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CLINICAL ASSESSMENT AND IMPLICATION OF OLFACTORY DYSFUNCTION IN NEUROPSYCHIATRIC DISORDERS OF CHILDHOOD AND ADULTHOOD: A REVIEW OF LITERATURE

ÇOCUKLUK ÇAĞI VE ERİŞKİN NÖROPSİKİYATRİK HASTALIKLARDA KOKU BOZUKLUĞUNUN KLİNİK DEĞERLENDİRİLMESİ VE ÖNEMİ: BİR LİTERATÜR DERLEMESİ

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Abstract

Olfactory function comes into prominence in the neuroscience study area after revealing that olfactory dysfunction is considered as an early diagnostic pre-motor biomarker of Parkinson's disease. Researchers have also examined the sense of smell in detail in patients with other neuropsychiatric disorders. Here, we present data from a systematic literature review in olfactory function in child and adult neuropsychiatric disorders. We have researched autism spectrum disorders (ASD), epilepsy, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, bipolar disorder, eating disorders, and obsessive-compulsive disorder (OCD). Due to smell test techniques and heterogeneity of studies, the total number of studies was limited. The disorders were grouped according to smell test techniques. The most commonly-used tests were Sniffin Sticks Test (SST) and the University of Pennsylvania Smell Identification Test (UPSIT). Although some researcher did not find any significant impairment in olfaction, most studies indicated that olfactory dysfunction was very striking, especially in disorders involving in the dopaminergic pathway (e.g., ADHD, autism, and schizophrenia). In this review, possible future diagnostic or prognostic markers of olfactory dysfunction in neuropsychiatric disorders have been discussed. More studies that combine imaging methods, the electrophysiologic system, and genetic research are needed to clarify the relationship between olfaction and neuropsychiatric disorders.

Keywords: Olfactory Dysfunction, Olfactory Assessment, Neuropsychiatric Disorders, University of Pennsylvania Smell Identification Test (UPSIT), Sniffin Sticks Test (SST)

Özet

Parkinson hastalığında koku bozukluğunun erken tanısal pre-motor belirteç olarak gösterilmesinden sonra, koku fonksiyonunun sinirbilim çalışma alanında önemi artmıştır. Araştırmacılar, koku duyusunu diğer nöropsikiyatrik hastalıklarda da detaylı olarak araştırmıştır. Bu çalışmamızda, çocukluk çağı ve erişkin nöropsikiyatrik hastalıklarda koku fonksiyonu üzerine sistematik bir derleme sunmaya çalıştık. Otizm spektrum bozuklukları (OSB), epilepsi, dikkat eksikliği/hiperaktivite bozukluğu (DEHB), şizofreni, bipolar bozukluk, yeme bozukluğu ve obsesif kompulsif bozukluk (OKB) araştırılmıştır. Koku testi teknikleri ve çalışmaların heterojen dağılımından dolayı, toplam çalışma sayısı kısıtlı kalmıştır. Çalışmalar koku testi tekniklerine göre ayrıldı. En sık kullanılan koku testleri Sniffin Sticks Testi (SST) ve Pensilvanya Üniversitesi Koku Tanımlama Testi (UPSIT) idi. Bazı araştırmacılar koku fonksiyonunda anlamlı bir bozulma bulmasalar da, çalışmaların çoğunda özellikle dopaminerjik yolağı ilgilendiren hastalıklarda (ör. DEHB, otizm ve şizofreni) koku bozukluğu dikkati çekmiştir. Bu derlemede, nöropsikiyatrik hastalıklarda koku bozukluğunun olası tanısal ve prognostik belirteç özelliği tartışılmıştır. Görüntüleme yöntemleri, elektrofizyolojik sistem ve genetik çalışmalarla entegre araştırmalar, koku ve nöropsikiyatrik hastalıklar arasındaki ilişkiyi aydınlatmak açısından önem taşıyacaktır.

Anahtar Kelimeler: *Koku bozukluğu, koku alma değerlendirmesi, nöropsikiyatrik hastalıklar, Pensilvanya Üniversitesi Koku Tanımlama Testi (UPSIT), Sniffin Sticks Testi (SST)*

1. Introduction

"Smell is the orphaned sense; it has been forgotten by medicine" (Birnbaum, 2011)

The sense of smell is currently arousing a great deal of interest in the neuroscience area. This distinct sense has some unusual features: that it is the only sensory system

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not to use the thalamus as a central relay station and that it maintains plasticity and exhibits neurodevelopment throughout life by regenerating approximately every 2–3 months (Turetsky et al., 2009) render the olfaction unique. Turetsky et al., (2009) postulated that the olfactory system offers an unparalleled opportunity to observe the developmental processes of neurogenesis and synapse formation that are no longer evident in other adult brain areas.

As the neuroanatomy of olfaction was revealed, the relation to some neuropsychiatric disorders was demonstrated. The complex association of the olfactory pathway with other brain areas such as the thalamus, amygdala, and hypothalamus, inferior frontal, lateral and medial temporal areas is necessary for olfactory identification, discrimination, and sensitivity (Kareken et al., 2003).

The important proximity of olfactory pathway to some certain neuropsychiatric disorders like schizophrenia has underlined the association of olfaction with these diseases. Schecklmann et al., (2013) indicated that specific alterations in olfactory function were found especially in disorders with dopaminergic pathology (e.g., ADHD, autism, and schizophrenia). Olfaction is mediated by neurotransmitters such as dopamine, and dopaminergic interneurons modulate odor detection and discrimination via D2 receptors (Hsia et al., 1999).

Within the sensory system, olfactory system is most closely associated with temporolimbic and frontal lobe regions (Fig. 1). These domains are related to affective and mnemonic functions, which are mainly impaired in schizophrenia (Turetsky et al., 1995). It has even been postulated that olfaction can be used to assess disease-related cognitive and emotional disturbances (Pause et al., 2008; Schneider et al., 2007).

