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Olfactory sulcus morphology in teenagers with first-presentation borderline personality disorder

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ABSTRACT

Gray matter reduction of the orbitofrontal cortex (OFC) has been reported in borderline personality disorder (BPD), but it remains unknown whether the BPD patients exhibit morphologic changes of the olfactory sulcus, a potential marker of forebrain development located on the OFC. We used magnetic resonance imaging to investigate the length and depth of the olfactory sulcus in 20 teenagers (15 females and 5 males) with first-presentation BPD and 20 healthy controls (15 females and 5 males). While there was no group difference in the length of the sulcus, the BPD patients (especially those with a history of trauma) had a significantly shallower right olfactory sulcus compared with controls. In addition, sulcus depth was negatively correlated with the severity of impulsivity and affective instability in the BPD patients. These preliminary findings may suggest a significant role of environmental risk factors (i.e., trauma exposure) during childhood to adolescence in the neurobiology of BPD.

1. Introduction

Gray matter reductions in fronto-limbic regions, such as the orbitofrontal cortex (OFC), have been implicated in emotional dysregulation and impulsivity in borderline personality disorder (BPD) (Chanen and Kaess, 2012; Krause-Utz et al., 2014). These findings are reported also in adolescent BPD (Chanen et al., 2008; Whittle et al., 2009), suggesting that neurobiological abnormalities in adult BPD may not solely be the consequence of chronic morbidity or prolonged medication use (Winsper et al., 2016). Further, a recent finding of altered OFC surface morphology in BPD (de Araujo Filho et al., 2014), which probably reflects cortical underdevelopment (Armstrong et al., 1995), may support neurodevelopmental theories of BPD suggesting that a neurobiological vulnerability interacts with environmental risk factors to increase risk of BPD (Crowell et al., 2009).

Morphology of the olfactory sulcus, a primary sulcus located on the surface of medial OFC, could be a marker of both fetal [i.e., around 16–25 weeks' gestation (Chi et al., 1977)] and postnatal [i.e., during childhood to adolescence (Alemán-Gómez et al., 2013)] forebrain development. An abnormally shallow olfactory sulcus has been reported in neuropsychiatric disorders such as schizophrenia and major depression (Takahashi and Suzuki, 2018), implicating abnormal neurodevelopment in the OFC region could be associated with emergence of various psychiatric conditions. Hypothesized neurodevelopmental theories and potential OFC pathology in BPD raise the possibility that the BPD patients exhibit a shallow olfactory sulcus and that environmental risk factors (e.g., trauma exposure during childhood to adolescence), which may lead to prefrontal cortical thinning (Kelly et al., 2013), affect the sulcus morphology. To our knowledge, however, no magnetic resonance imaging (MRI) studies have specifically examined the olfactory sulcus in BPD.

This MRI study examined olfactory sulcus morphology in teenage BPD patients with minimal treatment exposure and healthy controls. Based on the possible role of olfactory sulcus morphology as a marker of forebrain development, we predicted that the BPD patients would have a shallower olfactory sulcus compared to controls. We also examined the relationship between the sulcus morphology of the patients and their clinical characteristics (e.g., BPD phenomenology, environmental factors).

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Table 1
Sample characteristics and olfactory sulcus measures of the participants.

