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Research report

Attention networks and their interactions after right-hemisphere damage

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ABSTRACT

Unilateral spatial neglect is a disabling condition, frequently observed after right-hemisphere damage (RHD), and associated with poor functional recovery. Clinical and experimental evidence indicates that attentional impairments are prominent in neglect. Recent brain imaging and behavioral studies in neglect patients and healthy individuals have provided insights into the mechanisms of attention and have revealed interactions between putative attentional networks. We recruited 16 RHD patients and 16 neurologically intact observers to perform a lateralized version of the Attention Network Test devised by Posner and co-workers (Fan et al., 2002). The results showed evidence of interaction between attentional networks during conflict resolution. Phasic alertness improved the orienting deficit to left-sided targets, reducing the interference of distracters in the neglected visual field, thus facilitating conflict resolution in the majority of patients. Modulating alertness may be an important way of improving basic deficits associated with neglect, such as those affecting spatial orienting.

1. Introduction

Attention refers to a family of cognitive functions that prepare the individual to respond quickly and accurately to incoming information by selecting relevant and ignoring irrelevant stimuli. Traditionally conceived as a uniform concept, attention is now viewed as a composite function based on discrete neural substrates (Posner and Petersen, 1990). For example, Posner and his co-workers have proposed that three separate but linked brain networks contribute to the following attentional processes: orienting, alerting and executive control (Fan et al., 2002).

The orienting function has been traditionally studied by presenting stimuli preceded by orienting cues. When the cues correctly indicate the location of the upcoming target,

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participants' responses are faster and/or more accurate, indicating that spatial attention improves the processing of information (Posner, 1980). Influential functional Magnetic Resonance (fMRI) models propose a dorsal fronto-parietal network (including the bilateral intraparietal sulcus and frontal eye fields), involved in the orienting of attention, and a ventral fronto-parietal network (including the temporo-parietal junction – TPJ, and the inferior and middle frontal gyri) supporting attentional re-orienting to unexpected events (Corbetta and Shulman, 2002). Recent evidence has however demonstrated the causal role of TPJ (part of the ventral network) during the orienting of exogenous or involuntary attention (Chica et al., 2011).

The alerting system is believed to produce a general alert state that would be responsible for spreading attention over a broad area of space and is modulated by the locus coeruleus/norepinephrine system (Coull et al., 1999). A higher alert state allows faster processing of information, independently of its spatial location (Fernandez-Duque and Posner, 1997). We can voluntarily maintain our level of alertness over time, a function known as "sustained attention", which involves the right frontal cortex, inferior parietal lobe (IPL) and subcortical structures (Sturm and Willmes, 2001). The alertness level can also be modulated experimentally by presenting warning signals that carry information about when, but not where, targets will appear ("phasic alertness"). In addition to the (mainly right-lateralized) neural structures involved in sustained attention, phasic alertness is associated with activity in the left frontal cortex and thalamus (Sturm and Willmes, 2001).

A distinct dimension of attentional processes involves executive control, which requires both monitoring and conflict solving (e.g., flankers task, Eriksen and Eriksen, 1974). Brain areas associated with the executive control system are the dorsal anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC) (Bush et al., 2000), although more extensive areas are implicated when complex tasks are used (Fan et al., 2005).

Although behavioral and fMRI evidence support the theoretical independence of these attentional subsystems (Fan et al., 2005, 2002; Fernandez-Duque and Posner, 1997), other studies in neglect patients and healthy participants have emphasized the importance of their interactions (Posner and Petersen, 1990). These discrepancies with older studies were likely due to the paradigms used, which were not ideal to study the interactions between the three attentional networks. These studies measured alerting by using the presence/absence of spatial visual cues, which allows studying the main effect of each network, but not the interaction between alerting and orienting. Callejas et al. (2005, 2004) modified this paradigm in order to study not only the main effect of each network but also their interactions, by using a separate measure of alerting, manipulating the presence/absence of an auditory cue. They reported behavioral evidence supporting an interaction between the networks in a reaction time (RT) paradigm, where greater orienting effects were observed after the presentation of a warning tone that induced phasic alertness. Robertson et al. (1997) also showed that sustained attention deficits might predict the occurrence and severity of the orienting deficits demonstrated by neglect patients. Remarkably, modulating the alertness level by an alerting tone could overcome the spatial bias in visual awareness in eight neglect patients (Robertson et al., 1998).

Several studies have demonstrated that the degree of impairment of sustained attention is a strong predictor for the persistence of neglect (Hjaltason et al., 1996; Samuelsson et al., 1998). Alertness training can also improve lateralized spatial deficits in brain damaged patients by means of self-instructional (Robertson et al., 1995) or computerized methods (Sturm et al., 1997). Thimm et al. (2006, 2009) have reported ameliorations of neglect that are associated to increased activity in bilateral fronto-parietal regions such as the frontal gyri, the cuneus and precuneus, the angular gyrus, and the ACC (see also Manly et al. (2005), and Fimm et al. (2006), for the effects of alertness in sleep-deprived healthy participants).

