Characterization of Empathy Deficits following Prefrontal Brain Damage: The Role of the Right Ventromedial Prefrontal Cortex

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Abstract

■ Impaired empathic response has been described in patients following brain injury, suggesting that empathy may be a fundamental aspect of the social behavior disturbed by brain damage. However, the neuroanatomical basis of impaired empathy has not been studied in detail. The empathic response of patients with localized lesions in the prefrontal cortex (n = 25) was compared to responses of patients with posterior (n = 17) and healthy control subjects (n = 19). To examine the cognitive processes that underlie the empathic ability, the relationships between empathy scores and the performance on tasks that assess processes of cognitive flexibility, affect recognition, and theory of mind (TOM) were also examined. Patients with prefrontal lesions, particularly when their damage included the ventromedial prefrontal cortex, were significantly impaired in empathy as compared to patients with posterior lesions and healthy controls. However, among patients with posterior lesions, those with damage to the right hemisphere were impaired, whereas those with left posterior lesions displayed empathy levels similar to healthy controls. Seven of nine patients with the most profound empathy deficit had a right ventromedial lesion. A differential pattern regarding the relationships between empathy and cognitive performance was also found: Whereas among patients with dorsolateral prefrontal damage empathy was related to cognitive flexibility but not to TOM and affect recognition, empathy scores in patients with ventromedial lesions were related to TOM but not to cognitive flexibility. Our findings suggest that prefrontal structures play an important part in a network mediating the empathic response and specifically that the right ventromedial cortex has a unique role in integrating cognition and affect to produce the empathic response. ■

INTRODUCTION

Acquired damage to the prefrontal cortex (PFC) may result in severe impairment in interpersonal behavior (Stuss, Gallup, & Alexander, 2001; Damasio, Tranel, & Damasio, 1991; Stuss & Benson, 1986; Mesulam, 1985). Although it has been suggested that frontal damage may result in impaired perspective taking ability (Price, Daffner, Stowe, & Mesulam, 1990) and in ''acquired sociopathy'' (Blair & Cipolotti, 2000), the cognitive and neuroanatomical correlates of social impairment and the underlying mechanisms are still largely unknown. One concept that appears to have great utility in understanding personality alterations in neurological population is that of empathy (Brothers, 1989). *Empathy* in the broadest sense refers to the reactions of one individual to the observed experiences of another (Davis, 1980). While historical definitions of empathy have emphasized the emotional aspects of sharing an experience with the other (Mehrabian & Epstein, 1972), more recent accounts of empathy have underscored its cognitive aspects, emphasizing the importance of processes of cognitive perspective taking (Davis, 1994) in the understanding of the other. Thus, alterations in the empathic response may reflect impairment in a number of cognitive processes. One such process is the correct identification of affect: Failure to identify correctly the emotions displayed by another person may interfere with one's ability to adopt another person's perspective, and thus play a role in producing impaired empathic response.

However, perspective-taking is a complex cognitive process, which may also be impaired due to deficits in executive functions such as working memory or impaired cognitive flexibility. The latter refers to one's ability to shift a course of thought or action according to the demands of the situation. Such flexibility may be essential for the empathic response, which requires one to adopt the other person's point of view. Indeed, Grattan, Bloomer, Archambault, and Eslinger (1994) reported the expected relationship between the deficit in empathy and performance of cognitive flexibility tasks among patients with lesions in the PFC. However,

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among those with nonfrontal lesions, reduced empathy was not associated with impaired flexibility. This differential pattern may reflect the complexity of the construct of empathy, suggesting that the ability to respond empathetically may be impaired due to deficits in any of several cognitive and/or emotional processes, emerging following lesions to different brain regions.

Another process that may contribute to the empathic response is the ability to make inferences regarding the mental state of other individuals, which has been termed *theory of mind* (TOM) (Premack & Woodruff, 1978). Baron-Cohen (1995) has interpreted the inappropriate behavior observed among patients with PFC lesions in terms of damage to circuits mediating TOM. Failure to represent the other person's beliefs, knowledge, and intentions may result in failure to see things from another person's perspective and thus interfere with the empathic response.

The Neuroanatomical Basis of Empathy

Eslinger (1998) suggested that empathy may be disturbed by cerebral damage and more specifically by damage to the PFC. However, in a study comparing patients with lesions restricted to the PFC to patients with posterior cortical (PC) lesions, there were no differences between these groups in the overall empathy scores (Grattan et al., 1994). This failure to find specific lesions that result in impaired empathy may suggest that the complexity of the empathic ability renders it an unlikely candidate for strict localization, and a complex network may be involved in modulating empathy.

The Role of the Right Hemisphere in Social Behavior

A large literature, primarily from human lesion studies, has implicated the right hemisphere in processing of emotional and social information (Adolphs, 2001). The right hemisphere plays a crucial role in the perception of relationships among emotional interactions and in the determination of appropriate behavior for a given situation (Borod, 1992). Right hemisphere lesions have been associated with impaired recognition and expression of facial expressions (Montreys & Borod, 1998), affective prosody (Breitenstein, Daum, & Ackermann, 1998; Ross, Thompson, & Yenkosky, 1997), and impaired performance on TOM tasks, in which subjects are required to make mental representations of the other person's mental state (Happe, Brownell, & Winner, 1999; Winner, Brownell, Happé, Blum, & Pincus, 1998). Because identification of the other person's emotional state may be crucial for the empathic response, lesion asymmetry may prove an important variable contributing to the pattern of changes in empathic responses following brain damage, and different aspects of the empathic response may be differentially affected by lesions of the left or the right hemisphere. Yet, to the best of our knowledge, there are no reports comparing empathy in patients with unilateral lesions.

The Role of the Prefrontal Cortex in Empathy

As mentioned above, Eslinger (1998) has suggested that empathic processes might be especially impaired among patients with prefrontal lesions. This was based on reported deficits in self-awareness, loss of insight, impaired judgment, and impaired decision-making following such lesions (Damasio et al., 1991; Stuss & Benson, 1986). Although Grattan et al. (1994) could not demonstrate a difference in empathy scores between patients with PFC and those with PC lesions, further analysis reported in their study suggested that among patients with PFC lesions, those with orbito-frontal lesions were more impaired on empathy than those with dorsolateral PFC (DLC) lesions. Furthermore, empathy deficits were related to impaired cognitive flexibility in patients with lesions in the DLC, but not among those with orbito-frontal lesions. The number of patients within each of these subgroups was too small for meaningful statistical analyses. Nevertheless, there are indications in the literature to support a special role for the orbito-frontal/ventromedial (VM) frontal cortex in the mediation of the empathic response because lesions in this area have been associated with social and behavioral changes (Blair & Cipolotti, 2000; Rogers et al., 1999; Dias, Robbins, & Roberts, 1996; Damasio, 1994; Stuss & Benson, 1986).

