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Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions

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Recent evidence suggests that there are two possible systems for empathy: a basic emotional contagion system and a more advanced cognitive perspective-taking system. However, it is not clear whether these two systems are part of a single interacting empathy system or whether they are independent. Additionally, the neuroanatomical bases of these systems are largely unknown. In this study, we tested the hypothesis that emotional empathic abilities (involving the mirror neuron system) are distinct from those related to cognitive empathy and that the two depend on separate anatomical substrates. Subjects with lesions in the ventromedial prefrontal (VM) or inferior frontal gyrus (IFG) cortices and two control groups were assessed with measures of empathy that incorporate both cognitive and affective dimensions. The findings reveal a remarkable behavioural and anatomic double dissociation between deficits in cognitive empathy (VM) and emotional empathy (IFG). Furthermore, precise anatomical mapping of lesions revealed Brodmann area 44 to be critical for emotional empathy while areas 11 and 10 were found necessary for cognitive empathy. These findings are consistent with these cortices being different in terms of synaptic hierarchy and phylogenetic age. The pattern of empathy deficits among patients with VM and IFG lesions represents a first direct evidence of a double dissociation between emotional and cognitive empathy using the lesion method.

Keywords: Emotional empathy; cognitive empathy; mirror neurons; inferior frontal gyrus; ventromedial prefrontal cortex

Abbreviations: ANOVA = analysis of variance; BA = Brodmann area; EC = empathic concern scale; FS = fantasy scale; HC = healthy control; IFG = inferior frontal gyrus; IRI = Interpersonal Reactivity Index; MNS = mirror neuron system; PC = posterior lesion; PD = personal distress scale; PT = perspective-taking scale; ToM = Theory of Mind; VM = ventromedial prefrontal; WCST = Wisconsin Card Sorting Test.

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Introduction

Human empathy is a psychological construct regulated by both cognitive and affective components, producing emotional understanding. Impaired empathy is a central characteristic of several neurological and psychiatric conditions such as frontotemporal lobar degeneration (Rankin *et al.*, 2005, 2006) autism (Dziobek *et al.*, 2008) and schizophrenia (Lee *et al.*, 2004). Current evolutionary evidence suggests that there are several systems mediating empathy: phylogenetically early emotional contagion systems and more advanced cognitive perspective-taking systems (De Waal, 2007). The basic emotional contagion system is thought to support our ability to empathize emotionally ('I feel what you feel'). According to Preston and de Waal's (2002) perception-action hypothesis, perception of a behaviour in another automatically activates one's own representations for the behaviour, and output from this shared representation automatically proceeds to motor areas of the brain where responses are prepared and executed. This state-matching reaction has been related to the simulation theory and the mirror neuron system (MNS) (Gallese, 2007). The discovery of the MNS in the monkey's F5 region and in the human inferior frontal gyrus (IFG) demonstrates that a mechanism for translation is automatically elicited when viewing actions of others. While some models for empathy do not attribute any role to motor mirror neurons, activation of the motor

MNS involving the IFG has been shown recently to occur not only with respect to motor actions but to emotion recognition or evaluation (Carr *et al.*, 2003; Seitz *et al.*, 2008) and emotional empathy (Jabbi *et al.*, 2007; Schulte-Ruther *et al.*, 2007) as well. While the latter studies and other studies (Wicker *et al.*, 2003; Singer *et al.*, 2004) have also focused on the role of the insula in simulation of the others' emotional experiences, a recent study has emphasized the specific role of the IFG in emotional empathy (Schulte-Ruther *et al.*, 2007). Functional neuroimaging data demonstrating IFG activation during both imitation and passive viewing of emotional faces, are in line with this view (Dapretto *et al.*, 2006). Moreover, although Gazzola *et al.* (2006) have shown that individuals who score higher on a cognitive empathy scale [the perspective taking of the Interpersonal Reactivity Index (IRI)] activated the MNS more strongly, Kaplan and Iacoboni (2006) report a correlation between scores on an emotional empathy measure [the empathic concern scale (EC) of the IRI] and activity in IFG while watching action sequences. Thus, it appears that the core structure of emotional empathy is the IFG which appears to be involved mainly emotional contagion and emotion recognition.

However, the human empathic response is more than pure emotional contagion (Stotland and Dunn, 1963) and involves also cognitive perspective taking. Thus, the second empathy system requires more complex cognitive functions, including empathic perspective-taking and mentalizing (De Waal, 2007). This process of understanding another person's perspective, termed 'cognitive empathy' ('I understand what you feel') appears to depend upon higher cognitive functions such as cognitive flexibility (Decety and Jackson, 2004). Neuroimaging studies have implicated the medial frontal lobes as playing a critical role in a dedicated 'mentalizing' or 'Theory of Mind' (ToM) network in humans (Gallagher and Frith, 2003). However, others have questioned the role of these cortices (Bird *et al.*, 2004), suggesting that the temporoparietal junction (TPJ); (Saxe and Kanwisher, 2003; Samson *et al.*, 2004), as well as the superior temporal sulcus (STS); (Frith and Frith, 2003) are involved in ToM. Nonetheless, it has been repeatedly reported that cognitive empathy is related to ToM or mentalizing and that these abilities are impaired in patients with ventromedial prefrontal (VM) lesions (Eslinger, 1998; Shamay-Tsoory *et al.*, 2003). In accordance with this, increased VM activation during a mentalizing task, reported in fMRI studies (Mitchell *et al.*, 2006), further supports this region's role in cognitive empathy and ToM. Damage to the VM has been related to impaired higher decision making (Bechara *et al.*, 1998; Fellows and Farah, 2007; Koenigs and Tranel, 2007) and utilitarian moral judgements (Koenigs *et al.*, 2007), cognitive functions related to higher metacognition.