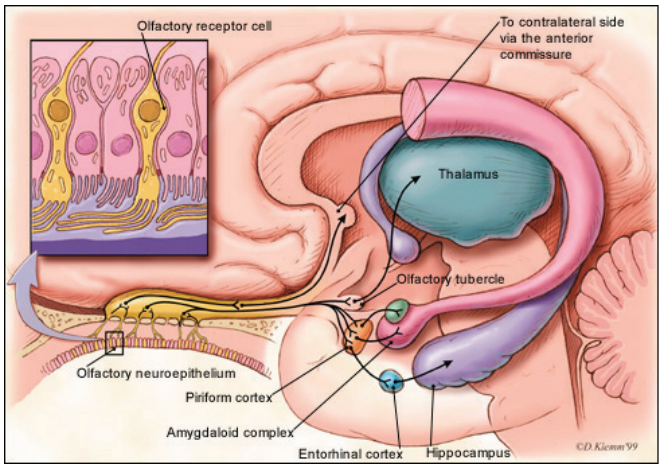

Figure 1: The simplified illustration of olfactory processing in the brain. From Bromley SM. (2000). Am Fam Physician, 61(2), 427-436. Copyright ©David Klemm (2000).

In some neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease (AD), general olfactory deficit (odor sensitivity, discrimination, and identification) has been detected. Furthermore, this olfactory deficit was considered as early diagnostic pre-motor biomarker of PD (Doty, 2007; Kranick and Duda, 2008). Along with valuable feature of olfactory testing in the differential diagnosis of idiopathic PD from a number of other neurodegenerative diseases (e.g., essential tremor, vascular Parkinsonism) (Katzenschlager et al., 2004), the disease predicting characteristics of olfactory loss in PD patients relatives (Ponsen et al., 2004) makes olfaction as a diagnostic tool in neurodegenerative disorders. Moreover, some researchers implied that olfactory dysfunction can be related to disease progression (Tissingh et al., 2001).

When olfactory dysfunction was shown in neurodegenerative disease, the field of neuropsychiatric disorders became a study area in terms of olfaction. The important dopaminergic pathway along with strategically anatomic proximity is maybe a key for studying olfaction in neuropsychiatric disorders.

The aim of this work was to provide a systematic review on olfactory function in neuropsychiatric disorders of childhood and adulthood. Due to smell test techniques and heterogeneity of studies, we focused on available literature about autism spectrum disorders (ASD), epilepsy, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, bipolar disorder, eating disorders, and obsessive-compulsive disorder (OCD). We tried to give some basic information to aid the discussion about potential diagnostic and clinical bio-markers of the olfactory system in neuropsychiatric disorders.

2. Materials and Methods

2.1. Assessment of Olfactory System

The assessment of olfactory system is mainly based on psychophysic and electrophysiologic tests. The applicability of these tests on children has been performed and shown that between age of 3 and 5 years the psychophysical tests were unreliable. After the age of 6 years, these tests can be applied for routine olfactory assessment. On the other hand, studies provided that it is possible to obtain an objective measurement of olfactory function in children from the age of 3.5 years using electrophysiologic tests (olfactory ERP recordings) (Hummel et al., 2007).

There are two common modalities in screening olfactory system; how the stimulus is given and how the stimulus is recorded.

Stimulus induction is mainly achieved with standardized odorants, which are given through the nasal aperture. Different odorants can be used like phenyl-ethyl alcohol for positive valence or isobutyraldehyde for negative valence. There are few differences in odor perception among study groups, but adaptation is the most frequently-used method. The technique of odorant stimuli is split into two ways. The first way uses olfactometers (Knecht and Hummel, 2004). By using an olfactometer device, odors are applied intranasally by means of a cannula that typically has an inner diameter of 2 to 3 mm. This cannula is inserted approximately 1 cm into the nostril to make it possible to stimulate directly olfactory mucosa. The device has two tubes into which air or odorant samples flow. Odorant samples can be diluted by mixing

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with air. Mixture percentages are important to identify the threshold levels in participants. The second way for odor stimuli uses psychophysical tests (Hummel and Welge-Luessen, 2006). This method use odors that are produced with a settled mixture of air-odor samples. This is different from the olfactometer because the odorant sample has to be inspired by the participant and the inter stimulus intervals (ISI) cannot be managed as strictly as in the olfactometer. The constant air flow is directed into the subject's nose mask for humidification (80% relative humidity) and thermostabilization (36°C) because dry, cool air produces nasal congestion, mucus discharge, and pain, which interferes with olfaction in many ways (Henkin et al., 2013). However, psychophysical tests are more widely used because of their simplicity and accessibility.

Recording data that comes from the olfactory system is the other important part of these studies. Psychophysical tests contain questions; participants are asked whether they can smell the odor sample (anosmia or threshold level), and to name the odor. Regional epigenetic confounding factors like being familiar or not with some odors were overcame by modifying the smell tests. (Tourbier and Doty, 2007).

Another way of collecting data about olfaction is through event-related potentials (ERPs). Olfactory-ERPs (OERPs) are electroencephalograph (EEG)-derived polyphasic signals. They originate from the activation of cortical neurons that generate electromagnetic fields (Rombaux et al., 2006). With OERPs, sequences of stimuli with different quality, intensity, duration, or inter stimulus interval can be analyzed. OERPs are direct correlates of neuronal activation and have a high temporal resolution in the range of microseconds. These characteristics allow the sequential processing of olfactory information to be screened and can be obtained independently of the subject's response bias, i.e., they allow the investigation of subjects who have difficulties in responding properly (e.g., children, aphasic patients, malingering) (Hummel and Welge-Luessen, 2006).

