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Difference of olfactory deficit in patients with acute episode of schizophrenia and major depressive episode

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ABSTRACT

Aim

Olfactory deficits are potential markers of early diagnosis, monitoring progress and predicting outcome in patients with schizophrenia and depression. We aimed to investigate differences in patterns and influencing factors of olfactory deficits between patients with acute episode of schizophrenia and major depressive episode (MDE).

Methods: Fifty-two patients with acute episode of schizophrenia, 75 patients with unipolar MDE and 199 healthy controls were included in this retrospective study. Following a structured interview, participants underwent olfactory tests (Sniffin' Sticks), assessment of psychiatric symptoms (Positive and Negative Syndrome Scale), depressive symptoms (Hamilton Depression Rating Scale), and cognitive function (color-word test and word generation test).

Results: Both patients with schizophrenia and MDE exhibited significant olfactory deficits, and MDE patients have poorer olfactory sensitivity than schizophrenia. Patients with MDE had a higher proportion of olfactory deficits (45.3% and 28%, respectively) but a better self-awareness (21.3% and 9.6%, respectively) than patients with schizophrenia. In patients with schizophrenia, PANSS scores was positively associated with olfactory sensitivity but negatively associated with olfactory identification, and olfactory discrimination was associated with word generation. In patients with MDE, olfactory discrimination was associated with word generation and age, but not disease severity. First-episode schizophrenia group showed significantly lower threshold scores than recurrent schizophrenia group, and first-episode MDE group had significantly lower threshold scores and higher discrimination scores than the recurrent MDE group.

Conclusions: Patterns and modulating factors of olfactory deficits in acute episode of schizophrenia and MDE are different, their differences should be considered when using olfactory deficits as marker in clinical practice.

1. Introduction

Olfactory deficits have been repeatedly reported in patients with psychiatric diseases, especially in schizophrenia and depression (Croy and Hummel, 2016; Moberg et al., 2014). It is well known that olfactory pathways overlap with many brain areas which are involved in emotional processing and psychological activities, such as amygdala, hippocampus and orbital-frontal cortex. Therefore, structural or functional abnormalities of these regions can not only cause mental disorders, but also lead to olfactory dysfunction (Marine and Boriana, 2014). Additionally, many studies suggest that in patients with schizophrenia and depression, olfactory deficits could serve as markers that could be helpful in early diagnosis (Chen et al., 2018a; Moberg et al., 2014), indicating disease severity (Pabel et al., 2018a; Corcoran et al., 2005; Good et al., 2010) and predicting therapeutic effects (Good et al., 2006; Negoias et al., 2016). However, it seems that olfactory deficits play different roles in schizophrenia and depression, and that they are associated with various factors.

Early studies have provided compelling evidence for the existence of olfactory deficits in patients with schizophrenia. A recent meta-analysis suggests that the effect size of olfactory deficits in patients with schizophrenia is medium-to-large (Moberg et al., 2014), and impairment of various olfactory domains including identification,

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olfactory threshold, discrimination, memory and hedonic judgement have all been reported (Moberg et al., 1999). Among various olfactory deficits, olfactory identification impairment is regarded as the most significant feature in schizophrenia (Good and Sullivan, 2015; Zou et al., 2018), and it has been reported to be correlated with negative symptoms (Corcoran et al., 2005; Good et al., 2010) and cognitive function (Compton et al., 2006; de Nijs et al., 2018). In addition, olfactory disturbance has been found to be positively correlated with self-reported anhedonia and negatively with self-reported anticipatory pleasure in patients with first-episode psychosis (Kamath et al., 2018), suggesting that olfactory deficits may be a useful indicator of disease severity in patients with schizophrenia. Furthermore, olfactory deficits may serve as a sensitive vulnerability marker of risk for schizophrenia, as a small effect of olfactory deficits was found in ultra-high-risk cohorts and first-degree relatives of schizophrenia patients, as well as people with schizotypal personality features (Cohen et al., 2012; Moberg et al., 2014). Recent studies also show that the olfactory deficit may be used as a predictor for poorer outcome in patients with schizophrenia. Specifically, poorer cognitive function, more negative symptoms and reduced functional outcome were associated with worse olfactory identification at baseline (Good et al., 2010; Good et al., 2006). In brief, olfactory deficits are promising markers for early diagnosis, monitoring progress and predicting outcomes in schizophrenia.

Different from schizophrenia, most of the studies suggested that patients with depression suffered from significant olfactory threshold impairment, and their olfactory identification was relatively intact (Marine and Boriana, 2014). It should be noted that depression is not uniformly associated with olfactory deficits, but relies on duration and course of depression. Pabel et al. reported that olfactory identification was negatively correlated with recurrent depressive disorders, and the longer duration of disease suggested poorer olfactory threshold (Pabel et al., 2018b). Khil et.al suggested that patients with recurrent depression also had an elevated odds of olfactory identification impairment compared to those with a first-time episode (Khil et al., 2016). Owing to the close relationship between olfaction and cognition, older people simultaneously suffering from depression and cognitive impairment tended to have a higher degree of olfactory identification impairment (Chen et al., 2018). Moreover, reduced olfactory identification scores contribute to early detection of high-risk individuals of Alzheimer's Disease in late-life depression (Chen et al., 2018b). Besides, the reciprocal interaction between olfaction and depression has been reported several times, such that depression can lead to an olfactory deficit, and that olfaction may also affect emotional regulation (Birte-Antina et al., 2018). Recent research indicated that enhanced olfactory input may serves as a new therapeutic strategy of depression, that depressive symptoms, cognitive function and olfactory threshold in elderly significantly improved following a 5-month olfactory training period (Birte-Antina et al., 2018).

