

Acute lesions that impair affective empathy

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Functional imaging studies of healthy participants and previous lesion studies have provided evidence that empathy involves dissociable cognitive functions that rely on at least partially distinct neural networks that can be individually impaired by brain damage. These studies converge in support of the proposal that affective empathy—making inferences about how another person feels—engages at least the following areas: prefrontal cortex, orbitofrontal gyrus, anterior insula, anterior cingulate cortex, temporal pole, amygdala and temporoparietal junction. We hypothesized that right-sided lesions to any one of these structures, except temporoparietal junction, would cause impaired affective empathy (whereas bilateral damage to temporoparietal junction would be required to disrupt empathy). We studied 27 patients with acute right hemisphere ischaemic stroke and 24 neurologically intact inpatients on a test of affective empathy. Acute impairment of affective empathy was associated with infarcts in the hypothesized network, particularly temporal pole and anterior insula. All patients with impaired affective empathy were also impaired in comprehension of affective prosody, but many patients with impairments in prosodic comprehension had spared affective empathy. Patients with impaired affective empathy were older, but showed no difference in performance on tests of hemispatial neglect, volume of infarct or sex distribution compared with patients with intact affective empathy.

Keywords: empathy; stroke; emotion perception; magnetic resonance imaging; prosody

Introduction

Nearly all human interaction requires that we make inferences about what other people think and feel. This ability to take the perspective of another person provides an important foundation for our relationships, communication, negotiations and other social activities. Perspective-taking is an important component of

empathy (de Waal, 2012), along with emotional contagion (Stotland and Dunn, 1963; de Waal, 2012), or sharing the other person's perceived emotional state. Several important neurological and neuropsychiatric diseases are known to disrupt various aspects of empathy, including autism (Dziobek *et al.*, 2008), frontotemporal dementia (Eslinger *et al.*, 2005; Viskontas *et al.*, 2007), traumatic head injury (Eslinger, 1998; McDonald and Flanagan, 2004; Neumann *et al.*, 2012) and schizophrenia (Shamay-Tsoory *et al.*,

2007; Lee *et al.*, 2011). Numerous functional imaging studies have investigated the brain regions engaged in empathy, and have found distinct regions involved in emotional contagion versus cognitive and emotional perspective-taking (the ability to infer what another person thinks or feels). These studies have led to the proposal that there are dissociable neural and cognitive systems of empathy. One is a developmentally and phylogenetically 'early' system of emotional contagion that may involve the mirror neuron system and the right inferior frontal gyrus (Bodini *et al.*, 2004; Shamay-Tsoory, 2011), as well as the right temporal pole, superior temporal gyrus, fusiform, insula and amygdala (Carr *et al.*, 2003). Emotional contagion may depend on areas of the brain that are activated in association with recognizing emotions of others through prosody (tone of voice), facial expression and gestures, in right fusiform cortex as well as superior temporal sulcus and amygdala (Gorno-Tempini *et al.*, 2001). The second 'later' system, which some think of as the second stage of empathy (Decety and Jackson, 2004) is a higher level perspective-taking system that depends on the medial prefrontal cortex (Eslinger, 1998; Shamay-Tsoory *et al.*, 2003). Perspective-taking can be further subdivided into cognitive and emotional perspective-taking. Perspective-taking may depend on a number of cognitive functions such as cognitive flexibility (Decety and Jackson, 2004; Rankin *et al.*, 2005), attention and working memory, abstract reasoning (Rankin *et al.*, 2006), belief attribution and assignment of agency (Saxe and Kanwisher 2003; Samson *et al.*, 2004; Saxe *et al.*, 2004; Decety and Lamm, 2007). Thus, affective empathy, the ability to recognize and make judgements about how another person feels, includes both emotional contagion and emotional perspective-taking.

The neural networks supporting affective empathy have been studied primarily through task-related and task-free ('resting-state') functional MRI. A task-free functional MRI study of neurologically normal adults investigated intrinsic functional dynamics of affective compared with cognitive empathy (Cox *et al.*, 2012). This study showed that a dominance of affective empathy compared to cognitive empathy was associated with functional connectivity between ventral anterior insula, orbitofrontal cortex, amygdala, and anterior cingulate, whereas a dominance of cognitive empathy was associated with functional connectivity between parts of the brainstem, superior temporal sulcus and ventral anterior insula. Task-related functional imaging studies also confirm an important role of various parts of the frontal cortex, anterior insula, anterior cingulate cortex and right amygdala in empathy, as revealed by large coordinate-based activation likelihood estimation meta-analyses. In one activation likelihood estimation meta-analysis of 112 experiments on affective empathy, Bzdok *et al.* (2012) reported that the following areas showed significant activation in association with empathy tasks across studies: bilateral dorsomedial prefrontal cortex, right greater than left inferior frontal cortex, bilateral anterior insula, anterior and posterior cingulate, bilateral temporoparietal junction, right amygdala, right middle temporal gyrus, right superior temporal sulcus, bilateral thalamus, right hippocampus, midbrain and right pallidum. A few meta-analyses have focused on a particular type of affective empathy: recognizing another person's negative emotion caused by pain. Gu *et al.* (2012) reported that anterior insula and anterior cingulate cortex

were the areas most commonly activated in association with recognition of another person's pain, on the basis of an activation likelihood estimation meta-analysis of 28 functional MRI studies on empathetic pain (using keywords 'empathy', 'empathetic', 'sympathy', 'emotional contagion', 'altruism' or 'compassion' combined with 'pain' and 'functional MRI'). Similarly, an image-based meta-analysis of nine independent functional MRI studies of empathy for pain and an activation likelihood estimation meta-analysis of 32 studies of empathy for pain identified activation in bilateral anterior insula, anterior cingulate, precuneus and thalamus, associated with empathy for other people's pain (Lamm *et al.*, 2011).