Collectively, the neuroanatomical evidence points to two possible empathy systems: an emotional system, which involves the IFG, and a more cognitive system involving the VM. Furthermore, the distinction between the emotional and cognitive empathic sub-processes is consistent with phylogenetic and developmental data. Whereas emotional contagion, the lowest common denominator of all empathic responses, is reported in birds and rodents, perspective-taking abilities are evident only in more phylogenetically advanced mammals such as great apes (De Waal, 2007). Moreover, developmentally, babies show emotional contagion in response to the distress of another individual without being able to separate their own and the other's distress (Singer, 2006). Only later during childhood and adolescence individuals become increasingly more capable of taking the other individual's perspective (Hoffman, 1977; Preston and de Waal, 2002; Gallese, 2003; Decety and Jackson, 2004).

Several theoretical models have addressed the issue of distinct emotional and cognitive facets of empathy processing (Adams, 2001; Preston and de Waal, 2002; Decety and Jackson, 2004; Leiberg and Anders, 2006). Most of the models support a theoretical framework in which the empathic process entails a hybrid of emotional as well as cognitive components which functionally intertwine to form the empathic state. However, none of these models address directly the relationship between the cognitive and emotional aspects of empathy. Two potential models may describe the possible relationship between emotional and cognitive based empathy. The first possible relationship between emotional and cognitive empathy is that of 'dependence'. Since emotional contagion is earlier, more automatic and basic both developmentally and phylogenitically than cognitive empathy, it may be proposed that cognitive empathy is based on, or may follow the basic emotional contagion and therefore emotional empathic processing is a pre-condition to cognitive empathy. According to this formulation, impairment in emotional empathy will necessarily result in impaired cognitive empathy as well. A second, equally plausible theoretical model is that of 'exclusivity'. This model suggests that emotional and cognitive empathy have different neural origins. The implication of this model would be that lesions that may impair emotional empathy will not have an effect on cognitive empathic abilities and vice versa.

While neuroimaging studies to date have been increasingly capable of characterizing the neural networks involved in emotional and cognitively based empathy (Hynes *et al.*, 2006; Vollm *et al.*, 2006; Schulte-Ruther *et al.*, 2007), only lesion studies can examine directly whether emotional empathy is 'necessary' for cognitive empathy or whether a neuroanatomical and behavioural double dissociation exists between these two components.

Therefore, the first goal of the current study was to investigate the neuroanatomical substrates underlying the emotional and cognitive empathy systems. Based on the above evidence we hypothesized that VM structures are necessary for cognitive empathy (and ToM) whereas IFG structures are necessary for affective empathy (and emotion recognition). The second goal of the present study was to

investigate the relationship between the two empathy systems. We reasoned that if a double dissociation between the systems is observed, then the exclusivity model better represents the relationship between these two components. However, if impairment in one component is related to impairment in the second component then the dependence model may better characterize the relationship between the two systems.

Materials and methods

Patients

Thirty neurological patients with localized damage limited to either the VM ($N = 11$) or IFG ($N = 8$) areas of the frontal cortex, or posterior lesions (PC, $N = 11$), and 34 healthy controls (HC) participated (Fig. 1).

Aetiologies included stroke, tumours (meningiomas) and head injury. The proportion of aetiologies was matched between groups (see Table 1) and chi-square analysis indicated no significant differences between patient groups in the proportions of aetiologies [$\chi^2(4) = 4.214$, NS]. Patients with diffuse axonal injury were excluded on the basis of MRI/CT scans. Patients with meningiomas were recruited at least 1 year following the resection of the tumours, when they were in a stable neurological condition, leading a relatively independent life. Inclusion criteria included postoperative imaging and behavioural changes. In addition, we did not include patients who underwent herniation or were stuporous prior to surgery and assume therefore that the tumour did not have an irreversible impact on distal brain structures. For the stroke and head-injury patients, testing was also conducted at the chronic phase of recovery (at least 6 months post-trauma), following signing of an informed consent form. Ethical approval was granted by the hospital's Ethics Committee. A neurologist who was blind to the study's hypotheses and the neuropsychological data carried out anatomical classification based on acute and recent CTs or MRIs. CT scans were used for 25 patients and MRIs for five patients. For patients with head injury, both the acute neuroradiological studies (performed within the first 24–48 h post-injury) and the chronic-recent scans were examined. Frontal and posterior lesions included cases with grey and white matter damage. Localization of lesions was determined using standard atlases (Damasio and Damasio, 1989) and were further transcribed from CT and MRI images to the appropriate slices of the MRIcro program (Rorden, http://www.sph.sc.edu/comd/rorden/mricro.html). We identified the specific regions that were damaged in each patient by superimposing their individual scans on a healthy brain template. Lesions were drawn by the first author and were independently verified by J.A.P., an expert neurologist with experience in neuroimaging. Where there were differences, J.A.P.'s decision was implemented. Based on other well-acknowledged lesion studies (Bechara *et al.*, 1998; Stuss and Levine, 2002; Fellows and Farah, 2007), the contour of the lesion was transposed manually onto the slices of the normal brain, taking into consideration the relation of the lesion and the identified pertinent anatomical landmarks. The MRIcro's 'Template Technique', in which lesions for all patients are drawn on a standard scan from a healthy individual, was applied. In this method, all lesions are presented in the same MNI stereotaxic space. In the next stage, the software's Brodmann map was used to document

