Olfactory sulcus morphology in patients with current and past major depression

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Abstract

Olfactory deficits have been reported in major depressive disorder (MDD). However, it remains largely unknown whether MDD is associated with abnormalities in olfactory sulcus morphology, a potential marker of olfactory system development. This magnetic resonance imaging study investigated the length and depth of the olfactory sulcus in 29 currently depressed patients, 27 remitted depressed patients, and 33 age- and gender-matched healthy control subjects. Both current and remitted MDD patients had significantly shallower olfactory sulci bilaterally as compared with controls. Only for male subjects, the right olfactory sulcus was significantly shorter in remitted MDD patients than in controls. The right sulcus depth was negatively correlated with number of depressive episodes in the entire MDD group and with residual depressive symptoms in the remitted MDD group. Medication status, presence of melancholia, and comorbidity with anxiety disorders did not affect the sulcus morphology. These findings suggest that abnormality of the olfactory sulcus morphology, especially its depth, may be a trait-related marker of vulnerability to major depression.

Key words: Depressive disorder; Magnetic resonance imaging; Olfaction; State factors; Trait factors

1. Introduction

Several lines of evidence have suggested that olfactory function is involved in emotional regulation, with common underlying neural substrates (Soudry et al., 2011; Takahashi et al., 2015). Although not consistently, patients with major depressive disorder (MDD) have been reported to have olfactory deficits, especially for olfactory sensitivity (reviewed by Burón and Bulbena, 2013; Schablitzky and Pause, 2014), which are associated with the severity of depressive symptoms and at least partly persist even after the clinical improvement (Naudin et al., 2012). These previous findings implicate a role for the olfactory system in the pathogenesis of depression (Yuan and Slotnick, 2014).

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). Regarding psychiatric disorders, an abnormally shallow olfactory sulcus has been reported in schizophrenia (Takahashi et al., 2013; Turetsky et al., 2009), supporting the notion that olfactory dysfunction may represent a marker of early neurodevelopmental abnormalities related to vulnerability to psychosis (Brewer et al. 2001, 2003; Kamath et al., 2014). On the other hand, several magnetic resonance imaging (MRI) studies in MDD have provided evidence for trait- and vulnerability-related alterations in volume (Lorenzetti et al., 2009 b, 2010; Opel et al., 2016; Takahashi et al., 2010) or surface morphology (Peng et al., 2015) of limbic and cortical structures, suggesting neurodevelopmental pathology in depressive disorders (Ansorge et al., 2007). Interestingly, Zhang et al. (2009) found decreased cortical gyrification in MDD, which may reflect neural underdevelopment during gestation, predominantly in the olfactory system structures (i.e., cingulate, insula, and orbitofrontal regions). However, it remains largely unknown whether MDD patients exhibit morphologic changes of the olfactory sulcus.

This MRI study investigated the length and depth of the olfactory sulcus in current depressed patients (cMDD), individuals with a history of major depression but who are currently in remission (rMDD), and healthy comparison subjects. This approach enabled us to examine whether abnormalities of the olfactory sulcus in MDD, if present, reflect state or trait markers of the disorder. On the basis of enduring olfactory deficits in MDD patients observed during episodes and after remission (Naudin et al., 2012), as well as the potential role of olfactory sulcus depth as a neurodevelopmental marker, we predicted that both cMDD and rMDD patients would have shallower olfactory sulci compared with controls, representing a trait-related feature of MDD. We also examined the influence of severity of depressive symptoms and subtypes of depression (e.g., co-morbid anxiety disorder, melancholic versus non-melancholic) on olfactory sulcus morphology in the MDD patients.

