward was linked to an abstract rule (i.e., the promise of reward for each detected target) and, as a consequence, homogenously distributed in space, because detecting a target on the left side of space did not provide more reward than detecting a target on the right side. Recent fMRI findings in healthy humans show that when rewards are randomly and homogeneously distributed in the egocentric space, the individual spatial-attentional bias works according to its default settings: the default bias is modified and abandoned when the non-random and spatially unbalanced distribution of rewards provide strategic advantages (Lee & Shomstein, 2013). Therefore, the results from the present study expand on previous findings on the effects of reward on spatial neglect and suggest that using "motivationally unbalanced" spatial task-sets, characterised by increased reward saliency of the contralesional space and reduced saliency of the ipsilesional one, could be a valuable strategy in counterbalancing the pathological ipsilesionally deviated default attentional bias of patients with left spatial neglect. Similar conclusions were also recently reached by Lucas et al. (2013) in an independent study on the "implicit" learning of reward in spatial neglect, that was published after the results of the present investigation were presented in a preliminary report (Lecce, Rotondaro, Tomaiuolo, & Doricchi, 2013). These authors found that in a multiple item cancellation task the preferential association of rewards with left-sided targets, biased the exploration towards the left neglected space even without any conscious awareness of the asymmetric reward distribution. The converging findings from these different studies point out that it might be important for future investigations to explore systematically whether the use of tasks characterised by the explicit or implicit learning of rewards preferentially released in the contralesional space, engenders better rehabilitative benefits compared to training exercises characterised by a spatially homogenous distribution of rewards or by the mere higher perceptual saliency of stimuli in the contralesional space.

6.1. *Cingulate neglect in the humans: insights from L.R. case*

A notable exception to the findings gathered from the study of the group of N+ patients was patient L.R. who, compared both to N+ and N− patients, showed a severe deficit in reward learning when rewards were frequently released (i.e., 75% trials) in the contralesional space and infrequently released (i.e., 25% of trials) in the ipsilesional space. A number of important clinical and experimental observations were made in this patient. First, compared to control groups of N+ and N− patients, L.R. had an additional lesion of the ACC and of the adjacent rostral sector of the corpus callosum. In L.R. the posterior attentional cortical areas were almost entirely spared: the lesion only affected the very rostral portion of the Supramarginal Gyrus in the inferior parietal lobe (IPL), whereas the Angular Gyrus, the Intra Parietal Sulcus (IPS), the medial and lateral aspects of the Superior Parietal Lobule (SPL), the PCC and the precuneus were intact. Primary visual pathways, striate and extrastriate cortex were also entirely spared. In addition, DTI tracking of white matter pathways showed that the second branch of the Superior Longitudinal Fasciculus, i.e., the pathway that links inferior parietal with prefrontal areas and that it is most frequently damaged in neglect patient (Bartolomeo et al., 2007; Thiebaut de Schotten et al., 2005, 2014; Doricchi & Tomaiuolo, 2003) was not anatomically disconnected. Second, in keeping with the large sparing of posterior attentional areas and despite the presence of neglect on conventional screening task, L.R. showed no lateral imbalance in the early phases of attentional processing as he detected with no failure very short single tachistoscopic visual and acoustic contralesional stimuli and, most importantly, showed no sign of contralesional extinction

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when the same stimuli were presented together with competing ipsilesional ones. These finding converge in suggesting that in L.R., the pathological ipsilesional bias of attention associated to contralesional neglect came into play at a relatively late stage of processing. As regards with the behaviour of L.R. during the performance of the reward-learning task, two additional clinical observations are relevant. First, with no exception and no cueing on the part of the examiner, in each trial L.R. immediately and spontaneously detected the appearance of a monetary reward in the left or the right side of the testing display and correctly judged whether the position of reward corresponded or not to that he had selected at the beginning of the trial. Second, when the two reward-boxes were vertically arranged one above the other and both presented within the contralesional space, L.R. showed preserved reward learning. These two observations, together with the absence of ipsilesional bias in early attentional processing, suggest that the lack of contralesional reward learning cannot be merely attributed to an ipsilesional bias of visual attention and that it was specifically observed when competing rewards were presented, even infrequently, in the ipsilesional space.