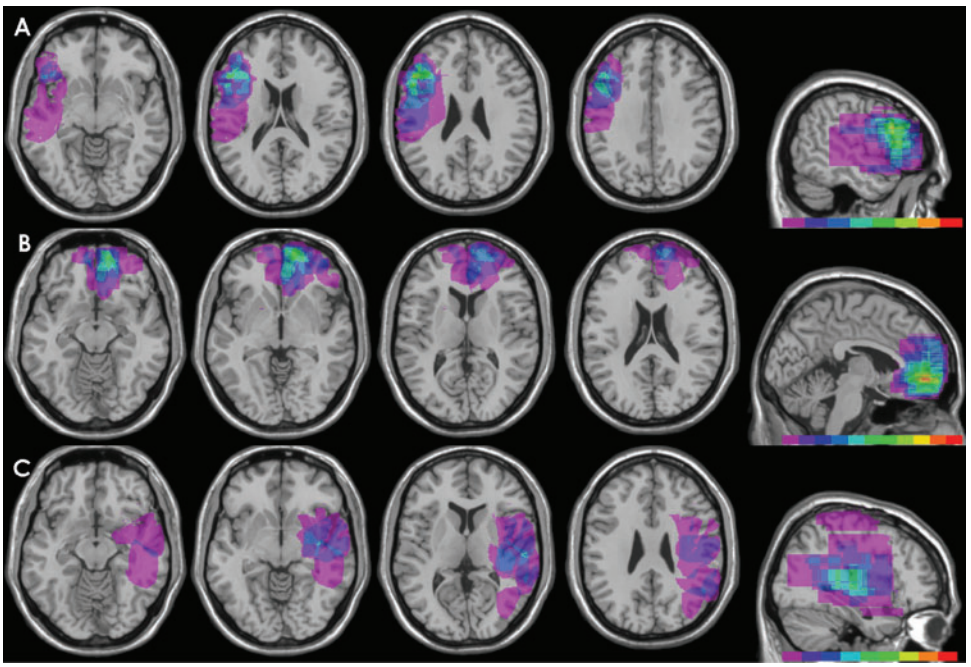

Fig. 1 Location and overlap of brain lesions. (**A**) Lesions of the eight subjects (eight males, mean age 32.75) with IFG damage. (**B**) Lesions of the 11 subjects (nine males, two females, mean age 38.0) with VM damage. (**C**) Lesions of 11 subjects (seven male, four females, mean age 36.45) with damage outside the frontal lobes (PC). Lesions are projected on four axial slices and one sagittal view of the standard Montreal Neurological Institute brain, oriented according to radiological convention (i.e. left is right). Areas damaged in one subject are shown in pink; brighter shades denote the degree to which lesions involve the same structures in two or more individuals, as indicated by the colour strip at the right-hand corner.

the Brodmann areas (BAs) involved in each lesion. In this manner, for each patient, each BA was rated as damaged or not damaged. To examine reproducibility of this transcription method, a random sample of 12 lesions was drawn by a third experimenter, a neuropsychologist trained in imaging. Correlation of lesion volumes between experimenters was highly significant ($r = 0.749$, $P = 0.005$), indicating the high reliability of this method across experimenters.

Subjects were then divided into three groups according to Damasio and Damasio (1989): the VM group, if damage involved mostly the orbitofrontal and/or the ventral portion of the medial wall of the frontal lobe (BAs: mesial 8 and 9, 10, 24 and 32, 10, 11 and 47); the IFG group, if damage involved mostly the Pars opercularis and the Pars triangularis (BAs 44, 45), and a group of patients with posterior lesion involving damage outside the frontal lobes comprising one of the two control groups. Figure 1 presents lesion superimposition for the VM, IFG and PC groups (lesions are flipped to one hemisphere to enhance anatomical overlap). In two cases, patients assigned to the IFG group had damage that extended to include portions of area 6; in four cases lesions involved also area 48 and in three patients the damage also included the temporal pole (BA 38) extending to the beginning of area 47. Among patients assigned to the VM group, four had a lesion extending to BA 46, and in one patient the lesion reached BA 25. While most of the patients had unilateral lesions, three patients from the posterior lesion control group had bilateral lesions. The volume of lesions ranged from 0.90 cm^3 to 145.317 cm^3 (mean = 33.71 cm^3, SD = 33.03 cm^3) and there were no significant differences in the size of lesions among the three lesion groups [$F(2,29) = 1.549$, NS], indicating that lesion sizes were not different between groups.

Experimental measures

Emotional and cognitive empathy

To assess empathy multi-dimensionally, we administered the IRI. The IRI (Davis, 1983), is a 28-item self-report questionnaire that measures both components of empathy. To date, it is the only published measure that allows a multi-dimensional assessment of empathy. The questionnaire contains four 7-item scales (two cognitive scales and two affective scales). The two cognitive scales are: (i) the perspective-taking scale (PT) which measures the reported tendency to adopt spontaneously the psychological point of view of others ('I sometimes try to understand my friends better by imagining how things looks from their perspective'); (ii) the fantasy scale (FS), measuring the tendency to imaginatively transpose oneself into fictional situations ('When I am reading an interesting story or novel I imagine how I would feel if the events in the story were happening to me'). The PT was found to be consistently related to measures of interpersonal functioning, social competence and high self esteem but not to affective empathy (Davis, 1983). The FS is highly related to verbal measures and intellectual abilities, especially verbal intelligence. Both scales were found to be positively correlated with other validated measures of cognitive empathy such as the Hogan empathy scale (Hogan, 1969), suggesting that these scales indeed measure cognitive empathy (Davis, 1983).

The two affective scales are the EC and the personal distress scale (PD). The EC scale taps the respondents' feelings of warmth, compassion and concern for others (e.g. 'I often have tender, concerned feelings for people less fortunate than me'). The PD scale assesses self-oriented feelings of anxiety and discomfort resulting from tense interpersonal settings (e.g. 'being in a tense emotional situation scares me').

Individual scores for each item (on a scale from 1 to 5) were transformed to a –2 to 2-point scale, therefore the scores of each sub-scale ranged between –14 and +14 points. Full-scale scores are not calculated as each scale has been shown to measure a discrete component of empathy (Davis, 1983). To assess cognitive empathy we used the mean score of the PT and the FS sub-scales whereas emotional empathy was assessed using the mean score of the EC and the PD sub-scales.

The factor structure of the IRI was confirmed in a study of female dieticians ($n = 217$) and dietetic interns ($n = 168$) (Spraggins *et al.*, 1990). The IRI has good internal consistency, with alpha coefficients ranging from 0.68 to 0.79 (Davis, 1983; Christopher *et al.*, 1993)

Emotion recognition task

A computerized task was designed to assess the ability to recognize various categories of emotional expressions (basic, complex, negative, positive). The test consists of 52 photographs of eyes reflecting 13 basic as well as complex emotions (Ekman and Freisen, 1976; Baron-Cohen *et al.*, 2001): happy, sad, afraid, surprised, distressed, disgusted, angry, interested, worried, confident, fantasizing, preoccupied, friendly and suspicious. At the bottom of each picture stimulus, two words are printed, one word describes the correct emotion expressed by the eyes and the other is a distracter of a different type. Scoring consisted of the percent of the total correct responses.