Collectively, the pattern of olfactory deficits in schizophrenia and depression seems to be different. However, due to the heterogeneity of various studies, the ambiguity of previous results and the lack of direct comparisons between schizophrenia and depression, their difference in patterns of olfactory deficits remains unclear. Understanding the difference of olfactory deficits in schizophrenia and depression are of great significance, because it can not only help psychiatrists to correctly use olfaction in clinical practice, but also to provide a better understanding of the relationship between olfaction and various psychiatric diseases. Therefore, the present study aimed to directly compare olfactory function between schizophrenia and depression, to explore their different patterns in olfactory deficits. Considering acute and remitted psychiatric patients may exhibit significant differences in olfactory function, and previous study included heterogeneous patient samples with acute episode and remitted or chronic schizophrenia with a risk of bias, only patients in acute episode were recruited in the current study. Information about factors (age, sex, smoking, disease severity, subtype of disease, type of episode, cognition etc.) that may be associated with olfaction were also collected, with the purpose of comparing their different associations with olfaction in schizophrenia and depression.

2. Method

2.1. Subjects

A total of 326 subjects were recruited at the Smell and Taste Clinic at the Department of Psychiatry and Department of Otorhinolaryngology of the TU Dresden, Germany. They consisted of three groups: patients with acute episode of schizophrenia ($n = 52$), patients with major depressive episode (MDE) ($n = 75$) and healthy controls ($n = 199$). Inclusion criteria of patients were (a) a diagnosis of schizophrenia and major depression disorders (MDD) according to Diagnostic and Statistical Manual, Fourth Edition, (DSM-IV) guidelines, which confirmed by an experienced psychiatrist; (b) an acute episode, defined as any new-onset or recurrent psychotic symptoms which required either initiation of antipsychotic treatment, change in existing treatment, or hospitalization. MDD is defined as having one or more MDE, and an MDE is defined as at least 2 weeks of depressed mood or loss of interest, accompanied by four or more of the following symptoms: change in appetite or weight, sleep disturbance, psychomotor agitation or slowing, fatigue or loss of energy, worthlessness or guilt, poor concentration or indecisiveness, and thoughts of suicide or death.

Exclusion criteria were (a) bipolar disorder; (b) physical illness that may induce emotion abnormalities (such as anaemia or hypothyroidism) or neurological disease (such as Parkinson's disease and Alzheimer's disease); (c) history of sinus surgery or nasal fracture. Healthy controls were part of our previous study (Oleszkiewicz et al., 2019), they did not exhibit major otorhinolaryngologic disorders or other disorders that would affect the sense of smell, like Parkinson's disease (Hummel et al., 2017), as well as history of sinus surgery or nasal fracture; they did not mention any disturbances of smell. All participants received a structural interview, a standardized test for olfaction, as well as assessment of clinical symptoms and cognition. Only participants who could understand the experimental tasks and questionnaires were included. This study was approved by the Ethics Committee at the University Hospital of the TU Dresden (protocol number EK251112006).

2.2. Assessment of olfactory function

Ortho-nasal olfactory function was measured using the extended “Sniffin' Sticks” test which is based on odor-containing felt-tip pens. This test consists of three subtests: threshold (sensitivity), discrimination, and identification test. For each subtest, the pen's cap was removed, and its felt-tip was presented about 2 cm in front of both nostrils of the subject for about 3 s. The testing procedure began with the threshold part in a triple-forced choice paradigm where participants had to discriminate the odor (phenyl ethyl alcohol (PEA)) from 2 blanks (filled with solvent propylene glycol). Starting with the lowest PEA concentration, a staircase paradigm was used where 2 correct or 1 incorrect answer led to a decrease or increase of concentration, the so-called turning point. The resulting threshold score was the mean of the last 4 turning points in the staircase. The higher threshold score means the lower olfactory threshold and higher olfactory sensitivity. The next subtest performed was the discrimination test, where 2 pens had the same odor while the other one had a different scent, which had to be identified. The last task was the identification test, where the subject was asked to choose the object that describes the odor the best using a 4-

alternative-forced choice from flash cards that had both the picture and name of the object. The scores of the olfactory subtests were then summed up building the overall TDI (threshold, discrimination and identification) score. The cut-off scores of normal olfaction and olfactory impairment is TDI 30.5 (Oleszkiewicz et al., 2019). Subjective olfactory sensitivity (normal/decreased/increased) was asked before the "Sniffin' Sticks" test. People whose TDI scores<30.5 and reported "Decreased" olfaction were considered to show "self-awareness of olfactory impairment", those reported "normal or increased" olfaction and a TDI score of <30.5 were considered to show a "lack of self-awareness of olfactory impairment".

