

# Impaired “Affective Theory of Mind” Is Associated with Right Ventromedial Prefrontal Damage

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**Objective:** To examine the hypothesis that patients with ventromedial (VM) frontal lesions are impaired in the affective rather than cognitive facets of theory of mind (ToM).

**Background:** Prefrontal brain damage may result in impaired social behavior, especially when the damage involves the orbitofrontal/VM prefrontal cortex (PFC). It has been previously suggested that deficits in ToM may account for such aberrant behavior. However, inconsistent results have been reported, and different regions within the frontal cortex have been associated with ToM impairment.

**Method:** The performance of 26 patients with localized lesions in the PFC was compared with responses of 13 patients with posterior lesions and 13 normal control subjects. Three ToM tasks differing in the level of emotional processing involved were used: second-order false belief task, understanding ironic utterances, and identifying social faux pas.

**Results and Conclusions:** The results indicated that patients with VM (but not dorsolateral) prefrontal lesions were significantly impaired in irony and faux pas but not in second-order false belief as compared with patients with posterior lesions and normal control subjects. Lesions in the right VM area were associated with the most severe ToM deficit. These results are discussed in terms of the cognitive and affective facets of “mind-reading” processes mediated by the VM cortex.

**Key Words:** theory of mind, ventromedial cortex, prefrontal cortex, empathy, right hemisphere

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Patients with prefrontal brain damage may show altered emotional and social behavior, such as disinhibition and misinterpretation of social situations, especially when the damage involves the orbitofrontal/ventromedial (VM) pre-

frontal cortex (PFC).<sup>1,2</sup> Clinical observations and experimental studies indicate that these patients develop a severe impairment in personal and social decision making, despite intact intellectual abilities.<sup>3,4</sup> Such behavioral deficits are most evident in social situations. However, there is a shortage of laboratory probes to measure this deficit and few satisfactory accounts of the neural and cognitive mechanisms underlying it.<sup>5,6</sup>

Several attempts have been made to delineate the role of the VM cortex in social behavior. Rolls et al<sup>7</sup> have suggested that the orbitofrontal cortex, through its connections with the limbic system, is involved in emotion-related learning. Damasio et al<sup>8</sup> propose that the VM participates in integrating information regarding body states evoked by experiences and the outcome of these experiences. Thus, it might be suggested that the VM mediates processes of integration between emotional and cognitive facets of behavior and that a breakdown of this integration may result in behavioral impairments observed in these patients.

Recently, attempts to explain the behavioral disturbances following prefrontal damage have emphasized the breakdown of “theory of mind” (ToM) processes in these individuals. ToM refers to the ability to understand and predict the behavior of other people through the process of making inferences regarding their mental states: their knowledge, intentions, and beliefs.<sup>9</sup> By demonstrating a selective ToM impairment in autistic children, Baron-Cohen et al<sup>10</sup> have put forward the possibility of a specific brain basis for “mind reading.” Operationally, subjects are credited with ToM if they succeed in tasks designed to test their understanding that an individual may hold a false belief. Tests of first-order false belief measure the ability of an individual to understand that another person can hold a belief that is mistaken, whereas tests of second-order false belief examine “belief about belief.”<sup>11</sup> Recently, Rowe et al<sup>12</sup> have reported that subjects with either right or left prefrontal lesions were impaired in ToM ability, as assessed by first- and second-order false belief tests. Stone et al,<sup>13</sup> however, have reported good performance on first-order and second-order ToM tests and impairment only on a more advanced ToM test (identifying a social faux pas) in subjects with bilateral orbitofrontal cortex but not in subjects with left dorsolateral PFC damage. “Faux pas” refers to incidents where someone said something they should not have said, not knowing or not realizing that they should not have said it. This study did not include patients with right dorsolateral damage. However, Stuss et al<sup>14</sup> have suggested that it is the right, rather than left, frontal lobe that plays an important role in the

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detection of deception, which these writers consider a classic instance of ToM.

Data from functional imaging have offered further support for the role of the PFC in ToM tasks. Yet, as in lesion studies, the imaging data point to involvement of different regions within the frontal lobes. Thus, using positron emission tomography, both Fletcher et al<sup>15</sup> and Goel et al<sup>16</sup> found left medial frontal activation during performance of ToM tasks, whereas Baron-Cohen et al<sup>17</sup> reported increased right orbitofrontal activation during recognition of mental states. A recent report from a functional magnetic resonance imaging (fMRI) study involving a story task and a cartoon task showed specific activation in the medial PFC.<sup>18</sup>

The diversity in prefrontal locations and differences in lesion asymmetry associated with ToM impairment may reflect the differences in the ToM tasks employed in these studies. The fundamental differences between the tasks used in the above-mentioned lesion studies (false belief and faux pas) suggest that these tasks involve different processes. Whereas performance of the second-order false belief task requires cognitive understanding of the difference between the speaker's knowledge and that of the listener, identification of social faux pas requires, in addition, an appreciation of the listener's emotional state.<sup>19</sup>

ToM paradigms have failed so far to consider the role that emotion plays in the process of representing the other. Clearly, the inferences one makes regarding others' mental states include not only knowledge about their thoughts and beliefs but also knowledge regarding their emotional states and feelings. It is possible that the behavioral deficits observed in patients with PFC lesions (and especially VM lesions) are not due to cognitive impairments such as understanding belief about belief but rather relate to impaired ability to integrate the cognitive and affective facets of ToM and thus understand belief about feelings. It appears that understanding others' emotional mental state involves empathic abilities; indeed, it has been previously suggested that VM lesions are associated with impaired empathy.<sup>20,21</sup> The VM cortex, through its rich connections with the limbic system, appears to be a likely candidate for such integration of cognition and affect. Therefore, these patients may have a specific difficulty in representing the other person's affective mental state but may be intact in representing that person's cognitive mental state.

To date, studies of ToM have not addressed the differences between the cognitive facets of ToM (belief about belief) and the affective facets of ToM (belief about feelings). Such distinction may be helpful in explaining the behavioral deficits of patients with VM prefrontal damage.

The goal of the current study was therefore to examine the effect of VM prefrontal damage on the performance of various tasks that assess ToM. Three ToM tasks were chosen on the basis of previous available data.<sup>13,22</sup> The tasks differed in the required level of emotional processing: from crude and basic ToM capacities, without involvement of emotional representation (second-order false belief task), through a task that demands a higher level of emotional processing (understanding ironic utterances), to complex ToM ability requiring both cognitive and emotional representations (identifying social faux pas).

## MATERIALS AND METHODS

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 (which was approved by the hospital's ethics committee). All patients gave informed consent. Patients were divided into frontal (PFC;  $n = 26$ ) and posterior (PC;  $n = 13$ ) cortex subgroups, on the basis of the location of the lesion. 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 who underwent removal of meningioma were included), and cerebrovascular accident. A neurologic examination was conducted prior to the cognitive assessment, and patients with 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 least 6 months post trauma or surgery (with the exception of one patient who was assessed 3 months after trauma).