Two recent studies have investigated the influence of neuropeptides that affect amygdala function on empathy. The first reported that intranasal oxytocin increased affective, but not cognitive empathy, as measured by a multifaceted empathy task; and improved learning performance on an association task when social, but not non-social, reinforcers were used (Hurlemann *et al.*, 2010). These authors also reported that two females with selective damage to bilateral amygdala due to Urbach-Wiethe disease were impaired in affective, but not cognitive, empathy on their multifaceted empathy task, and showed normal learning on an association task when non-social reinforcers, but not social, reinforcers, were used. Stone *et al.*, (2003) also reported cases of impaired empathy performance associated with bilateral amygdala lesions in two patients. More recently, investigators studied the effects of intranasal vasopressin, which is considered to have opposing effects of oxytocin, on activation in amygdala and other brain regions during empathy in a functional MRI study of affective empathy (Brunnelieb *et al.*, 2013). This study revealed that vasopressin modulated activation of right amygdala associated with affective empathy and increased connectivity between right amygdala and medial prefrontal cortex and inferior parietal cortex in association with the empathy task.

Together, these studies indicate an important role of at least the following areas in recognizing and making inferences about the emotions of another person (affective empathy): prefrontal cortex, orbitofrontal gyrus, anterior insula, anterior cingulate cortex, temporal pole and amygdala. The temporoparietal junction is another area that is nearly always activated in tasks that require perspective-taking (Corbetta *et al.*, 2008), but seems to be important for more general aspects of mentalizing or belief attribution than in affective empathy (Sebastian *et al.*, 2012). For example, it is equally engaged in third person visuospatial judgements as third person judgements of another person's feelings or emotions (Schnell *et al.*, 2011). Moreover, because it is not specific to emotional processing, we hypothesize that a unilateral lesion would not disrupt its role in assignment of agency or attributing a belief or feeling to another person. Rather, we expect bilateral damage to this region would be required to disrupt its role in empathy.

Lesions localized to some of the regions that are activated in functional imaging studies are reported to cause deficits specific to cognitive versus affective empathy (Hynes *et al.*, 2006; Shamay-Tsoory and Aharon-Peretz, 2007; Gu *et al.*, 2012). Such studies are important to the field, because it is critical to show that regions activated during a task are critical to that task, and not just

engaged by it (or actively inhibited during it), as 'activation' (blood oxygen level-dependent signal in a region that is correlated with the task) can reflect any of these possibilities (Thompson-Schill *et al.*, 1998; Fellows *et al.*, 2005). However, most of the studies of impaired empathy have been conducted in patients with poorly localized lesions, such as autism, dementia, and traumatic head injury. The few studies of affective empathy in patients with focal lesions, such as stroke, have included just one to two patients with focal lesions (Stuss and Anderson 2004; Samson *et al.*, 2005, 2007; Roldan *et al.*, 2011; Couto *et al.*, 2012) or have involved a heterogeneous population, of which only a few had stroke (and others had meningioma, head injury and other lesions) (Shamay-Tsoory *et al.*, 2003, 2005, 2009; Shamay-Tsoory and Aharon-Peretz, 2007). A voxel-based morphometry study of 123 patients with Alzheimer's disease, progressive supranuclear palsy, corticobasal degeneration and frontotemporal dementia using caregivers' ratings on the Interpersonal Reactivity Index (Davis, 1983) to evaluate empathy revealed that impairments in empathy measured by the sum of 'empathetic concern' (reflecting emotional contagion) and 'perspective-taking' significantly correlated with the volume of grey matter in right temporal pole, fusiform gyrus and medial inferior frontal region (Rankin *et al.*, 2006). Both empathetic concern and perspective-taking subscale scores alone correlated with volume of grey matter volume in right temporal pole. Other studies of behavioural variant frontotemporal dementia, a relatively focal neurodegenerative disease characterized by impaired social conduct and emotional function, including empathy, have also reported a role of right temporal pole and/or orbitofrontal atrophy in empathy deficits (Rankin *et al.*, 2005; Kipps and Hodges, 2006; Viskontas *et al.*, 2007). For example, a detailed study of a patient with hereditary multiple exostoses and frontotemporal dementia revealed severely impaired affective empathy associated with atrophy in right anterior temporal lobe and orbitofrontal gyrus (Narvid *et al.*, 2009). Right insula also showed atrophy. Therefore, we sought to test the hypothesis, derived from functional imaging studies in healthy participants and previous lesion studies, that lesions to components of a network of brain regions involving right prefrontal cortex, orbitofrontal gyrus, temporal pole, anterior insula, anterior cingulate cortex and amygdala cause deficits in affective empathy. We focused on patients with right hemisphere lesions because studies of neurodegenerative disease have consistently shown greater correlation between impairments in empathy and atrophy in the right hemisphere compared to the left hemisphere (Rankin *et al.*, 2005, 2006; Eslinger *et al.*, 2011). Older lesions studies, which frequently compared small numbers of right hemisphere stroke to left hemisphere stroke, without further lesion localization, also found a greater impact of right hemisphere on empathy (Brune and Brune-Cohrs, 2006). Finally, functional imaging studies have also indicated a specialized role of the right hemisphere in emotional aspects of empathy and sympathy (Decety and Chaminade, 2003). We also determined whether deficits in this type of empathy were related to lesion site alone, or also influenced by lesion volume, age, impairments of attention (neglect), or impairments of prosody comprehension. We tested these hypotheses in patients with acute stroke (within 48 h of onset), before the opportunity for reorganization of structure-function relationships,

rehabilitation, or recovery. This approach allowed us to determine if a lesion in a particular area had the predicted effect on the task.