2. Methods

2.1. Subjects

Eighty-nine subjects were recruited in the study, of which 29 received a current diagnosis of major depressive disorder (cMDD), 27 were currently medically and psychiatrically well individuals with a previous history of major depressive disorder (rMDD), and 33 were healthy controls (Table 1). Seven rMDD patients had a total Beck Depression Inventory (BDI; Beck and Steer, 1987) score > 18, but did not fulfill the criteria of MDD by the Structured Clinical Interview for DSM-IV (SCID-IV-TR; First et al., 2001). Demographic and clinical characteristics of the same MDD subjects, recruited through advertisement in the local media from the general community and via outpatient mental health clinics, have been described previously (Lorenzetti et al., 2009a). The relevant Human Research Ethics Review committees approved the study

protocol, and participants gave written informed consent after a complete description of the study.

Participant inclusion criteria were: age 18-50 years, English as a preferred language, and current IQ > 70. Exclusion criteria were: a history of significant head injury, seizures, impaired thyroid function and steroid use, neurological diseases, electroconvulsive therapy within the past 6 months, and gross brain abnormalities. All the depressed subjects with another current Axis I psychiatric disorder (other than anxiety disorders) were excluded, as well as any healthy controls who had a personal history of psychiatric illness, drug or alcohol dependence.

All participants underwent a clinical and neuropsychological assessment by experienced research psychologists at Orygen Youth Health, Melbourne. Participants were assessed with the SCID-IV-TR, the BDI, the Mood and Anxiety Symptom Questionnaire (MASQ; Watson et al., 1995), Positive Affect and Negative Affect Scale (PANAS; Watson et al., 1988), and the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1992). Measures of premorbid and current intelligence were obtained using the Wechsler Test of Adult Reading (Wechsler, 2001) and the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

Medication use in the preceding 6 months was also assessed. Thirty-three (21 cMDD and 12 rMDD) patients were on a stable medication regimen for at least 6 months preceding the scan. Of these, seventeen patients were on selective serotonin reuptake inhibitors, four on venlafaxine, three on mirtazapine, two each tricyclics and monoamine-oxidase inhibitors, and one each on lithium and reboxetine. Three patients were receiving combination therapy (paroxetine and benzodiazepine; escitolopram and mirtazapine; and lithium and dothiepin), while 3 cMDD and 6 rMDD patients were medication-naïve.

2.2. Magnetic resonance imaging procedures

MRI scans were acquired with a 1.5-T Magnetom Avanto scanner (Siemens Medical System, Inc., Erlangen, Germany) at the St. Vincent's Hospital Melbourne, Victoria. Structural 3D T1-weighted images were obtained with the following parameters: time to echo = 2.3 ms, time repetition = 2.1 ms, flip angle = 15°, matrix size = 256 x 256, voxel dimension = 1 x 1 x 1 mm. Additionally, MRI abnormalities were assessed using a high-resolution T2-weighted scan. The intracranial volume (ICV) was estimated from manual tracing on a sagittal reformat of the original T1-weighted images as previously described (Eritaia et al., 2000); the groups did not significantly 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 1-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 1-mm 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). While previous studies measured the sulcus depth by drawing a straight line on one coronal slice (Huart et al., 2011; Rombaux et al., 2009), we traced the surface of the intrasulcal gray matter on entire coronal slices containing the sulcus (approximately 40-50 slices) in order to reflect the contour of the sulcus into the measurement. The length of the sulcus in the anterior-posterior direction (mm) was equal to the number of these coronal slices. 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 [i.e., sulcus length (mm)]. Intra- and inter-rater (TT and DS)

intraclass correlation coefficients (ICCs) for the length and depth of the olfactory sulcus in a reliability data set of 10 randomly selected brains were over 0.90.

2.3. Statistical analysis

Clinical and demographic differences between groups were examined with one-way analysis of variance (ANOVA) or chi-square test.

The average depth and length of each olfactory sulcus were analyzed using the 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. Post hoc Scheffé tests were used to follow up the significant main effects or interactions yielded by these analyses.