Thirteen age-matched 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 or developmental disorders or any neurologic disease or systemic disease with CNS complications. Subjects with history of alcohol or drug abuse or previous head trauma with loss of consciousness were excluded. The three groups of subjects (PFC, PC, and normal healthy controls [HCs]) did not differ in age, education, or estimated overall level of intellectual functioning (as indicated by the Raven Progressive Matrices score) (see Table 1).

## Anatomic Classification and Analysis

Anatomic classification and analysis were based on visual quantitative evaluation of recent MR or computed tomography (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

**TABLE 1. Demographic Description of the Sample**

	Frontal Lesion ( $n = 26$ )	Posterior Lesion ( $n = 13$ )	Healthy Controls ( $n = 13$ )
Sex			
Male	20	8	10
Female	6	5	3
Age (y)			
Mean (SD)	34.12 (14.0)	40.46 (15.38)	34.2 (12.59)
Education (y)			
Mean (SD)	12.46 (1.9)	12.9 (2.1)	14.4 (3.4)
BDI			
Mean (SD)	14.03 (10.07)	10.07 (2.4)	5.5 (7.6)*
Raven (percentile)			
Mean (SD)	38.5 (24.23)	44.00 (34.58)	56.64 (28)

\*Significantly lower than both patient groups:  $F(2,56) = 4.032$ ,  $P < 0.023$ .  
BDI, beck depression inventory.

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.<sup>23</sup> Lesions were also transcribed from CT and MR images to the appropriate slices of the MRIcro program (Rorden, University of Nottingham, UK). To assess the extent of the lesion, we used a semiquantitative 3-point scale (0 = no lesions, 1 = 5-mm lesion, 2 = 10-mm lesion, 3 = 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 (Figs. 1–3).

The PFC subgroup consisted of 13 patients with unilateral lesion (left hemisphere = 6, right hemisphere = 7) and 13 patients with bilateral lesion. The PC subgroup included 13 patients with unilateral lesions (left hemisphere = 9, right hemisphere = 4).

Patients with frontal pathology were further assigned to one of three lesion groups: VM including the orbitofrontal and medial area (Brodmann areas: 6, mesial 8 and 9, 10, 11, 12, 24), dorsolateral (Brodmann areas: 44, 45, 46, dorsolateral 8 and 9), and mixed lesions (VM and dorsolateral [DLC]). There were 12 patients with VM lesions, 7 with DLC lesions, and 7 with mixed lesions (Table 2).

## ToM Tasks

The ToM tasks used were graded in the degree of emotional representation involved:

1. Second-order false belief: belief about belief, no emotional processing involved
2. Detection of irony: higher level of emotional processing
3. Identifying social faux pas: belief about belief as well as belief about emotion, both cognitive and emotional representations

These tasks were chosen also on the basis of previous reports of association between prefrontal damage and performance on these tasks.<sup>13,24,25</sup>

The Hebrew translation of the second-order and faux pas tasks<sup>13</sup> was validated on a group of normal subjects in a pilot study. For detection of irony, we used the task devised by Ackerman,<sup>22</sup> which was adapted to Hebrew by Lapidot et al.<sup>26</sup> For examples of these tasks, see Appendix.

## Second-Order False Belief Tasks

A second-order false belief task evaluates one's ability to understand what someone thinks about what someone else thinks.<sup>13</sup> In this task, the subject is required to understand that other people can represent mental states. The subject does not have to make any representation of the other's emotions, and no emotional processing is involved. This task requires simple inferences, and normal 6- to 7-year-old children perform it

successfully.<sup>13</sup> In each story, person A puts an object somewhere and leaves the room. Person B moves the object while person A is out of the room. However, person A is peeking back and watching what B does. Person B does not know that person A has seen the object being moved. The subject is then asked what person B knows regarding what person A thinks. An additional informative question is also asked, to control for misunderstanding of the story (see Appendix). Subjects were given eight stories. A copy of each story was handed to the subjects to control for memory load, attention, and working memory deficits. The subjects heard the story while at the same time using their printed copy to follow the story. They were allowed to reread it as many times as needed and to use it for answering questions, to control for attentional difficulties. The questions regarding the stories were explicit and unambiguous,<sup>13</sup> to prevent errors due to pragmatic deficits, as suggested by Siegal et al.<sup>27</sup> Scoring consisted of the number of errors made in response to the ToM questions and the control questions.

## Understanding Ironic Meaning

Irony is a common feature of everyday discourse used to convey feelings in an indirect way. It is characterized by opposition between the literal meaning of the sentence and the speaker's meaning<sup>28</sup> and has been assumed to involve the ability to create meta-representation. Sarcasm is a form of ironic speech used to convey implicit criticism and negative feelings. To detect sarcasm and irony, the listener first needs to make inferences about what the speaker knows and then infer the speaker's intentions.<sup>24</sup> Research with children has shown that the ability to understand irony is reliably demonstrated in children who are at least 6 years old<sup>22</sup> and that this ability is related to their ability to identify second-order false belief.<sup>28,29</sup> Others have suggested that even 5- to 6-year-old individuals understand sarcasm.<sup>30</sup> Happe<sup>31</sup> has demonstrated that the ability of autistic children to interpret irony depends on their ability to attribute mental states. Understanding ironic utterances, however, not only relies on the ability to understand second-order false beliefs but also requires emotional processing, since the subject also has to identify the affect conveyed indirectly. Poor performance on this task has recently been shown to be significantly correlated with empathic ability in patients with PFC damage.<sup>25</sup>

The task employed in the current study<sup>26</sup> consists of eight brief recorded stories, each describing an interaction between two characters. At the end of each interaction, one of the characters makes a comment directed at the other character. Each story is presented in two versions: a sarcastic one and a neutral one (total 16 stories, presented in randomized order). Whereas in the sarcastic version, the literal meaning of the speaker's comment is positive but the speaker's true meaning is negative, in the neutral version, both the literal meaning and the speaker's intended meaning are positive (for an example, see Appendix). The purpose of the neutral version was to identify patients' difficulties in story comprehension. Subjects who made more than two errors in these items were excluded. Scoring of an error was made when a subject failed to identify the negative meaning in the sarcastic version (the attitude