ToM: second-order false belief task

The second-order false belief task evaluates one's ability to understand what someone else thinks about what someone else thinks (Stone, 1998). In this task, the subject is required to understand that other people can represent mental states. In each story, Person 'A' puts an object somewhere and leaves the room. Person 'B' moves the object while Person A is out of the room. However, Person A is peeking back and watching what B does. Person B does not know that Person A has seen that he moved the object. The subject is then asked what person B knows regarding what person A thinks. Another informative question is asked to control for misunderstanding of the story. Subjects were given eight stories. A copy of each story was handed to the subjects to control for memory load, attention and working memory deficits. Patients who presented with difficulties in answering the control questions were excluded from the study.

Neuropsychological examination

All patients completed the Raven's Progressive Matrices to assess reasoning and to obtain an estimate of general intellectual functioning (Beaumont and Davidoff, 1992). Also, The Beck Depression Inventory (Beck *et al.*, 1987) was administered, to obtain a measure of depression among patients. Executive functions were assessed by The Wisconsin Card Sorting Test (WCST), administration and scoring followed (Heaton *et al.*, 1993) and Verbal Fluency [category (animals, fruit and vegetables) and letter fluency]. Two sub-scales from the WAIS-R were also administered: Digit Span (assessing attentional span) and Similarities (used to asses verbal reasoning).

Procedure

Prior to the experiment all patients were examined neurologically. Based on this screening and imaging data, suitable candidates were identified and contacted. Patients suffering from visual impairment, language deficits or motor limitations that might interfere with the performance of the neuropsychological tasks were excluded. All participants signed an informed consent form. Each participant was assessed individually for at least one session, with about a week interval between them. Tasks (ECs, ToM, emotion recognition and neuropsychological assessment) were performed in a random order. For two participants, the data for the IRI and emotional recognition task were lost due to technical failure (one subject did not have the IRI scores and one did not have the emotion recognition scores).

Results

Neuropsychological functioning

Analysis of variance (ANOVA) revealed no significant difference between the groups with regard to age [$F(3,59) = 1.203$, NS], estimated verbal IQ [$F(3,59) = 2.145$, NS], Raven's Progressive Matrices [$F(3,59) = 2.310$, NS], perseverative responses in the WCST [$F(3,59) = 0.890$, NS], Verbal Fluency [$F(3,59) = 0.854$, NS], or the score on the Beck depression inventory [$F(3,59) = 0.614$, NS] (all $P > 0.1$).

Emotional and cognitive empathy

The means, standard deviations, one-way ANOVA and *post hoc* (Duncan) analysis of group differences in the empathy sub-scales are reported in Table 2. As observed in the table the VM group was significantly different from the rest of the groups in the PT and FS sub-scales whereas the IFG group was significantly different from the other groups in the PD sub-scale. As described before, to further assess cognitive empathy we used the mean score of the PT and the FS sub-scales whereas emotional empathy was assessed using the mean score of the EC and the PD sub-scales.

To examine differences in performance on the different types of empathy (emotional and cognitive empathy scales), a repeated measures ANOVA was conducted with the lesion group as an independent variable and cognitive or emotional empathy as dependent variables. This analysis indicated a significant interaction between type of empathy and group [$F(3,59) = 5.613$, $P = 0.002$] and a significant

Table 1 Patients demographic details and performance on measurements of executive functions, RAVEN and BDI

	VM ($N = 11$)	IFG ($N = 8$)	PC ($N = 11$)
	Male = 9 Female = 2	Male = 8 Female = 0	Male = 7 Female = 4
Age, mean (SD)	36.45 (16.20)	32.75 (15.06)	38.00 (14.89)
Years of education, mean (SD)	11.70 (1.41)	14.12 (2.58)	13.36 (1.74)
Time since injury in years (SD)	9.36 (11.85)	7.25 (6.94)	7.27 (5.38)
Laterality	Right = 3 Left = 8 Bilateral = 3	Right = 5 Left = 3	Right = 3 Left = 8
Etiology	Head injury = 8 Tumor = 2 Stroke = 1	Head injury = 6 Tumor = 2	Head injury = 6 Tumor = 3 Stroke = 2
WCST set loss, mean (SD)	0.54 (1.21)	1.0 (1.26)	0.90 (1.19)
WCST perseverative errors, mean (SD)	11.27 (7.146)	15.67 (4.62)	13.10 (7.40)
WCST total errors, mean (SD)	22.90 (12.38)	31.33 (3.93)	23.80 (13.18)
Digit span, mean (SD)	8.22 (1.64)	8.00 (1.58)	7.88 (1.86)
Fluency phonemic, mean (SD)	9.18 (2.85)	12.25 (7.19)	12.00 (4.96)
Fluency semantic, mean (SD)	17.86 (5.44)	22.25 (7.19)	19.54 (5.56)
Raven, mean (SD)	39.40 (28.32)	40.00 (22.32)	60.25 (26.55)
Similarities, mean (SD)	9.50 (0.79)	11.40 (2.07)	11.00 (2.13)
BDI, mean (SD)	18.25 (8.68)	13.50 (11.36)	12.36 (7.21)

Table 2 Mean and standard deviation of the IRI scores

	Groups, Mean (SD)				
IRI Scales	VM	IFG	PC	HC	Group differences
PT	−2.50 (5.42)[a]	5.62 (3.26)	2.60 (2.97)	5.10 (6.21)	[$F(3,56) = 8.44$, $P = 0.0001$]
FS	−3.88 (6.17)[a]	2.71 (5.97)	0.00 (7.00)	3.00 (5.94)	[$F(3,56) = 2.83$, $P = 0.05$]
EC	2.88 (4.42)	6.32 (3.35)	3.20 (4.09)	6.00 (5.08)	[$F(3,56) = 2.34$, $P = 0.08$]
PD	2.38 (2.77)	0.09 (4.81)[a]	−5.40 (4.62)	−0.50 (5.38)	[$F(3,56) = 2.91$, $P = 0.04$]

[a]Significantly different from the others groups.

group effect [$F(3,59) = 5.713$, $P = 0.002$]. As shown in Fig. 2, *post hoc* (Duncan) analysis indicated that patients with VM lesions were impaired in cognitive empathy compared to the HC, patients with posterior lesions (PC) and patients with IFG lesions ($P < 0.05$). The IFG, HC and PC groups did not differ from each other. On the other hand, patients with IFG lesions were impaired in emotional empathy compared to the HC and the PC group ($P < 0.05$) and marginally different than the VM group ($P = 0.054$). The VM, HC and PC groups did not differ from each other.