The relationships between the olfactory sulcus measures and clinical variables were examined using Spearman's rank correlation coefficients because of a skewed distribution of clinical variables. The association of premorbid or current IQ (adequately normally distributed according to the Kolmogorov-Smirnov test) to the sulcus measures was examined using Pearson's partial correlation coefficients controlling for age and ICV. The volumes of the amygdala (Lorenzetti et al., 2010) and insula (Takahashi et al., 2010) were available for the subjects in this study; relationships between the olfactory sulcus measures and these volumetric data were also examined for each hemisphere using Pearson's partial correlation coefficients controlling for age and ICV. Statistical significance was defined as $p < 0.05$; Bonferroni correction was applied to the correlational analyses.

3. Results

3.1. Demographic and clinical data

Comparison of the groups revealed no significant differences in age, gender, and intelligence but, as expected, measures of depressive and anxiety symptoms were significantly different between groups (Table 1). The cMDD patients, as compared to rMDD patients, had an earlier age of onset, a higher proportion of participants on medication in the previous 6 months, and a higher rate of co-morbid anxiety disorder.

3.2. Depth and length of the olfactory sulcus

ANCOVA and post-hoc analyses showed that both cMDD and rMDD patients had significantly shallower olfactory sulci bilaterally as compared with healthy controls, but there was no difference between the two MDD groups (Table 2, Fig. 2). ANCOVA revealed a significant group by hemisphere by sex effect for olfactory sulcus length. Post-hoc analyses revealed that the right olfactory sulcus was significantly shorter in rMDD patients than in controls only for males (Table 2).

Dividing the patient group into those who were (n = 33) and those who were not (n = 19) taking medication in the preceding 6 months revealed no effect of medication status on the sulcus morphology [depth, F (1, 48) = 0. 31, p = 0.579; length, F (1, 48) = 2. 36, p = 0.131]. There were no differences in sulcus morphology when melancholic (n =10) and non-melancholic (n = 18) subgroups of cMDD patients [depth, F (1, 24) = 0.04, p = 0.845; length, F (1, 24) = 0.45, p = 0.508] or depressed patients with (n = 22) and without (n = 33) co-morbid anxiety disorder [depth, F (1, 51) = 0.26, p = 0.614; length, F (1, 51) = 0.07, p = 0.787] were compared.

3.3. Correlational analysis

Age and IQ (current, premorbid) did not correlate with the sulcus measures in

controls, the depression group as a whole, or the cMDD and rMDD subgroups. The right sulcus depth was negatively correlated with number of depressive episodes in the depressed patients as a whole (*rho* = -0.395, $p = 0.012$) and with MASQ scale reflecting general depression in the rMDD patients (*rho* = -0.588, $p = 0.002$). No significant correlations were found between the sulcus measures and other clinical variables (onset age, illness duration, total BDI score, PANAS subscale scores, and AUDIT score) after Bonferroni correction for multiple comparisons.

There was no significant relationship between the olfactory sulcus measures, amygdala volume, and insular cortex volume in the controls, the depression group as a whole, or the cMDD and rMDD subgroups.

4. Discussion

To our knowledge, this is the first MRI study to report morphologic changes of the olfactory sulcus in MDD patients. In this study, both current and remitted MDD patients had significantly shallower olfactory sulci as compared with healthy controls. The right sulcus depth was negatively correlated with number of depressive episodes in the depressed patients, which may reflect vulnerability to relapse, and with degree of residual depressive symptoms in the remitted patients. These findings suggest that abnormality of the olfactory sulcus morphology may represent a trait-related marker of vulnerability to major depression.