An important help in the functional interpretation of the contralesional reward learning deficit suffered by L.R. comes from the comparative study of patient G.P. who, notwithstanding an extended lesion in the right ACC, in the adjacent sectors of the corpus callosum and in the right mediobasal prefrontal cortex, showed normal contralesional and ipsilesional reward learning. At variance with L.R., G.P. had no contralesional neglect and no lesion in the lateral dorsal and ventral cortical attentional areas that are most frequently affected in neglect patients (Thiebaut de Schotten et al., 2014; Mort et al. 2003; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). Most important, in addition to their similar ACC and callosal damage, both L.R. and G.P. had lesions of subcortical structures participating in the processing of reward signals: the putamen and the caudate nucleus in L.R., the putamen, the caudate nucleus and the nucleus accumbens in G.P. These anatomical remarks suggest that the reward circuit in the right hemisphere was anatomically and functionally damaged in both patients, and that reward signals were probably mainly processed in the intact left hemisphere. Basing on this assumption, a number of hypotheses can be advanced to

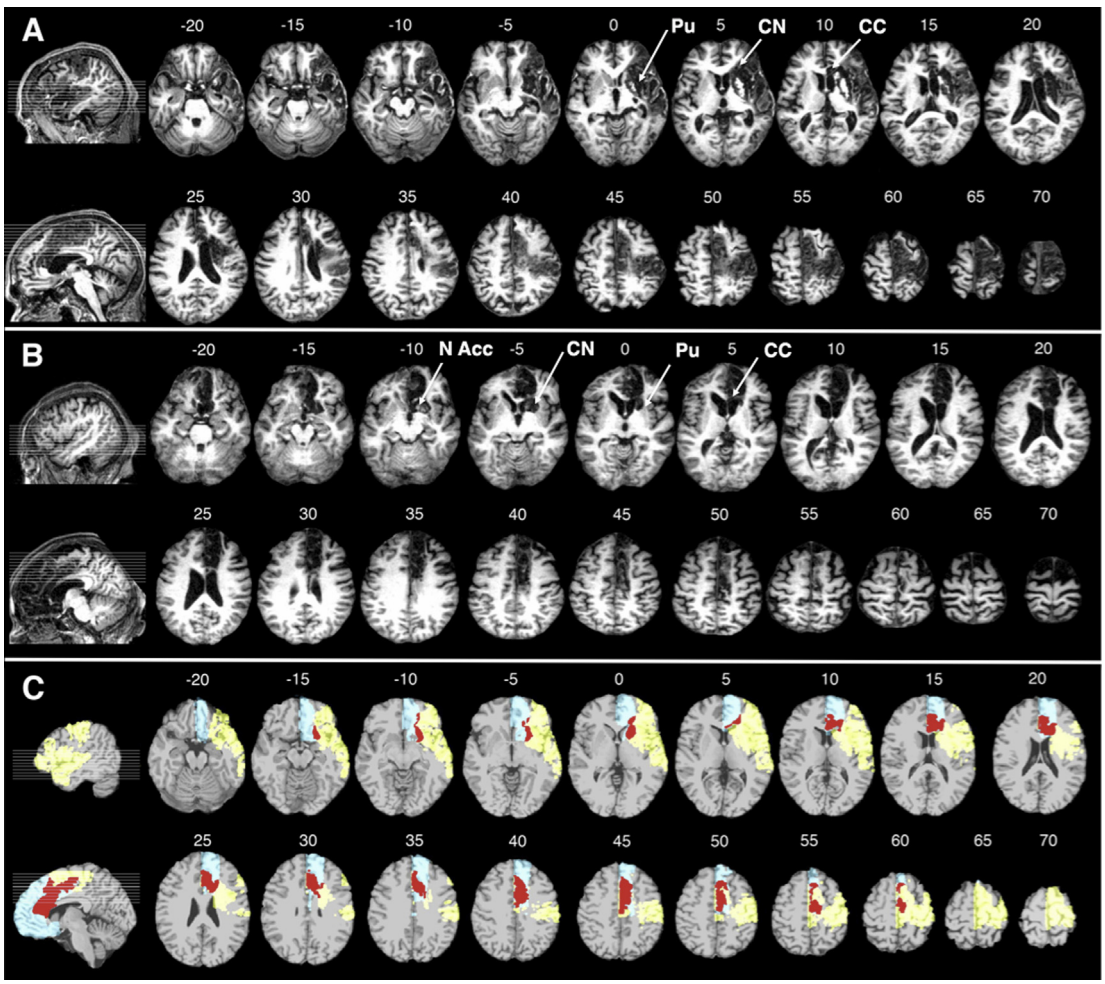

Fig. 6 – Study 3. Lesion comparison between case L.R. and case G.P. (A) L.R. MRI scan (Pu = Putamen; CN = Caudate Nucleus; CC: Corpus Callosum). (B) G.P. MRI scan (N Acc = Nucleus Accumbens; Pu = Putamen; CN = Caudate Nucleus; CC: Corpus Callosum). (C) Lesion comparison between L.R. (Yellow area) and G.P. (Light Blue area). Red area = lesion overlap.

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interpret the contralesional reward-learning deficit suffered by L.R. A first plausible hypothesis is that both in L.R. and G.P. reward signals processed in the ACC and in the other motivational and attentional structures of the left hemisphere (i.e., PCC, Precuneus, Posterior Parietal Cortex; Mohanty, Gitelman, Small, & Mesulam, 2008; Small et al., 2005; Tosoni et al., 2012) were transferred to the right hemisphere via spared posterior callosal connections. Starting from this point, two possible scenarios can be envisaged to explain L.R.'s contralesional reward learning deficit. The first is that reward signals arriving from the left hemisphere were ineffective in modifying the attentional saliency of the left side of space in the anatomically intact posterior-dorsal attentional areas of the right hemisphere, because the adjacent brain damage produced an important functional hypoactivation of these areas. Though plausible, this