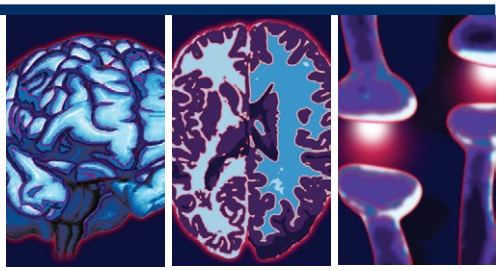

Impaired Behavioural Self-Awareness and Affective Theory of Mind Deficits Following Prefrontal Cortex Damage

FA Jonker[1,2†], MP Wattjes[3], EJA Scherder[2]

Abstract

Aim: The orbitofrontal cortex (OFC) and dorsomedial prefrontal cortex (dmPFC) are major subdivisions of the prefrontal cortex (PFC) involved in Theory of Mind (ToM) and behavioral self-awareness. Lesions of the OFC (Brodmann Area; 10,11,12,47) are associated with impairment in affective-ToM. Damage to dmPFC (Brodmann area: 8,9,10,24 and 32) is associated with the cognitive aspects of self-reference, including a consistent view of one's own behavior.

Method: we compared three dmPFC damaged patients (Brodmann Area; 8, 9, 10) with four OFC (Brodmann Area; 10, 11, 12) damaged patients, and compared them to a control group (N=22) on affective- ToM and behavioral self-awareness. Of the 20 patients in the pre-selection, only 7 patients had a lesion in a single sector of the PFC lesions. We measured behavioral-awareness with the Frontal System Behavioral Scale (FrSBe) subscales. Neuropsychological tests, including social cognitive tests and questionnaires were administered to patients and controls.

Results: The dmPFC group showed a significant difference with the control group concerning apathy ($\chi2(1, N=25) =5.319$, $p=0.021$). The OFC group differed significantly ($\chi2(1, N=26)=7.552$, $p=0.006$) from the control group concerning the Faux Pas empathy score (affective-ToM).

Conclusion: Both dmPFC and OFC are involved in a complex process of mentalizing with specific functions in relation to behavioral self-awareness irrespective of cognitive functioning.

Keywords

OFC damage, dmPFC damage, Affective- ToM, Behavioural self-awareness, Executive functions

Introduction

The prefrontal cortex (PFC) has been recognized as a key area for the 'social brain'; the ability to recognize and infer content of other minds, to empathize with others in order to predict future behaviors [1]. This sophisticated capability allows us to behave in a social appropriate way. The involvement of dorsomedial prefrontal cortex (dmPFC) and orbitofrontal cortex (OFC) in tasks that explicitly require mentalizing about social knowledge, Theory of Mind (ToM), including self-awareness processes in relation to social behavior has been well established [2-7]. Impaired self-awareness can be defined as a reduced capacity to reflect upon cognitive and social-emotional deficits, caused by impaired brain function, reflected in behavioral changes (i.e. personality changes) [8-12].In addition, self-awareness is associated with an affective ability to take a different perspective from the self, a skill that is necessary to understand the mental state of both self and others [9,13-17].

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The dmPFC includes Brodmann areas (BA) 8, 9, 10, 24, and 32 is associated with self-reference and self-appraisal, including a consistent view of the self and one's own behavior [4,18]. Neuroimaging studies show that the dmPFC is active during tasks that require social judgments, adjusting and updating the first initial impression and comparing oneself to others [19,20]. In a case study with a patient with dmPFC damage, it is concluded that the patient was impaired in updating his new self-concept (e.g. extraversion) based on given feedback [21]. Therefore, some researchers suggest that damage to the dmPFC is associated with impairment in metacognition and cognitive-ToM, mentalizing about thoughts and beliefs of others, and is related to deficits in behavioral self-awareness [6,22-24]. These findings are the more striking since studies also show that patients with dmPFC lesions show no impairment on standard neuropsychological tests appealing to executive functions [7, 25-27]. On behavioral level, lesions in the dmPFC are associated with apathy and processes related to drive [28].

Literature shows that lesions to the OFC, including BA 10, 11, 12 and 47 are strongly associated with changes in social-affective behavior, including impairment of affective-ToM, especially mentalizing about feelings and emotional states of others ('affective-ToM') [6,29-32]. The study of Shamay-Tsoory (2007) demonstrated that OFC damaged patients made more errors in affective-ToM compared to patients with extensive non-OFC lesions. According to the authors these group differences cannot be explained by executive dysfunctions. Damage to the OFC impairs the generation of social emotions which leads to the asymmetry between 'knowing how to behave' and 'behaving in an inappropriate way', which could be characterized as a deficit in behavioral self-awareness [33,34]. In a recent study on affective-ToM it was found that only damage to the left OFC and bilateral OFC lesions leads to impaired affective-ToM [35]. Lesions in exclusively the right OFC are in general associated with behavioral disinhibition [36-39].