2.3. Assessment of clinical symptoms and cognitive function

All the assessment of clinical symptoms and cognitive function were carried out at the same day as the olfactory test. Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess symptom severity of patients with schizophrenia. Scores of positive scale, negative scale and general psychopathology scale were calculated respectively, and they were summed as the PANSS total score. Patients with schizophrenia whose PANSS scores were in upper 50% were defined as "severe schizophrenia", and the low 50% as "mild schizophrenia". Hamilton Depression Rating Scale (HAMD) (Hamilton, 1969) was used to assess symptom severity of patients with depression. Patients with depression whose HAMD scores was in upper 50% was defined as "severe depression", and the low 50% as "mild depression". All the clinical rating scales were assessed by the same rater, an experienced psychiatrist who has received systematic training about the use of the PANSS and HAMD.

The Stroop Color Word Test and verbal fluency test (Strauss et al., 1991) were used to assess cognitive function due to their known relationship with olfaction (Takahashi et al., 2018; Chen et al., 2018). The Stroop Color Word Test includes 3 tests (A, B and C), time of finishing the tests were recorded, and the shorter time suggests better executive function and information processing speed. The verbal fluency test requires participants to produce as many words as possible from a category (objects in the supermarket, or words begin with F, A, S) in 60 s, the more words produced suggested better language function. Assessments of clinical symptoms, cognitive function and olfaction were performed in the same day.

2.4. Statistics

Statistical Package for Social Sciences version 25.0 (IBM SPSS 25.0, Chicago, IL, USA) was used for the statistical analyses. Differences of sex, smoking statute, type of episode and subjective olfactory sensitivity were evaluated with χ^2 analysis. Differences of olfactory functions were evaluated with one-way analysis of covariance (ANCOVA), and control variables included age and sex. Post hoc Least Significant Difference (LSD) tests were used for multiple comparisons. Differences of HAMD scores, PANSS scores, color-word test, word generation test were evaluated with two sample *t*-test analysis. Spearmen's correlations were calculated to assess the associations between olfactory function and different variables (age, duration, clinical symptoms and cognitive function). Stepwise multiple linear regression analysis was used to analyze the effect of different variables on olfactory scores, including age, sex, duration, episode recurrences, smoking status, clinical symptoms severity (PANSS total scores for schizophrenia and HAMD scores for depression) and cognitive function (sum of color-word scores and sum of word generation scores). For the regression model, the significance level for inclusion was set at $P < 0.05$, whereas the significance level for exclusion was set at $P > 0.01$.

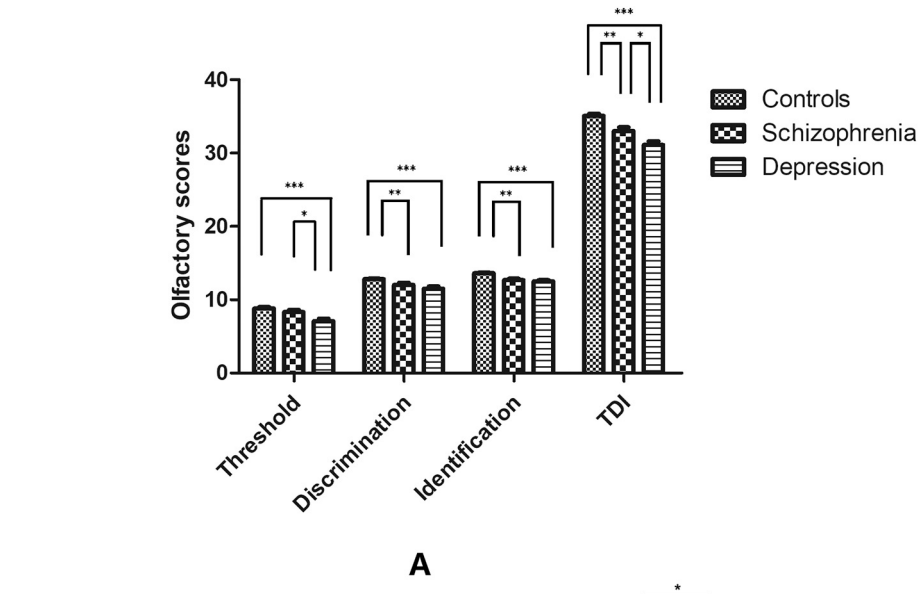
3. Results

Demographic data of healthy controls, patients with schizophrenia and depression are listed in Table 1. Information about type of drug in patients are listed in Supplemental Material. Dividing by the type of episode, there were 20 First-episode schizophrenia patients and 32 recurrent schizophrenia patients, 37 first MDE patients and 38 recurrent MDE patients. Dividing by the severity of symptom, there were 27 patients with mild schizophrenia and 25 with severe schizophrenia; 35 patients with mild MDE and 40 with severe MDE.