The most commonly-used tests for assessing the olfactory system are psychophysical tests. Some of these tests include the Barcelona Smell Test-24 (Cardesin et al., 2006), Sniff Magnitude Test (Frank et al., 2003), Connecticut Chemosensory Clinical Research Center (CCCRC) Test (Cain et al., 1988), Sniffin Sticks Test (SST) (Hummel et al., 1997) and University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al., 1984). The last two tests, SST and UPSIT, are the most commonly used and the best-validated olfactory tests in clinical study.

The Sniffin Sticks Test is performed using pen-like odor-dispensing devices (Fig. 2). As Hummel et al. explained in detail in their article, it comprises three tests of olfactory function, namely tests for odor threshold (n-butanol, testing by means of a single staircase), odor discrimination (16 pairs of odorants, triple forced choice) and odor identification (16 common odorants, multiple forced choice from four verbal items per test odorant) (Hummel et al., 1997). Odorants were presented in commercially available (unfilled) felt-tip pens. The tampon was filled with liquid odorants or odorants dissolved in propylene glycol. For odor presentation, the cap was removed by the experimenter and the pen's tip was placed circa 2 cm in front of both nostrils. For odor identification, 16 odorants were chosen. Criteria for the selection of odorants were as follows: First, subjects should be familiar with all odors used in the test; second, odorants included in the test should be similar with regard to both intensity and hedonic tone; and third, the successful identification of individual odorants from a list of four descriptors should be greater than 75% in healthy subjects. The identification test consists of 16 choices and requires the identification of the smelled odor from a choice of four verbally presented odors. For odor discrimination, triplets of 16 odorants were used. Subjects had to decide 16 times which stick out of three had a smell distinct from the other two. To prevent visual detection of the target sticks, subjects were blindfolded with a sleeping mask. For odor threshold, n-butanol or 2-phenylethanol was used as the odorant. A triplet of sticks was presented with one stick that contained a defined concentration of 2-phenylethanol / n-butanol and two odorless samples. The subject had to decide which of three sticks smelled "like a rose" (scent of 2-phenylethanol) or n-butanol. Using a staircase method, the concentration of odorant is varied and the individual sensitivity threshold can be obtained by averaging the last four reversal points. The sum of the three scores gives a definitive TDI score between 0 and 48, which determines whether the patient has normosmia (TDI > 30), hyposmia (TDI > 15 = 30) or anosmia (TDI ≤ 15) (Kobal et al., 2000).

Figure 2: Sniffin' Sticks. Phenyl ethyl alcohol or n-butanol odorants presented by felt-tip markers. Photo courtesy of Burghart Messtechnick GmbH, Wedel Germany.

The University of Pennsylvania Smell Identification Test (UPSIT) is another best-validated test used in neuropsychiatric disorders (Fig. 3). As Doty et al. described in their paper, it was just used for assessment of olfactory identification (Doty et al., 1984). As a highly standardized (from age 5–85 years) and validated scratch-and-sniff format test, the UPSIT consists of four booklets that contain 40 test items. Each page holds a microencapsulated strip onto which a suprathreshold odorant has been embedded and this can be released by scratching the surface with a pencil. Four possible responses appear on each page. The

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examiner scratches the label with a pencil and holds it under the participant's nose. The participant is instructed to smell the label and the experimenter pointed at and named each of the four picture responses on the picture card, such as "chocolate, pizza, peanut, or banana?" The answer was then recorded on the response sheet. Scores on UPSIT test range between 0 and 40, with each correct identification scoring 1 point. Normosmia is defined by a score > 34 for females and 33 for males. Mild microsmia is defined by a score of 31–34 for females and 30–33 for males. Moderate microsmia is defined by a score of 26–30 for females and 26–29 for males. Severe microsmia is defined by a score of 19–25 for females and males. Total anosmia is defined by a score of 6–18 (Cumming et al., 2011). The UPSIT contains also scores for children's smell identification abilities (from the age of 5 years).

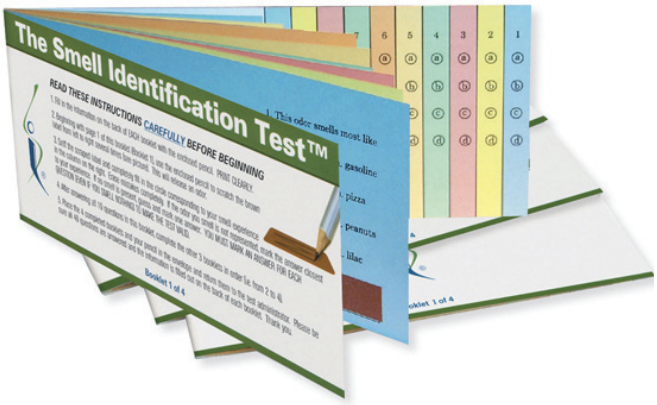

Figure 3: The 40-item University of Pennsylvania Smell Identification Test (UPSIT). Photograph courtesy of Sensonics International, Haddon Heights, New Jersey USA. Copyright©2013, Sensonics International.

Although it has not been definitely proved, it is strongly believed that the threshold parameter usually reflects the peripheral aspect of olfactory function (i.e mediated by lower-order neural pathways) while identification and discrimination parameters reflect central aspect of olfactory function (higher cortical function) (Hummel and Welge-Luessen, 2006). In accordance with these assumptions, patients with sinunasal disease showed a low threshold with normal olfactory identification and discrimination, whereas patients with diseases that involved the central nervous system demonstrated selective impairment of olfactory identification and discrimination with a normal threshold (Klimek et al., 1998; Koss et al., 1988). However, there are also controversial studies and arguments; it has been proposed that olfactory thresholds correlate highly with odor identification scores in controls and patients and the reliability of threshold determination is lower than that for other measures (Doty et al., 1994; Mesholam et al., 1998).