Where most neuroimaging studies focus on the relationship between neuroanatomy (e.g. dmPFC, OFC) and aspects of self-referential processes and affective ToM, the nature of behavioral functioning has not yet been described in empirical studies. We have chosen to study specific dmPFC and OFC lesions because it is clear from literature that both structures are involved in the complex process of mentalizing in relationship to behavioral awareness [2,14,40-44]. In the present study, we have chosen to study three dmPFC-damaged patients (BA; 8, 9, 10) and four OFC (BA; 10, 11, 12) damaged patients and compare them to a control group (N=22). All were subjected to a broad neuropsychological test battery, including affective-ToM, and a behavioral- questionnaire. Our main goal in this explorative study is to determine whether behavioral changes, if present, following dmPFC and OFC lesions are related to deficits in behavioral self-awareness. We also wanted to know whether this is associated with deficits in ToM.

Methods

■ Participants

A total of 7 patients with PFC damage were recruited from the Mental Health Institute Altrecht (Neuropsychiatry, Vesalius), The Netherlands. All patients are outpatients and were referred because of neuropsychiatric, social, and/or neuropsychological difficulties due to acquired brain injury (ABI). The control group (N=22) are patients with cognitive complains and were randomly selected based on: no structural damage and a complete neuropsychological battery. None of the controls met the criteria of mild traumatic brain Injury (mTBI), no posttraumatic amnesia (PTA) or loss of consciousness (LOC). The control group had no history of (severe) psychiatry, epilepsy or neurological impairment and had no structural abnormalities on the MRI/CT (Magnetic Resonance Imaging/Computerized Tomography). **Table 1** presents the clinical characteristics of the patients and controls. Compared to the controls, no differences are found with respect to the demographic characteristics. Mean time between assessment and the brain damage in the PFC group is 14,1 years (SD ± 15,1). Etiology of the lesion: traumatic brain injury (TBI) (57.1%), stroke (28.6%) sequelae after removal of benign primary tumor (14.3%). No significant difference between groups for level of education, age in year and sexes. None of the patients reported a history of premorbid chronic psychiatric disorders, neurodegenerative pathology or severe drug addiction. All patients were 18 years or older. All patients, including controls, gave written informed consent to take part in the study. Written informed consent was obtained from participants and caregivers

according to the Declaration of Helsinki, and local ethics committee approved the study.

■ Lesion location

The anatomical location is specified into Brodmann area's [45]. We used the following classification; dmPFC, 8, 9 and 10; OFC, 10, 11, 12 and 25. A radiologist carried out the first anatomic classification and etiology (where possible) of patients' lesions. We selected the patients with predominately classified PFC lesions. An independent senior (neuro) radiologist of the VU medical Centre, who is blind to the test results, classified the location of the focal brain damage according to the Brodmann areas. The identification of the Brodmann Areas has been performed by using a dedicated atlas of neuronanatomy. The MRI data of this retrospective study is based on a heterogeneous dataset including different MRI acquisition parameters (pulse sequences, spatial resolution, magnetic field strengths). The identification of the lesions was based on FLAIR and/or T2 weighted sequences. Of the 20 patients in the pre-selection, only 7 patients had lesion in a single sector of the PFC lesions **(Table 2)**.

■ Materials and Procedure

The existing framework of the standard diagnostic procedures of Mental Health institute Altrecht (Neuropsychiatry Vesalius) was used. All patients were given an extensive standard neuropsychological test battery, including questionnaires. Duration of the standard assessment varied from 2, 5 to 5 hr. depending on the severity of the mental fatigueness. In some cases an additional appointment was required. Demographic information and injury related information was collected from the patient file. All tests and questionnaire have been chosen to provide an added value within the population of care. A full neuropsychological report was provided to the patient.

■ Neuroimaging

All patients, including controls, have been subjected to a MRI. If a recent (<6 month) MRI has been made elsewhere, no additional MRI was requested. In all other cases a new MRI was made in the University Medical Center, Utrecht (UMCU), the Netherlands on 3.0 Tesla MRI machine (Philips NT). All patients (N=7) were given a new MRI, for the controls 18 new MRI's were requested. For all patients, sagittal slices with T1-SE sequence, transversal slices with T2-FLAIR, T2-FFE, T2-SSH-TSE, T2-Dual-TSE sequence and coronal slices with T1-IR, T1-SE, T2-FFE and T2-FlAIR sequences were acquired. Given the retrospective concept of this study, it is not possible to exactly determine the date and the whole range possible differential diagnosis. Most of the lesions represent focal tissue loss suggestive of secondary due to trauma or primary vascular ischemic.

■ Theory of mind

Patients are presented with two different tests to measure affective-ToM. One verbal task (Faux Pas test) and one non-verbal task (Reading the Mind in the Eyes Test, RMET). For each test, scores proposed by the authors are used.