In addition, there is increasing neurophysiological and anatomical evidence of these interactions between the alerting and the orienting systems. Clark et al. (1989) modulated the noradrenergic (NA) system by injecting intravenous drugs in healthy participants, producing changes in orienting attention on a cuing RT paradigm. Malhotra et al. (2006) have also observed an improvement of neglect with NA stimulation. Morrison and Foote (1986) studied the innervations of brain structures in monkeys and showed high density NA innervations in cortical and subcortical regions involved in attentional orienting (e.g., posterior parietal lobe – PPL).

The present study attempts to provide further behavioral data in right brain damaged patients emphasizing the importance of the interplay between attentional networks, which might contribute to the development of more efficient rehabilitation methods for patients presenting attentional deficits. We modified a computerized battery test (Attention Network Test – ANT) originally designed to determine the functional independence and efficiency of the three attentional networks discussed above (Fan et al., 2002). As in Callejas et al. (2004), we introduced an alerting tone before the cue was presented. This manipulation allows us studying not only the efficiency and independence of each network but also their interactions. Given that we were interested in studying lateralized spatial deficits (left- and rightward orienting of attention) as well as non-spatial deficits (alertness), and that we were especially interested in investigating their interactions, a lateralized version of the test proposed by Callejas et al. (2004) was designed. Based on previous research, we expected an abnormal orienting of attention to left-sided targets in right brain damaged patients (Bartolomeo and Chokron, 2001). If the attentional networks interact, the phasic alerting produced by the tone could ameliorate this orienting deficit in the patients, who might be faster and/or more accurate for validly cued left-targets. This better orienting might be able to improve conflict resolution at the attended location. Contrary, if the attentional networks do not interact, we will find faster RTs when the alerting tone is presented, but this will not influence neither orienting nor conflict resolution.

2. Methods

2.1. Participants

Sixteen patients (6 women; Table 1) and sixteen healthy controls (8 women) participated in the study. Patients were selected on the basis of the presence of unilateral damage to the right hemisphere, as assessed by magnetic resonance

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imaging (MRI) or computed tomography (CT) scans. For nine of the patients, high-resolution MRIs were obtained, and subsequently used for symptom-lesion mapping (see below, MRI protocol). For the rest of the patients, MRI or CT scans were not available at the time of the study. Brain lesions were ischemic, hemorrhagic, neoplastic or secondary to neurosurgical interventions. All patients had full visual fields on confrontational testing. Thirteen of the recruited patients showed pathological scores on a paper-and-pencil neglect battery (neglect evaluation battery – NEB; Table 1). However, hospital staff reported that all patients manifested signs of left unilateral neglect whilst carrying out everyday tasks (bathing, grooming, eating and dressing). Severe systemic and psychiatric illness, history of substance abuse and left hemianopia were all exclusion criteria for the study. Healthy controls were matched to patients in age [controls, mean ± standard deviation (SD), 62.1 ± 9.48 years; patients, 60.1 ± 10.96 years] and educational level (controls, 1.93 ± .57; patients, 1.87 ± .71; see Table 1). All participants were right-handed and reported to have normal or corrected-to-normal vision. All participants gave written informed consent prior to participation.

2.2. *MRI protocol*

Brain MRI scans included high-resolution T1 3D anatomical SPGR images [Repetition time (RT)] = 7164 msec, Echo time (TE) = 3124 msec, inversion time = 380 msec, flip angle = 15°, coronal orientation perpendicular to the double echo sequence, acquisition matrix = [0, 288, 256, 0], voxel resolution = .5 × .5 × 1.2 mm^3, slice thickness = 1.2 mm, spaces between slices = 1.2 mm) obtained on a 3T GE scanner with a standard head coil for signal reception.

2.2.1. *Neglect Evaluation Battery*

The battery consisted of target cancellation tests (bells, lines and letters), line bisection, drawings copy, writing and reading tasks (Bartolomeo and Chokron, 1999; Azouvi et al., 2002).

Target cancellation tests. Patients were asked to cancel the following stimuli on a horizontally oriented A4 sheet of paper: silhouettes of bells (Gauthier et al., 1989), lines (Albert, 1973) and “A” letters (Mesulam, 1985). The number of correctly canceled stimuli on the left half and on the right half of the test sheet was recorded. Scores were considered pathological if the difference between left and right omissions was larger than two (Bartolomeo et al., 1994).

Line bisection. Patients were asked to make a mark with a pencil in the middle of eight horizontal lines of different sizes, on a vertically oriented A4 sheet of paper (Bartolomeo and Chokron, 1999). The cumulative percentage of deviation from the true centre was calculated for all lines. Positive percentages denote rightward error and negative percentages denote leftward deviation. Scores were considered pathological if the deviation was greater than 10%.