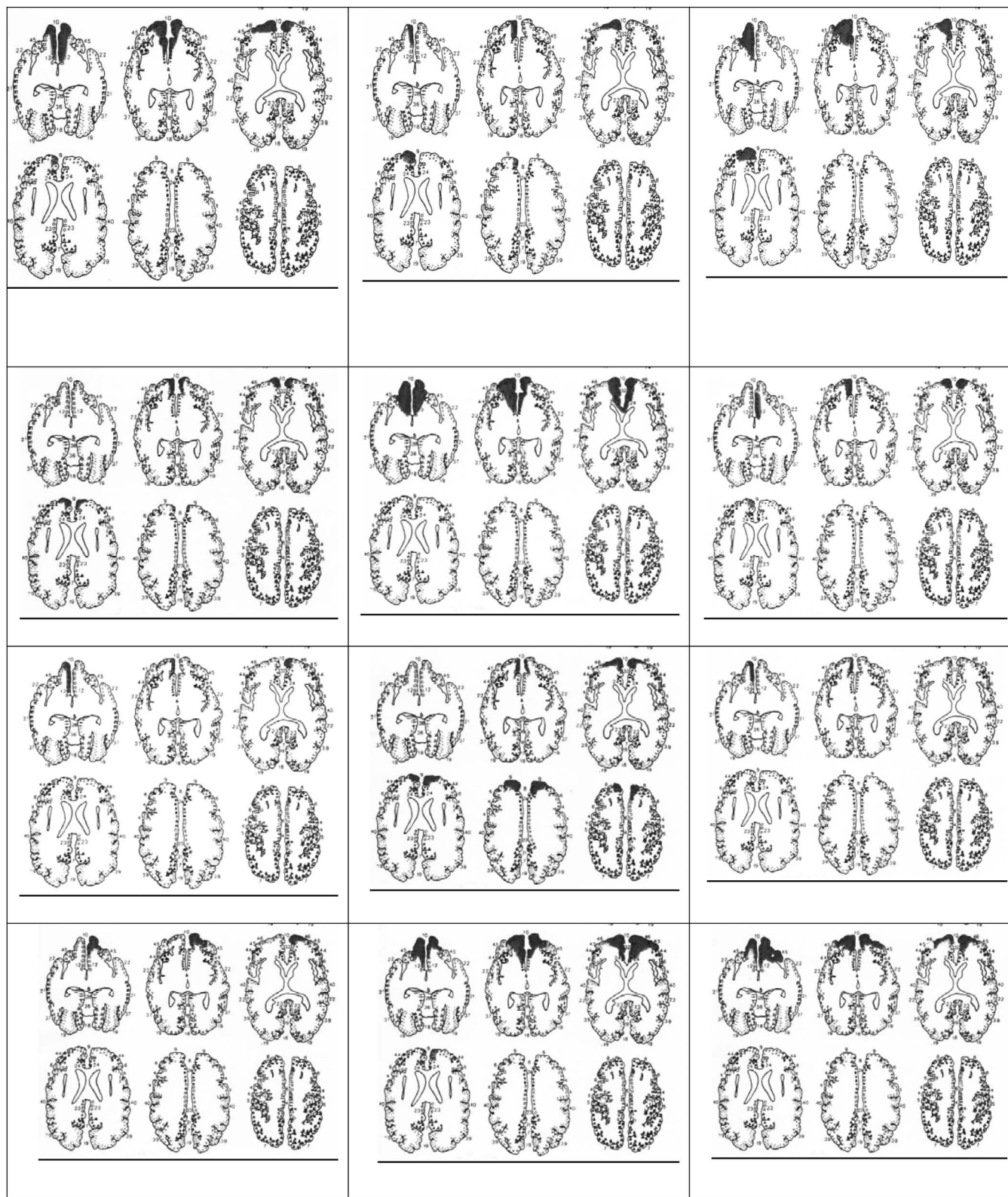
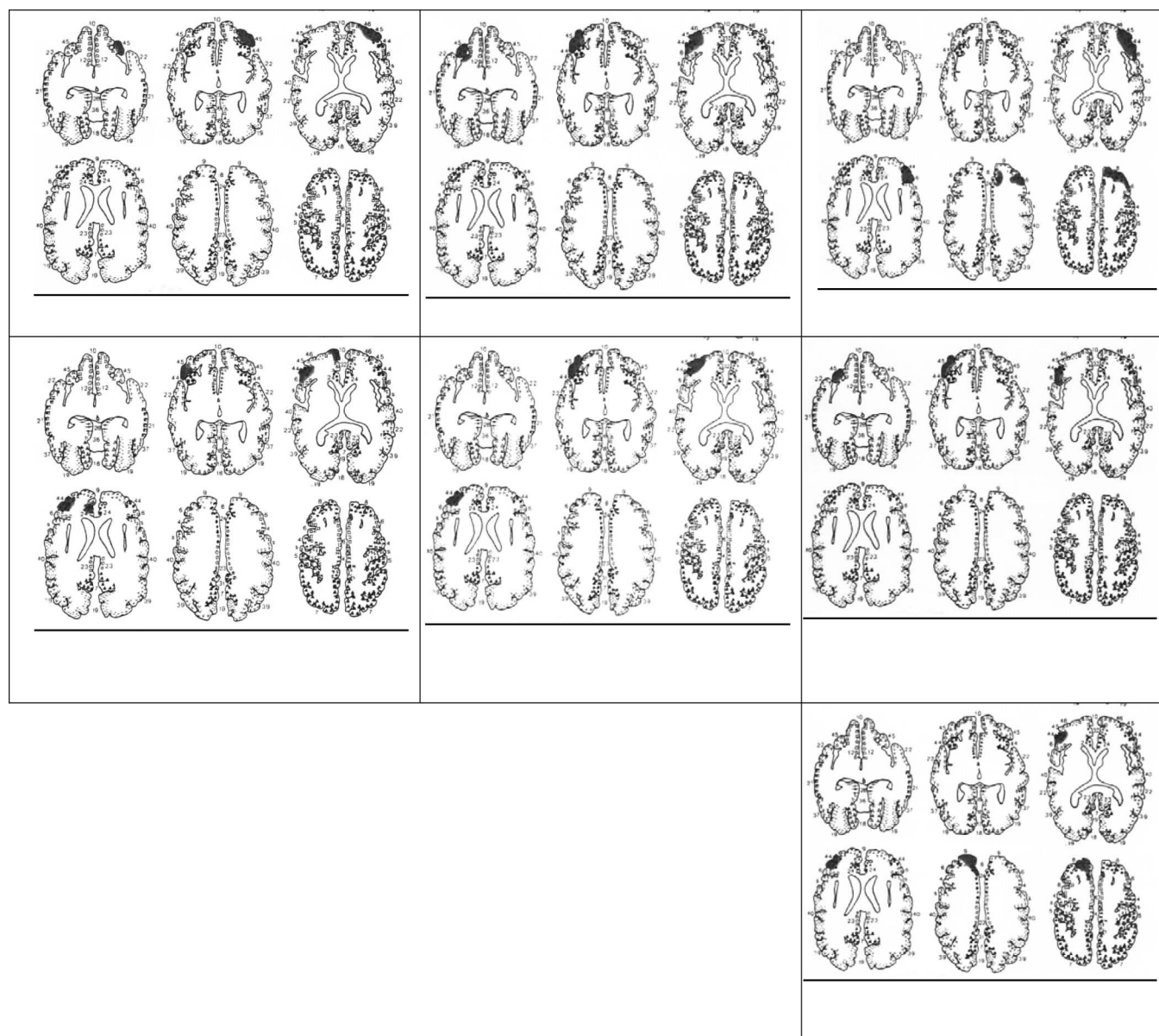


FIGURE 1. Summary of patient information: subject with VM lesions.