Materials and methods

Participants

We enrolled a consecutive series of 27 patients with acute ischaemic right hemisphere stroke who provided informed consent to participate in the study and had none of the following exclusion criteria: (i) neurological disease other than stroke; (ii) reduced level of consciousness or on-going sedation; and (iii) inability to have MRI due to claustrophobia, implanted ferrous metal, or weight >300 lb. We also enrolled 24 patients with transient ischaemic attack who had normal MRI and normal neurological examination at the time of testing to serve as normal controls as they had the same demographic characteristics and the same stressors of hospitalization as the stroke patients. They also had to have none of the exclusion criteria and no stroke.

Imaging

Patients underwent a stroke protocol MRI, including diffusion-weighted imaging, FLAIR and 3D time-of-flight angiography of the intracranial vessels. Diffusion-weighted imaging was acquired using single-shot spin-echo echo-planar imaging, in the transverse plane covering the entire brain with a b-value of 1000 (s/mm²) and with a least diffusion weighting (b₀).

Stroke volume measurement

To define boundaries of acute stroke lesion(s) (hereafter termed stroke map) to measure the stroke volume of each participant, a threshold of >30% intensity increase from the unaffected area in the diffusion-weighted image was applied, and then a neurologist (K.O.), who was blinded to the clinical information, manually modified the boundary to avoid false-positive and false-negative areas (Oishi *et al.*, 2009). This procedure was performed on RoiEditor (www.MRIstudio.org).

Image processing

The least diffusion weighted image (b₀) with T₂-weighted contrast was transformed to the JHU-MNI-b₀ atlas using affine transformation followed by the large deformation diffeomorphic metric mapping (Oishi *et al.*, 2009). The resultant matrices were applied to the stroke map for the normalization. Customized version of the JHU-MNI Brain Parcellation Map (cmrm.med.jhmi.edu) was overlaid on the normalized stroke map to investigate % volume of the selected anatomical structures (prefrontal cortex, orbitofrontal gyrus, anterior cingulate cortex, anterior insula, temporal pole and amygdala) affected by acute stroke (Fig. 1). This procedure was performed on DiffeoMap (www.MRIstudio.org).

Behavioural testing

Patients underwent cognitive testing within 24 h of admission to the hospital. Testing of affective empathy included eight questions requiring inference about emotions of individuals in short videotaped scenarios and two questions requiring inference about emotions of individuals in stories that were read to the patients (Box 1). To control for deficits in