■ Faux pas

A Dutch translation of the Faux Pas Test is used to assess affective- ToM [46]. The Faux Pas consists of 8 short verbal vignettes, chosen from the 20 stories of the original adult Faux Pas [47]. Half of the stories described a situation in which a faux pas occurred. The stories are read out by the experimenter, with a printed copy of the stories placed in front of the participants to control for memory load. After reading each story, the participants were asked: 'Did someone say something awkward?' The mental attribution about the feelings of the 'faux pas victim' can be seen as a measure for affective- ToM. The detection and correct identification of the person how commitment the Faux pas is considered a measure of cognitive ToM. The maximum score for both cognitive and affective- ToM is 4 [48]. To score and interpret the answers, the instructions of Stone *et al.* are used. Interrater reliability of the FP is shown to be high (r=0.98; [49]).

■ Reading the mind in the eyes test (RMET)

The Dutch translation of the Reading the Mind in the Eyes Test (RMET) is based on the original

Table 1: Means and Standard Deviations of demographic characteristics of prefrontal lobe patients and controls.

	Controls N=22 (M, SD)	Pre –frontal lesion N=7 (M,SD)	p*
Age years	38,4 ± 11,9	39,8 ± 9,6	.778
Sex (%female)	45.5%	28.0%	.438
Education level	4,9 ± 1,2	5,1 ± 0,3	.497
Time since injury years	-	14,1 ± 15,1	-
Etiology			
TBI (%)	-	57.1	-
Stroke (%)	-	28.6	-
Tumor (%)	-	14.3	-

Mann-Whitney U tests; *Significant p value P<0.05.
Etiology percentage: distribution of the different etiologies in the Pre-frontal lesion group

Table 2: Patient's lesion characteristic.

Patient	Sex	Age in years	Time since lesion years	Etiology	Side of lesion	OFC (BA: 10,11,12,25)	dmPFC (BA: 8,9,10)
	M	40.5	33.18	TBI	Bilateral	11	
	M	48.2	17.27	TBI	Bilateral	10,11,12	10
	F	46.6	1.11	TBI	Right	10,11	10
	M	41.0	4.04	Tumor	Right	10,11	10
	M	44.5	36.50	Stroke	Left	10	8,9,10
	F	38.5	4.82	TBI	Left		8
	M	19.4	2.36	Stroke	Right		9

BA (Brodmann area's): 8, 9, 10, 11, 12, 25

English version [50]. The RMET is a ToM task to measure affective- ToM by the emotion recognition of faces [51]. The RMET consists of 36 photographs showing the eye region of an equal number of males and females. On each trial, one photograph is accompanied with four mental state terms describing complex emotions (e.g. dispirited, jealous, panicked, and arrogant), presented at each corner of the photograph. The test is scored by totaling the number of items (photographs) correctly identified by the participant, i.e. the number of mental states correctly identified. The maximum total score on the test is therefore 36. Validity has been good [51]. The raw score of the RMET is used.

Behavioral self-awareness

■ Frontal systems behavioral scale (FrSBe)

The FrSBe is a 46-item rating scale designed to measure frontal systems behavioral syndromes. The FrSBe includes a Total Score, which is a composite of three subscales: Apathy, Disinhibition, and Executive Dysfunction [52]. Each item is rated on a one-to-five Likert scale, with one indicating 'almost never' and five 'almost always'. The FrSBe gathers information regarding behaviors from the patient (self-report) and a significant other and includes a composite score and thee subscales that assess apathy, disinhibition an executive function. Significant others who completed ratings in this study were the primary caregivers of the patients. We measured behavioral -awareness by calculating the discrepancy scores between (subtracting family ratings from the patients self-rating) the FrSBe subscales [53,54]. A compound for the total and sub-scores differences served as the behavioral awareness score. Higher difference scores indicate more severe deficits of behavioral awareness. The difference score method is considered a sensitive measurement of deficit in behavioral awareness after brain injury [55,56].

■ Cognitive measurements

Executive functions: The most widely used neuropsychological tests of executive functioning are the Stroop, Trail Making Test (TMT), verbal fluency test and the Wisconsin Card Sorting Test (WCST) [57].

The Stroop Colour Word Test (SCWT) measures speed of information processing and the capacity to suppress automatic response tendencies [57,58]. An interference measure is calculated by taking the time on Stroop III divided by Stroop II (STROOP III/II), with higher ratio scores reflecting greater interference.

The Trail Making Test (TMT A- B) measures divided attention [59]. Part B (Trail B) is considered a measure of cognitive flexibility, alternating attention, and ability to inhibit a dominant but incorrect response [60]. Calculating the ratio between Part B and Part A (Trails B/Trails A) is suggested for interpretation of executive deficits and eliminating the influence of visual and motor abilities on performance [61].

The Wisconsin Card Sorting Test (WCST) consists of four key cards and 128 response cards with three perceptual dimensions (color, form and number) [62]. This test requires participants to find the correct classification principle. This task measures specifically 'set-shifting' [63]. In our study, performance on the WCST is measured by scoring the number of categories achieved (CC) and the percentage of perseveration errors (PE) [62].

Letter fluency (DAT) is a phonemic memory task that requires patients to say as many words as possible beginning with a specific letter (the letters D, A, T are provided) [64]. Items were counted as correct if they met the constraints of the condition and were not repetitions. This test mainly measures switching to another letter or category group and is said to be associated

with frontal lobe damage [56]. Patients are instructed not to use people's names, places and numbers or to name sequences of words with the same prefix (e.g. superman, supercars, and supermarket). Letter fluency performance is based on the number of correct items produced by the participants. The total number of correct words was used in our analysis.

