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Review article

Olfactory dysfunction in frontotemporal dementia and psychiatric disorders: A systematic review

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ABSTRACT

Frontotemporal dementia (FTD) is a progressive neurodegenerative disease. Diagnosis of FTD, especially the behavioural variant, is challenging because of symptomatic overlap with psychiatric disorders (depression, schizophrenia, bipolar disorder). Olfactory dysfunction is common in both FTD and psychiatric disorders, and often appears years before symptom onset. This systematic review analysed 74 studies on olfactory function in FTD, depression, schizophrenia and bipolar disorder to identify differences in olfactory dysfunction profiles, focusing on the most common smell measures: odour identification and discrimination. Results revealed that FTD patients were severely impaired in odour identification but not discrimination; in contrast, patients diagnosed with schizophrenia showed impairments in both measures, while those diagnosed with depression showed no olfactory impairments. Findings in bipolar disorder were mixed. Therefore, testing odour identification and discrimination differentiates FTD from depression and schizophrenia, but not from bipolar disorder. Given the high prevalence of odour identification impairments in FTD, and that smell dysfunction predicts neurodegeneration in other diseases, olfactory testing seems a promising avenue towards improving diagnosis between FTD and psychiatric disorders.

1. Introduction

Our sense of smell is central to many aspects of life and health. It is important for alerting us to potential danger (e.g., smoke, chemicals, spoilt food) or orienting us towards pleasant stimuli (e.g., food, flowers) as well as for social and intimate relationships (Croy et al., 2013; Keller and Malaspina, 2013; Lundstrom et al., 2013). Losing the sense of smell, therefore, has serious implications for quality of life, physical safety and relationships, and is often associated with depression and social isolation (Miwa et al., 2001; Sivam et al., 2016).

Smell dysfunction is common in many neurodegenerative disorders, like Alzheimer's disease (Duff et al., 2002; Moberg et al., 1997a, Sun et al., 2012) (AD), frontotemporal dementia (FTD) (Pardini et al., 2009; Silva et al., 2019) and Parkinson's disease (Haehner et al., 2019; Postuma et al., 2015). Smell disturbance is also reported in psychiatric disorders, for instance in schizophrenia (Cumming et al., 2011; Kopala et al., 2001, Kopala et al., 1998a, Malaspina et al., 1994; Seidman et al., 1992; Striebel et al., 1999), depression (Taalman et al., 2017) and bipolar disorders (Parker et al., 2017). Importantly, changes in olfactory function often occur years before the clinical phase of these disorders and are therefore considered potential clinical markers and markers of disease progression (Haehner et al., 2011; Marin et al., 2018).

FTD and psychiatric disorders share a number of clinical features, which include neuropsychiatric symptoms such as psychosis or depression. As such, misdiagnoses across these conditions are not uncommon (Devenney et al., 2018; Gossink et al., 2016; Johnen and Bertoux, 2019; Lanata and Miller, 2016; Vijverberg et al., 2016). This symptomatic overlap between FTD and psychiatric disorders represents a challenge for timely and correct diagnosis (Ducharme et al., 2020).