Landscape drawing. Patients were asked to copy the drawing of a landscape consisting of a house and four trees (Gainotti et al., 1986). Two points were assigned to completely omitted items, one point to partially omitted items and 0 points to items entirely copied. Scores ranged from 0 (no omissions) to 9 (only the right half of one item copied). One or more omissions were considered pathological.

Reading and writing. Patients were asked to read aloud a passage of text, which contained 63 words to the left and 54 words to the right of the midline. One or more omissions were considered pathological. For the writing test, patients were asked to write some words on a blank sheet of paper. Left margins were measured and considered pathological when greater than 7.7 cm (Azouvi et al., 2002).

2.3. *Lateralized ANT – interactions*

2.3.1. *Apparatus*

Stimuli were presented on the 17-inch WXGA+ monitor of an Intel® Core Duo notebook PC running Windows® XP and SuperLab Pro™ 2.0 version software was used for stimulus

Table 1 – Clinical & demographic data: EL: educational level (1: <9 years of schooling; 2: 10–13 years; 3: >13 years); Onset: weeks since clinical onset; Cancellation tests (Bell, Line, Letter) show performance (left/right canceled items). Pathological scores are in bold.

Patient	Age	Sex	EL	Onset	Bell cancellation (max 15/15)	Line cancellation (max 30/30)	Letter cancellation (max 30/30)	Landscape drawing	Line bisection	Reading (max 63/54)	Writing
RHD1	56	M	2	24	**9/14**	30/29	**20/25**	**6**	**10.4**	63/54	0
RHD2	58	F	3	157	10/12	30/27	26/24	0	5.9	63/54	**13.5**
RHD3	40	M	1	22	11/13	30/30	29/29	0	3.3	63/54	1.5
RHD4	54	F	2	28	15/14	30/30	**27/30**	0	−.7	63/54	1
RHD5	56	M	1	42	13/12	30/30	28/29	0	.9	63/54	.8
RHD6	74	M	2	6	**5/11**	30/30	**10/21**	**1**	**17.3**	**51/53**	**18.5**
RHD7	43	F	2	46	12/13	**26/30**	**20/27**	**1**	−3.7	**57/48**	**11.5**
RHD8	62	F	3	23	15/15	30/30	**23/30**	0	−1.5	63/54	**13**
RHD9	63	F	3	60	**0/9**	**15/30**	**0/21**	**6**	4.2	**53/52**	**11**
RHD10	70	M	2	12	**10/13**	30/30	28/27	**8**	6.3	63/54	2
RHD11	60	F	2	23	14/15	30/30	29/30	0	4.2	63/54	2
RHD12	55	M	1	24	14/14	30/30	30/29	**1**	7.3	63/54	4.5
RHD13	73	M	1	10	**10/15**	**22/25**	**17/23**	**4**	8.4	**61/54**	6.5
RHD14	59	M	2	158	15/15	30/30	30/30	0	1.8	**30/54**	2
RHD15	57	M	2	7	**0/9**	28/30	28/29	**1**	.2	63/54	2.5
RHD16	83	M	1	20	**8/15**	**25/30**	**25/29**	**1**	.7	**53/45**	4.6

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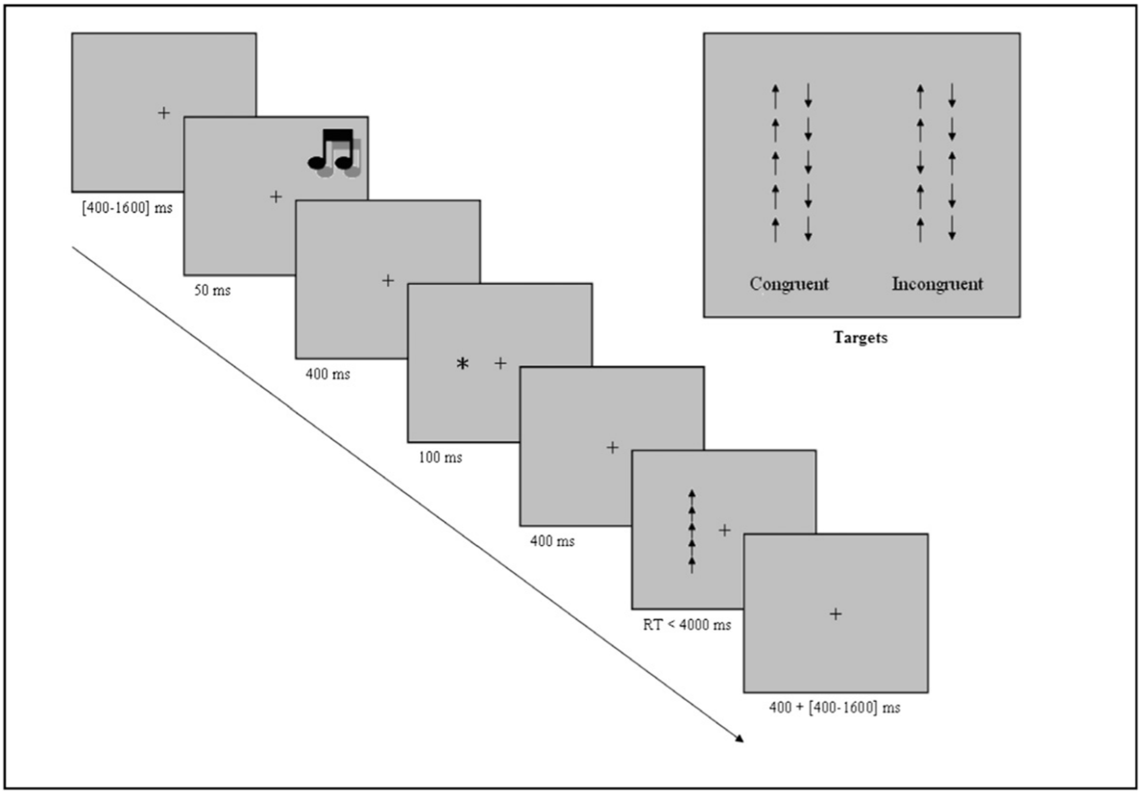