The Role of the Ventromedial Prefrontal Cortex in Social Behavior

Several attempts have been made to delineate the role of the VM PFC in social behavior. Stone, Baron-Cohen, and Knight (1998) have reported that orbito-frontal damage is associated with impaired TOM, whereas dorsolateral damage has no influence on such capacities. Functional imaging studies have also implicated the medial and orbital regions of the PFC in TOM (Calder et al., 2002; Gallagher et al., 2000; Fletcher et al., 1995; Goel, Grafman, Sadato, & Hallett, 1995; Baron-Cohen et al., 1994).

Rolls (1990) has suggested that the orbito-frontal cortex is involved in emotion-related learning. The learning deficits associated with damage to the orbito-frontal cortex in nonhuman primates include impaired extinction and impaired visual discrimination reversal. These impairments in human subjects may result in continued responding to a previously rewarded stimulus, leading to inappropriate emotional and social behavior (Rolls, 1996). Hornak, Rolls, and Wade (1996) have suggested that expression of voice and face may serve as reinforcers that VM patients fail to

respond to. The authors demonstrated impairments in the identification of facial and vocal emotional expression in patients with ventral PFC damage who had socially inappropriate behavior. This finding supports the previously mentioned hypothesis that empathic ability may be reduced due to impairment in the processing of affective stimuli such as facial expressions and affective prosody.

Blair and Cipolotti (2000) have reported a patient suffering from a PFC damage including the VM, who specifically showed impairment in the recognition of and autonomic responding to angry and disgusted expressions. The authors concluded that this impairment was due to a reduced ability to generate expectations of others' negative emotional reactions, in particular anger, and proposed that the VM may be implicated specifically either in the generation of these expectations or in the use of these expectations to suppress inappropriate behavior.

An alternative view of the role of the VM in social behavior has been put forward by Damasio et al. (1991) who suggested a ''somatic marker hypothesis'' for processes of decision-making. Damasio et al.'s ''somatic marker hypothesis'' proposes that the VM participates in integrating information regarding body states evoked by experiences and in the outcome of these experiences. The VM, through its connections with the limbic system and the autonomic nervous system, ''marks'' internal representations with somatic markers. These are the convergence zones for knowledge about the categorization of previous experiences and different profiles of emotional or biological states. In line with this hypothesis, Bechara, Damasio, Tranel, and Anderson (1998) found that VM patients exhibited difficulties with decision-making in a gambling task involving choices between actions that differ in terms of size and probabilities of their associated punishment and reward, but they did not show any deficit in a delayed response task. However, patients with lesions in the DLC showed the opposite pattern. Thus, it might be speculated that damage to the VM results in a failure to respond appropriately to a given situation, which—in social situations—may be expressed as lack of empathy.

The present study was designed to examine the relationships between the degree of impaired empathy following acquired brain lesions and the exact localization of the lesion. Specifically, the first goal of the present study was to examine to what extent cognitive empathy is impaired following damage to the PFC, and whether differential patterns of impaired empathy can be detected depending on the exact localization of the damage (VM vs. DLC) within the PFC. The second goal of the present study was to examine the relative effect that lesions in the right versus left hemisphere may exert on empathy. To examine further the hypothesis that the empathic response is complex and may depend on a variety of cognitive processes (which may be impaired differentially following damage to different brain regions), we also examined the relationship between empathic ability and the performance on tasks that assess cognitive, affective, and TOM processing in patients with localized lesions.

RESULTS

As Table 1 shows, the three groups of subjects (PFC, PC, and healthy controls [HC]) did not differ in age, education, or estimated overall level of intellectual functioning (as measured by the Raven's Progressive Matrices score), but differed significantly in the degree of depression, $F(2,56) = 4.032$, $p = .023$. Post hoc analysis indicated that both patient groups had significantly higher Beck Depression Inventory (BDI) scores than the HC (Scheffe, $p < .05$) but there was no difference between PFC and PC patients. Overall, BDI scores did not correlate with empathy scores. BDI scores did not differ significantly between patients with unilateral left and right hemisphere lesions nor were the BDI scores correlated with the extent of the lesion in the left versus right PFC.

Table 1. Demographic Description of the Sample

	Frontal Lesion (n = 25)	*Posterior Lesion (n = 17)*	*Healthy Controls (n = 19)*
Sex			
Male	19	11	15
Female	6	6	4
Age, mean (*SD*)	32.7 (12.4)	43.76 (16.26)	34.05 (15.81)
Education, mean (*SD*)	12.36 (1.9)	13.47 (2.3)	13.78 (3.1)
BDI, mean (*SD*)	14.03 (10.07)	11.64 (11.24)	4.92 (6.5)*
Raven (percentile), mean (*SD*)	38.5 (24.23)	43.72 (32.81)	56.64 (28)

*Significantly lower than both patients groups, $F(2,56) = 4.032$, $p = .023$.

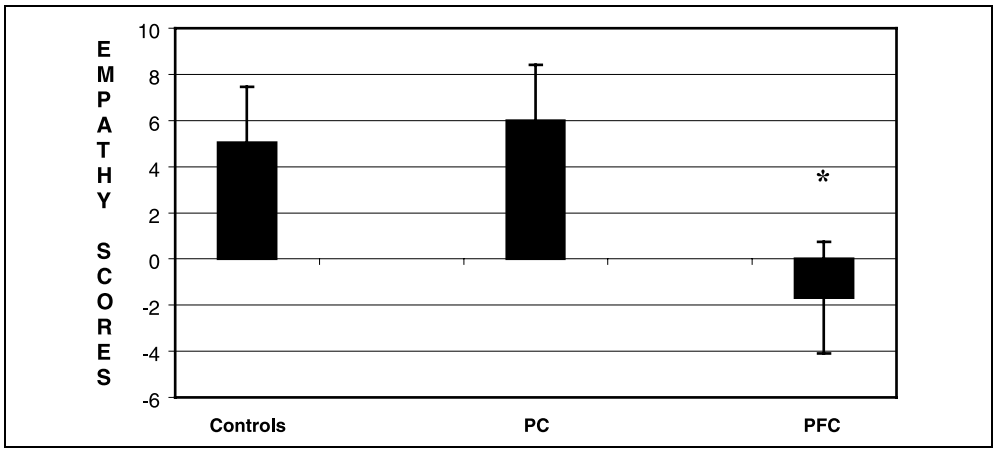

Figure 1. Empathy scores in patients with PC and PFC lesions and in HC. One-way ANOVA: $F(2,60) = 5.29$, $p = .008$. *Post hoc analysis: PFC significantly different from HC and PC ($p < .05$).