Depressed patients principally exhibit reduced olfactory sensitivity and deficits in the hedonic responses to olfactory stimuli, which are correlated with the severity of depressive symptoms (Atanasova et al., 2008; Yuan and Slotnick, 2014) but also partly persist even after remission (Naudin et al., 2012; Pause et al., 2001), and are probably not mediated by antidepressant treatment (Schablitzky and Pause, 2014). These olfactory findings, which may represent both state and trait abnormalities, might be

partly attributable to common underlying neural substrates for olfactory and emotional processing (i.e., limbic structures such as amygdala, insula, cingulate, and orbitofrontal cortex; Soudry et al., 2011). Indeed, increasing neuroimaging evidence has demonstrated morphologic and functional abnormalities of these olfactory system structures in MDD (reviewed by Atanasova et al., 2008; Lorenzetti et al., 2009b). The present MRI findings of abnormally shallow olfactory sulcus in MDD may also support these olfactory ability findings, as this anatomical abnormality could be associated with embryonic disruption of olfactory system development (Abolmaali et al., 2002; Hummel et al., 2003). These olfactory and neuroimaging findings may implicate the role of impaired olfactory system, which has a close relation with emotional regulation, in the pathophysiology of major depression.

In this study, not only currently but also remitted depressed patients, who were psychiatrically well but potentially vulnerable to illness relapse, showed significantly shallower olfactory sulcus as compared with healthy subjects. We also found shorter right sulcus only in male remitted patients, but this could not be generalized because of very small number of male remitted patients (n = 9). The olfactory sulcus morphology, which is thought to be stable at least during the period of adolescence to midlife (Takahashi et al., 2013), did not correlate with age or illness duration in this study. Given that olfactory sulci on the human brain appear at 16 weeks gestation and are prominent at 25 weeks (Chi et al., 1977), our findings may partly support the hypothesis by Ansorge et al. (2007) that neurodevelopmental factors affect the maturation of brain circuits involved in emotional function to increase diathesis to depressive disorder later in life. The olfactory sulcus depth did not correlate with symptom severity during depressive episodes, but our results suggested its association with vulnerability to relapse and residual depressive symptoms after clinical remission. In combination with the finding of enduring olfactory deficits in remitted MDD patients (Naudin et al., 2012) as well as MRI findings that altered surface morphology (e.g.,

gyrification), which probably reflects neural underdevelopment during gestation, predominantly in olfactory system structures (i.e., cingulate, insula, and orbitofrontal regions) in MDD (Peng et al., 2015; Zhang et al., 2009), our findings may provide support for the notion that abnormalities in olfactory system development during gestation and consequent olfactory deficits are at least partly reflect trait-related vulnerability factors. However, evaluation of whether olfactory sulcus morphology is a true trait marker of vulnerability to depression versus an enduring 'scar' of depressive episodes will require a future study in the subjects of various illness stages ideally including the vulnerable individuals prior to the onset of their first depressive episode.

Regarding other olfactory structures in the present MDD cohort, we have previously reported reduced insular cortex volume in both rMDD and cMDD groups (Takahashi et al., 2010) and increased amygdala volume only in the rMDD group (Lorenzetti et al., 2010). It is possible that abnormalities in one area in the olfactory circuits could cause secondary functional/structural alterations in other regions (Depciuch et al., 2015; Yuan and Slotnick, 2014). However, we found no direct relation between olfactory sulcus morphology and volumes of these olfactory structures, suggesting that distinct brain regions might be differentially involved in the neurobiology of MDD even within the olfactory circuits. These results may be partly consistent with recent functional MRI finding of imbalanced brain activity within the olfactory circuits in MDD patients (Zhang et al., 2016). On the other hand, brain morphology could change during the course of depression (Soriano-Mas et al., 2011), possibly reflecting stress-toxicity (Duman, 2002), neurohumoral changes (e.g., hypothalamic-pituitary-adrenal axis dysregulation; Lorenzetti et al., 2009a), and/or neuroplastic effects of medication (Frodl et al., 2008; Moore et al., 2000). Thus, further neuroimaging studies using longitudinal designs will be needed to clarify the characteristics of structural/functional abnormalities in the olfactory circuits during the course of major depression.