■ Depression

BDI-II- The Beck Depression Inventory was administered for depressive symptomology. The BDI-II is a 21-item self-report questionnaire that measure severity of depressive symptoms [66]. The total score of the BDI-II was used in our analysis. We administered the BDI-II to rule out the possibility of cognitive deficits resulting from a possible depression.

■ Data-analyses

All analyses were performed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, New York). For all statistical tests, the overall alpha level was set at 0.05. Mann-Whitney U Tests was used for the comparison between total PFC group and controls with additional effect sizes ($r=Z / (\sqrt{N})$). For de between group comparison (OFC, dmPFC, Controls) the non-parametric Kuskal- allis test is used.

Results

The mean score on the BDI-II for controls is 24,8 (SD ±12,1) and for the PFC group 24,5 (SD ±10,8) indicates moderate to severe depressive symptoms. A between-group comparison (Mann-Whitney U tests) for the patients and controls for the BDI showed no difference (U=65.000, Z =-.056, P=.955). **Table 3** shows the means and standard deviation (SD) and between-groups comparison (Mann-Whitney U tests) for affective- TOM, the FrSBe for the patients and controls. The total PFC group preforms significantly worse compared to controls on the empathy question of the Faux Pas (U= 23.000, Z=-2.95, P=.003, r=0.61).

■ Cognitive and affective- ToM

The assumption of homogeneity of variance was tested using a non-parametric levene's test and found tenable. Kruskal-Wallis Test shows that there is a statistically significant difference on the Faux Pas empathy score between groups, $\chi 2(2, N=29)=9.429$, p=.009, with a mean rank empathy score of 5.12 for the OFC group, 10.17 for the dmPFC group and 17.45 for the controls **(Table 4)**.

Post hoc comparisons indicated that the mean score of the empathy question of the Faux Pas is significantly different between the OFC group and controls, $\chi 2(1, N= 26)=7.552$, p=.006. With a mean rank empathy score of 4.50 for the OFC group and 15.14 for the controls. No other significant differences are found between the dmPFC group, OFC group and controls.

■ Behavioural self-awareness

The assumption of homogeneity of variance was tested using a non-parametric levene's test and found tenable. A Kruskal-Wallis Test shows that there is a statistically significant difference between groups for the discrepancy score of apathy; $\chi 2(2, N= 29)=6.028$, p=.049, with a mean rank for apathy of 10.38 for the OFC group, 25.67 for the dmPFC group and 14.39 for the controls **(Table 5)**.

Post hoc comparisons indicated that the mean score for the discrepancy score of apathy is significantly different between the dmPFC group and controls, $\chi 2(1, N=25)=5.319$, p=.021. With a mean rank score of 22.17 for the dmPFC group and 11.75 for the controls. No other significant differences are found between the dmPFC group, OFC group and controls for the discrepancy scores of the FrSBe **(Table 6)**.

■ Cognitive measures

The assumption of homogeneity of variance was tested using a non-parametric levene's test and found tenable. The Kruskal-Wallis Test shows

Table 3: Means and Standard Deviations of ToM and FrSBe- Questionnaire for the total PFC group and controls.

	Controls N=22 M (SD)	PFC lesion N=7 M (SD)	U	Z	P	r
Faux Pas						
Cognitive	3.72 (0.45)	3.28 (0.75)	51.00	-1.59	.111	0.33
Empathy	3.36 (0.65)	2.14 (0.89)	23.000	-2.95	**.003***	**0.61**
RMET	22.68 (5.54)	24.00 (4.74)	67.000	-0.51	.609	0.12
FrSBe discrepancy scores						
Total	-2.77 (23.3)	6.43 (40.9)	61.000	-0.81	.414	0.05
Apathy	-2.09 (10.2)	4.29 (17.8)	63.500	-0.69	.491	0.07
Dysexecutive	0.27 (9.4)	7.57 (11.1)	43.500	-1.71	.087	0.33
Disinhibition	-2.18 (8.9)	2.71 (6.4)	50.500	-1.35	.176	0.03

Mann-Whitney U tests; *Significant p value P<0.05.

Table 4: Affective-ToM between OFC & Control.

Test Statistics[a,b]	Faux Pas empathy	Faux pas Cognitive	Total score RMET
Chi-Square	7,552	1.314	1,836
	.006*	.252	.175

a. Kruskal Wallis Test
b. Grouping Variable: OFC, dmPFC, Controls

*Significant p value <0.05

Table 5: FrSBe discrepancy scores between dmPFC & Controls.				
Test Statistics[a,b]	**Total**	**Apathy**	**Disinhibition**	**Dysexecutive**
Chi-Square	,175	5,319	1,683	3,396
	.676	**.021***	.195	.065
a. Kruskal Wallis Test				
b. Grouping Variable: OFC, dmPFC, Controls				
*Significant p value < 0.05				

Table 6: Cognitive measures.					
Test Statistics[a,b]	**Stroop Ratio score**	**TMT Ratio score**	**Letter Fluency**	**WCST (PE)**	**WCST (CC)**
Chi-Square	0.632	2.157	2.274	1.459	3.556
df	2	2	2	2	2
Asymp. Sig.	.729	.340	.321	.482	.169
a. Kruskal Wallis Test					
b. Grouping Variable: OFC, dmPFC, Controls					
df: degree of freedom; Asymp. Sig: asymptotic significance					
*Significant p value < 0.05					

no significant difference between groups for the cognitive measures.

