



Olfactory function in neuropsychiatric disorders



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ABSTRACT

Recent clinical studies have identified olfactory dysfunction in patients with neuropsychiatric disorders. Although these studies showed differences in olfactory function between healthy individuals and neuropsychiatric patients, no studies have compared the differences in olfactory function among neuropsychiatric disorders. The aim of the present study was to investigate olfactory function among various neuropsychiatric disorders. Three-hundred and eighteen outpatients diagnosed according to the ICD-10 code participated in the study. Olfactory function was assessed using the Open Essence test. The differences in olfactory function among disorders were compared by analyses of (co-)variance. As expected, olfactory function was significantly affected by the age and marginally affected by the gender. We investigated the differences in olfactory function among patients with different neuropsychiatric disorders (*FO-F9*). Olfactory function significantly differed among the diagnostic groups. *Post hoc* analysis showed that patients with *FO* had decreased olfactory function compared to patients from the other diagnostic groups. In particular, patients with Alzheimer's disease (AD) had significantly poorer olfactory function compared to patients with other neuropsychiatric disorders. There were no differences among the other groups. These findings suggest that patients with AD had poorer olfactory function compared not only to healthy subjects but also to patients with several other neuropsychiatric disorders.

1. Introduction

One important function of the olfactory system is to detect danger, such as leaking gas, fires, and rotten food (Saito et al., 2006). Although the olfactory system exerts an important function in our lives, its function diminishes with age (Jimbo et al., 2011; Mobley et al., 2014). Impaired olfaction may prevent elderly people from detecting dangerous situations and may reduce the perception of offensive odors, such as the smell of burning. As a result, impaired olfaction increases the risk of serious accidents.

Olfactory function consists of several abilities, such as to detect, discriminate and identify odorants (Eibenstein et al., 2005). Olfactory identification and discrimination are closely associated with higher cognitive functions (Schubert et al., 2008; Sohrabi et al., 2009). Functional magnetic resonance imaging studies during an olfactory recognition memory task showed activation of a complex network of brain regions, including frontal, temporal and parietal gyri as well as hippocampus (Cerf-Ducastel and Murphy, 2006). Therefore, olfactory identification requires global cognitive processing including working memory, attention, judgment, language function and decision making.

Olfactory dysfunction is a common complaint during physician visits. Olfactory loss affects the quality of life and impairs the functions and activities of daily living. Impaired olfaction has been extensively reported in individuals with mild cognitive impairment (MCI) and patients with dementia, such as Alzheimer's disease (AD) and frontotemporal dementia (FTD), as well as in healthily aging individuals (Hori et al., 2015; Jimbo et al., 2011; Orasji et al., 2016; Seligman et al., 2013). In addition, impaired olfactory functions have been reported in various neuropsychiatric disorders, such as schizophrenia (Brewer et al., 1996; Zou et al., 2015), depression (Kohli et al., 2016; Sivam et al., 2016) and panic disorder (Buron et al., 2015).

Neuroscience studies in neuropsychiatric disorders generally rely on disease definitions based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD). Although the DSM or ICD consider different disorders as distinct entities, boundaries between disorders are often not as strict. To provide an alternative framework for research into neuropsychiatric disorders, the National Institute of Mental Health (NIMH) has recently developed the Research Domain Criteria (RDoC) (Casey et al., 2013). The RDoC is a research framework for new

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ways of studying neuropsychiatric disorders. It integrates many levels of information (from genomics to self-report) to better understand basic dimensions of functioning underlying the full range of human behavior from normal to abnormal. In the RDoC, five 'domains' reflect a brain system in which functioning is impaired, to different degrees, in different psychiatric conditions (<https://www.nimh.nih.gov/research-priorities/rdoc/constructs/rdoc-matrix.shtml>). In the cognitive domain, olfactory function is included although the way to examine the function has not been established. Therefore, evidence for how to examine the function, mechanisms underlying the function and the degrees of the dysfunction among disorders is needed. Although the differences in olfactory function between healthy individuals and those with neuropsychiatric disorders have been examined, no study has investigated the differences in olfactory function among patients with different neuropsychiatric disorders. The aim of the present study was to investigate olfactory function among several neuropsychiatric disorders using the Open Essence (OE) odorant identification test. We hypothesized that there may be more significantly impaired olfaction in one specific neuropsychiatric disorder when compared with the degree of impaired olfaction in other neuropsychiatric disorders. Considering that olfactory dysfunction precedes cognitive impairment in AD (Eibenstein et al., 2005), olfactory dysfunction is associated with the loss of hippocampal volume in AD (Murphy et al., 2003) and AD patients shows more severe cerebral atrophy than other neuropsychiatric disorder patients (Geuze et al., 2005), it is hypothesized that patients with AD may have more impaired olfaction than patients with other neuropsychiatric disorders.

2. Methods

2.1. Subjects

The subjects for this study consisted of 318 outpatients (43.4% males, 138 males/180 females, mean age \pm standard deviation: 44.7 ± 18.8 years) who came for their first visit to the psychiatric outpatient unit in the Kanazawa Medical University Hospital during the period of August 1, 2012 to October 31, 2015. All patients and their relatives, if available, underwent face-to-face interviews by at least two trained psychiatrists. The diagnosis was made according to the criteria of the ICD, 10th Revision. Clinical diagnoses based on the ICD-10 were mainly classified as follows: 'F0'- 'Organic, including symptomatic, mental disorders'; 'F1'- 'Mental and behavioral disorders due to psychoactive substance use'; 'F2'- 'Schizophrenia, schizotypal and delusional disorders'; 'F3'- 'Mood disorders'; 'F4'- 'Neurotic, stress-related and somatoform disorders'; 'F5'- 'Behavioral syndromes associated with physiological disturbances and physical factors'; 'F6'- 'Disorders of adult personality and behavior'; 'F7'- 'Mental retardation'; 'F8'- 'Disorders of psychological development' and 'F9'- 'Behavioral and emotional disorders with onset usually occurring in childhood and adolescence.' Patients who did not complete olfactory test or obviously understand explanation of the test were excluded from this study. Demographic information including age and gender is shown in Table 1. This study was performed according to the principles of the World Medical Association's Declaration of Helsinki and was approved by the Research Ethics Committee of Kanazawa Medical University.