Emotion recognition and ToM

Another repeated measures ANOVA was conducted to examine differences between groups on the ToM and emotional recognition measurements (a *z*-score was calculated for each variable in order to directly compare performance on these tasks). There was a significant interaction effect between the group and the tasks [$F(3,59) = 11.89$, $P = 0.0001$] and a significant group effect [$F(3,59) = 4.416$, $P = 0.007$]. *Post hoc* analysis indicated that patients with VM lesions were impaired in ToM compared to the HC, PC and IFG groups, ($P < 0.05$). Here again the IFG, HC and PC groups did not differ significantly from each other. While patients with VM lesions showed the most impaired performance in ToM, patients with IFG lesions were impaired in emotional recognition compared to the HC and the PC groups ($P < 0.05$) (Fig. 3). The VM and PC, HC groups did not differ from each other.

The relationship between ToM and cognitive empathy, emotion recognition and emotional empathy

To examine our definition of cognitive empathy as involving mainly ToM processing we conducted a correlation analysis (one-tailed) between the PT and the FS sub-scales and the ToM scores. This analysis indicated marginally significant correlation between the PT sub-scale and ToM ($r = 0.198$, $P = 0.07$). The FS sub-scale did not correlate with ToM ($r = 0.011$, NS).

The same analysis was conducted between the emotional empathy sub-scales (EC, PD) and emotion recognition. Only the PD sub-scale was significantly correlated with emotion recognition ($r = 0.286$, $P = 0.016$) whereas the EC scale did not ($r = 0.018$, NS).

The contribution of the STS to empathy

Although the PC group did not differ significantly from the HC group on any cognitive or affective measure of empathy, we further divided the PC groups into two new subgroups to test the contribution of the STS to cognitive and emotional empathy. The STS group included seven patients with lesions involving BAs 20, 21, 22, 37, 39 and 40 whereas the non-STS group included four patients with lesion involving BAs 1, 2, 3, 4, 19, 38, 41 and 43.

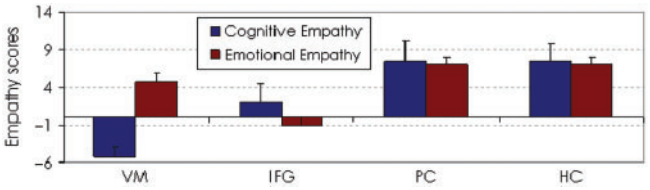

Fig. 2 Group and task (cognitive versus emotional empathy) interactions. Significant interaction between group and empathy type [$F(3,59) = 5.613$, $P = 0.002$]. Patients with VM lesions were impaired in cognitive empathy compared to the healthy controls (HC), patients with posterior lesions (PC) and patients with IFG lesions ($P < 0.05$) whereas patients with IFG lesions were impaired in emotional empathy compared to the HC, VM and the PC group.

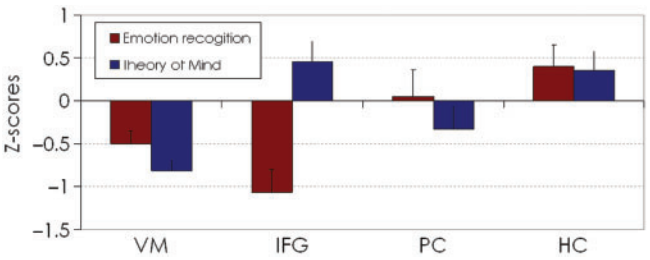

Fig. 3 Group and task (ToM versus emotional recognition) interactions. Significant interaction effect between the ToM task and the emotion recognition task. Patients with VM lesions were impaired in theory of mind compared to the HC, PC and IFG groups, ($P < 0.05$) whereas patients with IFG lesions were impaired in emotional recognition compared to the HC and the PC groups ($P < 0.05$).

First we examined the role of the STS in cognitive empathy. One-way ANOVA analysis indicated significant differences between the groups in both ToM [$F(4,58) = 8.354$, $P = 0.0001$] and cognitive empathy scales [$F(4,58) = 6.004$, $P = 0.0001$]. *Post hoc* analysis indicated that both the VM and STS groups were significantly impaired in ToM as compared to the rest of the groups ($P < 0.05$) whereas only patients with VM damage were impaired as compared to the rest of the groups in the cognitive empathy scales ($P < 0.05$).

The same analysis was conducted in emotional empathy. One-way ANOVA analysis indicated significant differences between the groups in both emotion recognition [$F(4,58) = 3.798$, $P = 0.008$] and emotional empathy scales [$F(4,58) = 4.350$, $P = 0.001$]. *Post hoc* analysis indicated that the IFG group was significantly impaired as compared to the HC in emotion recognition ($P < 0.05$) and significantly impaired as compared to the non-STS group in the emotional empathy scales.

Cognitive and emotional indices

For each participant, overall cognitive and emotional indices were calculated. To compute each index we computed *z*-scores for the four tasks and calculated the mean score of the emotional (emotional empathy, emotion recognition) and the cognitive (cognitive empathy, mentalizing) measures.