Empathy: Patients with Prefrontal versus Posterior Lesions and Control Subjects

Figure 1 shows the level of empathy scores of each of the three groups. Patients with lesions in the PFC had significantly lower empathy scores, compared to both patients with PC lesion and HC. The scores on the empathy scale were -1.68 ± 8.05 for the PFC group, 6.00 ± 10.16 for the PC group, and 5.05 ± 7.46 for the HC group, $F(2,60) = 5.294$, $p = .008$. Post hoc analysis revealed that PFC patients were significantly different from the two other groups (Duncan $p < .05$), but the PC and HC did not differ from each other.

Vendromedial versus Dorsolateral Lesions

The level of empathy displayed by patients whose lesions were limited to either the VM ($n = 12$) or the DLC ($n = 6$) was compared with that of the two control groups (PC and HC). As Figure 2 clearly demonstrates, the difference between these four groups was significant, $F(3,53) = 4.067$, $p = .012$, and post hoc analysis revealed that this difference was due to significantly lower empathy scores in the VM patients, as compared to patients with PC lesions and HC (Duncan, $p < .05$). The DLC group did not differ significantly from either the HC and the PC patients nor from the VM group.

Empathy Levels and Asymmetry of the Lesion

In order to examine whether the asymmetry of the lesion was an important factor contributing to the deficit in empathy, we compared empathy scores in patients whose lesions were unilateral. Patients with PFC lesions were not divided into VM and DLC lesions because of the small number of patients with clearly lateralized lesions in these subgroups.

As shown clearly in Figure 3, there was a significant difference between the four groups with strictly unilateral lesion, $F(3,28) = 4.981$, $p = .008$. Post hoc analysis revealed that left PC patients scored significantly higher

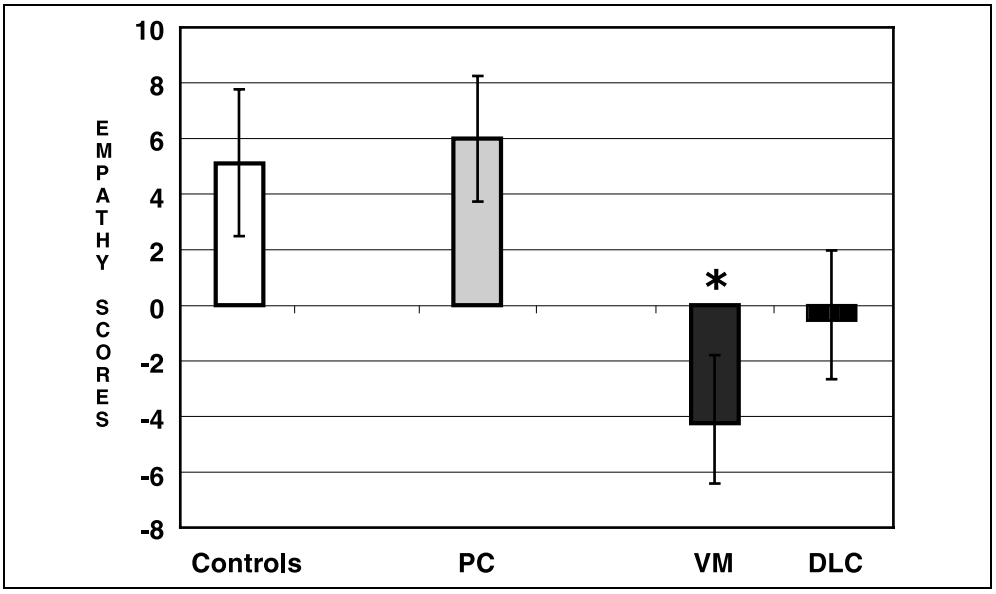

Figure 2. Empathy scores in patients with lesions limited to subregions of the PFC, compared to PC lesions and HC. VM = ventromedial prefrontal cortex; DLC = dorsolateral prefrontal cortex. One-way ANOVA: $F(3,53) = 4.067$, $p = .012$. *Significantly different from PC and controls, $p < .05$.

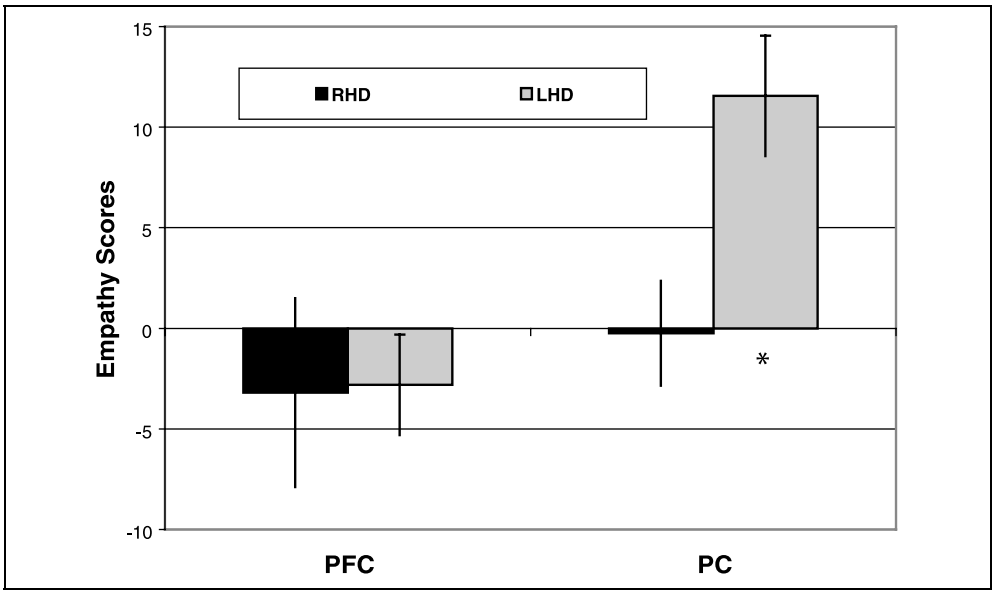

Figure 3. Empathy scores in patients with unilateral lesions. RHD = right hemisphere damage; LHD = left hemisphere damage. One-way ANOVA: $F(3,28) = 4.98$, $p = .008$. *Significantly different from all other groups, $p < .05$.

on empathy, as compared to the left and the right PFC groups (Duncan, $p < .05$). The right PC patients differed significantly only from the left PC patient (Duncan, $p < .05$), indicating that right posterior damage is associated with reduced level of empathy. There were no differences in empathy between HC and left PC lesions.