Variable	Controls (5M, 15F)	Whole BPD (5M, 15F)	BPD with trauma (2M, 7F)	BPD without trauma (3M, 7F)
Age (years)	19.0 ± 2.2	17.3 ± 1.1	17.5 ± 0.9	17.0 ± 1.1
Handedness (right/mixed/left)	18/0/2	18/1/1	9/0/0	8/1/1
Height (cm)[a]	168.2 ± 10.2	166.2 ± 11.5	163.9 ± 11.4	167.8 ± 12.5
premorbid IQ[a]	101.9 ± 9.1	100.9 ± 5.8	100.2 ± 5.7	100.8 ± 6.1
Number of parasuicidal episode	–	7.2 ± 9.4	3.2 ± 5.4	11.0 ± 11.4
Number of violent episode	–	2.9 ± 6.8	1.7 ± 3.3	4.0 ± 9.2
YASR or YSR subscale scores				
Internalizing	–	0.91 ± 0.49	0.92 ± 0.51	0.96 ± 048
Externalizing	–	0.76 ± 0.41	0.66 ± 0.38	0.91 ± 0.41
SCID-II total BPD score	–	21.0 ± 3.2	21.1 ± 2.6	21.5 ± 3.1
Intracranial volume (cm^3)	1363 ± 141	1370 ± 104	1366 ± 101	1371 ± 117
Olfactory sulcus length (mm)				
Left	44.7 ± 2.7	44 2 ± 3.2	43.5 ± 2.7	44.9 ± 3.6
Right	44.8 ± 3.7	45.6 ± 4.7	45.9 ± 3.5	45.7 ± 5.9
Olfactory sulcus depth (mm)				
Left	11.7 ± 1.4[b]	11.2 ± 0.8	11.2 ± 0.6	11.1 ± 0.9
Right	12.9 ± 1.2	11.2 ± 0.9[c]	10.7 ± 0.6[d]	11.7 ± 1.0

Values represent means ± SDs.
BPD, borderline personality disorder; F, female; M, male; SCID-II, Structured Clinical Interview for DSM-IV Axis II Disorders; YASR, Young Adult Self-Report; YSR, Youth Self-Report.
[a] Data missing for some participants.
[b] $p < 0.001$: compared with right hemisphere (Post hoc Scheffé's test).
[c] $p < 0.001$: compared with controls (Post hoc Scheffé's test).
[d] $p = 0.013$: compared with non-trauma BPD patients (Post hoc Scheffé's test).

2. Methods

2.1. Participants

Twenty teenagers meeting Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (First et al., 1997) criteria for BPD, who had never received specific treatment for BPD, and 20 healthy controls were included in this study (Table 1). The sample characteristics have been described in our previous study (Chanen et al., 2008), which reported gray matter loss of the OFC in the BPD group. Comorbid Axis I diagnoses included disruptive behavior disorders ($n = 10$), anxiety disorder ($n = 9$), mood disorder ($n = 7$), and/or substance abuse or dependence. Seventeen patients were medication-free, but three were taking antidepressants at the time of scanning. Lifetime trauma exposure, along with number of parasuicidal and violent episodes over the previous 6 months, were assessed by semi-structured interview. Interview data on abuse or trauma were available for 19 BPD participants; 10 denied any experience of abuse and 9 reported experience of physical ($n = 6$), sexual ($n = 5$), and/or emotional ($n = 5$) abuse (mean onset age of trauma experience = 5.6 ± 4.9 years, range = 0–15). The BPD participants completed the Youth Self-Report [YSR (Achenbach, 1991)] (age <18 years) or the Young Adult Self-Report [YASR (Achenbach, 1997)] (age ≥18 years).

Healthy controls were screened for personal or family history of psychosis, or substance abuse/dependence. BPD screens were performed using a checklist derived from the SCID-II. All participants were physically healthy, and none had a history of serious head injury, loss of consciousness (≥10 min), seizure, neurological diseases, thyroid disorder or other significant medical illness. The local Research and Ethics Committees approved this study. Written informed consent was obtained from participants or from a parent or guardian.

2.2. Magnetic resonance imaging procedures

The study participants underwent brain MRI with a 1.5-T GE Signa scanner. A three-dimensional volumetric spoiled gradient recalled echo sequence yielded a coronal series of 124 contiguous T1-weighted slices of 1.5-mm thickness (time repetition = 14.3 ms, time to echo = 3.3 ms, flip angle = 30°, field of view = 24 × 24 cm, matrix size = 256 × 256, and voxel dimension = 0.938 × 0.938 × 1.5 mm). The intracranial volume (ICV) was measured to correct for differences in head size as previously described (Eritaia et al., 2000).