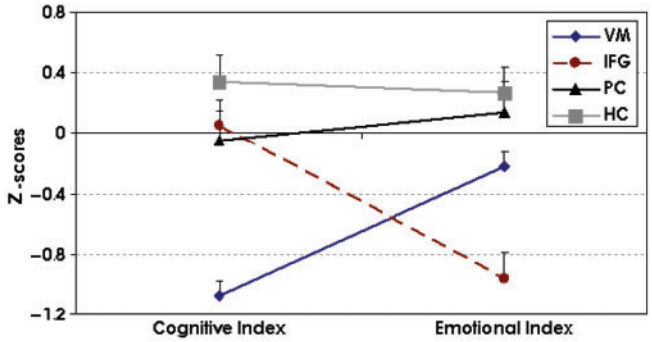

Fig. 4 Double dissociation between the emotional and cognitive indices. Significant interaction effect between empathy type (emotional versus cognitive) and lesion location. Patients with VM lesions were significantly impaired in the cognitive index as compared to the IFG, PC and HC groups, whereas patients with IFG lesions were impaired in the emotional index as compared to the VM, PC and HC group.

We then used these cognitive and emotional indices calculated in *z*-scores, to examine the performance of the VM versus IFG groups and the control groups across tasks. Repeated measures analysis revealed a significant interaction [$F(3,60) = 11.465$, $P = 0.0001$] between groups and the empathy index (cognitive versus emotional) (Fig. 4). Follow-up *post hoc* analysis indicated that patients with VM lesions were impaired in the cognitive index as compared to the IFG, PC and HC groups ($P < 0.05$), whereas patients with IFG lesions were impaired in the emotional index as compared to the VM, PC and HC groups ($P < 0.05$).

To examine separately the performance of the VM versus IFG groups across tasks and investigate whether a double dissociation exists between these brain areas, we conducted another repeated measures analysis with only the VM and the IFG groups. This analysis revealed a significant interaction [$F(1,17) = 15.809$, $P = 0.001$] between groups (VM versus IFG) and the empathy index (cognitive versus emotional), further highlighting the double dissociation between these two aspects of empathy. Again, patients with VM lesions were impaired in the cognitive index as compared to the IFG group ($P < 0.05$), whereas patients with IFG lesions were impaired in the emotional index as compared to the VM group ($P < 0.05$).

To rule out the possibility that different confounds such as age, number of years of education, lesion size, time since injury to study, intellectual abilities and BDI had an effect on the differences between groups, we reanalysed the data with each of these variables serving as a covariate. Repeated measures analysis revealed that the interaction between groups and the empathy index (cognitive versus emotional) remained highly significant after controlling for age [$F(1,16) = 14.177$, $P = 0.002$], time since injury [$F(1,16) = 15.275$, $P = 0.001$], years of education [$F(1,16) = 25.051$, $P = 0.0001$], estimated verbal intellectual abilities [$F(1,16) = 7.417$, $P = 0.02$], size of lesion [$F(1,16) = 13.672$, $P = 0.002$] and BDI scores [$F(1,16) = 16.491$, $P = 0.001$].

Additionally, to ensure that the division of groups was not affected by imaging method, another repeated measures ANOVA (VM/IFG*cognitive/affective index) was conducted with patients who had CT only (six patients from the IFG group and 10 from the VM group). The interaction between group and empathy type remained significant [$F(1,14) = 14.541$, $P = 0.002$], further confirming the dissociation between emotional and cognitive empathy.

Finally, the interaction effect between the IFG and the VM groups remained highly significant [$F(1,14) = 22.762$, $P = 0.0001$] when we omitted from the analysis three patients that have had bilateral lesions.

We further divided the lesion groups according to laterality of the lesion (right, left and bilateral VM; right and left IFG; right and left PC) and conducted one-way ANOVA to examine whether bilateral and unilateral lesions had different effects on task performance. This analysis indicated significant difference between groups in both the cognitive index [$F(7,56) = 13.116$, $P = 0.0001$] well as the emotional index [$F(7,56) = 5.991$, $P = 0.0001$]. *Post hoc* analysis showed that in the cognitive index the right VM as well as the left VM patients were significantly impaired as compared to the left IFG, right IFG, right PC, left PC and HC groups ($P < 0.05$). The bilateral VM and the right and left VM groups did not differ significantly from each other. In the emotional index, *post hoc* analysis indicated that the left IFG group was significantly impaired as compared to all the other groups excluding the right IFG which was significantly impaired as compared to the right and left PC, HC and the bilateral VM groups. These results confirmed that the performance of the patients with the bilateral patients did not differ significantly from the patients with the unilateral lesions.

Mapping of lesions

In addition to the analysis based on the standard anatomical groupings, we related performance to anatomy using a more precise mapping of the lesions. First, we used the cognitive and emotional indices to select the most impaired patients (at least 1 SD below average) and characterize a cognitive-empathy-impaired group and an emotional-empathy-impaired group. The cognitive-empathy-impaired group consisted of seven patients (five from the VM group, one each from the IFG the PC groups). The emotional-empathy-impaired group consisted of six patients (four from the IFG group and one each from the VM and PC groups). We then identified which Brodmann regions were damaged in the entire sample of thirty patients, to detect which of these areas were most related to impaired cognitive versus emotional empathy index. Thus, each BA in the IFG, VM and PC lesions was rated as damaged or not damaged in each patient. The BAs that were identified as damaged in one or more patients were: 9, 6, 22, 24, 32, 44, 45, 10, 11, 48, 47, 46, 1, 2, 3, 4, 20, 21, 25, 37, 38, 41, 43 and 19.

Analysis of the frequencies of damage in each area using Chi-square revealed that only lesions involving