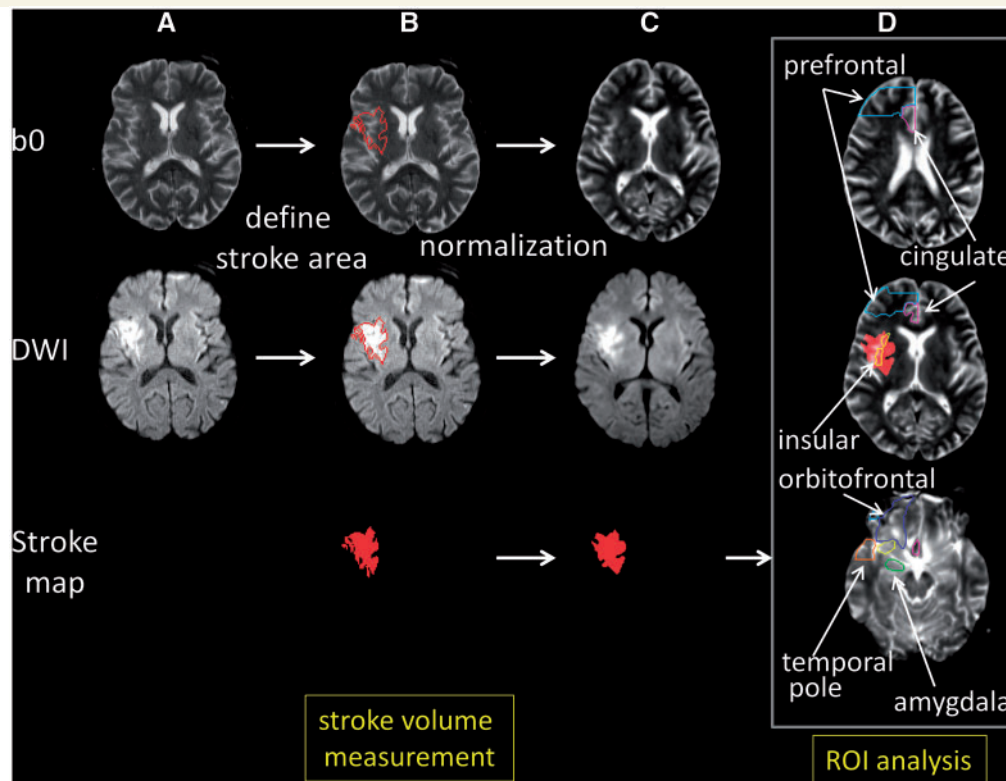


Figure 1 Procedures for the image processing. (A) Images in original space. (B) The diffusion weighted image (DWI) was used to 3D define the area with acute infarction (stroke map) shown as a red contour in the least diffusion weighted image (b0) and diffusion weighted imaging, and the red area in the stroke map. (C) The b0 image, with no or minimum signal intensity increase in the infarcted area, was normalized to the atlas space. The resultant transformation matrix was then applied to the stroke map. In this figure, the transformation matrix was also applied to the diffusion weighted imaging to qualitatively demonstrate the accuracy of image normalization. (D) A predefined set of 3D regions of interest (ROI) [right prefrontal (cyan contour), right anterior cingulate (purple contour), right anterior insula (yellow contour), right orbitofrontal (blue contour), right amygdala (green contour), and the right temporal pole (orange contour)] on the atlas space was overlaid on the normalized stroke map to report % volume of each region of interest affected by the infarction. In this figure, the normalized stroke map (red area) was overlaid on the normalized b0 image. Images are all in radiological convention.

general attention and recent memory, patients were also asked factual questions about the stories. To evaluate emotional contagion, the facial expressions, comments, and tone of voice of patients were evaluated when the patients watched the videos and listened to the stories.

Patients were also administered the Interpersonal Reactivity Index. This test is a self-administered test that includes four types of questions designed to evaluate cognitive empathy (perspective-taking and fantasy scales) and affective empathy (empathetic concern and personal distress).

Patients were also administered the prosody comprehension subtest of the Aprosodia Battery (Ross and Monnot, 2008) to evaluate for deficits in comprehension in affective prosody. In this test, participants listen to emotionally-neutral sentences, monosyllables (ba ba ba), or asyllabic tones (ah) produced in different tones of voice, and select (from written choices) the corresponding emotion (e.g. happy, sad, angry, surprised).

Patients were administered a general test of hemispatial neglect, including a test of detecting left versus right-sided gaps in circles scattered across a page (Ota *et al.*, 2001), and copying a scene of a house, two trees and a fence, and bisection of a 10-inch line.

Statistical analysis

We first identified a cut-off score for normal performance on the affective empathy test, by administering the test to 24 neurologically normal control subjects (transient ischaemic attack patients with normal MRI and normal neurological examination at the time of testing). We determined the range and distribution of scores for control subjects with comparable age, education and socioeconomic backgrounds of our stroke patients, which allowed us to identify a cut-off that would be outside of the normal range of scores for this population.

We then identified whether or not a lesion in the proposed network of areas critical for affective empathy (right prefrontal, orbitofrontal gyrus, temporal pole, anterior cingulate, anterior insula, or amygdala) in the right hemisphere is associated with impaired affective empathy, using Fisher's exact tests, for the entire network as a whole, including only the 27 stroke patients in the analysis. For the two areas most strongly associated with impaired affective empathy, we evaluated the Pearson correlation between severity of impairment (error rate on the affective empathy task) and percentage of damage in each of the two areas.

We then evaluated differences between stroke patients with lesions in this network and patients without lesions in this network (in a case

Box 1 Example of a story from the Affective Empathy Task

Participants listen to the following story, and then select a printed word that most accurately depicts the emotion in response to the question.

John was waiting for the bus that would bring his girlfriend, Cathy. He was planning to ask her to marry him. When the bus arrived, Cathy got off the bus, talking to a very handsome man. They were smiling at each other.

How do you think John feels?

Happy Jealous Scared Bored Excited Relieved

The story continues. Cathy saw John. She smiled and waved. She said, 'John, I would like you to meet my brother.'

How do you think John feels now?

Angry Jealous Scared Bored Excited Relieved

control study), with regard to score on our affective empathy test, tests of affective prosody, tests of hemispatial neglect, as well as age and volume of infarct.

Finally, we evaluated whether or not patients with impaired affective empathy were different from patients with spared affective empathy in terms of scores on prosody comprehension, volume of infarct, age, and scores on neglect.

Results

Affective Empathy Task: range of normal performance

The 24 control participants ranged in age from 35–79 years, mean \pm standard deviation (SD) = 52.5 ± 15.5 . The stroke patients were similar, ranging in age from 26–75 years, mean \pm SD = 54.5 ± 13.6 . In both the control group and the stroke group, 33% of patients were female.

The range of scores on the Affective Empathy Task for control patients was 0 to 20% errors. The mean score \pm SD was 5.8 ± 7.8 . The distribution of scores for controls was as follows: 58.3% made 0% errors; 25% made 10% errors; and 16.7% made 20% errors. Therefore, we used $>20\%$ errors as the cut-off for normal performance; $\geq 30\%$ errors was considered impaired. This score was more than 2 SD above the mean for normal controls.