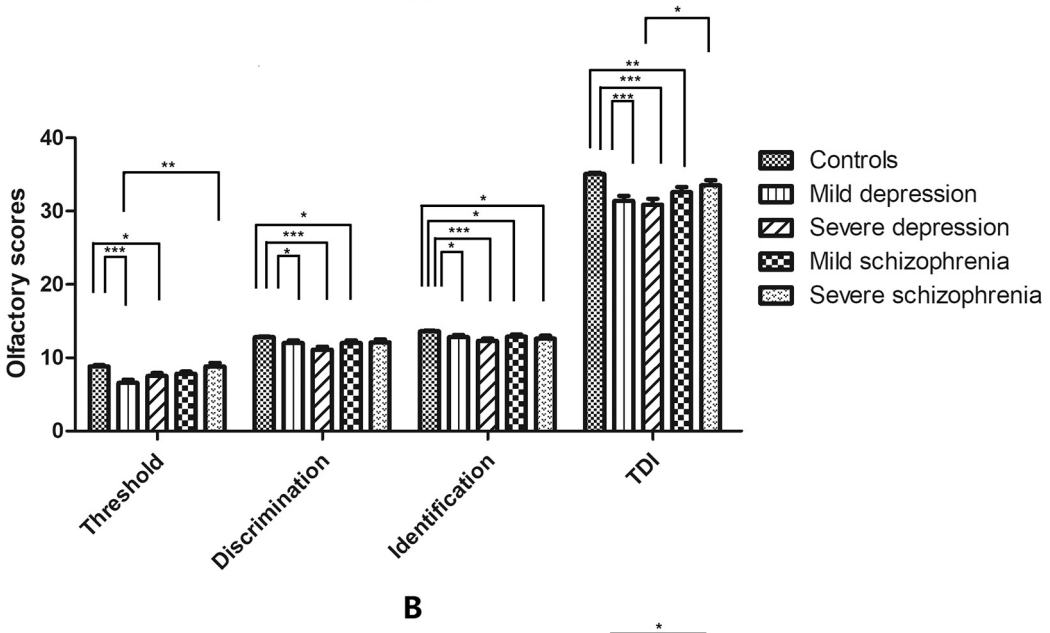
Both schizophrenia and MDE group had lower odor discrimination, identification and TDI scores than healthy controls, and only MDE group had lower threshold scores than healthy controls. Moreover, schizophrenia group has significant high threshold scores and TDI scores than MDE group (see Table 1 and Fig. 1A). Additionally, the proportion of olfactory impairment in patients

Table 1
Comparison of healthy controls, patients with schizophrenia and depression. * LSD was used for multiple comparison, A means healthy controls, B means patients with schizophrenia, C means patients with depression.

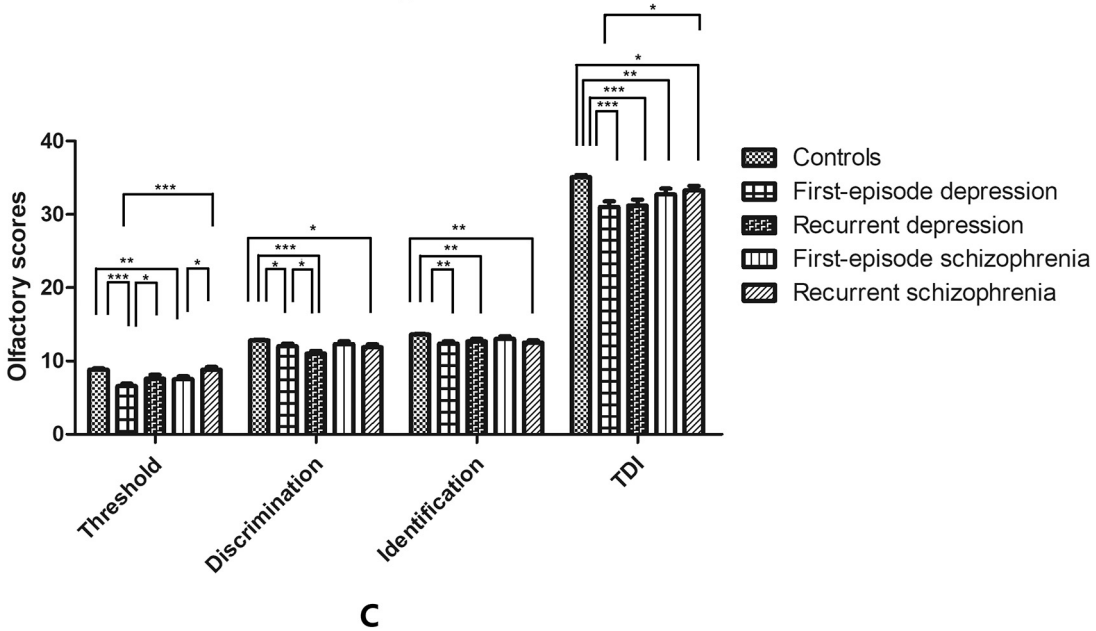
		Controls ($n = 199$)	Schizophrenia acute episode ($n = 52$)	Major depressive episode ($n = 75$)	$F/\chi^2/t$	P	Post hoc*
Age (m ± sd)		34.1 ± 11.9	32.7 ± 9.4	36.6 ± 10.0	2.10	0.124	–
Male/female (n)		90/109	22/30	23/52	4.78	0.920	–
Smoker (n)		–	25	26	2.30	0.130	–
Duration (year)(m ± sd)		–	4.9 ± 5.9	3.6 ± 2.8	1.18	0.237	–
First episode/Recurrent episode (n)		–	20/32	37/38	1.47	0.226	
Olfactory Threshold (m ± sd)		8.8 ± 3.1	8.3 ± 1.9	7.1 ± 2.6	8.69	<0.001	A, B > C
Olfactory discrimination		12.8 ± 1.8	12.0 ± 2.1	11.5 ± 2.5	9.63	<0.001	A > B, C
Olfactory identification		13.6 ± 1.9	12.7 ± 1.7	12.5 ± 1.8	6.15	<0.001	A > B, C
TDI		35.1 ± 4.5	33.0 ± 3.5	31.1 ± 4.6	18.82	<0.001	A > B > C
Olfactory impairment (TDI < 30.5)		–	15 (28%)	34(45.3%)	3.52	0.061	–
subjective olfactory impairment		–	5 (9.6%)	16(21.3%)	4.41	0.036	–
HAMD		–	–	23.8 ± 4.5	–	–	–
PANSS	Positive	–	14.7 ± 2.4	–	–	–	–
	Negative	–	17.3 ± 3.6	–	–	–	–
	General psychopathology	–	31.0 ± 5.8	–	–	–	–
	Total	–	62.2 ± 9.2	–	–	–	–
Severity (mild/severely)		–	27/25	35/40	0.34	0.560	–
Color word test	A	–	17.1 ± 4.3	16.6 ± 4.0	0.56	0.574	–
	B	–	27.4 ± 6.3	24.1 ± 4.8	3.34	0.001	–
	C	–	46.9 ± 15.4	41.5 ± 9.5	2.43	0.016	–
	C-A	–	19.9 ± 13.7	17.1 ± 7.6	1.38	0.170	–
Word generation tasks	Supermarket	–	21.7 ± 7.8	26.5 ± 8.1	3.36	0.001	–
	FAS	–	16.6 ± 6.9	18.7 ± 6.3	1.79	0.075	–