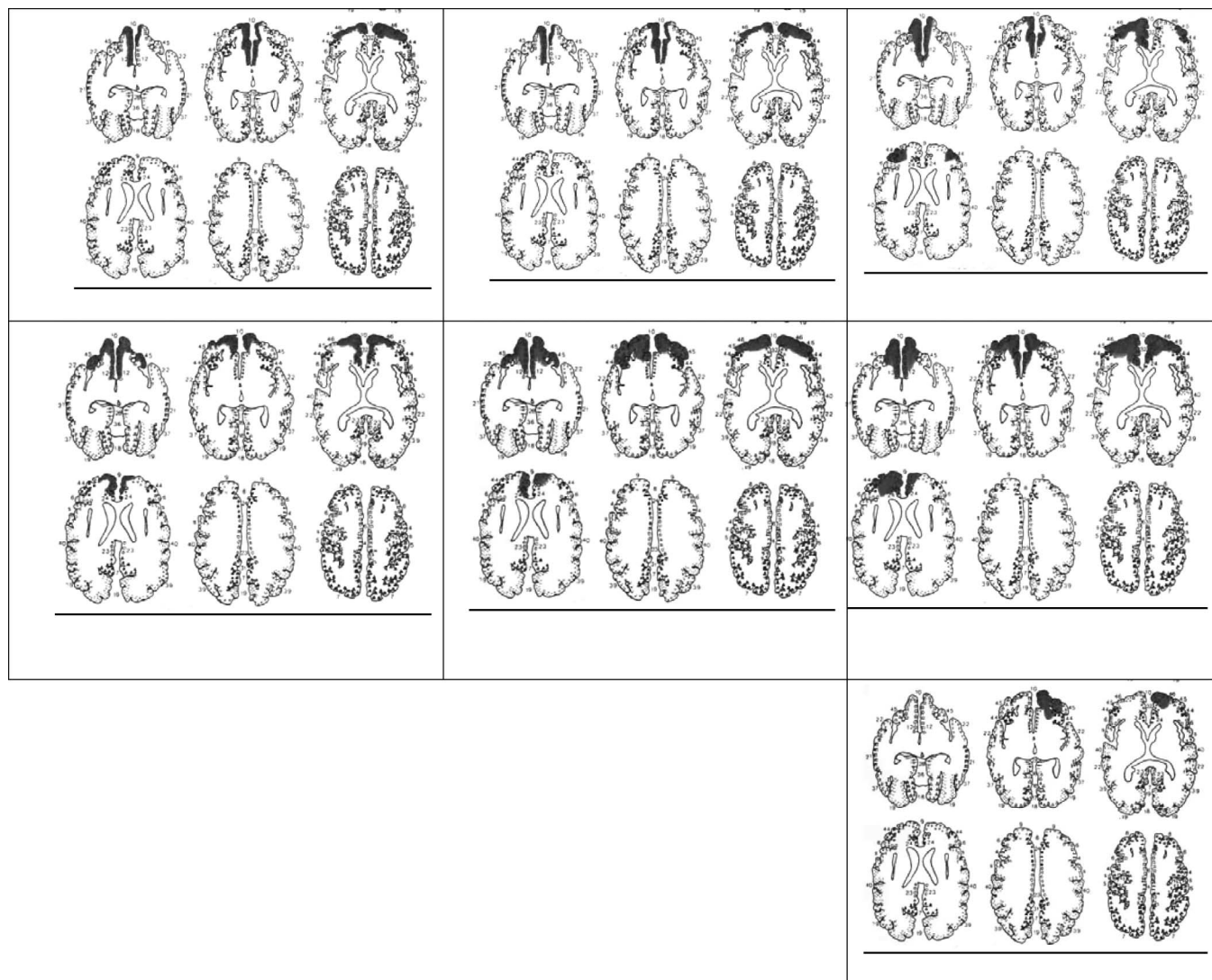
**FIGURE 2.** Summary of patient information: subjects with DLC lesions.

question). If the subject also made an error in the factual question, the item was not counted.

### Recognition of Faux Pas

This test of ToM, designed by Baron-Cohen et al.,<sup>32</sup> evaluates the ability of subjects to recognize a 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 (for an example, see Appendix). 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.<sup>32</sup> Since children cannot detect a 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.<sup>13</sup> 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.<sup>19</sup> A Hebrew version of the 20 faux pas stories used by Stone et al.<sup>13</sup> was employed: Subjects heard 10 stories in which a faux pas has occurred and 10 control stories (total 20 stories). Here again, the questions presented were unambiguous. The score consisted of the number of errors produced in response to the ToM questions and the control questions. As in the



**FIGURE 3.** Summary of patient information: subjects with VM and DLC lesions.

second-order false belief, 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. Subjects who made more than two errors in the control questions were excluded.

### Assessment of Empathy

Empathic ability was assessed to examine the relationship between the affective facets of ToM and the ability to empathize. To assess empathic ability, the questionnaire of the Interpersonal Reactivity Index (IRI)<sup>33</sup> was selected. While some investigators have considered empathy to be a cognitive phenomenon, emphasizing the ability to engage in the cognitive process of adopting another's psychological point of view, other investigators have used a definition of empathy stressing its emotional facets, referring to the capacity to experience affective reactions to the observed experiences of others.<sup>33</sup> The importance of the IRI lies in its recognition of the

multidimensional nature of empathy. It therefore consists of assessment of four separate dimensions (perspective taking, fantasy, empathic concern, and personal stress subscales). While the perspective-taking subscale assesses the cognitive facets of empathy (cognitive empathy), the empathic concern subscale assesses the emotional facets of empathy (affective empathy). In addition to the overall IRI scores, two separate scores were obtained for the perspective-taking and the empathic concern subscales to explore possible differential relationships between ToM tasks and the different facets of empathy. To provide information about the relationships between individual items in the IRI scale, reliability analysis of the Hebrew version of the scale was conducted and yielded high reliability coefficients ( $\alpha = 0.79$ ).

### Affective Processing

To determine whether, and to what extent, impaired ToM is related to the ability to identify another person's affective

**TABLE 2.** Detailed Description of Lesions

Site of Lesion	Size of Lesion	Etiology
Ventromedial (VM) n = 12		
Bilateral PFC	30	Meningioma
Left PFC	.125	Head-Injury: Contusion
Right PFC	1.38	Head-Injury: Contusion
Bilateral PFC	10.75	Head-Injury: Contusion
Bilateral PFC	.5	Head-Injury: Contusion
Bilateral PFC	22.125	Meningioma
Right PFC	8	Head-Injury: Hematoma
Bilateral PFC	5.8375	Head-Injury: Contusion
Right PFC	2.5	Meningioma
Bilateral PFC	4.125	Head-Injury: Contusion
Bilateral PFC	7.63	Head-Injury: Contusion
Right PFC	2.00	Encephalomalacia
Dorsolateral (DL) n = 7		
Left PFC	6.5	Head-Injury: Contusion
Right PFC	.625	Aneurysm
Right PFC	5	Meningioma
Right PFC	2.00	Head-Injury: Sub-Arachnoid Hematoma
Bilateral PFC	4.31	Head-Injury: Hematoma
Left PFC	7.625	Head-Injury: Contusion
Left PFC	1	Head-Injury: Hematoma
Mixed (Ventromedial + Dorsolateral) n = 7		
Bilateral PFC	31.25	Head-Injury: Craniectomy
Left PFC	.75	Meningioma
Bilateral PFC	11.5	Head-Injury: Contusion
Bilateral PFC	33.00	Head-Injury: Encephalomalacia
Left PFC	1	Head-Injury: Sub-Arachnoid Hematoma
Bilateral PFC	12.25	Head-Injury: Sub-Arachnoid Hematoma
Bilateral PFC	18.5	Head-Injury: Contusion, Epidural Hematoma

state and, more specifically, whether representation of the other person's affective state depends on the ability to identify specific emotions, subjects also performed two tasks: recognition of facial expression and recognition of affective prosody.