There are some other ways for assessing the olfactory system such as Olfactory ERP, Electroolfactrogram (EOG) and functional magnetic resonance imaging methods. As the focus of this paper is on psychophysical test, we tried to give some basic information about psychophysical assessment of olfactory function.

2.2. Literature Research / Study Selection

A computerized literature search for studies on olfaction (threshold, identification, and discrimination) in neuropsychiatric disorders performed in childhood and adulthood (autism spectrum disorders (ASD), epilepsy, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, bipolar disorder, eating disorders, and obsessive–compulsive disorder (OCD)).

We searched the PubMed database for English language studies between the date of June 2014 and November 2014. Keywords for olfactory system were "olfaction", "smell", "odor", "olfactory dysfunction" and "olfactory assessment". For neuropsychiatric disorders we used "autism spectrum disorder", "epilepsy", "attention deficit hyperactivity disorder", "schizophrenia", "bipolar disorder", "eating disorder", "obsessive compulsive disorder".

The papers were selected based on the titles and abstracts. In addition, manual searches were done by examining article references elicited through the database. We focused on certain neuropsychiatric disorders because the number of olfaction studies in children and adolescents is low. We limited our paper to certain trials that had been performed a few times and therefore a general idea could be concluded.

The first results were very heterogeneous even within the respective categories. Reasons for these heterogenic findings may be due to methodological design, especially the use of different olfactory testing procedures, and phenotypical heterogeneity of the samples. As the SST and UPSIT tests were the best-validated and most commonly-used psychophysical tests, only studies with SST and UPSIT were ultimately included. Studies with electrophysiologic and imaging techniques were excluded.

Table 1 shows an overview of study results. The alterations in the olfactory system were termed as "impaired" or "improved". The second bar contains the tests, SST or UPSIT, and the third bar contains the domains. Normally, SST tests include an olfactory threshold, olfactory identification, and discrimination tasks, whereas UPSIT test includes only olfactory identification task. However, some studies included olfactory threshold tests in addition to UPSIT.

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Table 1: Olfactory assessment and neuropsychiatric disorders according to smell test techniques

Disorder	Test	Domain	Results	Age Group	References
Autism SD	SST	OT OI OP* *(pleasantness)	No significance No significance No significance	Childhood	Dudova et al.2013
	UPSIT	OI	Significantly impaired	Childhood	May et al.2011
	SST	OT OI	Significantly impaired No significance	Childhood	Dudova et al.2011
	SST	OI	Significantly impaired	Childhood	Bennetto et al.2007
	UPSIT	OI	No significance	Childhood	Brewer et al.2008
Epilepsy	SST	OT OI	Significantly impaired Significantly impaired	Adulthood	Hummel et al.2013
	UPSIT	OT OI	No significance Significantly impaired* (*only right TLE, but not left TLE)	Adulthood	Kohler et al.2001
	SST	OT OD OI	No significance No significance* Significantly impaired** *(Significance after lobectomy) **(Significance both before and after lobectomy)	Adulthood	Haehner et al.2012
ADHD	SST	OT OD OI	Significantly improved No significance No significance	Childhood	Romanos et al.2008
	UPSIT	OI	Significantly impaired	Childhood	Karsz et al.2008
	SST	OT OI OD	No significance No significance Significantly impaired* *(improved by cessation of medication)	Childhood	Schecklmann et al.2011a
	SST	OT OD OI	No significance No significance No significance	Adulthood	Schecklmann et al.2011b

Disorder	Test	Domain	Results	Age Group	References
OCD	UPSIT	OI	Significantly impaired	Adulthood	Goldberg et al.1991
	UPSIT	OI	Significantly impaired	Adulthood	Barnett et al.1999
	SST	OT OD OI	Significantly impaired Significantly impaired Significantly impaired	Adulthood	Segalas et al.2011
	SST	OT OD OI	Significantly impaired Significantly impaired Significantly impaired	Adulthood	Segalas et al.2014
Eating Disorder *Anorexia Nervosa & Bulimia Nervosa*	UPSIT PEA	OI OT	No significance* No significance* (*Significance only in very-low-weight anorexics)	Adolescent/ Adulthood	Fedoroff et al. 1995
Anorexia Nervosa	SST	OT OD OI Overall	No significance No significance Significantly impaired No significance	Adulthood	Rapps et al. 2010
Anorexia Nervosa	UPSIT	OI	No significance	Adolescent/ Adulthood	Kopala et al.1995
Anorexia Nervosa	SST	OT OD OI	Significantly impaired Significantly impaired No significance	Adolescent	Roessner et al. 2005
Anorexia Nervosa & Bulimia Nervosa	SST	OT OD OI Overall	Significantly impaired* Significantly impaired No significance Significantly impaired *(only in BN)	Adolescent/ Adulthood	Dazzi et al.2013
Anorexia Nervosa & Bulimia Nervosa	SST	OT OD OI Overall	No significance Significantly impaired* No significance Significantly impaired* (*only in AN)	Adulthood	Aschenbrenner et al. 2009
Anorexia Nervosa	SST	OT OD OI	No significance No significance No significance* (*significantly improved in “pure anorexia nervosa group)	Adolescent	Schecklmann et al.2012
Anorexia Nervosa	SST	OT OD OI Overall	No significance* Significantly impaired Significantly impaired Significantly impaired *(significance only in hunger state)	Adulthood	Schreder et al.2008