Fig. 1 – Experimental procedure: example of a left valid warned congruent trial (the musical notation represents the alerting tone and was not presented visually).

presentation and response collection. A Thrustmaster® joystick was adapted to right-handed participants and its button registered only upward and downward responses. The alerting tone was administered through headphones, which were worn for the duration of the experiment.

2.3.2. *Stimuli*

Targets consisted of a black downward or upward pointing arrow presented at approximately 1.06° of visual angle to the right or left of a central fixation cross. Stimuli were presented against a gray background (Fig. 1). Targets were flanked by two arrows of equal size on each side (above and below), pointing in the same direction as the central target (congruent trials), or in the opposite direction (incongruent trials). Arrows (targets and flankers) subtended approximately .55° of visual angle and were separated by approximately .06°. The whole lateralized stimulus (central arrow plus four flankers) subtended approximately 2.99°. The orienting cue was an asterisk displayed at the same location as the upcoming target (valid cue) or in the other visual field (invalid cue). The alerting signal consisted of a 2000 Hz tone lasting 50 msec. All participants reported to hear the tone during the practice block.

2.3.3. *Procedure*

Each trial began with a fixation cross, which remained on the screen for a variable duration (random selection from 400, 800, 1200 or 1600 msec). On half of the trials, the fixation period was followed by the alerting tone (50 msec). After 450 msec, an orienting cue was presented in either the left or right visual field during 100 msec. Targets and flankers were displayed simultaneously at a 500 msec Stimulus Onset Asynchromy (SOA) after cue presentation,[1] and remained visible until a response was made or until 4000 msec had elapsed. Half of the spatial cues were valid and half invalid. Therefore, spatial cues were not informative about the future target location. There was an inter-trial interval of 400 msec during which the central fixation cross remained visible. Total trial duration depended on the fixation period and response times, and ranged between 2100 and 6950 msec.

Participants were seated at approximately 53 cm from the computer monitor. They were asked to respond as rapidly and as accurately as possible with their right thumb using the joystick button, pushing it upward when the target arrow pointed upward, and downward when the target arrow pointed downward. Participants were instructed to respond only to the targets and not to the orienting cues or to the alerting tones. They were informed about the non-informative value of the cues and the alerting tones. They were encouraged to keep their eyes on the central fixation cross during the entire test, and the experimenter controlled fixations using

[1] The 500 msec SOA used in this study is longer than the SOA normally used to observe facilitation in young healthy controls (~100–250 msec; Posner, 1980). However, this SOA was used given our sample's age and task difficulty. Facilitation with non-informative cues has been observed at longer SOA for elderly people (Castel et al., 2003), and for difficult discrimination tasks (Lupiáñez et al., 1997).

Table 2 – Mean correct RTs (SD in parentheses) for each group and experimental condition.