Empathy and Lesion Location within the Prefrontal Cortex

In order to identify the lesions that were associated with the most severe deficit in empathy, we converted the raw scores of all the subjects on the empathy scale into *Z* scores. We then examined the localization and extent of the lesions in nine subjects who displayed the lowest score (1 *SD* below the mean of all subjects).

Eight of the nine subjects with lowest empathy scores had PFC lesions (six VM, one DLC, and one mixed) and one had a right parietal lesion. Figure 4 provides an example of a computerized axial topography (CT) slice of one of the subjects, A. F. (see Table 2). Superimposition of the lesions of the eight PFC patients revealed that although the size of the lesions differed widely, the common lesion to seven

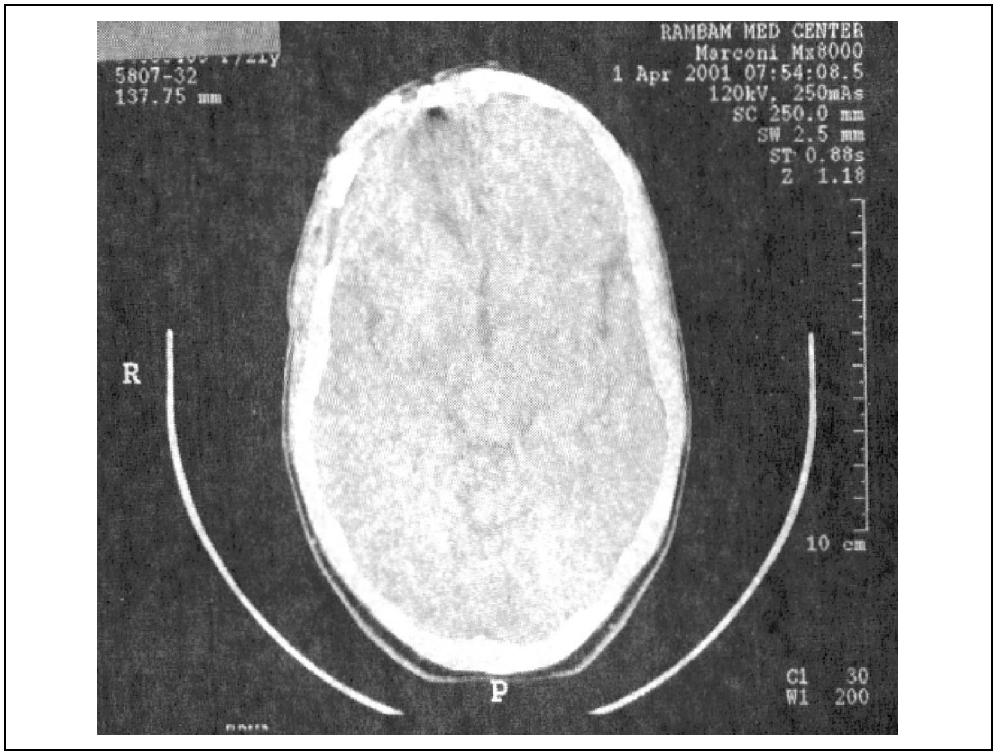

Figure 4. CT slice of one of patient (A. F.)—RVM damage.

Table 2. Detailed Description of the Patients with Frontal Lesions

		Size of Lesion		
Subject	*Lesion Site*	*Left*	*Right*	*Etiology*
Frontal Group				
D. T.	ventromedial+dorsolateral	1	0	head injury: subarachnoid hematoma
A. B.	ventromedial	0.125	0	head injury: contusion
H. H.	ventromedial	0	1.38	head injury: contusion
M. K.	dorsolateral	0.31	4.00	head injury: hematoma
E. G.	ventromedial	0.25	0.25	head injury: contusion
T. O.	ventromedial	10.5	11.625	meningioma
A. A.	ventromedial+dorsolateral	7.5	4.75	head injury: subarachnoid hematoma
D. J.	dorsolateral	0	2.00	head injury: subarachnoid hematoma
I. B.	ventromedial+dorsolateral	6.00	12.5	head injury: contusion, epidural hematoma
I. N.	ventromedial	1.00	3.125	head injury: contusion
M. L.	ventromedial	4	3.63	head injury: contusion
M. A. S.	ventromedial+dorsolateral	16.00	17.00	head injury: encephalomacia
E. S.	ventromedial	0	2.00	encephalomacia
A. G.	dorsolateral	6.5	0	head injury: contusion
K. R.	ventromedial+dorsolateral	3.5	8.00	head injury: contusion
S. H.	dorsolateral	0	0.625	aneurysm
S. S. H.	ventromedial+dorsolateral	0.75	0	meningioma
L. H.	ventromedial	8.25	2.5	head injury: contusion
M. S. I.	ventromedial	2.6125	3.25	head injury: contusion
I. S.	ventromedial	0	2.5	meningioma
D. O.	dorsolateral	7.5	0.125	head injury: contusion
S. M.	dorsolateral	1	0	head injury hematoma
D. B.	ventromedial+dorsolateral	15.25	16	head injury: craniectomy
A. F.	ventromedial	0	8	head injury hematoma
G. I.	ventromedial	14	16	meningioma

of these patients was in the right VM (RVM) region (Figure 5).

The contribution of the size of the lesion to the decline in empathy was examined first by comparing overall lesion size between the eight most impaired patients and all the other patients with PFC lesions. The two groups did not differ in lesion size, $t(24) = -0.461$, *ns*, indicating that the profound deficit in empathy could not be attributed to the lesion size alone. We then examined whether the degree of deficit in empathy was related to the extent of damage within the VM region and whether the side of lesion within that region was an important factor. To examine this, we calculated the overall size of the lesion for each patient in four separate regions: left and right VM (LVM and RVM, respectively) and DLC (Figure 6). As clearly seen, within the VM region, there were no significant differences in the extent of the lesion in the right and left hemispheres. However, the lesions in the RVM area were significantly larger than the lesions in either the left or right DLC regions. We then carried out the same analysis of lesion size in those patients with PFC lesions whose scores on the empathy scale were highest (1 *SD* above the group mean, $n = 8$). For this subgroup, there were no significant differences in the size of the lesion in these four regions (LVM, RVM, and DLC).