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Disorder	Test	Domain	Results	Age Group	References
Bipolar Disorder	UPSIT	OI	Significantly impaired	Adulthood	Lahera et al.2013
	UPSIT	OI	Significantly impaired	Adulthood	Cumming et al.2011
	UPSIT	OI	No significance	Adulthood	Hardy et al.2012
	SST	OT OI OP* *(pleasantness)	No significance No significance No significance	Adulthood	Swiecicki et al.2009
	SST	OT OD OI	No significance* No significance No significance *(event related impairment)	Adulthood	Krüger et al.2006
Schizophrenia	UPSIT	OI	Significantly impaired* *in male subjects	Adulthood	Kopala et al.1992
	UPSIT	OI	Significantly impaired	Adulthood	Houlihan et al.1994
	UPSIT	OI	Significant impairment* *in ultra-high-risk group who later developed schizophrenia spectrum disorder	Adulthood	Brewer et al.2003
	SST	OI OD OT	Significantly impaired Significantly impaired Significantly impaired	Adulthood	Clepce et al.2013
	UPSIT	OI	Significantly impaired* *in family members	Adulthood	Kopala et al.2001
	SST	OD OI	Significantly impaired* *in patients and youth at clinical risk Significantly impaired** *in paitents, at-risk youth and relatives	Adulthood	Kamath et al.2014
	UPSIT	OI	Significantly impaired* *Significantly worse scores in deficit syndrome patients than non-deficit patients	Adulthood	Malaspina et al.2002
	UPSIT	OI	Significantly impaired* *in early onset psychosis patients	Adolescent	Corcoran et al.2005
	UPSIT	OI	Significantly impaired* *Significantly lower baseline in patients with non-remission of negative and cognitive symptoms compared to patients with remission	Adulthood	Good et al.2006
	UPSIT	OI	Significantly impaired* *in pleasant odors	Adulthood	Crespo-Facorro et al.2001

2.3. Olfactory dysfunction in specific neuropsychiatric disorders

We presented the findings and interpreted them within subheadings respectively. In every category, some specific information about each disorder was given and then trials were discussed.

2.3.1. Autism Spectrum Disorders and Olfactory Dysfunction

Autism spectrum disorders (ASD) are neurodevelopmental conditions characterized by deficits in socialization, verbal and nonverbal communication, stereotyped patterns of behavior, and a range of interests (DSM-5).

The response to sensory stimuli or sensory perception in children with autism is often impaired. These sensory problems in ASD were reported by studies using sensory questionnaires including Short Sensory Profile (Kientz and Dunn, 1997; Lane et al., 2010; Schoen et al., 2009; Tomchek and Dunn, 2007), and interview methods including Diagnostic Interview for Social and Communication Disorders (DISCO) (Leekam et al., 2007). The mutual results of these types of studies showed significant sensory perceptional differences (especially sensory hypersensitivity) and clinical symptoms in children with autism. The main interest field of this paper, smell sensitivity, was also impaired in children with autism (Schoen et al. 2009; Lane et al. 2010) and the olfactory symptoms were more outstanding in ASD (Leekam et al., 2007).

Bennetto et al., (2007) investigated odor identification using SST in children with autism and showed significantly worse olfactory identification in ASD. Brewer et al., (2008) researched odor identification using UPSIT in children with high functioning autism (HFA) and showed no significant difference. However, smell identification ability was negatively associated with age in HFA. Dudova et al., (2011) reported significantly impaired odor detection thresholds using SST in children with Asperger's syndrome and high functioning autism but failed to show differences in odor identification. In that study, autistic participants were significantly better in identifying the odor of an orange and significantly worse at identifying the odor of cloves. The same team, Dudova et al., (2013) investigated olfactory dysfunction using SST among high-functioning patients (children) with ASD and showed no significant correlations between autism severity (as expressed by total CARS score) and odor-detection thresholds, odor identification or odor pleasantness. They argued that most of their patients had Asperger's syndrome (AS) (27 of 35 patients), which was atypical, and it did not represent the most common diagnosis in the ASD group. May et al., (2011) investigated the olfactory identification in a longitudinal study using UPSIT between children with high functioning autism (HFA) and Asperger's syndrome. There was a slight difference in olfactory identification between HFA and AS. The authors considered that the orbitofrontal cortex (OFC) was involved in the behavioral deficits of autism and AS. The psychophysical olfactory tests like SST and UPSIT are believed to be alternative ways to assess OFC function and development. Olfactory detection is mediated by lower-order neural pathways, whereas olfactory identification (OI), which requires recognition, is based on the OFC (Martzke et al., 1997; Qureshy et al., 2000). There are also OI deficits when the OFC is damaged in patients with cerebrovascular accidents (Savage et al., 2002). There are left-hemisphere deficits of orbitofrontal fascicules in HFA versus right-hemisphere deficits in AS (McAlonan et al., 2009); these differences might indicate the distinct neurologic development and different orbitofrontal functioning in AS and HFA.

2.3.2. Epilepsy and Olfactory Dysfunction

Epilepsy is one of the most common chronic neurologic disorders, which is characterized by recurrent and unpredictable seizure (Fisher et al., 2005). The International League against Epilepsy has classified seizures into two major types; generalized seizures and partial (focal) seizures. Temporal lobe epilepsy (TLE) is the most common type of partial epilepsy (Engel, 1996).

Sensation and perception are clearly involved in epilepsy and there is a perceivable correlation between sensation and epilepsy syndrome (Grant, 2005). For example, olfaction is commonly affected in temporal lobe epilepsy, whereas the processing of visual information is disturbed in occipital lobe epilepsy. Although many studies have shown impaired perceptual ability in epilepsy, heightened sensitivity has also been reported (Carroll et al., 1993; Grant, 2005; West and Doty, 1995).