Discussion

As far as we know, this is the first study that specifically compared structural dmPFC and OFC lesions due to ABI on measures of behavioural self-awareness and ToM in a clinical outpatient group. A major finding of our study is that we did find significant differences for the behavioral self-awareness level between groups on the apathy discrepancy score of the FrSBe. The mean discrepancy score of the dmPFC group is significantly higher (mean rank 25,67), suggesting impaired behavioral self-awareness / overestimation of one's own behavior. Our result shows that patients with dmPFC lesions do not report symptoms of apathy based on self-report whereas the proxy ratings do confirm severe apathy. This finding confirms that lesions to dmPFC (particularly the anterior cingulate cortex; ACC) are associated with self-awareness problems concerning apathy [6]. Recent studies suggest that the anterior parts of BA-10, as part of the dmPFC, is related to metacognition, including cognitive-ToM and self-knowledge and that its posterior part, as part of the OFC, is believed to play a coordinating role in affective-ToM [6,22,67]. One could suggest that damage to dmPFC disrupts a system that is involved in mechanisms that enables us to switch attention from external to intern self-representations [6, 67]. Given the fact that we did not find any deficits in cognitive-ToM in de dmPFC group might suggest more posterior lesions of the BA-10 in our group.

A second major finding is that the OFC group made more errors on the empathy question of the Faux Pas (affective- ToM) compared to controls and patients with dmPFC lesions. In line with literature we found that damage to the left OFC and bilateral OFC are more affected on affective ToM, a total of 60% left, bilateral sided OFC lesions in our study is in line with these findings [35]. In another study investigating emotional perspective taking, a task similar to affective- ToM, it was found that BA-11 (part of the OFC) is crucial for empathic processing [68]. In our OFC group 4 out of 5 have BA-11 damage. Theories state that the OFC is implicated with the 'somatic marker' [69]. This theory suggest that social decision-making is a process influenced by the amygdala and OFC, by marking input with a 'somatic marker' [69]. This might suggest that OFC patients do not experience a somatic marker in making empathic reactions (affective- ToM). Besides the fact that lesions in the right OFC are in general associated with behavioral disinhibition, a recent review on clinical case studies following OFC lesions concluded that affective-ToM is not specifically associated with behavioral changes [26]. In line with these findings this might explain why we did not find behavioral self-awareness deficits compared to dmPFC and controls. Given the mean time since the dmPFC and OFC lesions (14.1 years) one might conclude that some have learned to compensate for their behavioral changes [15]. For the reading the mind in the eyes test (RMET) we did not find a significant difference between groups. A possible explanation for this finding is that fMRI studies on the RMET shows increased activation in the dorsolateral prefrontal cortex (DLPFC), suggesting more cognitive processes in identifying emotions based on only the eyes [70-72].

A final finding of our study is that we found no cognitive dysfunctions, including executive functions, between groups. Much of what is known about neuropsychology is based on patients with DLPFC dysfunctions, which is mainly involved in cognitive functions, in particular executive functions [73,74]. Complex higher order cognitive functions of the PFC such as learning and adapting to changing reinforcement contingencies, behavioral-monitoring, decision making and social processing and affective-ToM does not coincide with standard neuropsychological functions [75]. Neuropsychological assessment of the OFC and dmPFC requires an integrative approach and must be augmented with MRI- data, tests that

are sensitive to the OFC and dmPFC with proxy ratings on behavioral level [7]. Indeed, part of the remaining puzzle is explaining the behavioral problems experienced by dmPFC-OFC damaged patients in real-life given their normal score on neuropsychological [7].

Limitations

There are limitations that need to be addressed. First, the number of patients with OFC and dmPFC lesions was limited. Bedsides, patients 2, 3, 4 and 5 had an overlap in BA-10. Despite the fact that literature agrees on the BA of the different PFC areas, this might have influenced the results. Although we grouped our patients in OFC and dmPFC the heterogeneity of the nature of acquired brain injury in our patient sample is high. TBI is more likely to cause not only one distinct anatomical injury but more diffuse white matter injury, which theoretically may cause more disruption between regions of the brain. The cross-sectional design of the study might have narrowed the range of possible outcomes. The high variability in time since injury might have influenced the test results. One can expect that patients with a more extended period of time since injury might have had more opportunities to learn to compensate for their deficits [15]. A final limitation is the use of the discrepancy scores as index for behavioral self-awareness. The limitation of this method is that the validity of this score depends on the ability of the family member to rate objectively the functioning of the patient post injury. It has been suggested that family members may give socially acceptable answers or even deny disability [76].