### Recognition of Facial Expression

This was evaluated using a modified version of the test devised by Ekman and Friesen.<sup>34</sup> Thirty-five pictures exhibiting seven emotional states from this battery (anger, disgust, happiness, surprise, fear, sadness, and neutral) were used. The total number of facial expressions detected correctly as well as the number of correct responses to each specific emotion were recorded.

### Recognition of Affective Prosody

We used the Hebrew version (adapted and validated by Lapidot et al)<sup>26</sup> of a task devised by Ross et al.<sup>35</sup> Subjects heard recorded sentences (constant in semantic content but varying among anger, sadness, happiness, surprise, disgust, and fearful emotional tones) and were asked to mark the exact affect conveyed in each presentation of the sentence, on a multiple choice answer sheet.

### Overall Intellectual Ability

The performance on the Raven Progressive Matrices was used to obtain an estimate of overall intellectual ability.<sup>36</sup>

## RESULTS

### False Belief, Faux Pas, and Irony: Effect of Lesion Location and Lesion Asymmetry

All statistical computations were performed using SPSS 11.0 (Chicago, IL). Unless otherwise specified, the level of significance was set at  $P < 0.05$  (two tailed).

Subjects' raw scores on the three ToM tasks were converted into  $z$  scores for comparison between tasks, and all the statistical analyses were performed on these  $z$  scores. The performance on the false belief task reflected a ceiling effect: Neither patients with brain lesion nor HC subjects made any errors on this task. As it did not discriminate between the groups, this task was not analyzed further.

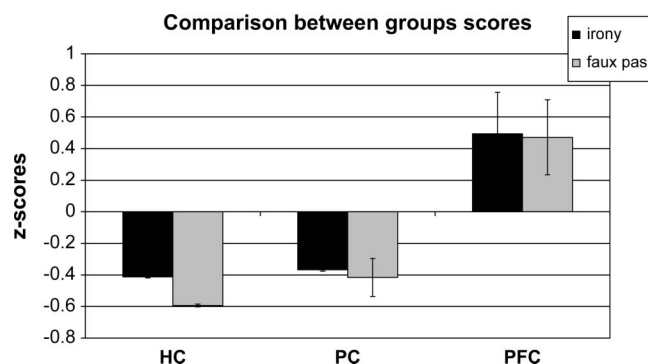
Although a one-tailed Pearson correlation analysis revealed that the numbers of errors made on the faux pas and the irony tasks were correlated ( $r = 0.247$ ,  $P = 0.04$ ), it was

apparent that subjects had greater difficulty in identifying social faux pas as compared with understanding ironic utterances. Forty-eight percent of the entire sample had at least one error in the faux pas task, whereas only 32% had errors in irony detection, suggesting that the former is somewhat more complex.

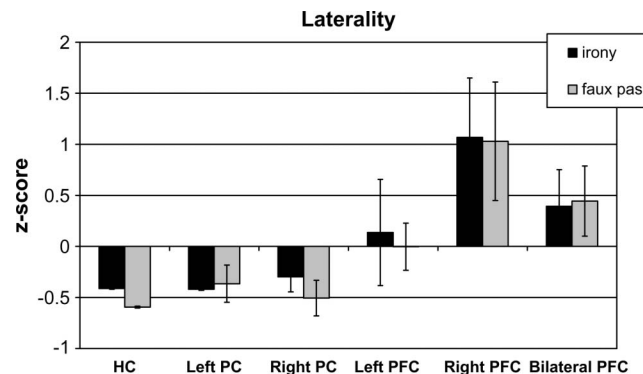
Figure 4 shows the ToM scores for the three groups. Compared with both patients with posterior lesions and HCs, patients with lesions in the PFC made significantly more errors in the faux pas ( $F[2,50] = 5.966, P = 0.005$ ) and in the irony ( $F[2,50] = 5.737, P = 0.006$ ) tasks. Post-hoc analysis revealed that PFC patients were significantly different from the two other groups (Duncan,  $P < 0.05$ ), but the PC and HC did not differ from each other, suggesting that only patients with lesions localized to the PFC were impaired on these tasks.

To rule out the possibility that impaired faux pas and irony could be related to depression, the differences in cognitive and affective scores were reanalyzed using the Beck Depression Inventory (BDI) scores as a covariate. Results indicated that although the BDI scores had a significant effect on performance of the irony task ( $F[2,50] = 5.92, P = 0.018$ ), the difference between the groups remained significant after covarying for the severity of depression ( $F[2,49] = 4.066, P = 0.023$ ). The BDI scores did not have a significant effect on the faux pas ( $F[2,50] = 3.7, NS$ ).

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 analysis of variance (ANOVA) of the performance of these subgroups and the HC group revealed a significant difference between the groups in both the faux pas ( $F[5,47] = 3.059, P = 0.018$ ) and the irony ( $F[5,47] = 2.618, P = 0.036$ ) tasks. Post-hoc analysis (Fig. 5) revealed that only patients with right PFC lesions were significantly different from patients with posterior (left or right) lesions and HC in both tasks. In addition, the right PFC and the bilateral PFC groups did not differ from each other.



**FIGURE 4.** Irony detection and faux pas scores in patients with posterior (PC) and prefrontal (PFC) cortex lesions and normal healthy control subjects (HC). One-way analysis of variance: faux pas ( $F[2,52] = 5.966, P = 0.05$ ); irony task ( $F[2,52] = 5.737, P = 0.006$ ). Duncan post-hoc analysis: PFC significantly different from HC and PC ( $P < 0.05$ ).

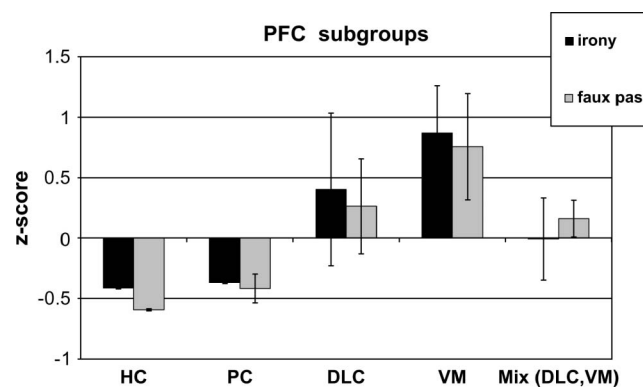


**FIGURE 5.** Irony detection and faux pas scores in patients with unilateral lesions. One-way analysis of variance: faux pas ( $F[5,52] = 3.059, P = 0.018$ ); irony ( $F[5,52] = 2.618, P = 0.036$ ). Duncan post-hoc analysis: prefrontal cortex (PFC) significantly different from healthy normal control (HC) and posterior cortex (PC) ( $P < 0.05$ ).