A few possible confounding factors may have affected our findings. First, we did not assess olfactory function or additional olfactory structures (e.g., olfactory bulb), representing a limitation of the study. Second, complete lifetime medication data of the patients were not available. However, no difference in sulcus morphology was found between patients who were and were not on antidepressant medication in the preceding six-month period. Third, in addition to a relatively small sample size especially for male subjects, potential heterogeneity between the MDD subgroups (e.g., earlier onset, lower current IQ, and higher prevalence of co-morbid anxiety disorders in the cMDD patients) might have biased our results. However, all of these potential confounding factors did not relate to sulcus morphology of the MDD patients in this study. Finally, given that the olfactory sulcus abnormalities are also reported in other psychiatric disorders such as schizophrenia (e.g., Takahashi et al., 2013) and reduced global sulcation appears to be a feature of major depression (Penttilä et al., 2009), the disease and regional specificities of our findings should be further tested.

In conclusion, the present study indicates that patients with unipolar depression have an abnormality of the olfactory sulcus morphology (especially its depth), which is also evident in remitted depressed subjects who are in a vulnerable clinical state. These findings are unlikely to be due to the effects of medication or co-morbid anxiety disorder, suggesting that the olfactory sulcus morphology may be a trait-related vulnerability marker of MDD. Further studies of both neuroimaging and olfactory ability assessments will be needed to examine possible role of the olfactory system, which has a close relation with emotional regulation (Soudry et al., 2011), in the pathophysiology of major depression.

Contributors

In this work, Drs. Yücel and Allen conceived the idea and methodology of the study. Dr. Nishikawa and Lorenzetti managed the literature searches and analyses. Drs. Takahashi, Nishikawa, and Sasabayashi analyzed MRI data. Dr. Takahashi undertook the statistical analysis and wrote the first draft of the manuscript. Drs. Yücel, Suzuki, Walterfang, Whittle, Allen and Pantelis provided supervision on interpretation of data and contributed in revising the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

None.

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References

Abolmaali, N.D., Hietschold, V., Vogl, T.J., Hüttenbrink, K.B., Hummel, T., 2002, MR evaluation in patients with isolated anosmia since birth or early childhood. Am. J. Neuroradiol. 23, 157-164.

Atanasova, B., Graux, J., El Hage, W., Hommet, C., Camus, V., Belzung, C., 2008. Olfaction: a potential cognitive marker of psychiatric disorders. Neurosci. Biobehav. Rev. 32, 1315-1325.

Ansorge, M.S., Hen, R., Gingrich, J.A., 2007. Neurodevelopmental origins of depressive disorders. Curr. Opin. Pharmacol. 7, 8-17.

Babor, T.F., De La Fuente, J.R., Saunders, J., Grant, M., 1992. TheAlcohol Use Disorders Identification Test: Guidelines for Use in Primary Health Care. World Health Organization, Geneva.

Beck, A.T., Steer, R.T., 1987. Beck Depression Inventory Manual. HBJ, San Antonio.

Brewer, W.J., Pantelis, C., Anderson, V., Velakoulis, D., Singh, B., Copolov, D.L., McGorry, P.D., 2001. Stability of olfactory identification deficits in neuroleptic-naive patients with first-episode psychosis. Am. J. Psychiatry 158, 107-115.

Brewer, W.J., Wood, S.J., McGorry, P.D., Francey, S.M., Phillips, L.J., Yung, A.R., Anderson, V., Copolov, D.L., Singh, B., Velakoulis, D., Pantelis, C., 2003. Impairment of olfactory identification ability in individuals at ultra-high risk for psychosis who later develop schizophrenia. Am. J. Psychiatry 160, 1790-1794.

Burón, E., Bulbena, A., 2013. Olfaction in affective and anxiety disorders: a review of the literature. Psychopathology 46, 63-74.

Chi, J.G., Dooling, E.C., Gilles, F.H., 1977. Gyral development of the human brain. Ann. Neurol. 1, 86-93.