The effect of acute ischaemic lesions in right hemisphere affective empathy network on affective empathy task performance

We examined the regions of interest in the right hemisphere that most commonly show activation during affective empathy tasks, to determine if a lesion in one or more of the components of the proposed network caused impaired affective empathy ($\geq 30\%$

error). The regions of interest included: right prefrontal cortex, orbitofrontal gyrus, anterior cingulate cortex, anterior insula, temporal pole and amygdala. We considered a region of interest as affected only if at least 1% of the area was infarcted on diffusion weighted imaging trace image. We identified 10 patients with lesions in one or more of the regions of interest. Nine (90%) of the 10 patients had impaired affective empathy. One patient with a lesion involving the anterior insula did not have impaired affective empathy using the 30% error cut-off, although the patient made 20% errors on the task.

Table 1 shows the percentage of infarct in each of the regions of interest for each of the 10 patients with damage to the network. All of these patients who had lesions in the temporal pole also had lesions in the anterior insula. The one patient who had insular damage but no damage to the temporal pole is the patient who made only 20% errors on the affective empathy task (in the normal range).

Of the 14 patients with impaired affective empathy, nine (64.3%) had lesions to one or more of the regions of interest we identified on the basis of the functional neuroimaging literature as engaged in affective empathy. The remaining five patients had lesions in the right thalamus (three patients) or right posterior superior frontal gyrus and middle frontal gyrus, posterior segment (two patients). One patient with a posterior superior and middle frontal gyrus lesion also had a lesion in the right precuneus. These are all areas that have shown activation in one or more of the functional imaging studies of affective empathy reviewed above.

There was a very strong association between the presence of a lesion in one or more region of interest in the network hypothesized to underlie affective empathy and impairments on our tasks of affective empathy (Fisher's exact = 0.004). Figure 2 shows examples of patients with impaired performance on the affective empathy task and lesions in each of the regions of interest. The strongest association (and only significant) associations were between impaired affective empathy and infarct in the temporal pole (Fisher's exact = 0.04) or in the anterior insula (Fisher's exact = 0.03). When we further divided the temporal pole into the pole of superior and middle temporal gyri, the strongest association was between impaired affective empathy and infarct of the superior temporal gyrus pole (Fisher's exact = 0.003). There were seven patients with both superior temporal gyrus pole and anterior insular lesions who had impaired affective empathy. For all 27 stroke patients, there was also a significant correlation between error rate on the affective empathy task and the volume of infarct in (i) temporal pole ($r = 0.48$; $P = 0.014$); (ii) superior temporal gyrus pole alone ($r = 0.49$; $P = 0.013$); and (iii) anterior insula ($r = 0.40$; $P = 0.047$). There were only a few patients with $>1\%$ damage to right prefrontal cortex ($n = 3$), anterior cingulate ($n = 2$), and amygdala ($n = 4$). Importantly, however, there were no patients with lesions to $>1\%$ of any of these three regions of interest or the temporal pole who had spared affective empathy on our test. Some lesions involved more than one of the regions of interest (Table 1).

As expected, there was no association between impaired affective empathy and a unilateral lesion involving the temporal parietal junction. There were three patients with impaired affective

Table 1 Error rate and percentage of damage to each region of interest in the 'empathy network' for the 10 patients with network lesions

Case:	1	2	3	4	5	6	7	8	9	10
Error rate:	30	30	30	30	50	40	30	100	100	20
Prefrontal cortex	0	0	0	8.8	0	0	49.8	6.7	0	0
Orbitofrontal gyrus	0	0	0	0	5.0	0	0	3.6	0	0
STG pole	14	0	2.4	1.4	86.7	1.5	3.5	84.3	0	0
MTG pole	0	0	0	0	66.0	0	0	57.8	0	0
Temporal pole	8.9	0	1.6	0.9	79.1	0.9	2.2	74.6	0	0
Anterior cingulate	0	1.3	0	0	0.6	0	0	2.5	0	0
Anterior insula	77.3	0	57.3	47.2	95.0	39.0	23.6	96.8	0	14.4
Amygdala	0	0	0	0	3.1	1.9	0	51.4	9.4	0

MTG = middle temporal gyrus; STG = superior temporal gyrus.

Given the strong association between impaired affective empathy and infarct in right temporal pole, we divided temporal pole into superior temporal gyrus pole and middle temporal gyrus pole, to identify the area most closely associated with impaired affective empathy.

empathy whose lesions included the temporal parietal junction, but also three patients with spared affective empathy whose lesions included that area.

Performance on affective empathy and other cognitive measures in patients with lesions in the hypothesized network supporting affective empathy versus lesions outside the network

Our second goal was to evaluate differences between stroke patients with lesions in the proposed 'affective empathy network' and patients with lesions outside this network, with regard to score on our affective empathy test, tests of affective prosody, tests of hemispatial neglect, as well as age and volume of infarct. To accomplish this goal, we carried out a very small case-control study including nine patients with lesions in the regions of interest hypothesized to underlie affective empathy, compared with nine patients with stroke, but not involving any of these six regions of interest, matched relatively closely for lesion volume, age and sex. To identify these patients, we excluded all patients with lesions $>100 \text{ cm}^3$ and $<1.45 \text{ cm}^3$. This exclusion yielded patients with the characteristics in Table 2. We compared the two groups using Mann-Whitney tests (because these data were not normally distributed).

Patients who had lesions in the proposed 'affective empathy network' (prefrontal cortex, orbitofrontal gyrus, anterior cingulate cortex, anterior insula, temporal pole, and/or amygdala) made significantly more errors on the affective empathy task than patients without lesions to the network (median = 30% versus 0%; $Z = -2.5$; $P = 0.01$). There were no significant differences between patients with and without lesions in the 'affective empathy network' with regard to lesion volume, age, neglect or prosody scores.

