

Brief report

Olfactory sulcus morphology in established bipolar affective disorder



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ABSTRACT

This MRI study examined the morphology of the olfactory sulcus, a potential marker of early neurodevelopment in 26 patients with bipolar I disorder and 24 matched controls. Bipolar patients had significantly shallower olfactory sulci bilaterally compared to controls, suggesting that neurodevelopmental abnormalities contribute to the neurobiology of bipolar disorder.

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1. Introduction

A large number of studies suggest a close relationship between olfactory and affective information processing, with common underlying neural substrates including limbic structures (Soudry et al., 2011). Although olfactory function in bipolar disorder (BD) has not been well documented (Burón and Bulbena, 2013), several recent studies have demonstrated olfactory dysfunction in BD (Cumming et al., 2011; Hardy et al., 2012; Lahera et al., in press) or in a BD subgroup with psychotic symptoms (Striebel et al., 1999).

The olfactory sulcus appears during fetal development at around 16 weeks of gestation (Chi et al., 1977), and its depth has been related to olfactory function in healthy subjects (Hummel et al., 2003). For psychiatric disorders, an abnormally shallow olfactory sulcus has been reported in schizophrenia (Turetsky et al., 2009a; Takahashi et al., 2013), supporting the notion that olfactory dysfunction is a prominent feature of schizophrenia and may represent a marker of early neurodevelopmental abnormalities (Brewer et al., 2001; Turetsky et al., 2009b; Kamath et al., 2014). In addition to clinical and biological commonality between BD and schizophrenia (Whalley et al., 2012; Tamminga et al., 2013), some neuroimaging (e.g., Takahashi et al. (2010)) and post-mortem studies suggest a possible embryonic developmental etiology also

in BD (reviewed by Sanches et al. (2008)). Furthermore, BD patients and their unaffected first-degree relatives are likely to share brain morphologic changes related to olfactory processing (e.g., anterior-limbic structures) (Matsuo et al., 2012; Nery et al., 2013), suggesting that abnormalities in the olfactory structures may be at least partly associated with vulnerability to BD. It remains largely unknown, however, whether BD patients exhibit morphologic changes of the olfactory sulcus.

This magnetic resonance imaging (MRI) study investigated the olfactory sulcus morphology in BD patients and matched controls. Based on previous olfactory ability findings in BD and the potential role of olfactory sulcus depth as a marker of early neurodevelopment, we predicted a shallower olfactory sulcus in BD patients compared with controls. We also investigated the association between olfactory sulcus morphology and clinical features of BD.

2. Methods

2.1. Participants

Twenty-six patients with DSM-IV bipolar I disorder and 24 age- and gender-matched healthy controls participated in this study (Table 1). Patients were recruited through advertisement and via a dedicated specialist bipolar disorder clinic based in Sydney, Australia. Diagnoses were made by a research psychiatrist (GM) using the Structured Clinical Interview for DSM-IV (SCID-IV-P) (First et al., 1998), supplemented by case note review. The majority of patients were euthymic at the time of scanning. Controls were recruited predominantly via advertisement, and they were screened for a personal and family history of psychiatric or neurological disorder using the SCID-IV nonpatient version (SCID-NP). Participants were right-handed and excluded if they had a history of ongoing substance misuse,

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Table 1
Sample characteristics and olfactory sulcus measures.

Variable	Healthy controls (N =24)	Bipolar patients (N =26)	Group comparison
Age (years)	38.7 ± 11.1	38.4 ± 10.9	ANOVA: $F(1,48)=0.01$, $P=0.928$
Male/female	7/17	8/18	Chi-square=0.02, $P=0.902$
NART-estimated IQ ^a	115.1 ± 9.6	113.8 ± 7.1	ANOVA: $F(1,47)=0.28$, $P=0.597$
Education (years)	14.6 ± 2.1	14.7 ± 2.8	ANOVA: $F(1,48)=0.02$, $P=0.899$
Illness duration (years)	–	13.5 ± 10.1	–
Number of manic episodes	–	8.8 ± 10.2	–
Number of depressive episodes	–	11.1 ± 10.8	–
Lithium dosage (mg, N=12)	–	975 ± 213	–
Valproate dosage (mg, N=12)	–	1437 ± 594	–
Intracranial volume (cm ³)	1461 ± 148	1476 ± 126	ANCOVA ^b : $F(1,47)=0.13$, $P=0.715$
Olfactory sulcus length (mm)			ANCOVA: $F(1,44) < 0.01$, $P=0.988$
Left	43.9 ± 4.7	44.1 ± 4.3	
Right	44.7 ± 4.7 ^c	45.4 ± 3.8 ^c	
Olfactory sulcus depth (mm)			ANCOVA: $F(1,44) = 51.55$, $P < 0.001$
Left	12.4 ± 1.2 ^d	10.6 ± 0.8	
Right	13.6 ± 1.3 ^{d,e}	11.4 ± 1.0 ^e	

Data are presented as mean ± SD.