Kohler et al., (2001) evaluated odor threshold (using the phenyl ethyl alcohol (PEA) test) and odor identification using UPSIT in patients (adults) with right- and left temporal lobe epilepsy and found significant impairment in odor identification in patients with right TLE but not in left TLE. The detection threshold sensitivity was normal in all groups. Haehner et al., (2012) researched odor threshold, odor identification, and odor discrimination using SST in patients (adults) with and without temporal lobe resection. Overall, there was no difference between groups in terms of odor threshold, but after temporal lobe resection, patients presented with significantly impaired bilateral discrimination and identification abilities compared with the healthy controls. The odor identification test results of patients with epileptic focus were lower than the results of the healthy controls. The authors concluded that olfactory function was only partially impaired preoperatively and would deteriorate further after partial resection of the epileptic focus. Hummel et al., (2013) reported significantly impaired olfactory function using SST in patients with TLE compared with healthy controls, both at threshold level and odor identification. They also showed smaller olfactory bulb volume by neuroimaging methods.

The reason why temporal lobe epilepsy was chosen for olfactory dysfunction study can be explained by close anatomic associations between the olfactory and limbic systems (Grant, 2005). Olfactory processing is performed in two ways. Primary processing occurs in the priform and entorhinal cortex, whereas secondary processing occurs in the orbitofrontal, mesial temporal, thalamic, and hypothalamic regions (Kohler et al., 2001; West and

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Doty, 1995). As temporal lobe epilepsy is a dysfunction of the temporo-limbic neural circuit (Kohler et al., 2001), olfaction is commonly affected and is a necessary topic of study. In such studies, the main olfactory tasks were identified as olfactory threshold, identification, and discrimination. Overall, studies showed that the odor detection threshold is not totally impaired in patients with epilepsy. The preservation of primary olfactory processing in epilepsy might mean that the odor threshold is more closely related with peripheral function (Hedner et al., 2010; Lötsch et al., 2008). However, the impairment of odor identification and discrimination in epilepsy could be explained by the involvement of secondary olfactory processing because odor identification and discrimination exhibit a significant relationship with higher cognitive proficiency (Hedner et al., 2010). The disruption of association of orbitofrontal cortex may be involved in odor discrimination as a higher cortical function in epilepsy. Through some studies, the expression of olfactory dysfunction in the right rather than the left TLE (Kohler et al., 2001) might be based upon olfactory processing asymmetry in the brain.

2.3.3. Attention Deficit Hyperactivity Disorders and Olfactory Function

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood-onset behavioral disorder characterized by clinical core symptoms such as inattention, impulsiveness, and hyperactivity (Tannock, 1998). The subtypes of ADHD can be classified as predominantly inattentive, predominantly hyperactive – impulsive, and combined group (DSM-5).

In the pathophysiology of ADHD, an inhibitory dopaminergic effect at striatal/prefrontal level is supported by neuroimaging, genetic, and stimulant medication studies (Levy and Swanson, 2001). Structural and functional changes in the prefrontal and striatal regions have also been implicated (Schneider et al., 2006). The orbitofrontal cortex, through its connections with other zones of the prefrontal cortex (PFC), plays a crucial role in controlling impulsivity (Davidson et al., 2000) and damage to this area has been associated with the symptoms of impulsive and inappropriate behavior (Berlin et al., 2004).

Olfaction is mediated by the olfactory nerve, which courses through the prefrontal cortex to the entorhinal cortex (Murphy et al., 2001). Damage to the prefrontal cortex can result in a decrease in olfactory sensitivity or identification (Varney and Menefee, 1993). The lesser activity of PFC in ADHD can imply the olfactory dysfunction in ADHD (Murphy et al., 2001). Romanos et al., (2008) interestingly revealed improved odor sensitivity (lower threshold) using SST in children with ADHD. However, patients given medication normalized their olfaction. These correlations may imply the close interaction between dopaminergic striatal system and olfaction. Karsz et al., (2008) reported significantly poorer olfactory identification using UPSIT in patients with ADHD. They emphasized that the decreased ability was consistent with prefrontal impairment in ADHD. Schecklmann et al., (2011) demonstrated using the SST test the normalization (increase) of olfactory discrimination after cessation of methylphenidate (MPH) in children. However, they found no medication effect on sensitivity in contrast to Romanos et al., (2008). The authors concluded that increased sensitivity in non-medicated patients and its normalization with MPH treatment as well as increased discrimination induced by cessation of MPH treatment in patients with chronic medication may be related to modulation of dopaminergic neurotransmission and to alterations in striatal dopaminergic function. Both the change in olfactory sensitivity (threshold) as a primary olfactory processing (peripheral function) and in olfactory discrimination as a secondary olfactory processing (higher cortical function) in patients with ADHD might indicate that there could be an important alteration / modulation extending from the olfactory bulb to orbitofrontal cortex in term of dopaminergic tone.

2.3.4. Obsessive-Compulsive Disorder (OCD) and Olfactory Dysfunction

Obsessive-compulsive disorder (OCD) is a psychiatric condition described as the presence of recurrent and persistent thoughts, urges or images (i.e. obsessions), and repetitive behaviors or mental acts in response to these (i.e. compulsions) (DSM-5). Various functional and structural changes have been observed in the gray and white matter areas, particularly in the cortical-striatal-thalamic-cortical (CSTC) circuits and orbitofrontal cortex (OFC) (Menzies et al., 2008; Peng et al., 2012; Piras et al., 2013; Rotge et al., 2010). Several neurocognitive domains have been investigated together with olfactory function in OCD because they are in close proximity (Shin et al., 2014).

The first study that assessed olfaction was by Goldberg et al., (1991) who used UPSIT for olfactory acuity. Although the number of subjects was limited, they found differences between the obsessional group (adults) and the otherwise healthy group.

Barnett et al., (1999) investigated olfactory identification in patients with OCD (adults) using UPSIT and they found that olfactory identification ability was significantly impaired in the patient group compared with the healthy controls. They added that most of the patients with OCD had moderate to mild degree microsmia but none of them were anosmic. However, there was no association between OCD severity and degree of dysfunction in olfactory abilities.