Conclusions and Recommendations

The present results are unique in it because that describes outpatients with specific PFC damage due to ABI in a chronic phase. Not be able to empathize with others is due to specific OFC lesions whereas a lack of behavioral awareness seems to be due to dmPFC lesions, irrespective of cognitive functioning. Both structures are involved in a complex process of mentalizing with specific functions. Neuropsychological assessment must be augmented with MRI- data, test that are sensitive to the dmPFC, OFC and with proxy ratings on behavioral level for an integrative approach. These findings should be taken into account in the aftercare of patients with dmPFC and OFC lesions. Chances are that these patients, similar to the patients in the present study, end up in neuropsychiatry due to their deficits in behavioural self-awareness and affective processing. This social disability should be recognized and should lead to appropriate counselling provided by caregivers.

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References

1. Frith CD, Frith U. The neural basis of mentalizing. *Neuron* 50(2), 531-534 (2006).
2. Mitchell JP, Banaji MR, Macrae CN. The link between social cognition and self-referential thought in the medial prefrontal cortex. *J. Cogn. Neurosci* 17(8), 1306-1315 (2005).
3. Gallagher HL, Frith CD. Dissociable neural pathways for the perception and recognition of expressive and instrumental gestures. *Neuropsychologia* 42(13), 1725-1736 (2004).
4. Gusnard DA, Akbudak E, Shulman GL, *et al.* Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc. Natl. Acad. Sci. USA* 98(7), 4259-4264 (2001).
5. Bramham J, Morris RG, Hornak J, *et al.* Social and emotional functioning following bilateral and unilateral neurosurgical prefrontal cortex lesions. *J. Neuropsychol* 3(1), 125-143 (2009).
6. Szczepanski SM, Knight RT. Insights into human behavior from lesions to the prefrontal cortex. *Neuron* 83(5), 1002-1018 (2014).
7. Zald DH, Andreotti C. Neuropsychological assessment of the orbital and ventromedial prefrontal cortex. *Neuropsychologia* 48(12), 3377-3391 (2010).
8. Larson MJ, Perlstein WM. Awareness of deficits and error processing after traumatic brain injury. *Neuroreport* 20(16), 1486-1490 (2009).
9. Trahan E, Pépin M, Hopps S. Impaired awareness of deficits and treatment adherence among people with traumatic brain injury or spinal cord injury. *J. Head. Trauma. Rehabil* 21(3), 226-235 (2006).
10. McDonald S. Impairments in social cognition following severe traumatic brain injury. *J. Int. Neuropsychol. Soc* 19(3), 231-246 (2013).
11. Spikman JM, Van Der Naalt J. Indices of impaired self-awareness in traumatic brain injury patients with focal frontal lesions and executive deficits: implications for outcome measurement. *J. Neurotrauma* 27(7), 1195-1202 (2010).
12. Herwig U, Kaffenberger T, Schell C, *et al.* Neural activity associated with self-reflection. *BMC. Neurosci* 13(1), 52 (2012).
13. Moriguchi Y, Ohnishi T, Lane RD, *et al.* Impaired self-awareness and theory of mind: An fMRI study of mentalizing in alexithymia. *Neuroimage* 32(3), 1472-1482 (2006).