Depciuch, J., Sowa-Kućma, M., Misztak, P., Szewczyk, B., Nowak, G., Pankiewicz, P., Parlińska-Wojtan, M., 2015. Olfactory bulbectomy-induced changes in phospholipids and protein profiles in the hippocampus and prefrontal cortex of

rats. A preliminary study using a FTIR spectroscopy. Pharmacol. Rep. 68, 521-528.

Duman, R.S., 2002. Pathophysiology of depression: the concept of synaptic plasticity. Eur. Psychiatry 17 (Suppl 3), 306-310.

Eritaia, J., Wood, S.J., Stuart, G.W., Bridle, N., Dudgeon, P., Maruff, P., Velakoulis, D., Pantelis, C., 2000. An optimized method for estimating intracranial volume from magnetic resonance images. Magn. Reson. Med. 44, 973-977.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2001. Structured Clinical Interview for Axis 1 DSM-IV Disorders. New York State Psychiatric Institute, New York.

Frodl, T., Jäger, M., Smajstrlova, I., Born, C., Bottlender, R., Palladino, T., Reiser, M., Möller, H.J., Meisenzahl, E.M., 2008. Effect of hippocampal and amygdala volumes on clinical outcomes in major depression: a 3-year prospective magnetic resonance imaging study. J. Psychiatry Neurosci. 33, 423-430.

Hummel, T., Damm, M., Vent, J., Schmidt, M., Theissen, P., Larsson, M., Klussmann, J.P., 2003. Depth of olfactory sulcus and olfactory function. Brain Res. 975, 85-89.

Huart, C., Meusel, T., Gerber, J., Duprez, T., Rombaux, P., Hummel, T., 2011. The depth of the olfactory sulcus is an indicator of congenital anosmia. Am. J. Neuroradiol. 32, 1911-1914.

Kamath, V., Turetsky, B.I., Calkins, M.E., Kohler, C.G., Conroy, C.G., Borgmann-Winter, K., Gatto, D.E., Gur, R.E., Moberg, P.J., 2014. Olfactory processing in schizophrenia, non-ill first-degree family members, and young people at-risk for psychosis. World J. Biol. Psychiatry 15, 209-218.

Lorenzetti, V., Allen, N.B., Fornito, A., Pantelis, C., De Plato, G., Ang, A., Yücel, M., 2009a. Pituitary gland volume in currently depressed and remitted depressed patients.Psychiatry Res. 172, 55-60.

Lorenzetti, V., Allen, N.B., Fornito, A., Yücel, M., 2009b. Structural brain abnormalities in major depressive disorder: A selective review of recent MRI studies. J. Affect. Disord. 117, 1-17.

Lorenzetti, V., Allen, N.B., Whittle, S., Yücel, M., 2010. Amygdala volumes in a sample of current depressed and remitted depressed patients and healthy controls. J. Affect. Disord. 120, 112-119.

Moore, G.J., Bebchuk, J.M., Wilds, I.B., Chen, G., Manji, H.K., 2000. Lithium-induced increase in human brain grey matter. Lancet 356, 1241-1242.

Naudin, M., El-Hage, W., Gomes, M., Gaillard, P., Belzung, C., Atanasova, B., 2012. State and trait olfactory markers of major depression. PLoS One 7, e46938.

Opel, N., Zwanzger, P., Redlich, R., Grotegerd, D., Dohm, K., Arolt, V., Heindel, W., Kugel, H., Dannlowski, U., 2016. Differing brain structural correlates of familial and environmental risk for major depressive disorder revealed by a combined VBM/pattern recognition approach. Psychol. Med., 46, 277-290.

Pause, B.M., Miranda, A., Göder, R., Aldenhoff, J.B., Ferstl, R.. 2001. Reduced olfactory performance in patients with major depression. J. Psychiatr. Res. 35, 271-277.

Peng, D., Shi, F., Li, G., Fralick, D., Shen, T., Qiu, M., Liu, J., Jiang, K., Shen, D., Fang, Y., 2015. Surface vulnerability of cerebral cortex to major depressive disorder. PLoS One 10, e0120704.