interpretation is probably not entirely congruent with the absence of a pathological lateral bias in the early phases of attentional processing and with the preserved ability of L.R. in detecting spontaneously the release of rewards in the contralesional space. These observations allow drawing a second scenario. According to the Critic-Actor distinction introduced by Holroyd and Coles (2002), the ACC plays the role of a "Critic" evaluating stimuli and actions in terms of expected reward. This information is passed to high-level motor areas, insula and basal ganglia. These areas play the role of an "Actor" selecting actions along the guidelines provided by the "Critic". From an empirical standpoint, several sources of evidence demonstrate that one important role of the ACC is linking reward-related information to the selection of alternative actions, especially in response to diminished reward. As an example, Williams, Bush, Rauch, Cosgrove, and Eskandar (2004) showed that in humans, surgical ablation of the ACC produces severe impairments in changing the direction of a simple motor response upon the release of diminished reward. In agreement with this finding, Camille, Tsuchida, and Fellows (2011) recently documented a double dissociation in human patients, showing that lesion in the ACC disrupts value-based choice between alternative actions whereas lesion in the orbitofrontal cortex disrupt value-based choice between alternative sensory stimuli. Based on these findings one can hypothesize that in L.R. reward signals arriving from the left hemisphere actually modified the attentional saliency of the left side of space in the posterior attentional areas of the right hemisphere and that his contralesional reward learning impairment originated from a later processing deficit, consisting in the defective association of reward-related spatial signals with the selection of appropriate motor responses. In terms of Holroyd and Coles' Critic-Actor distinction (2002), this would mark a dysfunctional "Actor" system. It is important to note that in L.R. the reduced frequency of "left" contralesional choices made before the release of rewards, cannot be ascribed to contralesional "motor" neglect or hypokinesia, because upon presentation of reward in the contralesional space, L.R. indicated with no hesitation and no cuing on the part of the examiner the (contralesional) position of reward. In this respect, L.R.'s deficit seems therefore limited to the planning and selection of an attentional-motor choice in the contralesional direction, when this choice must be guided by cumulated knowledge on the spatial distribution of rewards.