Using Dr. View software (Infocom, Tokyo, Japan), the images were realigned in three dimensions and reconstructed into contiguous coronal images with a 0.938-mm thickness, perpendicular to the anterior commissure-posterior commissure line. As described in detail elsewhere (Takahashi et al., 2013), one rater (TT), who was blind to the subjects' identity, measured the depth of the olfactory sulcus in all coronal slices where the sulcus could be identified (Fig. 1). On each coronal slice, the olfactory sulcus was traced beginning with the deepest point of the sulcus and ending inferiorly with a tangent line connecting the top surfaces of the gyrus rectus and medial orbital gyrus (Rombaux et al., 2009). The average depth of the sulcus on each hemisphere was calculated as follows: sum of the depth in all slices containing the sulcus / slice number. The length of the sulcus in the anterior-posterior direction (mm) was determined by the multiplication of the number of these coronal slices by 0.938. Intra- and inter-rater (TT and YN) intraclass correlation coefficients (ICCs) for the length and depth of the olfactory sulcus in 10 randomly selected brains were over 0.83.

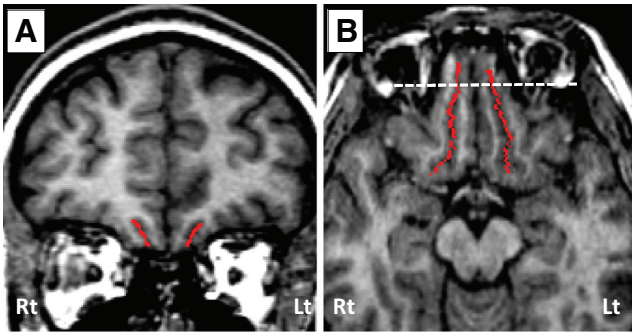

Fig. 1. Olfactory sulci on coronal (A) and axial (B) views, which were colored on 0.938-mm consecutive coronal slices. Panel A and the dotted line on panel B show the plane of the posterior tangent through the eyeballs.

2.3. Statistical analysis

The average depth and length of the olfactory sulcus were analyzed using the repeated measures ANCOVA, with age, gender, and ICV as covariates, diagnosis as a between-subject factor, and hemisphere as a within-subject variable. We then compared the olfactory sulcus measures between BPD subgroups on the basis of violent and parasuicidal episodes, trauma exposure, and comorbid disorders. Post hoc Scheffé's test was employed.

The relationships between the sulcus measures and clinical variables in BPD patients (YSR/YASR subscale scores, number of parasuicidal and violent episodes, age of trauma onset, and each of nine SCID-II BPD criteria score) as well as the OFC gray matter volume (Chanen et al., 2008) were examined by Pearson's partial correlation coefficients, controlling for age and ICV. The number of parasuicidal and violent episodes was log-transformed because of their skewed distribution. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Sample characteristics

The BPD participants and healthy controls were matched for gender, handedness, height, and IQ, but the controls were older than the BPD group [F (1, 38) = 2.97, $p = 0.003$] (Table 1). There was no significant difference in any demographic or clinical variable between BPD patients with ($n = 9$) and without ($n = 10$) trauma exposure (Table 1).

3.2. Length and depth of the olfactory sulcus

ANCOVA of the sulcus depth showed significant main effects of diagnosis [F (1, 35) = 9.91, $p = 0.003$] and hemisphere [F (1, 38) = 19.04, $p < 0.001$] and a diagnosis-by-hemisphere interaction [F (1, 38) = 16.91, $p < 0.001$]. However, ANCOVA of the sulcus length showed no significant effect of diagnosis or hemisphere. Post-hoc analyses showed that right olfactory sulcus depth was significantly shallower in the BPD patients compared with controls (Table 1). There was no effect or interaction involving gender on the sulcus depth [males ($n = 10$), left = 11.4 ± 1.2 mm, right = 12.0 ± 1.4 mm; females ($n = 30$), left = 11.5 ± 1.1 mm, right = 12.1 ± 1.4 mm] when we used gender also as the independent variable.