Penttilä, J., Paillère-Martinot, M.L., Martinot, J.L., Ringuenet, D., Wessa, M., Houenou, J., Gallarda, T., Bellivier, F., Galinowski, A., Bruguière, P., Pinabel, F., Leboyer, M., Olié, J.P., Duchesnay, E., Artiges, E., Mangin, J.F., Cachia, A., 2009. Cortical folding in patients with bipolar disorder or unipolar depression. J. Psychiatry Neurosci. 34, 127-135.

Rombaux, P., Grandin, C., Duprez, T., 2009. How to measure olfactory bulb volume and olfactory sulcus depth? B-ENT 5 Suppl 13, 53-60.

Schablitzky, S., Pause, B.M., 2014. Sadness might isolate you in a non-smelling world: olfactory perception and depression. Front. Psychol.5, 45.

Soriano-Mas, C., Hernández-Ribas, R., Pujol, J., Urretavizcaya, M., Deus, J., Harrison, B.J., Ortiz, H., López-Solà, M., Menchón, J.M., Cardoner, N., 2011. Cross-sectional and longitudinal assessment of structural brain alterations in melancholic depression. Biol. Psychiatry 69, 318-325.

Soudry, Y., Lemogne, C., Malinvaud, D., Consoli, S.M., Bonfils, P., 2011. Olfactory system and emotion: common substrates. Eur. Ann. Otorhinolaryngol. Head Neck Dis. 128, 18-23.

Takahashi, T., Yücel, M., Lorenzetti, V., Tanino, R., Whittle, S., Suzuki, M., Walterfang, M., Pantelis, C., Allen, N.B., 2010. Volumetric MRI study of the insular cortex in individuals with current and past major depression. J. Affect. Disord. 121, 231-238.

Takahashi, T., Nakamura, Y., Nakamura, K., Ikeda, E., Furuichi, A., Kido, M., Kawasaki, Y., Noguchi, K., Seto, H., Suzuki, M., 2013. Altered depth of the olfactory sulcus in first-episode schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 40, 167-172.

Takahashi, T., Itoh, H., Nishikawa, Y., Higuchi, Y., Nakamura, M., Sasabayashi, D., Nishiyama, S., Mizukami, Y., Masaoka, Y., Suzuki, M., 2015. Possible relation between olfaction and anxiety in healthy subjects. Psychiatry Clin. Neurosci. 69, 431-438.

Turetsky, B.I., Crutchley, P., Walker, J., Gur, R.E., Moberg, P.J., 2009. Depth of the olfactory sulcus: a marker of early embryonic disruption in schizophrenia? Schizophr. Res. 115, 8-11.

Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. J. Pers. Soc. Psychol. 54, 1063-1070.

Watson, D., Clark, L., Weber, K., Assenheimer, J., Strauss, M., McCormick, R., 1995. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. J. Abnorm. Psychology 104, 3–14.

Wechsler, D., 1999. Manual for the Wechsler Abbreviated Scale of Intelligence. The Psychological Corporation, San Antonio, Texas.

Wechsler, D., 2001. Manual for the Wechsler Test of Adult Reading (WTAR). The Psychological Corporation, San Antonio, Texas.

Yuan, T.F., Slotnick, B.M., 2014. Roles of olfactory system dysfunction in depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 54, 26-30.

Zhang, X., Di, X., Lei, H., Yang, J., Xiao, J., Wang, X., Yao, S., Rao, H., 2016. Imbalanced spontaneous brain activity in orbitofrontal-insular circuits in individuals with cognitive vulnerability to depression. J. Affect. Disord. 198, 56-63.

Zhang, Y., Yu, C., Zhou, Y., Li, K., Li, C., Jiang, T., 2009. Decreased gyrification in major depressive disorder. Neuroreport 20, 378-380.