In our Study 3, we have found that patient G.P. who had a right unilateral lesion in the ACC, in the adjacent SMA and in the medial orbitofrontal cortex did not suffer contralesional spatial neglect. This is apparently at variance with the findings by Watson, Heilman, Cauthen, and King (1973), who documented contralesional neglect in monkeys following unilateral surgical ablation of the right ACC. Before surgery, monkeys were trained to explore the left side of space (i.e., opening the left side of a double-hinged door to obtain a biscuit) upon stimulation of the left leg or upon simultaneous stimulation of both legs and to explore the right side of space upon stimulation of the right leg. The main consequence of right cingulectomy was that on bilateral stimulation monkeys showed a pathological bias to open the door on the right side, just as if the touch of the left leg was attentionally extinguished. Most important, however, no spatial bias (i.e., neglect) was observed in spontaneous exploration as the animals "spontaneously opened both doors". The findings reported by Watson et al. (1973) seems therefore imputable to post-operatory impairments affecting the attentional processing of somatosensory inputs rather the spontaneous allocation of attentional resources in extrapersonal space.

6.2. *Future lines of clinical inquiry*

The interpretation that we have proposed for the reward learning impairment that we have observed in L.R., points at a late processing deficit that comes into play during a task requiring the explicit exploration and the strategic exploitation of reward, thus strongly implying endogenously guided attention. However, several investigations have extensively demonstrated that reward can also have an automatic influence on early phases of perceptual and attentional processing by direct conditioning basic sensory features of environmental stimuli. This modulatory influence escapes observer's awareness and might constitute the phylogenetically oldest form of attentional control (Hickey et al., 2010). Studies in animals and humans have well characterised the behavioural and neural correlates of these automatic effects. Reward can directly modulate the response of spatially selective neurons in primary sensory and associative cortex and in subcortical sensory and motor related structures. Interestingly, in humans reward modulation of responses in primary visual cortex (V1) can be mediated both by direct and indirect mechanisms. Serences (2008) documented value-related modulation of the BOLD response in spatially selective visual areas, including V1 (see also Serences & Saproo, 2010). These modulatory effects were driven by recent prior rewards rather than by the subjective reward value assigned to stimuli. In contrast, Frontal (left Superior Frontal Sulcus, ACC, left and right Inferior Frontal Gyrus) and parietal areas (PCC, left and right IPS and Precuneus) were sensitive to the differential value between alternative response options. Weil et al. (2010) showed that verbal-auditory feedback following a visual choice, increased the activity of visual areas beyond primary visual cortex (i.e., V3): however, in the ensuing trial, the increased response in V3 enhanced, in turn, the response in the sectors of the primary visual cortex representing the

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features rewarded in the preceding trial. From a behavioural standpoint, the most important observation is that within a set of trials, the automatic influence of reward is determined by immediate preceding rewards rather than by the discovery and exploitation of the rule regulating reward release across the entire trial set. In a series of investigations, Della Libera and Chelazzi (2006; 2009) showed that RTs to visual targets intermixed with distracters, were fast when targets were characterized by a colour that in the previous trial was associated with a high monetary reward and slow when in the previous trial reward was associated to the colour of distracters. These effects were matched to an enhancement of the P1 wave and the N2pc wave signalling the allocation of attention, in the cortex contralateral to the reward-associated colour (see also Kiss, Driver, & Eimer, 2009).

Based on this set of findings, we think that it would be an important matter for future clinical research to establish whether automatic reward effects can be maintained in brain damaged patients suffering deficits in the explicit discovery and exploitation of reward rules and, vice versa, whether training in the explicit learning of reward rules can counteract the pathological reduction of automatic reward influences.