Olfactory scores
40
30
20
10
0
Threshold
Discrimination
Identification
TDI
Controls
Schizophrenia
Depression

A


Olfactory scores
40
30
20
10
0
Threshold
Discrimination
Identification
TDI
Controls
Mild depression
Severe depression
Mild schizophrenia
Severe schizophrenia

B


Olfactory scores
40
30
20
10
0
Threshold
Discrimination
Identification
TDI
Controls
First-episode depression
Recurrent depression
First-episode schizophrenia
Recurrent schizophrenia

C

with MDE (45.3%) was higher than in patients with schizophrenia (28%), but this did not reach the significant level ($P = 0.061$). And there were significantly more patients with MDE had self-awareness of olfactory impairment than patients with schizophrenia (see Table 1).

3.1. Associations between olfactory functions with sociodemographical, clinical variables and cognition in schizophrenia acute episode and MDE patients

In patients with schizophrenia, olfactory threshold scores were correlated with PANSS scores (total scores ($r = 0.37$, $P = 0.007$), and general psychopathology ($r = 0.48$, $P < 0.001$)). Olfactory discrimination was correlated with word generation (supermarket) ($r = 0.276$ $P = 0.047$). No such correlations were found for the odor identification and TDI scores (see Fig. 2). Women (34.2 ± 3.4) had higher TDI scores than men (31.5 ± 3.0) ($t = 2.96$, $P = 0.012$). No significant difference in olfactory function was found between smokers/nonsmokers.

In patients with MDE, no significant correlation was found between olfactory sensitivity and other factors. Olfactory discrimination was correlated with age ($r = -0.28$, $P = 0.015$), disease duration ($r = -0.26$, $P = 0.023$), word generation (supermarket ($r = 0.26$, $P = 0.026$) and FAS ($r = 0.35$, $P = 0.002$)). Olfactory identification was correlated with time of color-word C-A ($r = -0.25$, $P = 0.047$). TDI was correlated with age, word generation (supermarket) ($r = 0.35$, $P = 0.002$) (see Fig. 2). No significant difference in olfactory function was found between men/women, smokers/nonsmokers.

3.2. Regression analysis

In patients with schizophrenia, olfactory sensitivity was associated with sex and PANSS total scores. Olfactory identification was associated with PANSS total scores. TDI was correlated with sex (see Table 2). In patients with MDE, olfactory discrimination was associated with word generation and age. TDI was associated with age (see Table 2).

3.3. Olfactory functions and episodes severity in schizophrenia and MDE patients compared with healthy controls

No significant difference in olfactory scores was found between mild and severe schizophrenia groups, nor mild and severe MDE groups. Additionally, there was neither a difference in olfactory scores between mild schizophrenia and mild MDE, nor severe schizophrenia and severe MDE (see Fig. 1B).

3.4. Olfactory functions and episode recurrences in schizophrenia and MDE patients compared with healthy controls

First-episode schizophrenia group showed significantly lower threshold scores than recurrent schizophrenia group, and first-episode MDE group had significantly lower threshold scores and higher discrimination scores than recurrent MDE group. No difference was found in olfactory scores between first-episode schizophrenia and first-episode MDE, nor recurrent schizophrenia and recurrent MDE (see Fig. 1C). First-episode schizophrenia showed younger age ($t = 3.821$, $P < 0.001$), shorter duration ($t = 5.629$, $P < 0.001$) than recurrent schizophrenia, and first-episode MDE showed younger age ($t = 2.176$, $P = 0.033$), shorter duration ($t = 6.649$, $P < 0.001$) than recurrent MDE.

4. Discussion

Previous studies about patterns of olfactory deficits in patients with schizophrenia and depression are inconsistent (Cohen et al., 2012; Croy and Hummel, 2016), which may result from their mixture of patients in acute and remitted status. The current study merely included patients with acute episode of schizophrenia and MDE in a relatively large sample size and revealed 4 major results:

(1) both patients with schizophrenia and MDE exhibited significant olfactory deficits, and MDE patients have poorer olfactory sensitivity than schizophrenia patients. (2) Patients with MDE had a higher proportion of olfactory impairment but better self-awareness than patients with schizophrenia. (3) In patients with schizophrenia, PANSS scores were positively associated with olfactory sensitivity and negatively associated with olfactory identification; in patients with MDE, olfactory discrimination was positively associated with word generation and negatively associated with age. (4) First-episode schizophrenia group showed significantly lower threshold scores than recurrent schizophrenia group, and first-episode MDE group had significantly lower threshold scores and higher discrimination scores than recurrent MDE group.