The two subgroups of patients with PFC lesions (most and least impaired on empathy) did not differ in age, education, or estimated overall level of intellectual functioning, nor did these two groups differ in the level of depression, indicating that none of these

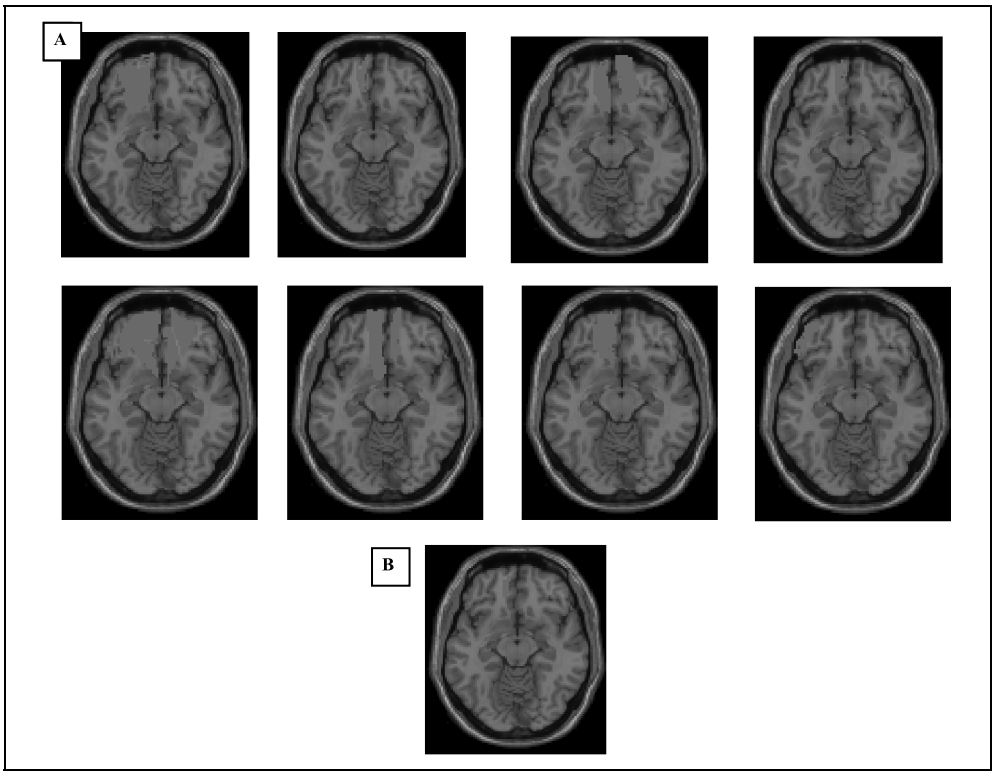

Figure 5. Lesions associated with impaired empathy. (A) Reconstruction of the PFC lesions in eight patients with the most impaired empathy scores. (B) Overlap of lesions in seven of the eight patients shown in A. All seven lesions included the RVM region.

demographic variables contributed to the degree of deficit in empathy.

Performance of Theory of Mind and Cognitive and Affective Tasks

Theory of Mind

Compared to both patients with PC lesions and HC, patients with lesions in the PFC made significantly more errors in the faux pas task, $F(2,52) = 5.966$, $p = .05$. Post hoc analysis revealed that PFC patients were significantly different from the two other groups (Duncan, $p < .05$), but the PC and HC did not differ from each other, suggesting that only patients with lesions localized to the PFC were impaired on this task.

In order to examine whether the asymmetry of the lesion was an important factor contributing to the deficit in TOM, we divided the patients into subgroups, depending on the side of the lesion (right, left, and bilateral frontal, left and right posterior lesion). A multivariate ANOVA of the performance of these subgroups revealed a significant difference between the groups in the faux pas task, $F(5,52) = 3.059$, $p = .018$. Post hoc analysis revealed that patients with right PFC made significantly more errors than patients with either right or left PC lesion and HC (Duncan, $p < .05$). However, the three PFC groups (right, left, and bilateral lesion) did not differ from one another.

Performance on the TOM task of patients whose lesions were limited to either the VM ($n = 12$) or the DLC ($n = 7$) was compared with that of the two control groups (PC and HC). The difference between these groups was significant, $F(4,52) = 3.659$, $p = .011$, and post hoc analysis revealed that this difference was due to significantly poorer performance by the VM group, as compared to patients with PC lesions and HC (Duncan, $p < .05$). The DLC group did not differ significantly from either the HC and the PC patients or from the VM group.

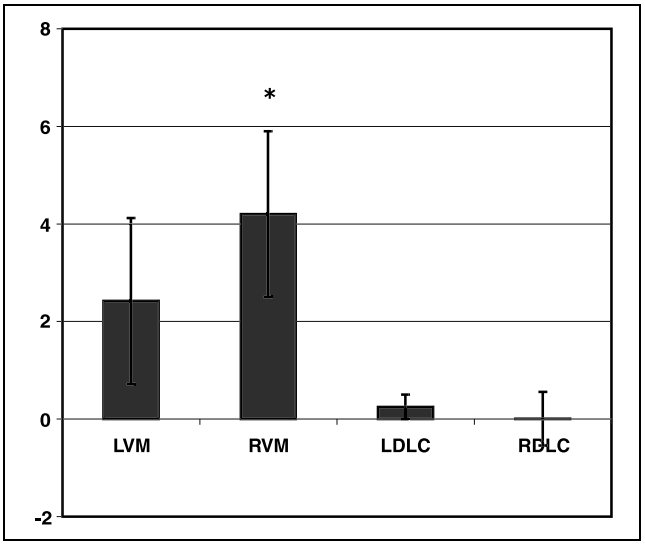

Figure 6. Average lesion size in the four prefrontal subregions. Comparison of lesion size in the LVM, RVM, left dorsolateral (LDLC), and right dorsolateral (RDLC) prefrontal cortices in eight patients with lowest empathy scores.

Cognitive Flexibility

One-way ANOVA (comparing HC to patients with PC and PFC lesions) revealed overall significant differences in the performance of phonemic fluency, $F(2,58) = 7.85$, $p = .001$, and alternate uses, $F(2,57) = 9.53$, $p = .000$. Post hoc analysis showed that only the PFC group was significantly different from the HC group on both tasks (Duncan, $p < .05$).

Comparison of left, right, and bilateral lesions indicated that right hemisphere damage was associated with poorer performance on the Wisconsin Card Sorting Test (WCST; fewer number of categories [8.4 vs. 6.4 for the left and right hemisphere lesions, correspondingly, $p < .05$] and more perseverative errors [11.07 vs. 21.93 for the left vs. right lesions, $p < .05$]). Patients with right hemisphere lesions also gave fewer responses in alternate uses (23.4 and 14.6 for the left and right lesioned groups, respectively, $p < .05$).