14. Morin A. Self-recognition, theory-of-mind, and self-awareness: what side are you on? *Laterality* 16(3), 367-383 (2011).
15. Flashman LA, McAllister TW. Lack of awareness and its impact in traumatic brain injury. *NeuroRehabilitation* 17(4), 285-296 (2002).
16. Sherer M, Boake C, Levin E, *et al.* Characteristics of impaired awareness after traumatic brain injury. *J. Int. Neuropsychol. Soc* 4(4), 380-387 (1998).
17. Hart T, Seignourel PJ, Sherer M. A longitudinal study of awareness of deficit after moderate to severe traumatic brain injury. *Neuropsychol. Rehabil* 19(2), 161-176 (2009).
18. Schmitz TW, Johnson SC. Relevance to self: A brief review and framework of neural systems underlying appraisal. *Neurosci. Biobehav. Rev* 31(4), 585-596 (2007).
19. Philippi CL, Duff MC, Denburg NL, *et al.* Medial PFC damage abolishes the self-reference effect. J. *Cogn. Neurosci* 24(2), 475-481 (2012).
20. Denny BT, Kober H, Wager TD, et al. A Meta-analysis of Functional Neuroimaging Studies of Self- and Other Judgments Reveals a Spatial Gradient for Mentalizing in Medial Prefrontal Cortex. *J. Cogn. Neurosci* 24(8), 1742-1752 (2012).
21. Philippi CL, Feinstein JS, Khalsa SS, *et al.* Preserved self-awareness following extensive bilateral brain damage to the insula, anterior cingulate, and medial prefrontal cortices. *PLoS. One* 7(8), e38413 (2012).
22. Stuss DT, Alexander MP. Is there a dysexecutive syndrome? *Philos. Trans. R. Soc. Lond. B. Biol. Sci* 362(1481), 901-915 (2007).
23. Powers KE, Chavez RS, Heatherton TF. Individual differences in response of dorsomedial prefrontal cortex predict daily social behavior. *Soc. Cogn. Affect. Neurosci* 11(1), 121-126 (2016).
24. Adolphs R. The neurobiology of social cognition. *Curr. Opin. Neurobiol* 11(2), 231-239 (2001).
25. Fujii T, Suzuki M, Suzuki K, *et al.* Normal memory and no confabulation after extensive damage to the orbitofrontal cortex. *J. Neurol. Neurosurg. Psychiatry* 76(9), 1309-1310 (2005).
26. Jonker F, Jonker C, Scheltens P, *et al.* The role of the orbitofrontal cortex in behaviour and cognition. *Rev. Neurosci* 26(1), 1-11 (2015).
27. Namiki C, Yamada M, Yoshida H, *et al.* Small orbitofrontal traumatic lesions detected by high resolution MRI in a patient with major behavioural changes. *Neurocase* 14(6), 474-479 (2008).
28. Holroyd CB, Yeung N. Motivation of extended behaviors by anterior cingulate cortex. *Trends. Cogn. Sci* 16(2), 122-128 (2012).
29. Funayama M, Mimura M, Koshibe Y, *et al.* Squalor syndrome after focal orbitofrontal damage. *Cogn. Behav. Neurol* 23(2), 135-139 (2010).
30. Hornak J, Bramham J, Rolls ET, *et al.* Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain* 126(7), 1691-1712 (2003).
31. Shamay-Tsoory SG, Aharon-Peretz J (2007) Dissociable prefrontal networks for cognitive and affective theory of mind: a lesion study. *Neuropsychologia* 45(13), 3054-3067 (2007).
32. Stone VE, Baron-Cohen S, Knight RT (1998) Frontal lobe contributions to theory of mind. *J. Cogn. Neurosci* 10(5), 640-656 (1998).
33. Beer JS, John OP, Scabini D, et al. Orbitofrontal cortex and social behavior: integrating self-monitoring and emotion-cognition interactions. *J. Cogn. Neurosci* 18(6), 871-879 (2006).
34. Slachevsky A, Peña M, Pérez C, *et al.* Neuroanatomical basis of behavioral disturbances in patients with prefrontal lesions. *Biol. Res* 39(2), 237-250 (2006).
35. Leopold A, Krueger F, dal Monte O, *et al.* Damage to the left ventromedial prefrontal cortex impacts affective theory of mind. *Soc. Cogn. Affect. Neurosci* 7(8), 871-880 (2012).
36. Jonker FA, Jonker C, Scheltens P, *et al.* The role of the orbitofrontal cortex in cognition and behavior. *Rev. Neurosci* 26(1), 1-11 (2015).
37. Poletti M, Lucetti C, Bonuccelli U. Out-of-control sexual behavior in an orbitofrontal cortex-damaged elderly patient. *J. Neuropsychiatry Clin. Neurosci* 22(2), E7 (2010).
38. Ogai M, Iyo M, Mori N, *et al.* A right orbitofrontal region and OCD symptoms: a case report. *Acta. Psychiatr. Scand* 111(1), 74-76 (2005).
39. Nyffeler T, Regard M. Kleptomania in a patient with a right frontolimbic lesion. *Neuropsychiatry. Neuropsychol. Behav. Neurol* 14(1), 73-76 (2001).
40. Damasio AR, Tranel D, Damasio H. Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. *Behav. Brain. Res* 41(2), 81-94 (1990).
41. Flagan T, Beer JS. Three ways in which midline regions contribute to self-evaluation. *Front. Hum. Neurosci* 7(1), 450 (2013).
42. Northoff G, Heinzel A, de Greck M, *et al.* Self-referential processing in our brain--a meta-analysis of imaging studies on the self. *Neuroimage* 31(1), 440-457 (2006).
43. Henry JD, Phillips LH, Crawford JR, *et al.* Theory of mind following traumatic brain injury: the role of emotion recognition and executive dysfunction. *Neuropsychologia* 44(10), 1623-1628 (2006).
44. Platek SM, Critton SR, Myers TE, *et al.* Contagious yawning: the role of self-awareness and mental state attribution. *Brain. Res. Cogn. Brain. Res* 17(2), 223-237 (2003).
45. Rowe AD, Bullock PR, Polkey CE, *et al.* Theory of mind' impairments and their relationship to executive functioning following frontal lobe excisions. *Brain* 124(3), 600-616 (2001).
46. Spek AA, Scholte EM, Van Berckelaer-Onnes IA. Theory of Mind in Adults with HFA and Asperger Syndrome. *J. Autism. Dev. Disord* 40(3), 280-289 (2010).
47. Stone VE, Baron-Cohen S, Knight RT. Frontal Lobe Contributions to Theory of Mind. *J. Cogn. Neurosci* 10(5), 640-656 (1998).
48. Bivona U, Riccio A, Ciurli P, *et al.* Low Self-Awareness of Individuals With Severe Traumatic Brain Injury Can Lead to Reduced Ability to Take Another Person's Perspective. *J. Head. Trauma. Rehabil* 29(2), 157-171 (2013).
49. Gregory C, Lough S, Stone V, *et al.* Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: theoretical and practical implications. *Brain* 125(4), 752-764 (2002).
50. Baron-Cohen S, Wheelwright S, Hill J, *et al.* The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child. Psychol. Psychiatry* 42(2), 241-251 (2001).
51. Ahmed FS, Stephen Miller L. Executive function mechanisms of theory of mind. *J. Autism. Dev. Disord* 41(5), 667-678 (2011).
52. Stout JC, Ready RE, Grace J, et al. Factor analysis of the frontal systems behavior scale (FrSBe). *Assessment* 10(1), 79-85 (2003).
53. Hoerold D, Dockree PM, O'Keeffe FM, *et al.* Neuropsychology of self-awareness in young adults. *Exp. Brain. Res* 186(3), 509-515 (2008).
54. Hoerold D, Pender NP, Robertson IH. Metacognitive and online error awareness deficits after prefrontal cortex lesions. *Neuropsychologia* 51(3), 385-391 (2013).
55. Hart T, Whyte J, Polansky M, *et al.*