### VM Lesions

Performance on ToM tasks of patients whose lesions were limited to either the VM ( $n = 12$ ) or the DLC ( $n = 7$ ) as well as a group of patients with mixed lesions ( $n = 7$ ) was compared with that of the two control groups (PC and HC). As Figure 6 clearly demonstrates, the difference between these groups was significant for both irony ( $F[4,48] = 4.293, P = 0.005$ ) and faux pas ( $F[4,48] = 3.659, P = 0.011$ ), and post-hoc analysis revealed that this difference was due to significantly poorer performance by the VM group as compared with patients with PC lesions and HC (Duncan,  $P < 0.05$ ). The VM group did not differ from the mixed group. The DLC group did not differ significantly from either the HC or the PC patients or from the VM group.

As the performance on the faux pas and irony tasks was significantly correlated ( $r = 0.247, P = 0.04$ ) and the pattern of deficit in these tasks was clearly similar, a new variable was



**FIGURE 6.** Irony detection and faux pas scores in patients with lesions limited to subregions of the prefrontal cortex (PFC) compared with posterior cortex (PC) lesions and normal healthy controls (HC). One-way analysis of variance: irony ( $F[4,52] = 4.293, P = 0.005$ ); faux pas ( $F[4,52] = 3.659, P = 0.011$ ). Duncan post-hoc analysis: PFC significantly different from HC and PC ( $P < 0.05$ ). VM, ventromedial prefrontal cortex; DLC, dorsolateral prefrontal cortex.



computed: A ToM score was calculated for each subject, by averaging the  $z$  scores of this subject on the irony and faux pas tasks. This ToM score was used to identify the patients with impaired performance on both irony detection and faux pas. To identify the most critical lesion location associated with the most severe deficit in ToM, PFC subjects were further assigned into one of two groups according to their ToM scores. The first group consisted of 13 patients with preserved ToM (scoring at group mean and above mean score), and the second consisted of 13 patients who were impaired (ToM score below group mean scores). We then examined the localization and extent of the lesions of the 13 impaired patients.

The contribution of the size of the lesion to the deficit in ToM was examined first by comparing overall lesion size between the ToM-impaired patients and all the nonimpaired patients with PFC lesion. The two groups did not differ in lesion size ( $t[25] = -0.461$ , NS), indicating that the profound deficit in ToM could not be attributed to the lesion size alone. We then examined whether the degree of deficit in ToM 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 and left and right dorsolateral PFC (Fig. 7). Repeated measures analyses revealed significant differences between sizes of lesions ( $F[3,10] = 3.762$ ,  $P = 0.048$ ). Post-hoc analysis revealed that the lesions in the right VM area were significantly larger than the lesions in the left VM ( $P = 0.047$ ), left DLC ( $P = 0.009$ ), and right DLC ( $P = 0.022$ ) regions. We then carried out the same analysis of lesion size in the 13 patients

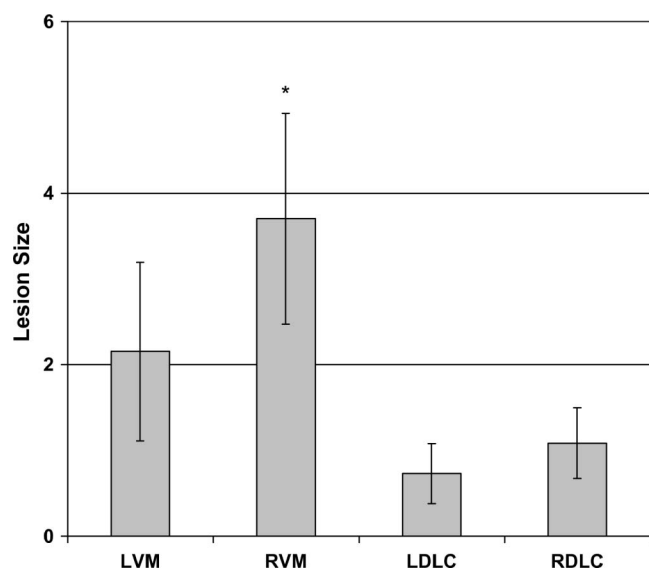
whose ToM scores were highest. For this subgroup, there were no significant differences in the size of the lesion in these four regions (left and right VM and DLC).

Furthermore, superimposition of the lesions of the ToM-impaired patients (8 VM, 2 DLC, and 3 with lesions extending to both VM and DLC), revealed that although the size of the lesions differed widely, in 9 of these 13 patients, the right VM region was involved (Fig. 8).

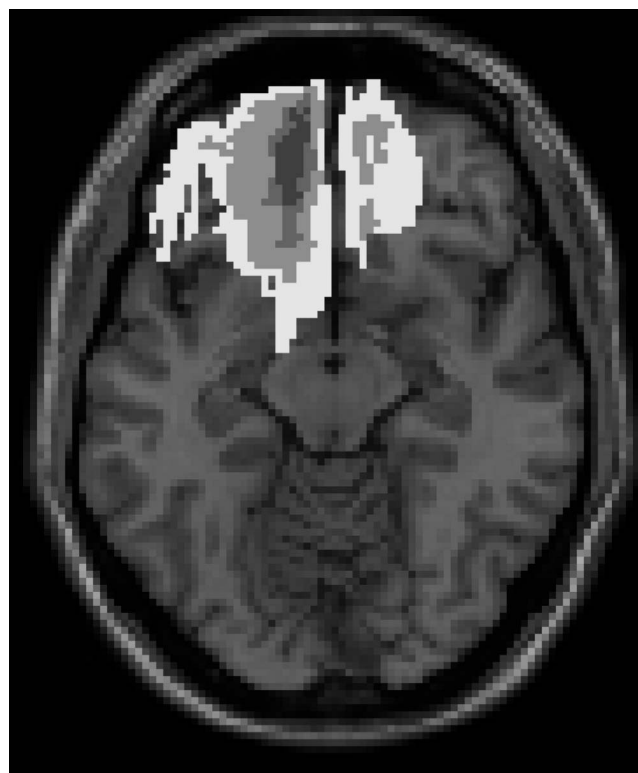
## ToM and Affective Processing

A one-way ANOVA of group differences in prosody and facial expression did not reveal significant differences. Compared with HCs, both patients with lesions in the PFC and with posterior lesions did not make significantly more errors in either the prosody ( $F[2,50] = 2.71$ ,  $P = 0.075$ ) or the irony ( $F[2,50] = 2.35$ ,  $P = 0.106$ ) task. However, a significant difference between the patients with the right hemisphere damage and those with left hemisphere damage was revealed both for prosody ( $F[1,29] = 15.246$ ,  $P = 0.001$ ) and for facial expression ( $F[1,29] = 6.228$ ,  $P = 0.019$ ), indicating that patients with right hemisphere damage made significantly more errors than patients whose damage was limited to the left hemisphere.