	Alert	Left				Right			
		Congruent		Incongruent		Congruent		Incongruent	
		Invalid	Valid	Invalid	Valid	Invalid	Valid	Invalid	Valid
Controls	Absent	705 (139)	671 (140)	798 (133)	730 (145)	702 (139)	686 (148)	787 (131)	738 (150)
	Present	688 (136)	650 (139)	777 (131)	722 (135)	686 (132)	656 (147)	786 (142)	732 (152)
Patients	Absent	1166 (471)	1106 (462)	1319 (476)	1292 (525)	1045 (375)	1039 (415)	1208 (386)	1140 (390)
	Present	1119 (445)	1090 (476)	1315 (455)	1193 (442)	1035 (376)	956 (321)	1161 (357)	1072 (365)

a mirror during the practice trials. Trials were organized in three blocks of 128 trials each and participants were allowed to rest between blocks. The three experimental blocks were preceded by 24 practice trials, in which participants received feedback concerning their speed, accuracy and eye movements. Practice trials were discarded from the analyses. Each block had 8 trials per condition resulting in a total of 24 identical trials per condition. Every block lasted for about 6 min for controls, and approximately 10 min for patients.

3. Results

3.1. *Response times*

RT outliers were discarded from analyses by using the following trimming procedure. First, mean RTs and SD for each participant were calculated separately for left- and right-sided targets. Separate means were calculated in order to avoid excluding mostly RTs to left-sided targets, which were likely to be much slower than RTs to right-sided targets in right-hemisphere damaged (RHD) patients. Then, RTs exceeding 2.0 SD below or above each participant's mean were excluded from the analyses. This resulted in the exclusion of 3.10% of the trials for controls and 4.94% for RHD patients.

We performed a Levene test that proved the variance of the two groups to be different. Therefore, separate repeated-measures analyses of variance (ANOVAs) were performed for each group. Mean correct RTs for each condition (Table 2) were subjected to an ANOVA with target side (left, right), orienting cue (valid, invalid), conflict (congruent, incongruent), and alerting tone (absent, present) as within-participant factors.

3.1.1. *Control group*

The three main effects of orienting, conflict and alerting were reliable. Participants responses were faster on valid than invalid trials, $F(1,15) = 27.85$, $p < .001$. They also showed longer RTs on incongruent trials than on congruent trials, $F(1,15) = 87.98$, $p < .001$. And responses were faster when responding to warned trials than to non-warned trials, $F(1,15) = 10.02$, $p = .006$.

Orienting interacted with side, $F(1,15) = 4.57$, $p < .049$, because the orienting effect was slightly larger for left-sided targets (invalid *vs* valid RTs = 50 msec) than for right-sided targets (invalid *vs* valid RTs = 37 msec). Orienting and conflict also interacted, $F(1,15) = 14.84$, $p = .001$, indicating that when participants' attention was oriented to the target location there was a reduced interference from incongruent flankers (Callejas et al., 2005; Fan et al., 2002). The interaction between side, orienting and alerting was also reliable, $F(1,15) = 4.84$, $p = .044$, because the validity effect was slightly larger (10 msec) for right-sided targets in the presence of the alerting tone. Alerting interacted with conflict, $F(1,15) = 4.84$, $p = .044$, because the conflict effect increased in the presence of the alerting tone. This is consistent with previous studies demonstrating an inhibitory relationship between the alerting and executive networks (Posner, 1994).

3.1.2. *RHD patients group*

Again, the three main effects of orienting [$F(1,15) = 19.99$, $p < .001$], conflict [$F(1,15) = 69.56$, $p < .001$], and alerting [$F(1,15) = 28.86$, $p < .001$] were reliable. The main effect of side was significant in the patient group, $F(1,15) = 6.48$, $p < .022$, because RTs were 127 msec larger for left-sided stimuli. As in the control group, there was a reliable interaction between orienting and alerting, $F(1,15) = 21.71$, $p < .001$, because the orienting effect increased by 36 msec when the alerting tone was present. The interaction between side, orienting, conflict and alerting was also reliable, $F(1,15) = 8.16$, $p = .012$. In order to explore this complex interaction, we performed two separate ANOVAs for left- and right-sided targets. When RHD patients responded to left-sided targets, the interaction between orienting, validity and tone was significant, $F(1,15) = 5.06$, $p = .040$. The warning tone reduced conflict in valid trials as compared to invalid trials, $F(1,15) = 4.94$, $p = .042$, whereas the conflict effect was similar for valid and for invalid trials when there was no tone, $F < 1$ (Fig. 2). From a different perspective, for RHD patients the orienting effect for left incongruent trials was much larger on warned than on non-warned trials. Thus the usual interaction between orienting and alerting observed in controls with a shorter SOA (Callejas

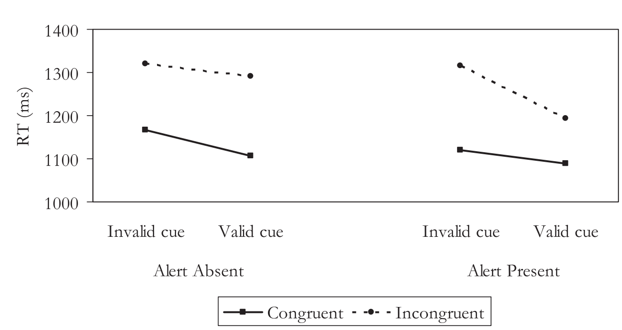

Fig. 2 – Mean RT of RHD patients to targets presented on the left visual field. Note that interference is dramatically reduced on alert present valid cue trials. This reduction is due to dramatic reduction in RT on alert present valid cue incongruent trials.