Affect Recognition

One-way ANOVA of all experimental groups revealed that both patient groups performed significantly worse than HC on measures of affective prosody, $F(2,57) = 4.08$, $p = .021$, and facial expression, $F(2,57) = 3.46$, $p = .037$. There were no significant differences between PFC and the PC groups in measures of affective prosody and facial expression both in the total number of errors of the tasks and in the specific emotions. However, Comparison of left, right, and bilateral lesions indicated that right hemisphere damage was associated with more errors in identifying affective prosody and that right frontal and right posterior damage were associated with more errors in identifying facial expressions. These groups were significantly different from the normal controls and the left posterior patients, $F(5,57) = 2.8$, Duncan $p < .05$, confirming the right hemisphere's role in affective processing. The VM and the DLC groups did not differ from each other in measures of affect recognition.

Cognitive Correlates of Empathy

The correlations between empathy scores and the performance on the various cognitive tasks were calculated separately for each PFC subgroup. This was done in order to examine the hypothesis that the deficit in empathy, which is observed following lesions in different brain regions, might be associated with different cognitive processes.

As Table 3 shows, in the VM group, empathy level correlated neither with measures of cognitive flexibility nor with measures of affective processing. However, empathy did correlate significantly with measures of faux pas. In the DLC group, empathy correlated with cognitive flexibility but not with faux pas, affective prosody, or the identification of facial expression, suggesting that the decline in empathy observed in this group of patients is associated with specific deficits in cognitive flexibility.

Table 3. Correlations between Empathy and Cognitive Tasks in the VM and DLC Patient Groups

	DLC Patients (n = 7)	*VM Patients (n = 12)*
WCST		
Number of perservative responses	−.784*	−.376 *ns*
Number of set losses	−.768*	−.391 *ns*
Torrance		
Number of responses	.891**	.259 *ns*
Alternate Uses		
Number of responses	.818*	−.002 *ns*
Verbal Fluency		
Number of correct responses	.048 *ns*	.173 *ns*
Design Fluency		
Number of correct responses	.734*	.452 *ns*
Affective Prosody		
Number of errors	−.241 *ns*	.088 *ns*
Facial Expression		
Number of errors	−.362 *ns*	.266 *ns*
TOM (Faux Pas)		
Number of errors	−.429 *ns*	−.556*

*$p < .05$.

**$p < .01$.

DISCUSSION

Our findings indicate that patients with lesions restricted to the PFC were significantly impaired in empathic ability, as assessed using a cognitive empathy scale. Lesions in the VM region appear to be associated with greater deficit in empathy, although they did not differ significantly from the DLC group. The present findings also suggest that the localization of the lesion along the anterior–posterior axis is not the only factor: When the lesion is confined to the posterior cortex, involvement of the right, but not left, hemisphere is associated with impaired empathic responses. However, both left and right prefrontal lesions resulted in equally severe deficits in empathy. Despite this apparent lack of asymmetry within the PFC, the most severe deficit in empathy in this group was noted among patients whose lesion

involved the RVM region, again suggesting that both the asymmetry of the lesion and the localization within the hemisphere are important in determining the degree of deficit in empathy.

The present results confirm the significant role played by the PFC in mediating the empathic response and add to previous clinical observations of aberrant behavior (Blair & Cipolotti, 2000) and profound disturbances in social interactions (Eslinger & Damasio, 1985), associated with lesions of the VM PFC. The PFC is known to play an important role in processes that demand holding information on line (Goldman-Rakic, 1987; Baddeley, 1986), set shifting according to external feedback (Cicerone, Lazar, & Shapiro, 1983), abstract interpretation, and indirect forms of communication (Alexander, Benson, & Stuss, 1989). Indeed, when compared to the HC group, our PFC patients were impaired on the various measures of cognitive flexibility employed in the present study. Of greater interest, however, is the finding that the relationships between empathy scores and performance on measures of executive functions, affect recognition, and TOM revealed a differential pattern in the two subgroups of PFC lesions. Thus, in the DLC group, empathic ability was related to cognitive flexibility but not to TOM, whereas in the VM group empathy was related to TOM but not to cognitive flexibility. In fact, the VM group had both the lowest empathy scores and the greatest number of errors in the TOM task. These results suggest that deficits in the ability to make an inference regarding another person's mental state may account for the profound deficit in empathic ability observed in the VM group. Adolphs (1999) suggested that our ability to judge other people's emotions, behavioral dispositions, beliefs, and desires might draw substantially on our ability to empathize with them, and alterations in the empathic ability may be related to deficit in processes involving ''metarepresentations'' (Leslie & Frith, 1987). These results are also in line with Baron-Cohen (1995) who suggested that the impairment of PFC patients with acquired sociopathy can be accounted for in terms of damage to neural circuits that mediate TOM.

Unlike cognitive flexibility and TOM, empathy scores did not correlate with measures of recognition of facial expression and affective prosody in either of the PFC lesioned groups. This is surprising, in view of previous reports in the literature, suggesting that the PFC, and the VM in particular, plays an important role in the interpretation of the significance of emotional information. Rolls (1996) related aberrant behavior to dysfunction in altering behavior appropriately in response to reinforcement contingency changes. Hornak et al. (1996) suggested that expression of face and voice are used as natural environmental stimuli that are normally detected and used as reinforcers to alter behavior and demonstrated that impaired recognition of emotions is associated with behavioral changes.

A different interpretation was proposed by Blair and Cipolotti (2000) who argued that impaired ability to recognize anger and disgust reflect a reduced ability to generate expectations of others' emotional reaction. The lack of correlation between recognition of affect and empathy observed in the present study fails to support the hypothesis that impaired empathy is due to dysfunction in altering behavior appropriately in response to reinforcement contingency changes as suggested by Rolls. In addition, the PFC group did not differ from the PC group in all measurements of affect recognition, including anger and disgust, suggesting that the formulation offered by Blair and Cipolotti (2000) cannot account for the impaired empathy observed in the present study.

Considering the multifaceted nature of empathy, it is only to be expected that it should be mediated by a complex neural network. Decreased empathic response may be due to deficits in a variety of cognitive and emotional processes, mediated by different neural systems. Our findings suggest that the right hemisphere also plays an important role in the mediation of empathy. This is not surprising, considering that the right hemisphere contains essential components of systems specialized in the processing of emotion (Borod, 1992; Ross, 1981; DeKosky, Heilman, Bowers, & Valenshtein, 1980; Ley & Bryden, 1979). In the present study, affective possessing (as measured by prosody and facial expression identification) was associated with right hemisphere damage. In addition, the empathic response was decreased in all patients with right hemisphere damage. These findings confirm yet again the role of the right hemisphere in social interactions and social aspects of personality, as suggested by evidence of social dysfunction of patients with known right hemisphere damage (Happe et al., 1999; Voeller, 1986).