6.3. *Dopaminergic agents and reward-based rehabilitation of spatial neglect*

Given the well-established role of dopaminergic structures in the evaluation and exploitation of rewards, it would be also useful to assess whether the possible effects of reward-based rehabilitation tasks can positively interact and potentiate the therapeutic effects that dopaminergic agonists can produce on spatial neglect. The use of dopaminergic agonists in the therapy of unilateral spatial neglect has been the subject of research and debate. In the rat, unilateral lesion of dopaminergic structures in the VTA produces ipsilesional turning and contralateral neglect. Both of these pathological effects are suppressed after administration of apomorphine, a D1/D2 agonist. In the same animals, apomorphine is also effective in reducing neglect caused by unilateral lesion of the dorsomedial frontal cortex, which normally receives dopaminergic inputs. Studies in human patients, have reported contrasting results on the effect of bromocriptine, a strong selective D2 agonist. Fleet, Valenstein, Watson, and Heilman (1987) reported positive results in two patients whereas Grujic et al. (1998) observed worsening of neglect. These authors concluded that while unilateral lesion of dopaminergic structures in the mesencephalon produces hypersensitivity of dopaminergic receptors in the ipsilesional striatum and cortex, so that the administration of dopaminergic agonists can be effective in boosting the activity of these structures and in reducing neglect, lesions that affect directly the striatum and the cortex might reduce the sensitivity of these structures to dopaminergic agents. In this latter case dopaminergic stimulation might have greater impact on striatal and cortical structures in the intact hemisphere thus increasing the ipsilesional attentional-motor bias. In human patients, more encouraging and homogenous results seem provided by the administration of D1 and D1/D2 agonists. Geminiani, Bottini, and Sterzi (1998) observed improvement from neglect in a motor-pointing task following administration of the D1/D2 agonist apomorphine, despite the presence of drowsiness as a side effect (Geminiani et al., 1998). In a more recent investigation (Gorgoropatis et al., 2012), administration of D1-agonist rotigotine improved performance on cancellation tasks requiring focussing of attention on targets and resistance to attentional capture from distractors. Rotigotine produced no change in measures of sustained attention. All together, these findings suggest that dopaminergic treatment of neglect might have poor, no or even detrimental effect on motivation and arousal and that the use of "arousing" reward-based spatial rehabilitation tasks might complement the effects of pharmacological intervention and potentiate its beneficial therapeutic influence. This possibility finds support in animal lesion studies showing that, alike our findings in the group of N+ patients, contralesional neglect can be produced independently of concomitant spatial-motivational deficits and can follow lesion of dopaminergic motor-related structures though not of dopaminergic reward-related ones. Christakou, Robbins, and Everitt (2005) found that in the rat combined unilateral lesion of the dorsal striatum and the medial prefrontal cortex produce a severe and long lasting pathological ipsilesional exploratory bias in the absence of lateralised motivational impairments, as lesioned animals were still able of associating visual stimuli in the left or right side of space with the release versus no-release of food pellets (i.e., "Autoshaping task"; Bussey et al., 1997). Carli, Evenden, and Robbins (1985); Carli, Jones, and Robbins (1989) showed that in rats performing a task requiring orientation toward or away from visual stimuli that were unpredictably presented in the left or right side of space, contralesional neglect was observed after unilateral dopamine depletion in the motor-related structures of the dorsal striatum (i.e., caudate nuclei) but not after depletion in reward-related structures of the ventral striatum (i.e., nucleus accumbens). In line with the results of the present study, the clear dissociation between motivational and attentional impairments documented by these animal studies suggests that in neglect patients reward-related structures in the lesioned hemisphere should not be necessarily anatomically or functionally damaged and that boosting their activity, whether pharmacologically or through the combination of pharmacological intervention and behavioural rehabilitation with reward-based spatial tasks, can be a therapeutic strategy that is worth exploring. In agreement with this possibility, recent and very interesting findings reported in a preliminary report by Malhotra and co-workers (Li, Soto, Russell, Balaji, & Malhotra, 2013), suggest that L-Dopa can potentiate the reduction of contralesional neglect produced by monetary reward in multiple item cancellation tasks.

7. Conclusions

To summarise, the observations reported in the present series of studies provide promising insights on the pathological anatomical and functional conditions that in right brain damaged patients lead to severe and spatially modulated deficits in the integration between motivational inputs and the representation of space and motor actions. The same set of findings demonstrate that voluntary learning and exploitation of rewards released in the contralesional space is

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generally spared in RBD patients with neglect. In line with evidence from other recent investigations, this latter result supports the conclusion that preserved reward sensitivity and learning can be exploited to improve rehabilitation training programs for the spatial neglect syndrome.

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