Segalàs et al., (2011) evaluated odor identification, threshold and discrimination with Sniffin Sticks Test (SST), along with nonverbal memory, anxiety levels, depression levels, and Axis I diagnosis. There were statistically significant olfactory impairments in the patient group (adults) for all three olfactory domains. However, after excluding patients with Axis I comorbidities, no significant differences were observed between the OCD patients and healthy controls. Scores for olfactory identification were negatively correlated with depression and anxiety levels in patients with OCD and it did not change after discarding the patients who had Axis I comorbid disorders. A significant

negative correlation was also present between olfactory identification dysfunction and disease intensity in patients without comorbid psychiatric diagnoses. There were no significant association between nonverbal memory and olfactory dysfunction. The authors concluded arguing that symptoms of obsession, compulsion, and depression might alter olfaction, particularly olfactory identification in patients.

The same research group examined the association between regional gray matter volume, as assessed by analysis of magnetic resonance images (MRI), and olfactory function using SST in adult patients with OCD (Segalàs et al., 2014). They found significantly impaired olfactory function (threshold, identification and discrimination) and association with volumetric changes in brain areas (left anterior cingulate cortex and left medial orbital gyrus) in patients with OCD. Olfactory dysfunction in patients with OCD can indicate that frontal and temporal lobe circuits are related to both disease activity and olfaction owing to their close strategic proximity.

2.3.5. Eating Disorder and Olfactory Dysfunction

Eating disorders are chronic conditions defined as disturbances of eating or eating-related behavior, which result in impairment of physical health and psychosocial function (Treasure et al., 2010). The complexity associated with these disorders derives from its high morbidity (up to 20%) and comorbidity rates (Hoek, 2006; Treasure et al., 2010). Pica, rumination disorder, avoidant/restrictive food intake disorder, anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder are categorized as eating disorders in the new edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

Disturbances of sensation and perception towards internal and external stimuli are believed to play an important role in the development and progress of eating disorders (Connan et al., 2003). Distorted perception of body size, physical properties of food (Berry et al., 1995), hunger and satiety (Halmi and Sunday, 1991; Rolls et al., 1992) as well as diminished hedonic capacity to respond to olfactory, gustatory and visual food related stimuli were previously reported.

A variety of psychophysical tests are used to show olfactory disturbances in people with eating disorders. However, the results are controversial. The very first studies that investigated olfactory dysfunction in eating disorders, Koppala et al., (1995) used UPSIT and found no differences in olfactory identification ability between patients with anorexia nervosa and the healthy control. On the other hand, Fedoroff et al., (1995) recruited patients who had food-restricting type anorexia, anorexia with bulimic features, and bulimia nervosa and found olfactory detection and identification impairment only in the very-low-weight anorexic group using UPSIT and the phenyl ethyl alcohol (PEA) test.

In more recent years, Roessner et al., (2005) used the SST test to examine olfactory dysfunction in patients with anorexia and stated that significantly higher scores were detected in odor threshold and impairment was found in odor discrimination, but not in odor identification. They argued that these findings indicated that patients with anorexia showed a reduction of peripheral olfactory perceptual ability.

Supporting findings were obtained from a study conducted by Dazzi et al., (2013) who found poorer outcomes in olfactory discrimination in patients with AN and olfactory threshold and discrimination in patients with BN. When comparing overall function (TDI scores in SST), patients with both AN and BN fell on the hyposmic range, which was significantly higher than the control group.

In a longitudinal study, Aschenbrenner et al., (2008) compared AN patients with BN patients and a healthy control group. They reported that patients with AN had a small but significant decrease in odor discrimination and overall olfactory function compared with healthy controls and patients with BN. In the same study, an improvement in olfactory function was observed after effective treatment in patients with AN.

Conversely, Schecklmann et al., (2012) argued that the conflicting results of previous studies might be derived from selection criteria and designed a study with adolescent girls who had never smoked and a well-matched healthy control group. They defined a subgroup of patients who had received no medication and had no psychiatric comorbidity, this subgroup was called "pure anorexia nervosa". Using SST, there were no difference between patients and healthy controls in any olfactory domain. Higher olfactory identification was observed in the "pure anorexia nervosa group", which could be attributed to increased attentional processing towards food-related stimuli.

Schreder et al., (2008) investigated olfactory dysfunction of patients with anorexia nervosa in hunger and satiety conditions using SST. They performed threshold tests in a hungry and satiated state, but odor discrimination and odor identification only when satiated. The olfactory discrimination and identification abilities of patients with AN were significantly lower. The olfactory threshold sensitivity for isoamyl acetate (food-related odor) was only significantly lower in hunger. Hence, hunger and satiety state may be considered to be other determinant factors of sensation and perception disturbances.

2.3.6. Bipolar Disorder and Olfactory Dysfunction

Bipolar disorder is a psychiatric disorder that causes shifts in a person's mood, energy, and ability to function (DSM-5). It is characterized with episodes of mania and depression, and accompanied by impaired executive function and emotional dysregulation (Hardy et al., 2012).

The etiology of bipolar disorder is unknown, but functional and anatomic differences have been found in imaging studies in patients with bipolar disorder, especially in the amygdala, anterior cingulate, striatum, ventromedial prefrontal cortex, and orbitofrontal cortex (Agarwal et al., 2010; Keener and Phillips, 2007). In the last two studies, it was demonstrated that euthymic patients with bipolar disorder have a decreased regional cerebral blood flow in the orbitofrontal cortex at rest and a stronger decrease after provocation with a sad mood–

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induction paradigm compared with healthy volunteers using positron emission tomography (PET). These regions have also been shown to play important roles in olfactory processing, particularly the amygdala, hippocampus, and orbitofrontal cortex receive projections from the piriform cortex and are key secondary olfactory areas (Kivity et al., 2009). It has been postulated that olfactory dysfunction might be accompanied by bipolar disorder on the basis of the anatomic and functional relationships (Hardy et al., 2012).