Although patients were administered the Interpersonal Reactivity Index, which has been shown to be a reliably measure of cognitive and affective empathy in neurologically normal

individuals and some patient populations (Rankin *et al.*, 2005), we could not use it to detect deficits in empathy in our population. Only one participant had a score that was >1.5 SD below normal on the perspective-taking subscore; and this participant was a transient ischaemic attack (neurologically normal) control subject. Likewise, only one participant (an acute stroke patient) showed performance on the empathetic concern subscore that was >1.5 SD below the mean for normal controls.

We also did not use the scores for emotional contagion based on observations of facial expressions during the videotapes, because nearly all patients were scored as 'happy' (given choices of happy, jealous, scared, bored, excited or relieved). The patient testers found it difficult to assess the participants' emotions while watching the videos. Most patients did not show outward signs of emotion, such as change in facial expression or make spontaneous comments about their feelings. They were scored as happy if they were pleasant and judged to be happy to continue the experiment.

Differences between patients with impaired affective empathy versus patients with spared affective empathy

Our final goal was to identify any significant differences between patients with impaired affective empathy and patients with spared affective empathy, in terms of scores on prosody comprehension, volume of infarct, age and scores on neglect. We compared all stroke patients with impaired performance on the affective empathy task ($\geq 30\%$ errors; $n = 14$) to those with normal performance on the affective empathy task ($\leq 20\%$ errors; $n = 13$) using Mann-Whitney tests.

A subset of 25 of the patients completed the prosody comprehension testing. Patients with deficits in affective empathy were significantly more impaired in comprehension of affective prosody compared to patients with normal performance on the affective empathy task (overall median error rate on prosody comprehension: 61% versus 40.3% errors; $Z = -2.6$; $P = .009$) (see Table 3 for mean and standard deviations). All patients with impaired affective

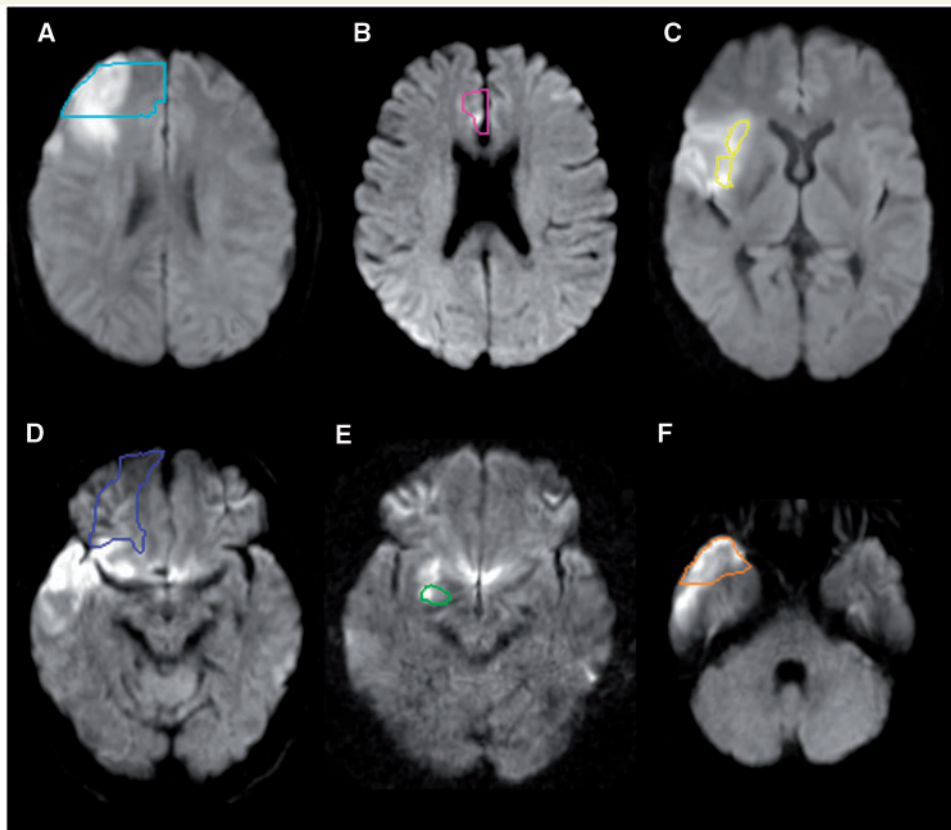


Figure 2 Representative individuals with acute infarction in the prefrontal cortex (A, cyan contour), anterior cingulate cortex (B, pink contour), anterior insular cortex (C, yellow contour), orbitofrontal cortex (D, blue contour), amygdala (E, green contour) and the temporal pole (F, orange contour). Diffusion weighted images were normalized to the JHU-MNI atlas space and predefined regions of interest were overlaid on the normalized images. Images are all in radiological convention.