Figure Legends

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

Fig. 2. Scatter plots of olfactory sulcus depth in healthy controls, currently depressed patients (cMDD), and remitted depressed patients (rMDD). Horizontal bars indicate means of each group. *$p < 0.01$.

Table 1
Demographic and clinical characteristics of the participants

	Controls (n = 33)	cMDD (n = 29)	rMDD (n = 27)	Group comparisons[a]
Age (years)	34.0 ± 9.9	32.5 ± 8.3	35.1 ± 10.0	F (2, 86) = 0.52, p = 0.595
Male/female	12/21	7/22	9/18	Chi-square = 1.13, p = 0.568
Age of onset	-	21.1 ± 8.0	26.0 ± 9.4	F (1, 54) = 4.56, p = 0.037; cMDD < rMDD
Number of episodes	-	3.7 ± 3.4	3.1 ± 2.6	F (1, 38) = 0.37, p = 0.547
First episode/recurrent	-	7/22	-	-
Melancholic/atypical	-	10/3	-	-
Medication past 6 months: yes/no	-	21/6	12/13	Chi-square = 4.96, p = 0.026
Current anxiety disorder: yes/no	-	18/10	4/23	Chi-square = 14,02 p < 0.001
Current IQ	111.1 ± 10.9	104.9 ± 8.7	111.4 ± 9.9	F (2, 85) = 4.03, p = 0.021; not significant (Scheffé test)
Premorbid IQ	111.6 ± 12.3	107.5 ± 11.4	111.7 ± 8.9	F (2, 86) = 1.41, p = 0.250
Beck Depression Inventory	3.6 ± 4.1	36.8 ± 8.9	13.0 ± 11.7	F (2, 86) = 120.57, p < 0.001; cMDD > rMDD > controls
MASQ general distress	27.9 ± 8.3	50.5 ± 7.8	40.4 ± 10.3	F (2, 81) = 49.21, p < 0.001; cMDD > rMDD > controls
general depression	19.5 ± 7.2	47.3 ± 9.2	35.0 ± 11.7	F (2, 82) = 66.85, p < 0.001; cMDD > rMDD > controls
general anxiety	16.4 ± 6.4	32.2 ± 8.7	24.7 ± 7.7	F (2, 82) = 32.31, p < 0.001; cMDD > rMDD > controls
anxious arousal	22.0 ± 4.4	42.0 ± 12.2	28.9 ± 7.7	F (2, 79) = 40.47, p < 0.001; cMDD > rMDD > controls
high positive affect	81.1 ± 14.3	43.6 ± 13.5	65.0 ± 12.4	F (2, 80) = 57.19, p < 0.001; cMDD < rMDD < controls
loss of interest	14.7 ± 5.0	31.6 ± 6.4	23.5 ± 6.8	F (2, 82) = 58.68, p < 0.001; cMDD > rMDD > controls
PANAS positive affect	32.9 ± 7.3	21.6 ± 6.5	28.7 ± 8.0	F (2, 82) = 18.57, p < 0.001; cMDD < rMDD, controls
negative affect	11.2 ± 1.6	21.2 ± 8.5	14.2 ± 4.7	F (2, 83) = 24.98, p < 0.001; cMDD > rMDD, controls
AUDIT	4.6 ± 3.0	5.4 ± 6.2	5.7 ± 4.8	F (2, 83) = 0.42, p = 0.662
Intracranial volume (cm^3)	1493 ± 143	1477 ± 138	1470 ± 150	F (2, 85) = 0.20, p = 0.816[b]

The values represent mean ± SD. AUDIT, Alcohol Use Disorders Identification Test; cMDD, currently depressed patients; MASQ, Mood and Anxiety Symptom Questionnaire; PANAS, Positive and Negative Affect Schedule; rMDD, remitted depressed patients.

[a] Difference between the degree of freedom across measures is due to missing data.

[b] ANCOVA with age as a covariate and group as a between-subject factor was used.