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et al., 2005, 2004) was observed with the longer 500 msec SOA in patients on the more difficult trials (left incongruent trials). For right-sided targets the interaction between orienting, validity and tone was far from significance, $F(1,15) = 1.72$, $p = .210$.[2]

In our design, the spatial cue carried out temporal information about when the target would be presented. However, this cannot explain the validity effect (faster responses for valid than invalid trials) or its modulation by the alerting tone, given that the temporal information was identical for valid and for invalid locations. Therefore, the main effect reported in the paper (decreased conflict on valid trials after the alerting tone for left-sided targets) cannot be accounted for the temporal information provided by the cue.

3.2. *Accuracy*

Accuracy rates were arcsin-transformed and subjected to repeated-measures ANOVA with the same factors as the RT analysis.[3]

The analysis of the control group could not be performed given the lack of variance of the data (performance was close to 100% correct in most of the conditions). In the patient group, only the main effect of congruency was significant, $F(1,15) = 10.61$, $p = .005$, with more accurate responses for congruent than incongruent conditions.

3.3. *Misses*

The percentages of missed trials for each condition were subjected to repeated-measures ANOVA with the same intra-participants factors as the previous analyses. Only results from the RHD patients were analyzed because the data showed no variance for controls (they only missed .15% of the targets *vs* the 4.06% of the targets missed by RHD patients).

RHD patients responded to fewer targets on valid than on invalid trials, $F(1.15) = 14.65$, $p = .001$. The interaction between Congruency, Orienting and Side was also significant, $F(1,15) = 4.61$, $p = .048$. Least significant difference (LSD) Fisher post-hoc comparisons revealed that this interaction was due to the fact that participants missed more left incongruent targets for valid versus invalid trials ($p = .002$). None of the other main effects or interactions were significant.

3.4. *Brain damage anatomy*

By detailed visual inspection of the digital images of the nine patients for whom high-resolution MRIs were available, brain lesions were plotted using MRIcro software (Rorden and Brett, 2000, www.mricro.com) and a graphics tablet (WACOM Intuos A6, Vancouver, Washington, USA) on 12 equidistant slices of a T1-weighted template (Fig. 3). The area of damage on the original MRIs and the lesions delineated on the template were separately reviewed and corroborated by P.M., clinical neurologist.

3.4.1. *Lesion mapping*

In order to assess whether specific brain damaged areas were associated with the interaction between alerting, orienting and conflict, the nine patients for whom high-resolution MRI scans were available were divided in two groups. The lesions of the six patients showing reduction of conflict by a warning tone in valid trials as compared to invalid trials were subtracted from the three patients showing no reduction of conflict by a warning tone using the MRIcro software. The region of maximum overlap in the group with no reduction of conflict was located in the gray matter of the right insula (Fig. 4, Talairach coordinates 35, −27, 20), and the underlying white matter close to the superior portion of the acoustic radiations, as mapped in a post mortem white matter atlas (Bürgel et al., 2006).

4. Discussion

The current study aimed at exploring the efficiency of, and interactions between, attentional networks by using a lateralized version of the ANT (Fan et al., 2002), which allowed us to assess these interactions separately for each visual field. RHD patients, who typically manifest deficits of spatial attention (e.g., rightward orienting bias) and non-spatial attention (e.g., sustained attention, Husain and Rorden, 2003), provide a clinical and scientific challenge to our understanding of attentional processes and of their neural bases (Bartolomeo, 2007, 2008; Bartolomeo and Chokron, 2002; Husain, 2008; for recent reviews). The present results are in agreement with those of previous studies concerning the attentional impairments found in RHD patients. Firstly, RHD patients had overall longer RTs (mean = 1159 msec) than healthy controls (mean = 721 msec) for targets in both visual fields. Non-lateralized deficits (Husain and Nachev, 2007; Robertson, 2001) could account for this overall difference between groups. Secondly, RHD patients showed a rightward bias of attention, as evidenced by slower responses to left-sided targets than to right-sided targets (Bartolomeo and Chokron, 2002).

Our results demonstrate that phasic alerting can improve the attentional orienting to left-sided targets in RHD patients, and this amelioration in orienting can ameliorate conflict resolution.[4] Robertson et al. (1998) have previously shown an interaction between alertness and orienting in neglect patients, suggesting that phasic alertness might affect the

[2] Given that 3 of the patients did not show signs of neglect in the paper and pencil tasks, we performed these same analyses with the 13 patients showing neglect. The results proved to be identical, with a significant interaction between alerting, orienting and conflict for left-sided targets, $F(1,12) = 4.99$, $p = .045$; the same interaction for right-sided targets resulted far from significance, $F < 1.3$.