BPD patients with trauma exposure had a shallower right olfactory sulcus compared with those without (subgroup-by-side interaction, F (1, 17) = 8.52, $p = 0.010$) (Table 1, Fig. 2). However, there were no significant group differences of the sulcus measures when dividing the BPD patients on the presence or absence of parasuicidal episodes, violent episodes, or each comorbid Axis I disorder. These results did not change even when we excluded the BPD patients who were taking antidepressants ($n = 3$) or we examined only female subjects.

3.3. Correlational analysis

The sulcus measures did not correlate with age and IQ in BPD or healthy subjects. Sulcus depth was negatively correlated with SCID-II BPD impulsivity (right, $r = -0.528$, $p = 0.024$) and affective instability (left, $r = -0.577$, $p = 0.012$) scores, although this was not significant after Bonferroni correction. Other clinical variables (including the age of trauma onset) and the OFC volume did not correlate with the sulcus measures.

4. Discussion

To our knowledge, this is the first MRI study to report the morphologic changes of the olfactory sulcus in BPD. The adolescent BPD patients, especially those with a traumatic experience, had significantly shallower right olfactory sulcus compared to controls, but there was no group difference in its anterior-posterior length. In addition, the sulcus depth of the BPD patients was weakly associated with impulsivity and affective instability. These findings suggest that environmental risk factors of BPD may significantly affect neurobiological abnormalities related to BPD phenomenology.

The depth of the olfactory sulcus, which appears at around 16 weeks and is prominent at 25 weeks of gestation (Chi et al., 1977), relates to olfactory function in healthy subjects and is usually deeper on the right hemisphere in association with functional lateralization in the olfactory system (Hummel et al., 2003). Therefore, an altered olfactory sulcus depth observed in various neuropsychiatric disorders such as schizophrenia spectrum and affective disorders (e.g., Nishikawa et al., 2016; Takahashi et al., 2013, 2016) has been thought to reflect an embryonic disruption of the olfactory system, which is closely related to emotional regulation with common underlying neural substrates (e.g., limbic structures and the OFC; Soudry et al., 2011). The present finding of abnormally shallow olfactory sulcus in BPD and its relation to high BPD scores may also support the functional overlap between olfactory and emotional processing. Our results also demonstrated that such a morphologic change is present early in the disorder, while the present cross-sectional study cannot directly address whether our findings reflect intrauterine abnormalities, postnatal changes, or both of these factors.

One major finding of the present study is a significant effect of trauma exposure on the olfactory sulcus morphology in BPD. Our findings are in line with previous observation that early stress (e.g., childhood maltreatment) may lead to reduced gray matter volume (Hanson et al., 2010) or cortical thickness (Kelly et al., 2013) in the right OFC. It remains unclear why these environmental factors predominantly affect the right hemisphere, but age-related changes in asymmetry, which reflect on-going changes in functional localization,

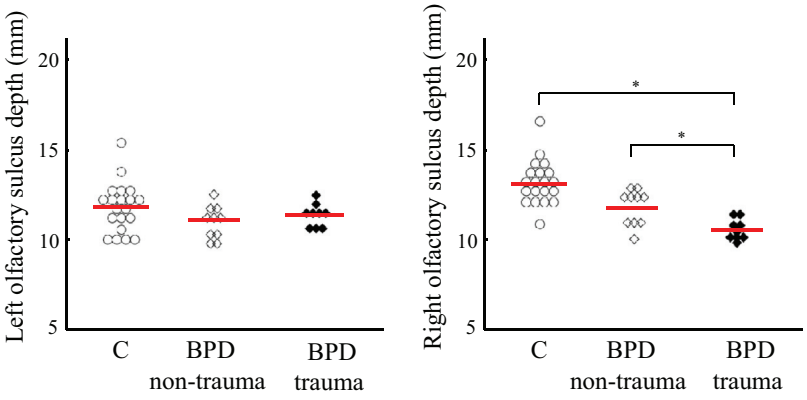

Fig. 2. Scatter plots of sulcus depth in the controls, BPD patients with trauma exposure, and BPD patients without trauma exposure. C, controls; BPD, borderline personality disorder. Horizontal bars indicate means of each group. *$p < 0.05$.