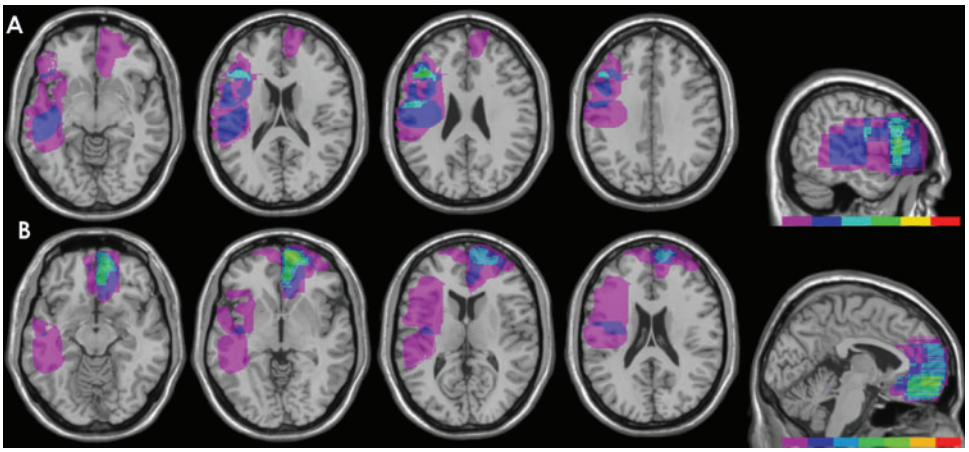

Fig. 5 Location and overlap of brain lesions according to emotional versus cognitive empathy impairment-groups. (**A**) Lesions of the emotional-empathy-impaired group ($n = 6$). Four patients had an IFG damage involving area 44, one had a VM damage and one had a PC damage. Chi-square analysis revealed that lesions involving area 44 were significantly more frequent in this group as compared to the non-impaired group [$\chi^2(1) = 7.071$, $P = 0.008$]. (**B**) Lesions of the cognitive-empathy-impaired group ($n = 7$): five had VM damage involving area 10 and 11, one had an IFG damage and one had a PC damage. Chi-square analysis revealed that lesions involving area 10 [$\chi^2(1) = 6.04$, $P = 0.010$] and area 11 [$\chi^2(1) = 5.185$, $P = 0.023$] were significantly more frequent in this group as compared to the non-impaired group.

area 10 [$\chi^2(1) = 6.04$, $P = 0.010$] and area 11 [$\chi^2(1) = 5.185$, $P = 0.023$] were significantly more frequent in the cognitive-empathy-impaired group as compared to the non-impaired group, indicating that areas 10 and 11 are critical for cognitive empathy. On the other hand, only damage to area 44[$\chi^2(1) = 7.071$, $P = 0.008$] was significantly more frequent in the emotional-empathy-impaired group as compared to the non-impaired group, indicating that this area is critical for emotional empathy. Superimpositions of lesions are shown in Fig. 5.

Discussion

Consistent with a growing body of recent evidence our results demonstrate that both the IFG and the VM are involved in emotional and cognitive empathy, respectively. As predicted, patients with VM damage show consistent and selective deficit in cognitive empathy and ToM, while presenting with intact emotion recognition and emotional empathy. Patients with IFG lesions, on the other hand, displayed extremely impaired emotional empathy and emotion recognition. Specifically, BA 44 was found most critical for emotional empathy while areas 11 and 10 were found critical for cognitive empathy. Interestingly, area 44, which has been reported as cytoarchitectonically homologous to F5 (Petrides *et al.*, 2005), was identified as a central part of the MNS (Rizzolatti, 2005). Thus, although some doubt has been voiced with respect to the role played by MNS in social cognition (Jacob and Jeannerod, 2005), these results present an empirical evidence that the MNS is essential for emotional empathy.

Nonetheless, although area 44 has been clearly related to social cognition, it is not a region which is typically associated with the emotional aspect of social cognition. How can one explain the essential role of BA 44 in emotional empathy observed in the present study? First, beyond language related functions, neuroimaging studies have suggested a central role of BA 44, as a neural substrate for imitation (Iacoboni *et al.*, 1999, 2001; Nishitani and Hari, 2000, 2002; Tanaka *et al.*, 2001; Koski *et al.*, 2002; Tanaka and Inui, 2002; Carr *et al.*, 2003; Grezes *et al.*, 2003; Rizzolatti and Craighero, 2004). Second, BA 44 have been increasingly implicated in emotion recognition tasks such as identification of emotional intonation (Wildgruber *et al.*, 2005) and judgement of facial expressions (Kesler-West *et al.*, 2001). Additionally, as noted above, activation of BA 44 has been shown recently to occur not only with respect to motor actions but to emotion recognition (Carr *et al.*, 2003). Furthermore, Adolphs *et al.* (2002) have found deficits in emotion recognition from faces and from prosody after damage to either the frontal operculum (involving BA 44) or right somatosensory cortices. Taken together, it appears that of BA 44 is particularly involved in imitation and emotion recognition. It may be interesting to speculate whether imitation, the heart of emotional contagion, is even more enhanced when emotional social stimuli rather than neutral stimuli are presented. Thus, we believe that experiencing emotions may encourage and motivate imitation and therefore depend on intact MNS. This conclusion is compatible with a recent report by Nummenmaa *et al.* (2008) who propose that emotional empathy facilitates motor representation of other peoples' emotions, and results in more vigorous mirroring of the observed bodily and emotional states than cognitive empathy.

These results provide strong support for the existence of two behavioural systems for understanding others: an early emotional matching/mirroring system involving the MNS and a more advanced system for cognitive understanding of mental states, involving the VM cortices. Furthermore, the fact that area 44 was found most critical for emotional

empathy while BA 11 and 10 are necessary for cognitive empathy is consistent with these cortices being, in terms of synaptic hierarchy, unimodal and heteromodal, respectively (Mesulam, 2000). Additionally, areas 10 and 11 differ from area 44 cytoarchitectonically according to the layering of the cortex (Brodmann, 1909): while among the six layers of the isocortex layer IV is not fully developed in BA 44, it is fully developed in areas 11 and 10. Therefore, whereas BA 44 is classified as dysgrangular, areas 11 and 10 are considered as granular cortex. This could be taken as indirect evidence for these parts of area 44 being phylogenetically older than areas 10 and 11.

It should be noted that most of the patients in this study sustained a closed head injury. Although cases of apparent diffuse axonal injury were excluded and the proportion of patients with head injury was matched between the different groups, it is impossible to completely rule out the possibility that in some patients lesions were more diffuse.

Additionally, it should be acknowledged that attempting to convert stereotaxic coordinates based on MRI/CT scans to BAs based on cytoarchitecture is problematic, and therefore the conclusions regarding cytoarchitectonic differences should be treated with caution, particularly since most of our patients had CT scans rather than MRI scans.