To determine whether impaired ToM is related to processing of emotional stimuli, a correlation analysis was conducted between recognition of facial expression, recognition of affective prosody, faux pas, and irony. Examination of the pattern of correlations between ToM scores and the performance



**FIGURE 7.** Average lesion size in the four prefrontal subregions. Comparisons of lesion size in the left ventromedial (LVM), right ventromedial (RVM), left dorsolateral (LDLC), and right dorsolateral (RDLC) prefrontal cortices, in 13 patients with lowest theory of mind scores. Lesions in the right VM area are significantly larger than the lesions in either the left VM ( $t[12] = 2.209$ ,  $P = 0.047$ ), the left DLC ( $t[12] = -3.099$ ,  $P = 0.009$ ), or the right DLC ( $t[12] = -2.634$ ,  $P = 0.022$ ) regions.



**FIGURE 8.** Lesions associated with impaired theory of mind. Overlap of lesions in 13 patients with the lowest theory of mind scores. In nine patients, the right ventromedial region was involved.

on the affective processing tasks among patients with PFC lesions revealed that performance in the faux pas and irony task correlated neither with performance of prosody nor with performance of facial expression. No significant correlation was found between the measures of prosody and irony ( $r = 0.131$ , NS), prosody and faux pas ( $r = 0.337$ , NS), facial expression and irony ( $r = 0.324$ , NS), and facial expression and faux pas ( $r = -0.254$ , NS).

Furthermore, to determine whether affective processing affected the ability to identify social faux pas and irony, we reanalyzed the performance of the two patient groups and control subjects on faux pas and irony, using the scores of affect recognition as covariates. Neither facial expression (ANOVA:  $F[2,50] = 2.00$ , NS) nor prosody (ANOVA:  $F[2,50] = 2.02$ , NS) was found as a factor contributing to the group differences in faux pas. Similarly, neither facial expression (ANOVA:  $F[2,50] = 2.87$ , NS) nor prosody (ANOVA:  $F[2,50] = 0.00$ , NS) was found as a factor contributing to group differences in irony.

A similar ANOVA comparing the VM, DLC, mixed, PC, and HC groups showed that neither facial expression ( $F[4,48] = 1.84$ , NS) nor prosody ( $F[4,48] = 3.2$ , NS) contributed to the observed group differences in faux pas. Likewise, neither facial expression (ANOVA:  $F[4,48] = 2.71$ , NS) nor prosody (ANOVA:  $F[4,48] = 0.102$ , NS) was found as a factor contributing to group differences in irony.

In each of the above analyses, the deficit in ToM in the PFC and in the VM groups as compared with the control group remained highly significant, indicating that the group differences in ToM could not be accounted for by difficulties in processing of affective stimuli.

## ToM and Empathy

The two subgroups of patients with PFC lesions (most and least impaired on ToM) did not differ in age, education, or estimated overall level of intellectual functioning, indicating that none of these demographic variables contributed to the degree of deficit in ToM. They did, however, differ significantly in the level of empathic ability, and patients with impaired ToM had significantly lower empathy scores than those patients who performed well on the ToM tasks ( $F[1,24] = 4.863$ ,  $P = 0.038$ ). When the correlation between empathy scores and the performance on ToM tasks was analyzed for the entire group, a significant correlation between ToM variable scores and the IRI scores ( $r = -0.357$ ,  $P = 0.012$ ) was observed, suggesting that poorer faux pas and irony performance were associated with lower level of empathy. However, when the relationships between the affective (empathic concern) and cognitive (perspective taking) subscales of the IRI and the ToM tasks were tested separately, only the cognitive empathy subscale correlated significantly with ToM ( $r = -0.509$ ,  $P = 0.0001$ ), whereas affective empathy did not correlate with the ToM tasks ( $r = -0.014$ , NS).

## DISCUSSION

This study found that prefrontal lesions, particularly in the right VM, may result in impaired ToM. Unlike the work of Rowe et al,<sup>12</sup> all prefrontal patients exhibited intact perfor-

mance in the second-order false belief tasks. However, despite the fact that patients with lesions in the VM area did not have any difficulty on a second-order false belief task, their performance on a faux pas task was impaired. This pattern of performance is in agreement with Stone et al,<sup>13</sup> who interpreted the dissociation in developmental terms, comparing orbitofrontal patients with 7- to 8-year-old individuals who fail in more "advanced" ToM tasks. However, the impairment of our VM patients in understanding ironic utterances points against such a developmental explanation, since 5- to 6-year-old children have been shown to understand irony.<sup>30</sup> An alternative explanation is that the tasks used in the current study differ qualitatively from other ToM tasks. To understand irony and even more so to detect faux pas, one is required not only to understand the knowledge of the others but also to have empathic understanding of their feelings. Thus, good performance of these tasks requires integration between the cognitive and affective facets of a given situation, whereas in the false belief task, no affective processing is needed. In the current study, the VM patients performed without difficulty a task that requires understanding belief about belief but were impaired in tasks that involved understanding belief about emotions. This was not due to difficulty in identifying emotions (either through facial expression or through prosody), as patients with lesions in the VM did not differ from the other patients in their ability to identify a wide range of emotions, and their performance on tasks of recognition of affect was not correlated with performance on any of the ToM tasks.

We believe that the performance of patients with damage to the VM reflects impaired "affective" ToM rather than "cognitive" ToM. A similar distinction between affective and cognitive ToM (ie, the representation of the cognitive state of others and the representation of their affective and motivational state) has been made by Brothers and Rings<sup>37</sup> and is referred to as the distinction between "cold" and "hot" aspects of ToM. Blair and Cipolotti<sup>38</sup> have also suggested dissociable systems involved in social cognition. The authors reported a patient who, following trauma to the right frontal region, including the orbitofrontal cortex, presented with "acquired sociopathy." The patient's pattern of performance suggested the existence of a distinct system involved in "cold" social cognition (ie, ToM), which was dissociated from a "hot" social cognition (processing others' emotional signals).

To the best of our knowledge, there are no reports in the literature regarding the neuroanatomic substrates involved in mediating the affective aspects of ToM. The attempts to explain social deficits in terms of ToM have emphasized the cognitive facets of a theory one creates with respect to another person's mental states.<sup>10</sup> These accounts, however, say very little about the role of emotions. As the current study suggests, an account of the behavioral impairment accompanying damage to the VM region that excludes the role of emotion is insufficient, because mental states are inseparable from emotional processes. Constant integration between cognitive and affective components is needed to respond adaptively. Our findings suggest that the right VM region plays an important role in integrating the affective (or "hot") aspects of ToM.

The VM region appears to be especially suitable for integrating diverse cognitive and emotional processes. It receives

projections from all sensory modalities<sup>39</sup> and has extensive bidirectional connections with the hippocampus and the amygdala.<sup>40</sup> Furthermore, in a series of studies using a gambling task, Bechara et al<sup>41</sup> found that subjects with VM lesions made poor choices on the task and did not acquire any subjective feeling regarding their choices. They also had impaired anticipatory skin conductance response (SCR) during risk-related decision making.<sup>42</sup> Recently, imaging findings have suggested that somatic arousal (indexed by SCR) is represented in the VM, indicating that cognitive and emotional aspects of behavior are integrated with information regarding peripheral autonomic states of arousal, particularly in the VM and orbitofrontal cortex.<sup>43</sup>

Taken together, these findings highlight the role of the VM in attaching emotional valence to stimuli. Thus, damage to the VM may result in a failure to represent the affective components of mental states, and such a failure may result in inappropriate behavior in social situations.