The present study suggested that both acute episode of schizophrenia and MDE patients suffer from olfactory deficits. To some extent, abnormalities of olfactory pathway in schizophrenia and depression are similar. In both diseases the volume of olfactory bulbs and the hippocampus has been shown to be reduced (An et al., 2011; Chen et al., 2018b), and there are morphological abnormalities of olfactory sulci (Takahashi et al., 2016; Turetsky et al., 2009a, 2009b), and dysfunction of high-level olfactory areas (Chen et al., 2018b; Croy et al., 2014; Kiparizoska and Ikuta, 2017). However, the underlying mechanism of olfactory deficits in these two diseases are different. Olfactory deficits may originate from deficiency of embryonal development in schizophrenia (Turetsky et al., 2009a, 2009b), and they are not only associated with central dysfunction but also peripheral damage (Turetsky et al., 2009a, 2009b; Borgmann-Winter et al., 2016). Additionally, many studies suggested that olfactory identification impairment may be a trait marker of schizophrenia (Good et al., 2010; Zou et al., 2018), which can also be found in their first-degree family members and youths at-risk for psychosis (Cohen et al., 2012). On the contrary, most of the studies suggested that olfactory threshold impairment was more pronounced than other olfactory domains in patients with depression (Buron and Bulbena, 2013; Marine and Boriana, 2014), and their olfactory deficits are reversible after successful antidepressive treatment (Birte-Antina et al., 2018). Croy et al. assumed that olfactory deficits in depression may be associated with reduced attention and reduced turn-over rate of olfactory receptor neurons in the olfactory epithelium, and that the decreased volume of the olfactory bulb may lead to reduced signaling from OB to central olfactory areas and exacerbate depressive symptoms (Croy and Hummel, 2016).

Consistent with the previous researches, differences in the pattern of olfactory deficits between acute episode of schizophrenia and MDE were found in the current study, that MDE patients showed worse olfactory sensitivity than schizophrenia patients. Moreover, there was a large number of patients with acute episode of schizophrenia and MDE with hyposmia, but their rates of self-awareness were relatively low. Lack of insight is one of the most critical symptoms in schizophrenia (Palmer et al., 2015), while depression patients are prone to have better self-awareness.

Fig. 1. Comparison of olfactory function between patients and healthy controls. **A**, comparison between patients with acute episode of schizophrenia and major depressive episode (MDE). **B**, comparison among mild/severe MDE, mild/severe schizophrenia and healthy controls. **C** comparison among first-episode/recurrent MDE, first-episode/recurrent schizophrenia and healthy controls.