during postnatal cortical maturation (Remer et al., 2017) may partly explain our lateralized results. In normal brain development, the prefrontal cortex flattens during adolescence probably due to synaptic pruning, myelination, and other processes (Alemán-Gómez et al., 2013). Our findings, including the lack of normal asymmetry of the olfactory sulcus, in the BPD patients are consistent with the hypothesis that early stress affects the prefrontal developing processes, which could lead to reduced hemispheric differentiation as well as precocious but stunted cortical maturation (Teicher et al., 2003). Our previous BPD study demonstrated the lack of normal (right > left) asymmetry also in OFC gray matter volume (Chanen et al., 2008), but the OFC gray matter volume did not correlate with any of the clinical variables or with the olfactory sulcus measures. Thus, our results may suggest that the sulcus depth, rather than the gray matter volume, in the OFC region could be a marker of biological vulnerability to BPD that arises during childhood to adolescence.

Several limitations to this study are noteworthy. First, we examined only a focal anatomical abnormality in this study without functional or anatomical connectivity measures. Thus, functional significance and possible relation with other brain abnormalities of our olfactory sulcus findings should be further tested ideally by using multimodal neuroimaging investigations. Second, the small sample size (especially for each BPD subgroup) and older age of the control subjects compared to BPD patients might have biased our results, although we used age as a covariate in all analyses. In addition, the effect of age alone could not explain the difference in the olfactory sulcus depth between the BPD subgroups (with and without trauma), as these subgroups were matched for age. Third, although we recruited teenagers with first-presentation BPD sample in order to reduce potential confounding effects of prolonged illness or medication, BPD is a heterogeneous disorder and is arguably more so in teenagers (Bondurant et al., 2004). It is possible that heterogeneity with respect to the later course of the disorder and psychiatric comorbidity might have influenced the findings, while we found no effect of comorbid disorders on the sulcus morphology. Fourth, although the onset age of trauma experience did not correlate with the sulcus morphology in this study, potential role of the degree (e.g., severity and duration) of trauma experience in the neurobiology of BPD needs to be tested in future studies. Finally, as an altered olfactory sulcus morphology is reported in various psychiatric disorders (Takahashi and Suzuki, 2018), further studies should examine whether the relation of early stress to orbitofrontal development is specific to BPD patients.

In conclusion, we demonstrated a shallow olfactory sulcus in early course of BPD, which was associated with the BPD phenomenology. Although it remains unclear when such a brain morphologic change occurs, our findings suggested that environmental risk factors such as traumatic experience might significantly contribute to biological processes associated with BPD.

CRediT authorship contribution statement

Tsutomu Takahashi: Conceptualization, Investigation, Methodology, Formal analysis, Funding acquisition, Writing - original draft. **Yumiko Nishikawa:** Formal analysis, Investigation, Validation. **Dennis Velakoulis:** Conceptualization, Data curation, Methodology, Resources. **Michio Suzuki:** Conceptualization, Funding acquisition, Methodology, Writing - review & editing. **Patrick D. McGorry:** Conceptualization, Data curation, Methodology, Resources. **Christos Pantelis:** Conceptualization, Data curation, Funding acquisition, Methodology, Resources, Writing - review & editing. **Andrew M. Chanen:** Conceptualization, Data curation, Methodology, Resources, Supervision, Writing - review & editing.

Declaration of Competing Interest

None.

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