The correlation between the poor performance of the “affective” ToM tasks and impaired empathy, reported in the current study, suggests that affective “mind reading” may, in fact, be an empathic response. However, the significant correlation between “affective ToM” and “cognitive empathy” (and insignificant correlation with “affective empathy”) imply that although inferences of feelings and emotional experiences in other people involve affective processes, they are nonetheless still cognitive. It has been previously suggested that whereas affectively based empathy involves vicarious arousal and experience of another’s feeling state, cognitively based empathy involves the ability to take another’s viewpoint and infer that person’s feelings.<sup>44</sup> On the basis of this, it may be assumed that “affective ToM” has to do with processes of cognitive empathy, which are involved in the inference of other people’s emotions.

Indeed, Adolphs<sup>45</sup> suggested that we judge other people’s emotions, behavioral dispositions, beliefs, and desires on the basis of our ability to empathize with them. He suggested that emotion and social cognition are closely related in terms of shared processing strategies and in terms of neural substrates such as the VM, the amygdala, and the right somatosensory-related cortices. Thus, it appears that the empathic response requires both cognitive and affective ToM. This is supported by previous reports regarding impaired empathy, in which the most severe deficit in empathy was observed following damage to the PFC.<sup>20,21</sup>

Two different approaches attempt to account for the cognitive mechanisms that subserve the ability by which we represent and predict another person’s behavior. The “theory” theorists (or ToM theorists) maintain that mental states attributed to other people are conceived of as unobservable, theoretical posits, invoked to explain and predict behavior, something akin to a scientific theory.<sup>46</sup> On the other hand, the “simulation” perspective<sup>47</sup> suggests that the others’ mental states are represented by tracking or matching their states with resonant states of one’s own. Thus, the attributer tries to covertly mimic the mental activity of the target. This is based on findings regarding “mirror” neurons in the monkey’s ventral precentral motor cortex that respond both when a particular action is performed by the recorded monkey and

when the same action, performed by another individual, is observed.<sup>47</sup>

Although it would be expected that “affective ToM” requires simulation mechanism, the correlation between cognitive empathy and affective ToM may imply that affective ToM involves cognitive ToM abilities. However, this does not imply that ToM and simulation processes are necessarily mutually exclusive, and the proposal that affective ToM involves also simulation mechanisms cannot be rejected altogether by the current study results. Therefore, we suggest that simulation mechanism is essential at the beginning of the affective ToM process and is further used for making inferences regarding the other person’s affective mental state. As the current study indicates, not all ToM abilities are impaired in VM patients: These patients have the basic ability to make inferences regarding beliefs and knowledge; yet, ToM abilities that involve affective processing appear to be impaired in these patients. Perhaps, therefore, it is this key connection—the interplay between mind and emotion—that is particularly problematic for individuals with VM lesions.

One disorder in which a similar pattern of behavioral profile has been described is Asperger syndrome, a mild subtype in the spectrum of autistic disorders. Individuals with Asperger syndrome pass basic ToM tests such as first- and second-order false belief but fail in advanced ToM tasks such as faux pas.<sup>19</sup> Recently, we have described two cases diagnosed with Asperger syndrome, who displayed severely impaired empathy and impaired performance on the faux pas task. Interestingly, the errors these patients made on this task reflected their inability to integrate cognition and emotion and make representations of the other person’s emotional state.<sup>48</sup> Dawson et al<sup>49</sup> have suggested that autism is related to dysfunction of the medial temporal and orbital frontal cortex rather than to dorsolateral PFC. In a first fMRI study of childhood Asperger syndrome, frontal activation patterns demonstrated some differences between patients and normal subjects.<sup>50</sup> Future investigations are needed to examine more closely the processes and patterns of deficits that are involved in developmental disorders such as autism and impaired social behavior following acquired brain damage.

The three tasks used in the current study differed in complexity and thus in attentional demands. However, it is highly unlikely that the patients’ low scores in the faux pas and irony tasks were due to difficulties in coping with the complexity of the tasks. First, working memory and memory load demands were controlled by allowing the subjects to reread the story as many times as needed. Also, subjects who made more than two errors in the control questions in either task were excluded. A qualitative analysis of the responses indicated that all the patients, including those with VM lesions, understood the stories well enough to reply correctly to the control (content) questions, and yet many of them failed to recognize when sarcasm was used or faux pas occurred.

This study suggests that the deficit in affective ToM is associated with VM lesions (especially in the right hemisphere) rather than damage to other brain areas. We do not wish to claim that affective ToM is localized to the right VM. Rather, we believe that our results indicate that the right VM region plays a major part in a network mediating affective

ToM. Baron-Cohen<sup>51</sup> has proposed that ToM is mediated by a distributed circuit involving the orbitofrontal cortex and the limbic system. Frith and Frith<sup>52</sup> described an alternative network, comprised by the superior temporal sulcus, the inferior frontal regions, and the medial PFC. Based on the current results, we suggest that the VM is a crucial component of this circuit. Therefore, a lesion in any of these regions may result in impairment of some aspect of ToM. These results reflect the major role played by the VM in integrating the various processes of ToM, thus facilitating the formation of affective ToM.

In the current study, all patients performed the false belief task at ceiling. We interpreted this as indicating that only "affective" ToM was impaired in our patients, whereas "cognitive" ToM was intact. However, it is possible that the false belief task was too easy, and a more complicated false belief task may have revealed some deficits in cognitive ToM as well as in affective ToM. We did not attempt to clarify the relationships between the cognitive and affective facets of ToM in detail. The detailed investigation of possible dissociations between these facets awaits future studies.

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## APPENDIX

### Second-Order False Belief

Hana and Benny are sitting in the office, talking about their meeting with their boss. Benny is putting an open bottle of ink on his desk. As he is doing so, some ink spills, so he leaves the office to look for a towel to clean up the spilled ink. While Benny is out of the office, Hana moves the ink bottle to the cabinet. While Benny is outside the office, he looks back through the keyhole and sees Hana moving the ink bottle.

Benny enters the office.

Following each story, four questions were asked:

*Belief question:* Where will Hana think that Benny thinks the ink bottle is?

*Reality question* (assessing story comprehension): Where, actually, is the ink bottle?

*Memory question:* Where did Benny put the ink bottle?

*Inference question:* Where would there be ink stain?

Participants were tested individually and answered the experimenter's questions spontaneously.

### Irony

*A sarcastic version item:* Joe came to work, and instead of beginning to work, he sat down to rest. His boss noticed his behavior and said: "Joe, don't work too hard!"

*A neutral version item:* Joe came to work and immediately began to work. His boss noticed his behavior, and said: "Joe, don't work too hard!"

Following each story, two questions were asked:

1. *Factual question* (assessing story comprehension): Did Joe work hard?
2. *Attitude question* (assessing comprehension of the true meaning of the speaker): Did the manager believe Joe worked hard?

Participants were tested individually and marked "yes" or "no" in a test booklet.

### Recognition of Social Faux Pas

Mike, a 9-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 cubicle, 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 said it?

Why did they say it?

*Control question* (assessing story comprehension):

In the story, where was Mike while Joe and Peter were talking?