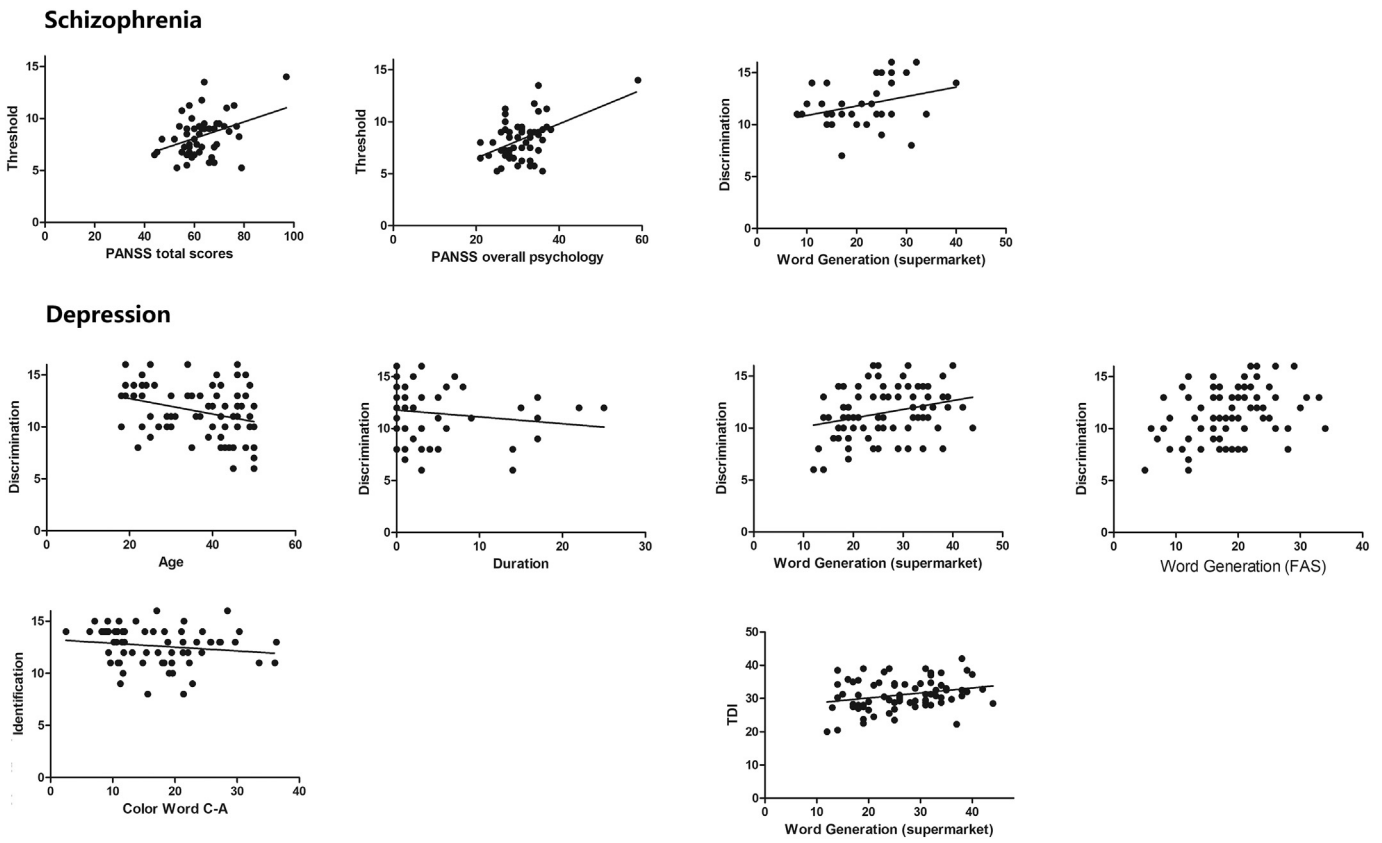


Fig. 2. Associations between olfactory function and sociodemographical variables and cognition in schizophrenia acute episode and MDE patients.

Current results suggested that poor self-awareness of olfactory deficits may also be one symptom related to the lack of insight. This emphasizes that objective assessment should be used to evaluate olfaction of psychiatric patients particularly in schizophrenia, because their self-report is not reliable and may cause misdiagnosis.

With regard to the modulating factors of olfaction, several similarities and difference between schizophrenia and depression were showed in the current study.

First, olfactory identification decreased while olfactory sensitivity increased as disease progress in patients with schizophrenia, and there was no significant association between olfaction and disease severity in MDE group. Previous studies suggested that olfactory deficits may serve as markers of disease severity in both schizophrenia (Pabel et al., 2018b; Good et al., 2010), because decreased olfactory function is associated with brain abnormalities. However, olfactory thresholds behaved inversely compared with olfactory identification in the current results. A previous meta-analysis also reported a higher level of positive symptoms were associated with less olfactory deficit, and it was hypothesized to reflect an increased vigilance to external and internal stimuli in patients with more predominant Schneiderian symptomatology (Moberg et al., 2014). Our possible explanation for this positive association may be a compensatory mechanism. Olfactory threshold partly relate to peripheral olfactory function, and, hence, to modulators of olfactory function like turn-over rate of olfactory receptors, number of olfactory receptor neurons (ORNs), loss of specificity of olfactory receptor expression, and magnitude of the membrane depolarization in ORNs (Croy and Hummel, 2016; Turetsky et al., 2009a, 2009b). Interestingly, in patients with schizophrenia there are reports of increases in electro-olfactogram (EOG) recordings (representing summated generator potentials of ORN in the olfactory epithelium) (Borgmann-Winter et al., 2016; Turetsky et al., 2009a, 2009b), increased G protein activation in response to DA and 5HT (Borgmann-Winter et al., 2016), increased number of immature ORNs (Arnold et al., 2001), increased mitosis and greater cell proliferation (Feron et al., 1999; McCurdy et al., 2006), and increased expression of multiple genes related to cell proliferation,

Table 2
Linear regression analysis of factors which are associated with olfactory scores in patients with schizophrenia and depression.

		Variable	β	t	P	95%CI
Schizophrenia	Threshold	PANSS	0.448	3.54	0.001	(0.041, 0.150)
	$R^2 = 0.253$	sex	0.346	2.73	0.009	(0.359, 2.364)
	Discrimination	–				
	Identification	PANSS	−0.308	−2.290	0.026	(−0.109, −0.007)
	$R^2 = 0.095$					
	TDI	Sex	−0.378	−2.891	0.006	(−4.466, −0.805)
	$R^2 = 0.143$					
Depression	Threshold	–	–	–	–	–
	Discrimination	Word generation	0.280	2.565	0.012	(0.012, 0.094)
	$R^2 = 0.171$	Age	−0.266	−2.435	0.017	(−0.118, −0.012)
	Identification	–	–	–	–	–
	TDI	Age	−0.290	−2.573	0.012	(−0.232, 0.029)

differentiation and neurogenesis in olfactory epithelium (McCurdy et al., 2006). Therefore, we hypothesize that their decreased olfactory threshold may be a compensatory mechanism for dysfunction at higher levels of the olfactory system. The (hypothetically) larger activation of the peripheral olfactory system may be a mechanism to offset the dysfunction at a higher level. Such top-down influences form the brain on peripheral levels have been shown to exist in humans (Cavazzana et al., 2018). Future studies with magnetic resonance imaging, electro-olfactogram and biopsy to assess the activity of olfactory pathway and olfactory epithelium could verify this hypothesis.