Table 2 Characteristics of patients with and without lesions in the 'Affective Empathy Network' (right prefrontal cortex, orbitofrontal gyrus, temporal pole, anterior insula, anterior cingulate, amygdala), excluding those with lesions $> 100 \text{ cm}^3$ and $< 1.45 \text{ cm}^3$

	Patients with empathy network lesions		Patients without network lesions		Z	Exact significance
	Median	Mean \pm SD	Median	Mean \pm SD		
Empathy error rate	30%	34.4 \pm 27	0%	8.8 \pm 17	-2.5	0.01
Prosody error rate	60%	51.3 \pm 18	36.5%	37.2 \pm 6	-1.7	0.11
Neglect: gap detection error rate	0%	0.82 \pm 2.3	0%	0.91 \pm 2.0	-0.18	0.89
Line bisection deviation (in % of)	2.2%	5.5 \pm 11.2	2.7%	3.1 \pm 1.6	-1.12	0.27
Scene copy error rate	5.6%	15.9 \pm 28.0	2.9%	8.7 \pm 13.4	-0.98	0.33
Volume of infarct in cm^3	30.6	26.6 \pm 15.9	15.0	16.6 \pm 16.1	-1.2	0.22
Age	52	51.3 \pm 13	49	50.7 \pm 13	-0.088	0.93
% Female	44%		33%			1.00

empathy had impaired affective prosody comprehension; however, there were 13 patients with impaired affective prosody comprehension who had normal performance on the affective empathy task.

In contrast, performance of patients with impaired affective empathy was not significantly different from that of patients with normal affective empathy on tests of hemispatial neglect (Table 3). Those with impaired affective empathy were older

(median 60.8 versus 49.1 years; $Z = -2.3$; $P = 0.02$); they were no more likely to be male (71% versus 62%; not significant).

Discussion

Previous functional neuroimaging studies have consistently shown that particular areas of the brain are engaged during tasks that

Table 3 Characteristics of patients with and without impairments in affective empathy

	Patients with impaired affective empathy		Patients with intact affective empathy		Z	Exact Significance
	Median	Mean \pm SD	Median	Mean \pm SD		
Prosody error rate	65%	61.4 \pm 12	37%	38.0 \pm 14	-2.5	0.008
Neglect: gap detection error rate	0%	0.4 \pm 1.0	0%	1.1 \pm 2.4	-0.02	1
Line bisection deviation (in % of line neglected)	2.6%	4.8 \pm 9.4	2.7%	3.1 \pm 1.7	-0.47	0.65
Scene copy error rate	4.2%	11.3 \pm 23.9	5.5%	10.1 \pm 14.5	-0.06	1
Volume of infarct in cm ³	9.8	26.5 \pm 45.8	16.5	33.6 \pm 58.1	-0.82	0.43
Age	61	60.8 \pm 11.4	46	48.6 \pm 13.8	-2.3	0.02
% Female	29%	38%	1			

involve recognizing and making inferences about how another person feels, sometimes called affective empathy. However, lesion studies have produced more inconsistent results, only some of which indicate that the areas that show activation during affective empathy are also required for this function. One limitation of previous studies is that patients have been heterogeneous in aetiology and time post-onset of lesion. Some lesions, such as meningiomas and other slow growing tumours, often fail to produce deficits, even when they arise in areas of the brain where a stroke or other sudden onset lesion would typically cause a specific deficit. Furthermore, when patients are studied a long time after stroke or other focal lesion, they may have originally had the deficit associated with the lesioned area, but may have recovered due to rehabilitation or spontaneous recovery, as other areas of the brain can assume the functions of the damaged ones. The few previous lesion studies of empathy have included patients with slow growing tumours or patients who are a long time post onset of stroke or other focal injury. We tried to correct for these particular limitations of previous studies by studying patients immediately after onset of acute stroke, before the opportunity for reorganization, recovery or rehabilitation.

We were able to confirm that lesions within the hypothesized network were associated with an error rate on an affective empathy task that is outside the error rate made by neurological normal controls. We also showed, in a small case-control study that patients with lesions involving the network had higher error rates on the affective empathy task than a fairly well-matched group of patients with similar sized lesions that do not involve the network.

The most commonly affected areas in the patients with impaired affective empathy in this study were the anterior insula and the temporal pole (specifically the pole of the superior temporal gyrus). The anterior insula is an area that is commonly affected in acute middle cerebral artery stroke (Finley *et al.*, 2003). Nevertheless, we found that those who had impaired affective empathy were more likely to have lesions in the anterior insula than those who did not have impaired affective empathy. The temporal pole is not an area commonly involved in stroke (Caviness *et al.*, 2002). Yet, 50% of the patients with impaired affective empathy had lesions in temporal pole, and no patients with lesions in temporal pole had normal performance on the

affective empathy task. In both areas, percentage of damage correlated with error rate on the affective empathy task. All patients with temporal pole lesions had anterior insular lesions, raising the possibility that damage to only one or the other may be associated with affective empathy. However, there are converging data from other sources for a role of each of these areas in affective empathy. As reviewed above, the anterior insula nearly always shows activation in association with affective empathy tasks in functional imaging studies (Bzdok *et al.*, 2012). The temporal pole is an area where it has been more difficult to reveal activation in functional imaging studies, but recent studies have shown activation in association with affective empathy (Jimura *et al.*, 2010). Furthermore, both right anterior insula and right temporal pole atrophy have been associated with impaired affective empathy in neurodegenerative disease (Rankin *et al.*, 2005, 2006; Kipps and Hodges, 2006; Narvid *et al.*, 2009; Lee *et al.*, 2012). These areas were not the only critical components of the network; other areas included right prefrontal and fronto-orbito cortex, anterior cingulate and amygdala.