[3] Error rates are prone to compression at both extremes. Therefore, raw proportion correct is rarely normally distributed. A possible solution is to apply an arcsin transform to the data, which typically makes the data more normally distributed, and therefore enhances the statistical power of the ANOVA.

[4] Note that the reported effects were observed in RT but not in accuracy measures. This was expected given that our participants presented mild rather than severe neglect. Severe neglect patients would have not been able to perform our task, which required selecting the relevant target out of distractors both in the intact, right visual field, but also in the neglected, left visual field.

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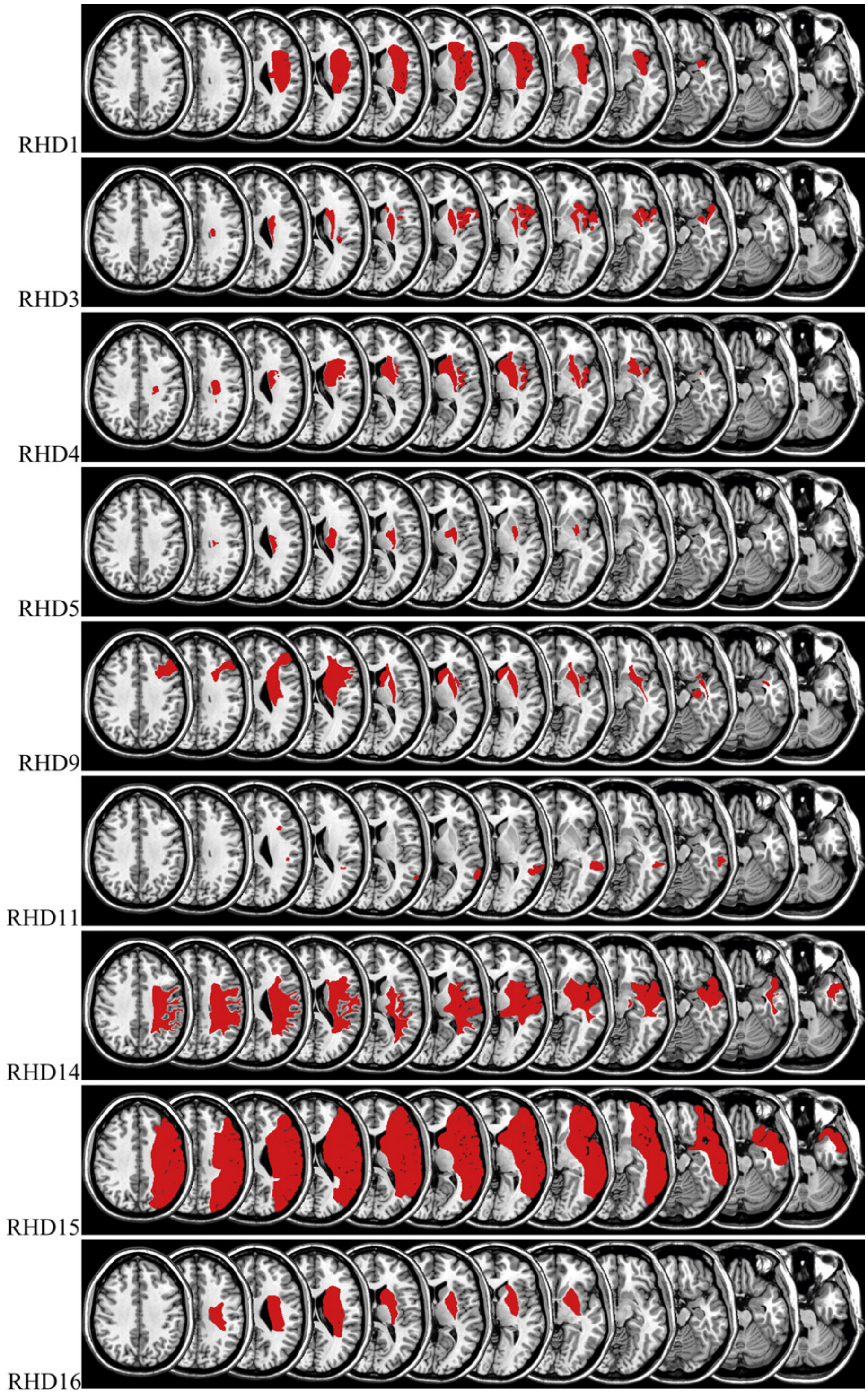

Fig. 3 – Lesions of nine RHD patients.