It should be noted that the low scores of disease severity in some patients could also be a result of treatment, because many antipsychotic and antidepressant drugs may influence olfactory receptors change olfactory thresholds. Therefore, the effect of drugs may also contribute to the positive correlation between olfactory threshold and disease severity. With regards to the effect of drugs on olfaction, the types, doses and using time of drugs may matter. Morberg et.al suggested that both overall medication and chlorpromazine equivalents showed no effect on olfaction, but patients taking typical or first-generation antipsychotics exhibited greater olfactory deficits than those taking atypical or second-generation antipsychotics (Moberg et al., 2014). However, drug combinations, irregular medication changing of types and doses of drug are very common during the course of the disease in patients with schizophrenia and depression, which makes it difficult to clarify the effect of different drugs in the present study. Future specialized study considering comprehensive information about duration, change of type and dose, as well as combinations of different drugs could provide a better understanding of the relationship between medication and olfaction in acute episode psychiatric patients. Besides, it should be noted that current results derived from cross-sectional comparison, further longitudinal studies could provide a deeper understanding of the role which olfaction plays in schizophrenia and depression.

Second, olfactory discrimination was positively associated with word generation scores in both acute episode of schizophrenia and MDE. The close relationship between olfaction and cognition has been repeatedly reported, and the olfactory pathway overlaps with many brain areas dominating cognitive processing, such as hippocampus, amygdala and orbitofrontal cortex (Marine and Boriana, 2014). Furthermore, dysfunction of these overlapping areas has been shown in schizophrenia and depression (Kiparizoska and Ikuta, 2017; Croy et al., 2014b; Chen et al., 2018b), indicating their impairment of olfaction, cognition and emotional processing. Collectively, the current results suggest that olfactory discrimination deficit could be used a marker of cognitive impairment in both schizophrenia and depression.

Third, first-episode schizophrenia/MDE were prone to have worse thresholds than patients with recurrent schizophrenia/MDE, and first-episode MDE had higher discrimination scores than recurrent MDE. Previous studies suggest that age and disease course have a significant impact on olfaction (Pabel et al., 2018b; Doty, 2018). Therefore, the better discrimination in first-episode patients may be associated with their younger age and shorter disease course than recurrent patients in the current study. While the lower thresholds scores in first-episode patients compared to recurrent patients could also be explained by the compensatory mechanism discussed above, in that the abnormalities of olfactory and mental processing in recurrent patients may trigger the activation of the peripheral olfactory system. Because of the less pronounced impairment of olfactory discrimination, the compensatory mechanism in first-episode patients may not be as active as it is in recurrent patients, and their relatively short duration of the disease may not allow the compensatory mechanism to fully operate. Another possible explanation may be the longer duration of antidepressant treatment in recurrent MDE patients, as antidepressants could improve olfactory threshold.

5. Limitations

First, although olfactory threshold, discrimination and identification between schizophrenia and depression were compared in the present studies, some other olfactory indexes such as hedonic ratings of odors and odor memory tests were absent. As impairment of olfactory hedonicity and odor memory have been shown in patients with schizophrenia and depression in earlier studies, further research should include these comparisons. **Second**, the differences in olfactory function was only compared at a behavioral level in current study. Future studies using neuroimaging and electrophysiological techniques could provide a deeper understanding of their different neural mechanism. **Third**, in the current study we only collected information on the type but not the dose of drugs and treatment duration, and “current smoker or not” but not the burden of smoking, which prevents us from a deeper understanding of the influence of drugs and smoking on olfaction. Future studies recording comprehensive information about duration, change of type and dose, and combination of different drugs, as well as smoking burden (pack-years, pack-days) could clarify these relationships. **Forth**, previous studies suggested that memory and attention were also associated with olfaction in patients with schizophrenia and depression, but patients in acute episode were difficult to cooperate with, which did not allow for extensive testing of all cognitive domains. Future studies using comprehensive cognitive test batteries could better explore the different relationship between cognitive function and olfaction in schizophrenia and depression. **Fifth**, concerning the significant differences in clinical symptoms, disease course and mechanism between schizophrenia and depression, mild/severe and first-episode/recurrent in the two patient groups were divided by different criteria in current study. Therefore, comparing the influence of episode severity and episode recurrences should be interpreted with caution. **Last**, we include a homogenous group of patients with acute episode (schizophrenia and depression) and we cannot generalize our results for patients in remission or with residual symptoms.

6. Conclusions

To sum up, the current study emphasis the general presence of olfactory deficits and the importance of objective olfactory assessment in patients with acute episode of schizophrenia and MDE. Schizophrenia and depression have different patterns of olfactory deficits, and their sense of smell is influenced by a variety of factors. Their differences should be carefully considered when using olfactory deficits as a marker in clinical practice.

Contributors

Ben Chen: conception and design, acquisition of data, analysis and interpretation of data; drafted the article; gave final approval of the version to be published.

Rita Klarmann: conception and design, acquisition of data, gave final approval of the version to be published.

Matthias Israel: revised the manuscript critically for important intellectual content, gave final approval of the version to be published.

Yuping Ning: revised the manuscript critically for important intellectual content; gave final approval of the version to be published.

Romain Colle: revised the manuscript critically for important intellectual content, gave final approval of the version to be published.

Thomas Hummel: conception and design, acquisition of data, analysis and interpretation of data; revised the manuscript critically for important intellectual content, gave final approval of the version to be published.

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Declaration of competing interest

The authors declare no conflict of interest.

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No.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.08.004.

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