While empathy was reduced following right posterior damage, the empathic response was most severely impaired following lesions within the right frontal structures and, most notably, the RVM region of the PFC, suggesting a greater role for right PFC structures in the mediation of empathy. Posterior right regions are involved in emotional perception whereas the right frontal lobe is crucial for choosing the appropriate emotional response to situations, as well as the expression of mood and emotions (Edwards-Lee & Saul, 1999; Ross, 1981). We suggest, therefore, that right posterior damage results in impaired empathy due to deficits in affect recognition whereas the right frontal damage influences the expression of the response.

A surprising, although not statistically significant, finding was that of the empathy scores of patients with left PC lesions, which appear to be somewhat higher than those of the HC subjects. Sullivan and Gratton (1999) have proposed the existence of a left cortical inhibitory control of the emotional expression of the

right hemisphere. If this were the case, the higher empathy score of patients with left PC lesion may reflect the release of the right PC, thus facilitating the expression of the empathic response.

Another cognitive process that may be important for the empathic response involves reactivating one's past experiences, which may then be related to the other person's experience. The right frontal lobe has been associated with processes of episodic retrieval (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Recently, it has been suggested that a right hemispheric network of temporal, together with posterior, cingulate, and PFC areas, is engaged in retrieval of autobiographical information (Fink et al., 1996). Thus, we suggest that the PFC mediates the empathic response by integrating reactivated past scenarios (which are processed in the right hemisphere) with other affective and cognitive processes mediated by the PFC.

In the present study, the most severe deficit in empathy was associated with damage to the VM region of the PFC. This is consistent with other views regarding the role of ventral–medial areas connecting affective information (or somatic states) and cognitive information in mechanisms of decision-making (Damasio, 1994). Damasio proposed that impairment in a ''somatic marker system'' causes aberrant social behavior (e.g., Damasio, 1994). This system tags and marks internal representations with a somatic (body state) marker, that is, an autonomic nervous system response. These somatic markers aid decision making by forcing attention on the negative outcome to which a given action may lead and function as an automated alarm.

The VM mediates the integration of information in convergence zones regarding body states evoked by experiences and the outcome of these experiences. Thus, damage to the VM impairs these convergence zones and may lead to failure to integrate the emotional and cognitive facets of a social interaction. A subject with VM damage may understand a social interaction but might fail to comprehend the emotional outcome of this interaction and as a result respond inappropriately to a given situation, thus displaying lack of empathy.

Our results suggest that the RVM region plays a major part in a network mediating the empathic ability. The components of this network include processing of affective information (posterior right hemisphere), retrieving past personal events (right PFC), and aspects of executive functions (such as cognitive flexibility, among others) that are mediated by the DLC. Therefore, a lesion in any of these regions may result in impaired empathic response. The importance of the VM area reflects its major role in integrating these various processes (together with input from other brain regions, most importantly, the amygdala and the autonomic nervous system), thus facilitating the formation of the empathic response.

We propose a complex network for the organization of the empathic response. This network is divided into a core system and an extended system. The core system is comprised of the VM region of the PFC where integration of several cognitive and affective processes takes place. The extended system includes the DLC region of the PFC and circuits within the right hemisphere, which are involved in the identification and processing of affective information. Each component in this system has some specialization, yet this specialization is not absolute because lesions to different parts of the network can have similar effects on the empathic ability. Each region plays a prominent, but not exclusive, role in controlling a certain aspect of empathy.

Other regions of the brain may also be involved in this network. Specifically, the amygdala has been shown to play an important role in the mediation of social behavior. Brothers (1995) has described a neural circuit including the orbito-frontal cortex, the amygdala, the anterior cingulate gyrus, and the temporal pole, suggesting that this circuit functions as a unitary social ''editor'' specialized in the processing of others in a social interaction. Baron-Cohen (1995) has also suggested a neural circuit including the amygdala and the VM, which is involved in the mediation of TOM processes. In addition, the amygdala has been shown to respond to negative emotions such as fear and sadness (Blair, Morris, Frith, Perrett, & Dolan, 1999; Anderson & Phelps, 1997; Calder et al., 1996).

The patients in the present study suffered from localized cortical damage and none of the PFC lesions included the amygdala. However, neuroanatomical data suggest that the VM region of the PFC is one station in an extensive circuitry (including the ventral striatum and amygdala) that is implicated in processes of reinforcement and incentive motivation and under strong influence from mesocorticolimbic dopamine input (Koob & Bloom, 1998). In addition, the orbitofrontal cortex is known to receive strong inputs from the amygdala and projects back to temporal lobe areas (Price, Carmichael, & Drevets, 1996). We therefore believe that empathy deficits similar to those observed in the VM group may also be observed in patients with damage to the amygdala. This suggestion is supported by a recent case study presented by Fine, Lumsden, and Blair (2001). These authors have reported a patient with early left amygdala damage who was found to be severely impaired in his ability to represent mental states.

Finally, the present results suggest that empathy and TOM may be closely related, because patients with damage in the VM showed the most severe empathy deficits and poorest performance on the TOM task. However, our study does not allow a more complete analysis of the nature of the relationships between these two constructs. Further study is needed in order to elucidate this issue more fully.

METHODS

Subjects

Patients with well-defined, localized, acquired cortical lesions, who were referred for a cognitive assessment at the Cognitive Neurology Unit, Rambam Medical Center, were recruited for participation in this study. All patients gave informed consent for participation in the study (which was approved by the hospital's Ethics Committee). Patients were divided into frontal (PFC, $n = 25$) and posterior (PC, $n = 17$) subgroups, based on the location of the lesion. In order to obtain a sufficient number of circumscribed lesions, patients with different etiologies were accepted, including head injury (excluding all cases where there was evidence for diffuse axonal injury), tumors (only patients that underwent removal of meningioma were included), and cerebrovascular accident. A neurological examination was conducted before the cognitive assessment and patients suffering from visual impairment (other than corrected vision), language deficits, or motor limitations that might interfere with the performance of the neuropsychological tasks were excluded. Testing was conducted at the chronic phase of recovery at least 6 months post-trauma or surgery (with the exception of one patient, who was assessed 3 months after trauma). Nineteen age-matched healthy volunteers served as controls (see Table 1 for demographic details). All participants were fluent in Hebrew and none had a history of psychiatric illness predating the injury, developmental disorders, or suffered from any neurological disease or systemic disease with central nervous system complications. Subjects with history of alcohol or drug abuse or previous head trauma with loss of consciousness were excluded.