ANCOVA, analysis of covariance; ANOVA, analysis of variance; IQ, intelligence quotient; NART, National Adult Reading Test.

^a Data missing for one bipolar patient.

^b Age was used as a covariate.

^c $P=0.007$: longer than in left hemisphere (post hoc Scheffé's test).

^d $P < 0.001$: deeper than in bipolar patients (post hoc Scheffé's test).

^e $P < 0.001$: deeper than in left hemisphere (post hoc Scheffé's test).

neurological disease or, in patients, if there was a co-morbid Axis I or II DSM-IV diagnosis that required treatment. All participants gave written informed consent and the local Hospital and University ethics committee approved the study.

At the time of scanning, eight patients were taking lithium, seven were taking valproate, and four were taking a combination of both. One patient was taking valproate and carbamazepine, and another was taking carbamazepine alone, while five patients were medication free. All patients had previously been exposed to antipsychotic medication, although none within 12 months of entering the study. Ten patients had a family history of major affective disorders (bipolar disorder, $N=3$; unipolar depression, $N=5$; and both, $N=2$), while 12 had no family history of affective disorders and four had an unknown family history. Sixteen patients had a history of psychosis (hallucinations and/or delusions) during at least one affective episode.

2.2. MRI procedures

T1-weighted MR scans were acquired with a 1.5-T GE Signa scanner. Imaging parameters were as follows: echo time, 5.3 ms; repetition time, 12.2 ms; field of view, 24.9 cm; voxel dimensions, $0.98 \times 0.98 \times 1.6$ mm thick coronal slices. The intracranial volume (ICV) was measured as previously described (Eritaia et al., 2000); the groups did not differ in their ICVs (Table 1).

For the assessment of the olfactory sulcus, the images were processed on a Linux PC using Dr. View software (AJS, Tokyo, Japan). Brain images were realigned in three dimensions and reconstructed into contiguous coronal images with a 0.98-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 was clearly seen. 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) (Fig. 1). The length of the sulcus in the anterior-posterior direction (mm) was determined by the multiplication of the number of these coronal slices by 0.98. Intra- and inter-rater (TT and YN) intraclass correlation coefficients for the length and depth of the sulcus in 10 randomly selected brains were over 0.8.

2.3. Statistical analysis

The average depth (sum of the depth in all slices containing the sulcus/slice number) and length of the olfactory sulcus were analyzed using repeated measures analysis of covariance (ANCOVA), with age and ICV as covariates, diagnosis and gender as between-subject factors, and hemisphere as a within-subject variable. The sulcus morphology of the patient subgroups (psychotic and nonpsychotic, with and without a family history, with and without lithium or valproate treatment at scanning) was also analyzed by ANCOVA, covarying for age and ICV. Post-hoc Scheffé's tests were used.

The relationships between the olfactory sulcus measures and clinical variables were examined using Pearson's partial correlation coefficients controlling for age

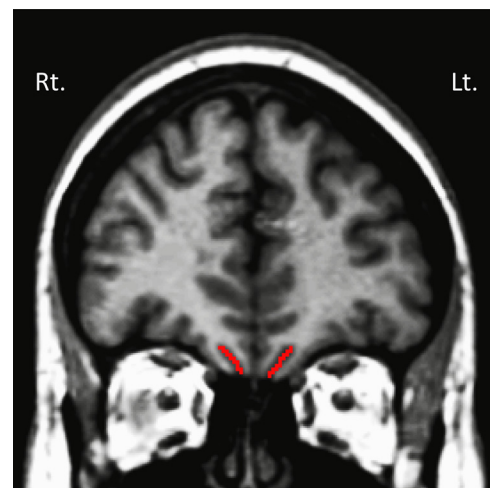


Fig. 1. T1 coronal image of the olfactory sulcus at the level of PPTe (posterior tangent through the eyeballs).

and ICV. The number of manic/depressive episodes was log-transformed because of their skewed distribution. Statistical significance was defined as $P < 0.05$.

3. Results

ANCOVA of the sulcus depth revealed significant main effects for diagnosis [$F(1, 44)=51.55$, $P < 0.001$] and hemisphere [$F(1, 46)=83.14$, $P < 0.001$] but no interaction between these factors; the BD patients had a shallower sulcus than controls, and the sulcus was deeper in the right than in the left hemisphere (Table 1, Fig. 2). There was no group difference in the sulcus length, but the olfactory sulcus was longer in the right hemisphere [$F(1, 46)=6.88$, $P=0.012$] (Table 1). No significant effect involving gender was found.

There were no significant differences in the sulcus measures between the patient subgroups on the basis of psychotic symptoms, family history, and lithium treatment status. The BD patients taking valproate had a longer sulcus bilaterally compared with those who were not on valproate treatment [$F(1, 22)=7.73$, $P=0.011$].

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