All but five patients with significant impairments in affective empathy had lesions in one or more of the regions of interest in the proposed network. Two of these patients had small lesions in part of the right posterior superior frontal gyrus and middle frontal gyrus, close to ventromedial prefrontal cortex (ventral superior frontal gyrus). It is possible that a larger part of the frontal cortex, rather than just ventromedial prefrontal cortex, as proposed by some authors, is critical for affective empathy.

The three remaining patients with impaired affective empathy had right thalamic infarcts. The thalamus has an important role in relaying sensory and multimodal information to the prefrontal cortex for further processing. It is reasonable to assume that it may play an important role in perception of auditory and visual cues about another person's emotions, and relaying this information to the cortex to enable inferences to be drawn. Four out of nine patients with right thalamic infarcts had impairments in affective empathy. The thalamus consists of several nuclei with quite distinct functions, so whether or not affective empathy was disrupted may have depended on the nuclei involved. However, the resolution of our imaging was not adequate to determine which nuclei were included in the infarct. Of note, consistent with our hypothesis that the thalamus may be important in affective

empathy, the activation likelihood estimation meta-analysis of 112 functional MRI studies of affective empathy revealed the right posterior thalamus and left anterior thalamus among the areas commonly activated in association with empathy (Bzdok *et al.*, 2012).

The temporoparietal junction is an area that consistently is engaged in 'mentalizing' or cognitive perspective-taking, although it does not appear to be specific to empathy (Decety and Lamm, 2007; Schnell *et al.*, 2011; Sebastian *et al.*, 2012). Although one study has indicated that a right parietal lesion might cause impairment in empathy (Shamay-Tsoory *et al.*, 2003), most studies have raised the possibility that either temporoparietal junction alone might be adequate to handle the role in perspective-taking, which may include attributing a belief to another person (Shamay-Tsoory *et al.*, 2003). In this case, a unilateral temporoparietal junction would not be expected to substantially impair empathy. Consistent with this view, in our study, lesions in this area alone were not associated with impaired affective empathy.

Not surprisingly, patients with impaired affective empathy also had significantly higher error rates in the closely related task of recognizing the emotion in tone of voice. However, we do not believe that impaired recognition of prosody was responsible for the deficit in affective empathy, because recognition of emotion from tone of voice was not required to answer any of the questions correctly. Furthermore, a patient with severely impaired recognition and production of prosody performed this task accurately (and scored normally on the Interpersonal Reactivity Index) (Dara *et al.*, 2012). Furthermore, in this study, 13 patients had impaired prosody comprehension, but normal performance on the empathy task. Rather, we believe that some of the areas of the brain necessary for affective empathy may also be necessary for comprehension of affective prosody.

Finally, we found that impairments in affective empathy appear to be independent of impairments in spatial attention (neglect) after right hemisphere stroke, indicating that it is not likely to simply be a marker of 'severe' right cortical stroke.

One limitation of the study is that we were not able to demonstrate a dissociation between perspective-taking and emotional contagion; that is, we could not distinguish between neurologically normal participants and stroke patients in emotional contagion, either using the self-administered Interpersonal Reactivity Index or technicians' observations of facial expressions, gestures, and tone of voice during videos and stories. Acute right hemisphere stroke patients are known to have other deficits that interfere with expression of emotional concern (e.g. impaired expression of emotion through prosody; Ross *et al.*, 1997) and self-assessment of deficits (anosognosia, perhaps including changes in emotional contagion compared to baseline). Therefore, if they have impaired emotional contagion, we were unable to detect it using the Interpersonal Reactivity Index or observation of facial expression/gestures. Our task of affective empathy may have conflated emotional contagion and affective perspective-taking, because the questions about videos may have been answered in part by recognizing and sharing in the emotions of another person. Future studies may use the caregiver assessments of emotional contagion as well as perspective-taking, as has been done for patients with frontotemporal dementia, who also have limited insight (Rankin

et al., 2006; Eslinger *et al.*, 2011). Like our stroke patients, patients with frontotemporal dementia showed no difference from controls on their self-assessment of empathy, although caregivers rated them as having impaired perspective-taking and empathetic concern at the same time (Eslinger *et al.*, 2011). Alternatively, emotional contagion can be assessed with autonomic responses, such as skin conductance response and heart rate changes, when presented with emotional scenes or stories (Balconi and Bortolotti, 2012).

Another limitation is that we did not assess patients with left hemisphere stroke in this study. Previous studies of dementia (Rankin *et al.*, 2006; Eslinger *et al.*, 2011) and focal lesions (Shamay-Tsoory *et al.*, 2003, 2005) have indicated that right hemisphere lesions are more likely than left hemisphere lesions to cause deficits in empathy. However, one study of penetrating traumatic brain injuries found that lesions involving left but not right ventromedial frontal cortex affected performance on affective theory of mind tasks (Leopold *et al.*, 2012). One might argue that penetrating traumatic brain injuries, although they have a focal component, also have a more diffuse and bilateral impact that may have affected performance. Nevertheless, the role of the left medial prefrontal cortex deserves further investigation.

Despite its limitations, our study is a relatively large study of the effect of acute focal ischaemic lesions in carefully selected regions of interest on affective empathy. This study provides converging evidence that areas identified as engaged in the task are indeed necessary for the task. Furthermore, the study indicates that one or more nucleus of the right thalamus also likely plays an important role in this network.

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