Anatomical Classification and Analysis

Anatomical classification and analysis was based on visual quantitative evaluation of recent magnetic resonance (MR) or computerized axial topography (CT) data. A neuroradiologist who was blind to the study's hypotheses and the neuropsychological data carried out this analysis. The final rating was based on two evaluations of the same imaging data for each subject, which were performed in different sessions. Only cases where the scoring obtained in the two sessions was identical were included in the statistical analysis. For inclusion, lesions had to be localized to either frontal or nonfrontal cortical regions. Frontal lesions included cases with gray and white matter lesions. Lesions extending to the basal ganglia were excluded. Patients with evidence of diffuse axonal injury following head trauma were excluded. Lesions were localized with standard atlases and transferred to templates following Damasio and Damasio (1989). To assess the extent of the lesion, we used a semiquantitative three-point scale (0 indicates no lesions, 1 indicates a 5-mm lesion; 2 indicates a 10-mm lesion, 3 indicates a 15-mm lesion). The size of the lesion was quantified for each axial slice in which the lesion was evident and an overall score for the lesion size was obtained by summing up the scores for the separate slices. A separate score was derived for the left and right hemispheres in each slice. The lesions were then transcribed from CT and MRI images to appropriate slices of the MRIcro program, for further analysis. The PFC subgroup consisted of 12 patients with unilateral lesion (left hemisphere = 6, right hemisphere = 6) and 13 patients with bilateral lesion. The PC subgroup included 17 patients with unilateral lesions (left hemisphere = 9, right hemisphere = 8).

Patients with frontal pathology were further assigned to one of three lesion groups (see Table 2): (1) ventromedial (Brodmann's areas: 6, medial 8 and 9, 10, 11, 12, 24), (2) dorsolateral (Brodmann's areas: 44, 45, dorsolateral 8 and 9, and 46), and (3) mixed lesions (VM and DLC). There were 12 patients with VM lesions, 6 with DLC lesions, and 7 with mixed lesions.

Assessment of Empathy

Empathic ability was assessed using self-report scales for which a valid and reliable Hebrew version was available. The Cognitive Empathy Scale was designed to assess the capacity to adopt cognitively the point of view of others. It consists of two subscales from the Hebrew version of the Interpersonal Reactivity Index, which includes four seven-item subscales, each tapping a separate facet of empathy (Davis, 1980). The two subscales used in the present study were the (1) perspective-taking subscale, which measures the reported tendency to adopt spontaneously the psychological point of view of others, (2) fantasy subscale, which measures the tendency to imaginatively transpose oneself into fictional situations. The scores on the cognitive empathy scale range from −56 to +56. Reliability analysis of the Hebrew version of the empathy scales in the present study yielded high reliability coefficients (alpha = .79).

Recognition of Faux Pas

This test of TOM designed by Baron-Cohen, Jolliffe, Mortimore, and Robertson (1997) evaluates the ability of subjects to recognize social faux pas. A faux pas occurs when a speaker says something without considering that the listener might not want to hear it or might be hurt by what has been said (e.g., see Stone et al., 1998). This task was selected on the basis of previous findings that individuals with Asperger syndrome could pass easier TOM tasks such as first- and second-order false-belief tasks but were impaired on the faux pas task (Baron-Cohen et al., 1997). Because children cannot detect the faux pas until ages 9–11, this task is considered as tapping a more advanced capacity to make inferences regarding another person's state of mind (Stone et al.,

1998). Detection of faux pas requires both an understanding of false or mistaken belief and an appreciation of the emotional impact of a statement on the listener (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999). A Hebrew version of the 20 faux pas stories was employed (see Appendix): Subjects heard 10 stories in which faux pas has occurred and 10 control stories (total 20 stories). The score consisted of the number of errors produced in response to the TOM questions and the control questions. Subjects used printed copies of the stories while listening to the story being read. They were permitted to look for answers to the question in their copy to control for memory load and inattentiveness.

Neuropsychological Assessment

All subjects completed the Raven's Progressive Matrices to assess reasoning ability and to obtain an estimate of overall intellectual functioning. The BDI (Beck, 1987) was also administered to obtain a measure of depression among patients and controls and to evaluate the possible contribution of depressive mood to empathic response.

To examine whether specific cognitive processes contribute to the level of empathy displayed by our subjects, we administered a number of neuropsychological tests which sample two cognitive domains: (1) cognitive flexibility and (2) identification of emotions. As discussed above (see Introduction), deficits in each of these domains may be related to a person's ability to respond empathetically.

Cognitive Flexibility

The following measures were used:

1. *Wisconsin Card Sorting Test (WSCT):* Administration and scoring followed Heaton, Chelune, Talley, Kay, and Curtiss (1981).

2. *Fluency Tests:* (a) *Verbal Fluency:* This included category (animals, fruit, and vegetables) and letter fluency. For each condition, the score consisted of the number of correct responses given within 60 sec. (b) *Design Fluency:* Subjects were given 4 min in which they were asked to draw as many different drawings as possible, each made of four lines, and excluding actual objects or nameable abstract forms (Jones-Gotman & Milner, 1977).

3. *Alternate Uses Test:* Subjects were asked to describe as many uncommon uses for a set of six objects (can, carton, shoe, glass, tire) as come to mind (Lezak, 1995).

4. *Torrance Test of Creative Thinking (The Circles subscale):* Subjects were presented with a page on which 30 identical circles were drawn. They were asked to draw as many different drawings of meaningful objects, each of which included at least one circle (Torrance, 1974).

Assessment of Emotional Processing

Two tasks were administered:

1. *Recognition of facial expression:* This was evaluated using a modified version (adapted and validated for the use with Israeli population) of the test devised by Ekman and Friesen (1976). Thirty-five pictures exhibiting seven emotional states from this battery (anger, disgust, happiness, surprise, fear, sadness, and neutral) were used. Subjects were asked to identify the emotion depicted in each photograph.

2. *Recognition of affective prosody:* We used the Hebrew version (adapted and validated by Lapidot, Most, Pik, & Schneider, 1998) of a task devised by Ross et al. (1997). Subjects heard a recorded sentence (constant in semantic content but varying among anger, sadness, happiness, surprise, disgust, and fearful emotional tones) and were asked to choose the exact affect conveyed in the sentence from a multiple-choice answer sheet.

Appendix

A Faux Pas item
Mike, a nine year old boy, just started at a new school. He was in one of the cubicles in the toilets at school. Joe and Peter, two other boys at school, came in and were standing at the sinks talking. Joe said, ''You know that new guy in the class? His name's Mike. Doesn't he look weird? And he's so short!'' Mike came out of the cubicles, and Joe and Peter saw him. Peter said, ''Oh, hi, Mike! Are you going out to play football now?''

The subject is then asked the following questions:
Detection of the Faux Pas question:
Did anyone say anything they shouldn't have said?
Who said something they shouldn't have said?
Why shouldn't they have say it?
Why did they say it?
Control question:
In the story, where was Mike while Joe and Peter were talking?

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