Concordance of patient and family report of neurobehavioral symptoms at 1 year after traumatic brain injury. *Arch. Phys. Med. Rehabil* 84(2), 204-213 (2003).

56. O'Keeffe F, Dockree P, Moloney P, *et al.* Awareness of deficits in traumatic brain injury: a multidimensional approach to assessing metacognitive knowledge and online-awareness. *J. Int. Neuropsychol. Soc* 13(1), 38-49 (2007).

57. Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. *Neuropsychol. Rev* 16(1), 17-42 (2006).

58. Stuss DT. The frontal lobes are necessary for `theory of mind'. *Brain* 124(2), 279-286 (2001).

59. Reitan RM, Herring S. A short screening device for identification of cerebral dysfunction in children. *J. Clin. Psychol* 41(5), 643-650 (1985).

60. Kortte KB, Horner MD, Windham WK. The trail making test, part B: cognitive flexibility or ability to maintain set? *Appl. Neuropsychol* 9(2), 106-109 (2002).

61. Corrigan JD, Hinkeldey NS. Relationships between parts A and B of the Trail Making Test. *J. Clin. Psychol* 43(4), 402-409 (1987).

62. Nyhus E, Barceló F. The Wisconsin Card Sorting Test and the cognitive assessment of prefrontal executive functions: a critical update. *Brain. Cogn* 71(3), 437-451 (2009).

63. Miyake A, Friedman NP, Emerson MJ, *et al.* The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn. Psychol* 41(1), 49-100 (2000).

64. Strauss E, Sherman EMS, Strauss SO, *et al.* A compendium of neuropsychological tests: Administration, norms, and commentary. In: New York: Oxford University Press. 1216. Oxford University Press (2006).

65. Reverberi C, Laiacona M, Capitani E. Qualitative features of semantic fluency performance in mesial and lateral frontal patients. *Neuropsychologia* 44(3), 469-478 (2006)

66. Beck AT, Steer RA, Brown GK. Manual for Beck Depression Inventory-II. *San Antonio. TX Psychol. Corp* (1996).

67. Roca M, Torralva T, Gleichgerrcht E, *et al.* The role of Area 10 (BA10) in human multitasking and in social cognition: a lesion study. *Neuropsychologia* 49(13), 3525-3531 (2011).

68. Hynes CA, Baird AA, Grafton ST. Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. *Neuropsychologia* 44(3), 374-383 (2006).

69. Bechara A, Damasio AR. The somatic marker hypothesis: A neural theory of economic decision. *Games. Econ. Behav* 52(1), 336-372 (2005).

70. Adolphs R, Baron-Cohen S, Tranel D. Impaired recognition of social emotions following amygdala damage. *J. Cogn. Neurosci* 14(8), 1264-1274 (2002).

71. Baron-Cohen S, O'Riordan M, Stone V, *et al.* Recognition of faux pas by normally developing children and children with Asperger syndrome or high-functioning autism. *J. Autism. Dev. Disord* 29(5), 407-418 (1999).

72. Haxby JV, Hoffman EA, Gobbini MI. Human neural systems for face recognition and social communication. *Biol. Psychiatry* 51(1), 59-67 (2002).

73. Duffy JD, Campbell JJ. The regional prefrontal syndromes: a theoretical and clinical overview. J. Neuropsychiatry. *Clin. Neurosci* 6(4), 379-387 (1994).

74. Stuss DT, Levine B. Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annu. Rev. Psychol* 53(1), 401-433 (2002).

75. Hanna-Pladdy B. Dysexecutive syndromes in neurologic disease. *J. Neurol. Phys. Ther* 31(3), 119-127 (2007).

76. Sherer M, Hart T, Nick TG. Measurement of impaired self-awareness after traumatic brain injury: a comparison of the patient competency rating scale and the awareness questionnaire. *Brain. Inj* 17(1), 25-37 (2003).