2.2. Open Essence test

To assess olfactory function, we used the OE odorant identification test (Wako Pure Chemical Industries, Ltd., Osaka, Japan) (Okutani et al., 2013). The 40-odorant University of Pennsylvania Smell Identification Test (UPSIT) or its shorter version; the three-item Quick Smell Identification Test (Q-SIT), were developed in the USA (Doty et al., 1996). Although the UPSIT has been translated into many languages and has been administered to patients with neuropsychiatric disorders worldwide (Devanand et al., 2015; Doty et al., 1984; Gill

Table 1.

Demographic variables for the diagnostic groups included in this study.

ICD-10 code	N (%)	Age (years)	Gender (M/F)	OE score (95%CI)
F0	23 (7.2)	68.4 \pm 14.0	11/12	3.4 \pm 3.2 (2.4 – 4.4)
F1	9 (2.8)	66.4 \pm 10.8	6/3	6.0 \pm 2.6 (4.4 – 7.6)
F2	20 (6.3)	36.4 \pm 15.2	6/14	7.3 \pm 1.9 (6.2 – 8.3)
F3	82 (25.8)	43.0 \pm 15.3	35/47	7.7 \pm 2.3 (7.2 – 8.2)
F4	135 (42.5)	44.5 \pm 17.7	55/80	7.3 \pm 2.5 (6.9 – 7.7)
F5	31 (9.7)	40.4 \pm 20.9	17/14	7.8 \pm 2.1 (6.9 – 8.6)
F6	5 (1.6)	32.4 \pm 21.9	1/4	9.0 \pm 2.3 (6.9 – 11.1)
F7	1 (0.3)	42.0	1/0	6.0 (1.3 – 10.7)
F8	5 (1.6)	28.8 \pm 14.9	4/1	8.8 \pm 2.4 (6.7 – 10.9)
F9	7 (2.2)	24.0 \pm 15.6	2/5	8.1 \pm 2.2 (6.4 – 9.9)
Total	318	44.7 \pm 18.8	138/180	7.2 \pm 2.6

OE: Open Essence test; M: male; F: Female; F0: Organic, including symptomatic, mental disorders; F1: Mental and behavioral disorders due to psychoactive substance use; F2: Schizophrenia, schizotypal and delusional disorders; F3: Mood [affective] disorders; F4: Neurotic, stress-related and somatoform disorders; F5: Behavioral syndromes associated with physiological disturbances and physical factors; F6: Disorders of adult personality and behavior; F7: Mental retardation; F8: Disorders of psychological development; F9: Behavioral and emotional disorders with onset usually occurring in childhood and adolescence. Means \pm standard deviations are shown.

et al., 2014), some odorants in the original UPSIT are unfamiliar to people in countries outside the USA, including Japan (Ayabe-Kanamura et al., 1998). Therefore, the OE test containing odorants familiar to Japanese people was developed (Okutani et al., 2013; Shiga et al., 2014). The OE test has also been administered to patients with various diseases, such as dementia and Parkinson's disease (Homma et al., 2013; Sanke et al., 2014). The OE test uses 12 odorants: (1) condensed milk, (2) cooking gas, (3) curry, (4) cypress wood (Japanese cypress, *hinoki*), (5) India ink, (6) Japanese orange (*mikan*), (7) menthol, (8) perfume, (9) roasted garlic, (10) rose, (11) sweaty clothes, and (12) wood. The OE contains 12 cards folded in two and sealed with a special glue that is sensitive to extremely high pressure (Fig. 1). The subjects received the odor cards from the experimenter, opened them, and then sniffed and identified the odorant in a four-plus alternative choice paradigm. Once the cards are opened, they cannot be closed again. The score from the OE test ranges from 0 (poor olfactory function) to 12 (good olfactory function).

2.3. Statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics 19.0 software (IBM Japan, Tokyo, Japan). The effects of the diagnostic status (F0-F9) on olfactory function were analyzed by analyses of variance (ANOVA) with the OE test scores as the dependent variables and the diagnostic status based on the ICD-10 code as the independent variables. *Post hoc* testing with Fisher's Least Significant Difference (LSD) was used to evaluate the statistical significance of the differences among the diagnostic groups. The correlation between the OE test score and age was assessed using Spearman's ρ test. To control for confounding factors, such as age and gender, we performed analyses of covariance (ANCOVA) with the OE test scores as the dependent variables, the diagnostic status based on the ICD-10 code as the independent variables, and age and gender as covariates. We further performed a preliminary ANCOVA with the OE test scores as the dependent variables, the diagnostic status (AD or non-AD groups) as the independent variables, and age and gender as covariates. Standardized effect sizes were calculated using Cohen's *d* method (<http://www.uccs.edu/faculty/lbecker>). The significance level for all statistical tests was set at two-tailed $p < 0.05$.

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