speed of perceptual processing in the neglected visual field. In their study, a temporal order judgment task was used, and the alerting tone speeded the processing of left-sided stimuli, overcoming their rightward bias of attention. Here, we report an interesting consequence of this leftward shift of attention. Enhancing phasic alertness improved the way in which RHD patients dealt with irrelevant spatial information on the neglected visual field. When the cues were not preceded by a warning signal, RHD patients were less able to focus attention on the valid location and thus they were unable to use the orienting of attention to resolve the conflict. The use of warning signals, however, helped the patients to orient attention to the cued location, reducing the conflict effect on warned left-sided targets. Therefore, alerting improved the functioning of the orienting of attention, which might have improved conflict resolution by either helping to filter out distracting information

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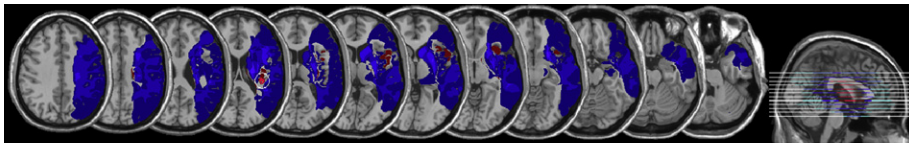

Fig. 4 – Damaged brain area associated with the interaction between alerting, orienting and conflict, located in gray matter of the right insula. In red to orange, regions damaged in the three patients with no reduction of conflict and spared in the six patients with reduction of conflict. Regions in blue denote areas affected in patients presenting reduction of conflict but spared in patients with no reduction of conflict.

or enhancing response selection. No interaction between the three attentional networks was observed for right-sided targets. This might result from attention being easily captured by these targets in neglect patients (D'Erme et al., 1992), which might in turn determine near-optimal performance on the discrimination task. This pathological magnetic attraction is associated to some inadaptative functions such as the revisiting behavior (Danckert and Ferber, 2006).

The three patients whose performance did not benefit from auditory warning tones had damage implicating the right insula and the underlying white matter. The right insula has been associated with sustained attention (Thakral and Slotnick, 2009) and has important connections to the ACC (Augustine, 1996), a structure crucial for cognitive control and conflict resolution (Botvinick et al., 1999; Fan et al., 2003). This suggests that conflict resolution can be improved in neglect patients by modulating alerting and orienting, but only if critical structures for conflict resolution such as the insula are spared. The extension of the lesion in these patients into the white matter might also have damaged the acoustic radiations, probably preventing auditory input to reach cortical structures in the right hemisphere, although this hypothesis should be confirmed in further studies.

Malhotra et al. (2009) have also recently demonstrated an interaction between sustained attention and spatial attention after right parietal damage. Neglect patients presented a vigilance decrement but only when the task involved spatial components. These vigilance decrements were associated with lesions to the posterior parietal cortex. These results further suggest an important interaction between the alerting and the orienting network, although this time, alerting is not phasic, as in our experiments, but tonic (sustained attention). This is consistent with studies of neurologically intact individuals showing that increased working memory load can interact with the ability to sustain attention (Caggiano and Parasuraman, 2004).

It has been proposed that in order to prevent inappropriate responses to irrelevant stimuli, the activity of the ventral fronto-parietal network, underlying re-orienting to unexpected targets, is suppressed by the sustained activation of the dorsal fronto-parietal network, responsible for endogenous orienting processes (Corbetta et al., 2008). If the interaction within and between fronto-parietal networks is partially dysfunctional in neglect patients (Bartolomeo, 2006; He et al., 2007), then enhancing the locus coeruleus/norepinephrine system (Coull et al., 1999) output by an alerting tone could partially restore the equilibrium between them, improving attentional orienting to left-sided stimuli.

The interactions between alerting, orienting and executive control found here point to an important interplay between these attentional processes. A deficit in sustained attention exacerbates a defective orienting process, which impairs the ability to resolve conflict with maximal efficiency. This is an important finding because previous studies had pointed to the independence of these attentional networks (Fan et al., 2005, 2002; Fernandez-Duque and Posner, 1997). Here we propose that they work closely together, one network modulating the efficiency of the other in order to reach maximal efficiency in complex situations.

Our results have also provided further evidence on how the alerting network can modulate the rightward bias of attention observed in neglect (Husain and Nachev, 2007; Husain and Rorden, 2003; Robertson et al., 1995). We have shown that enhancing the alerting state might improve the disengagement deficit found in these patients. This is also an important finding because this deficit has been associated with the severity of neglect (Losier and Klein, 2001; Morrow and Ratcliff, 1988), and could underlie part of its disabling consequences on everyday tasks. Therefore, modulating alertness might affect mechanisms linked with those clinical findings.

In summary, our data have contributed to the understanding of attentional mechanisms in two ways. Firstly, we have shown that alertness can improve the orienting of attention to left-sided events, improving conflict resolution on the neglected visual field. And secondly, our results demonstrate that the attentional networks interact, and modulating alertness may be an important way of improving basic mechanisms associated with neglect, such as the orienting deficits.

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