Nevertheless, evidence other than cytoarchitectonic and the synaptic hierarchy differences suggests distinct emotional and cognitive empathy systems. As noted above, developmental studies also indicate that emotional contagion is observed earlier in younger babies than perspective-taking abilities, which are acquired during cognitive development (De Waal, 2007). Chakrabarti and Baron-Cohen (2006), for example, have proposed a model in which the emotional component of empathy develops earlier as compared to higher level mechanisms, such as ToM and cognitive empathy.

Collectively, the neuroanatomical, cytoarchitectonic and developmental evidence point to a consistent dissociation between two empathy systems that comprises the empathic response. Our model of two separate systems that operate in an exclusive manner is depicted in Fig. 6. According to our model, in normal circumstances every interaction with a protagonist may trigger independently both an emotional response (emotional empathy) as well as cognitive evaluation of his state of mind and perspective (cognitive empathy). Although both emotional and cognitive components of empathy are working autonomously, every empathic response will evoke both components to some extent, depending on various variables such as the social context, the level of distress (Jackson *et al.*, 2005) and the perceived similarity between the individual and the protagonist (Mitchell *et al.*, 2005). According to our theoretical model, the protagonist's emotions are 'shared', activating brain areas involved in simulation and mirroring, including the IFG. However, the present study shows that one necessary area of this state-matching network is area 44, which is homologous to F5 region in the monkey brain. As

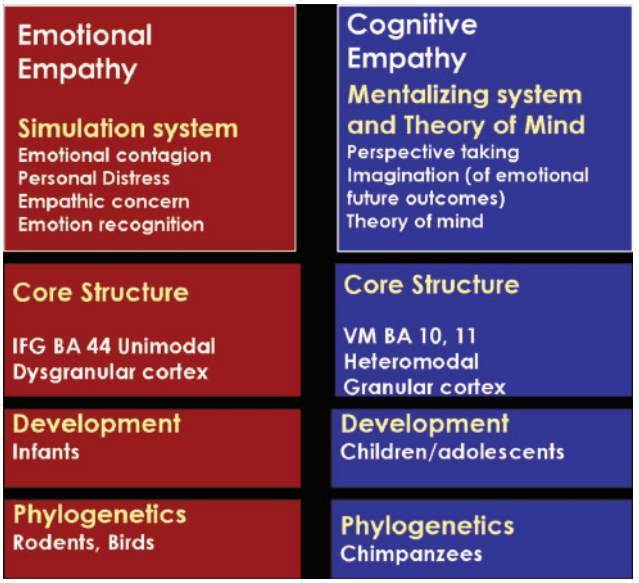

Fig. 6 Two separate systems for emotional and cognitive based empathy. The two upper panels (rows) of the model summarize the present study's behavioural and neuroanatomical double dissociation. Behaviourally, emotional empathy involves personal distress, empathic concern and emotion recognition. Anatomically the IFG appears to be responsible for emotional empathy. We have added phylogenitic, cytoarchitectonic and developmental evidence to support the early, basic and automatic role of emotional empathy (two lower panels). Cognitive empathy, on the other hand, involves perspective taking, the fantasy scale and theory of mind and is mediated by the VM. Phylogenitic, cytoarchitectonic and developmental evidence support its role in higher forms of empathy.

noted above, this system is phylogenetically older and can be observed in rodents and even in birds. Independently, the ability to accurately infer the other's perspective and imagine the protagonist perspective and state of mind is also involved in every social interaction. This process may require the intentional suppression of one's own viewpoint (Keysar *et al.*, 2003; Royzman *et al.*, 2003; Van Boven and Loewenstein, 2003; Bernstein *et al.*, 2004) in order to represent other people's mental states (Frith and Frith, 2003) and take the other's perspective (Decety and Jackson, 2004). Additionally, cognitive empathy requires the ability to imagine the other's perspectives as well as the future outcomes of these perspectives (Davis, 1983). Indeed, the VM has been shown to be a critical neural structure for triggering the affective signals associated with the imagination of future outcomes. For example, increased activity in the VM was reported for the imagination of positive versus negative future events (Sharot *et al.*, 2007). In accordance with this, the VM has been recently associated with imagining and envisioning emotional events (D'Argembeau *et al.*, 2008).

Both functional and lesion studies in humans, as well as the present study's results, suggest that the VM, approximately corresponding to BAs 10 and 11, may play a crucial role in the network performing this mentalizing cognitive

empathic function. This system is phylogenetically younger and is unique to primates and humans adults.

Yet, it is important to point out that although a clear double dissociation was observed in the present study, one may wonder whether emotional and cognitive empathy systems are nevertheless partially overlapping. In this regard Heberlein and Saxe (2005) postulate that a double dissociation does not imply that two processes are always separate, but that they can be separated, which may lead us to a third potential model of empathy in which both cognitive and emotional empathy are partially related. Indeed, although not statistically significant it appears that VM as well as IFG lesions have a general effect on cognitive and emotional empathic abilities. The small number of patients and the variability in lesion aetiologies in each group may have reduced this general effect. Thus, it is possible that both empathic abilities are closely related and that while the VM is the core structure of cognitive empathy it also participates to some extent in emotional empathy and therefore VM lesions would produce mainly cognitive empathy deficits but also some emotional empathy deficits and vice versa.

Finally, it should be noted that other brain regions are predicted to also participate in these empathy systems. Although it is speculated that the VM is the core of the cognitive system, a widespread neural network which has been reported as involved in mentalizing including the TPJ (Samson *et al.*, 2004), the STS and the temporal poles (Gallagher and Frith, 2003), is also involved in cognitive empathy and ToM. Indeed, when we separated a subgroup of patients with lesions involving the STS from the PC group it was evident that this group was also impaired in ToM, further supporting the role of the STS in mentalizing. Additionally, other brain regions such as the amygdala, right somatosensory cortex, right temporal pole and insula have also been implicated in this kind of subjective emotional experience (Reiman *et al.*, 1997; Blair, 2003; Carr *et al.*, 2003; Wicker *et al.*, 2003; Singer *et al.*, 2004) and are predicted to be involved in emotional empathy. Therefore, it may be concluded that these two systems are mediated by two neural networks with two core components which are triggered and operate independently.

Supplementary material

Supplementary material is available at *Brain* online.

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