In two recent studies, patients (adults) with bipolar disorder showed significant impairment in olfactory identification compared with healthy controls (Cumming et al., 2011). Krüger et al., (2006) showed a close relation between olfactory function and mood regulation. In that study, a heightened olfactory acuity in patients with bipolar disorder whose mood episodes were triggered by emotional events was demonstrated. It has been reported that depressive symptoms were related to increased sensitivity (the ability to detect odors at a lower concentration) and mania symptoms were related to decreased sensitivity for odor detection (Hardy et al., 2012). On the other hand, comparatively intact olfactory function in bipolar disorders have also been shown (Swiecicki et al., 2009).

2.3.7. Schizophrenia and Olfactory Dysfunction

Schizophrenia is a neuropsychiatric disorder characterized by disruptions in thought processes, perceptions, and emotions. In the pathophysiology of schizophrenia, there are abnormalities in the temporolimbic and frontal lobe regions (Seidman et al., 1995). These areas, namely the temporolimbic and orbitofrontal cortex, have been shown to be responsible for olfactory information process in animal studies (Tanabe et al., 1975). The alteration in these areas might be associated with olfactory dysfunction because these regions serve for the affective and mnemonic functions, and these functions are most intimately related to olfaction among sensory processing (Turetsky et al., 2009).

The impairment of sensation in schizophrenia can be explained by olfactory dysfunction due to strategic anatomic proximity. The assessment of olfactory dysfunction among patients with schizophrenia has also been broadly done by various methods including psychophysical tests such as UPSIT (Houlihan et al., 1994; Kopala et al., 1993) and SST (Clepce et al., 2013; Kamath et al., 2013).

The decreased threshold sensitivity in schizophrenia has been shown by some studies (Rupp et al., 2005; Serby et al., 1990). Olfactory identification deficits in patients with schizophrenia have been reported by numerous studies to be independent of sex, neuroleptic use, and smoking status (Moberg et al., 1999). However, identification deficits significantly correlate with duration of illness (Moberg et al., 1997). In addition, olfactory memory is proven to be impaired (Wu et al., 1993) and this finding was supported by more recent studies (Moberg et al., 2014).

Many studies have also explored olfaction in association with positive and negative symptoms in schizophrenia. In these studies, there is a greater correlation of olfactory dysfunction with the degree of negative symptoms (Corcoran et al., 2005; Good et al., 2006; Malaspina et al., 2002). Patients with schizophrenia also have deficient response to emotional stimuli and decreased hedonic capacity to odorant stimuli, especially to pleasant ones but not unpleasant odors (Crespo-Facorro et al., 2001; Kamath et al., 2011; Moberg et al., 2003; Strauss et al., 2009).

Olfactory dysfunction has been investigated in patients with schizophrenia and also in high-risk individuals, healthy first-degree family members, and people with schizotypal personality features (Kopala et al., 2001; Brewer et al., 2003; Kamath et al., 2014;). Although the findings were controversial for individuals with schizotypal personality features (Compton and Chien, 2008), there were positive associations between olfactory dysfunction and the high-risk population as well as healthy first-degree relatives of schizophrenia patients when compared with the control groups. These findings suggest that impaired olfactory abilities may be considered as a susceptibility marker or an endophenotypic feature for schizophrenia.

3. Discussion and Conclusion

Although olfactory loss often goes unnoticed, data suggest that olfactory dysfunction (loss) might guide us in the way of determining the risk of some certain neurodegenerative and neuropsychiatric diseases. Olfactory dysfunction occurs before any movement or cognitive disorder in Parkinson's disease, Alzheimer's disease (AD) (Hawkes, 2006), and hyposmia; anosmia in particular significantly increased the risk of subsequent cognitive failure in AD (Graves et al., 1999).

Due to strategic anatomic proximity, it has been shown that olfactory loss is coexistent in ADHD, autism, and schizophrenia. The dopaminergic pathway within temporolimbic and frontal lobe regions revealed this association, especially in disorders that involve this pathway (e.g., ADHD, autism, and schizophrenia) showed olfactory dysfunction. Improved olfactory function in ADHD and normalization by dopaminergic medication was also shown. Overall olfactory deficit (threshold, identification and discrimination) is possible in OCD. Olfactory identification may be especially impaired in ASD and epilepsy. Impairment in olfactory discrimination has been reported in anorexia nervosa, and deficits in olfactory identification in schizophrenia might be especially described.

High-risk individuals for neuropsychiatric disorders are targets for determining the biomarker feature of olfaction and several recent studies detected positive associations between olfactory dysfunction and this risk group (Brewer et al., 2003; Kamath et al., 2014). Based upon these trials, olfactory dysfunction might precede the pending diseases as in neurodegenerative disorders. However, risk- group studies have thus far been limited to schizophrenia.

Methodologic design, sample heterogeneity, control groups, inconsistent findings, low number of studies in childhood and adolescence are primary concerns for

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drawing certain conclusions. The putative biomarker features of olfactory dysfunction in neuropsychiatric disorders remain unclear, especially because of the limited number of risk group studies.

More studies with better methodologic design are required for absolute conclusions. Longitudinal studies that start from childhood might provide more important information about the putative prognostic features of olfactory dysfunction. The applicability problem of smell tests in childhood might be overcome with electrophysiologic tests. Along with developmental screening tests, studies in ADHD and ASD and in their risk groups could be valuable for determining the diagnostic role of olfaction in neuropsychiatry. Imaging and genetic techniques may add supplementary information to these purposes.

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