The purpose of this systematic review is to evaluate profiles of

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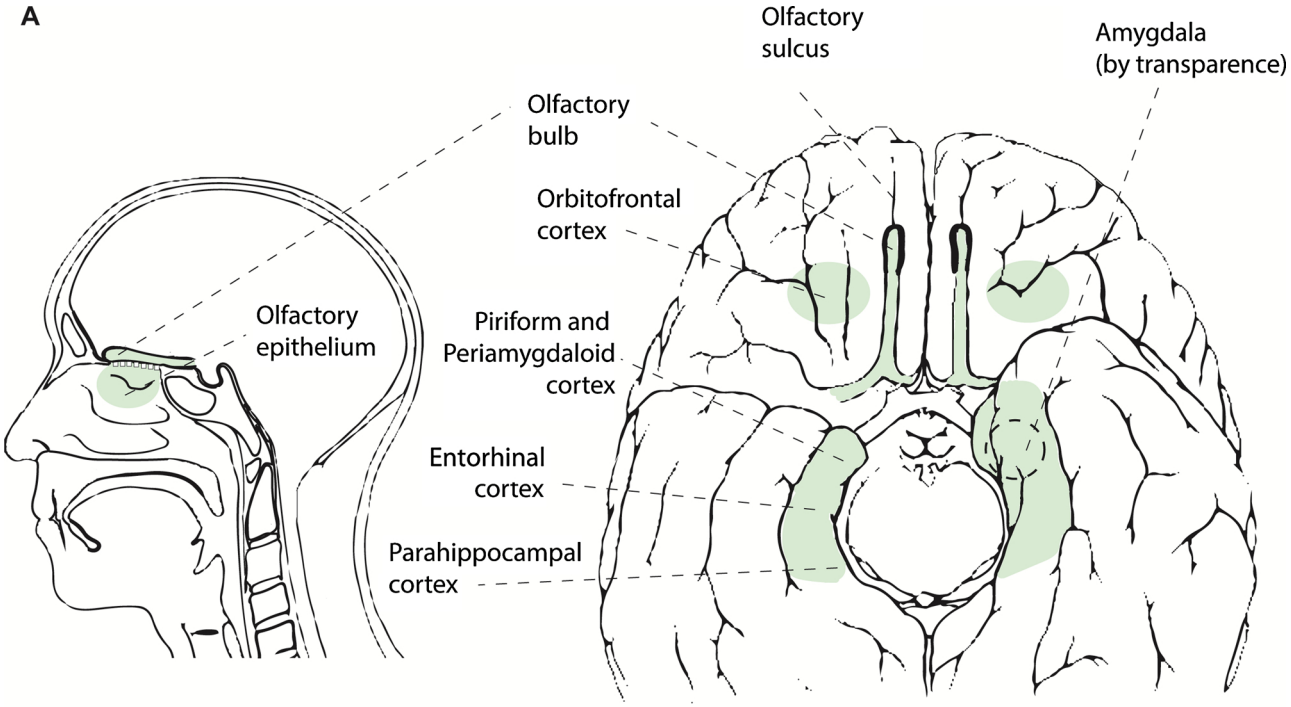

B

	FTD	Schizophrenia	Depression	Bipolar disorder
Olfactory epithelium		✕		✕
Olfactory sulcus		✕	✕	✕
Olfactory bulb	✕	✕	✕	
Piriform cortex	✓	✕		
Amygdala	✕	✕	✕	✕
Hippocampus / Parahippocampal gyrus	✕	✕	✕	Mixed
Entorhinal cortex	✕ SD / ✓ bvFTD	✕	✕	✕
Thalamus	✕	Mixed	✓	Mixed
Anterior cingulate cortex	✕	Mixed	✕	Mixed
Orbitofrontal cortex / Medial frontal cortex	✕	✕	✕	✕
Insula	✕	✕	✕	✕
Prefrontal cortex	✕	✕	✕	✕
Temporal neocortex	✕	✕	Mixed	Mixed

Fig. 1. Olfactory system and structural/functional brain changes in frontotemporal dementia, schizophrenia, depression and bipolar disorder. **(A)** Olfactory system. Green areas depict the olfactory system. The olfactory pathway begins at the level of the olfactory epithelium. This epithelium contains neurons with axons projecting to the olfactory bulb, which houses the first relay of olfactory information that projects to the primary olfactory cortex including the piriform and periamygdaloid cortex, the entorhinal cortex and parahippocampal cortex. The secondary olfactory cortex includes the orbitofrontal cortex, which processes multimodal sensory cues. **(B)** Overlapping structural or functional brain changes involving the olfactory system in frontotemporal dementia (FTD), schizophrenia, depression and bipolar disorder. **Key:** orange = abnormalities; green = preserved; grey = mixed findings; white = not investigated.

olfactory function in FTD and the psychiatric disorders that FTD patients are most commonly misdiagnosed with, namely, depressive disorders, schizophrenia and bipolar disorder. We discuss these findings in terms of divergent symptomatology, underlying neural processes, and the validity of current smell tests in this context and propose ways of improving olfactory evaluation for neurodegenerative and psychiatric disorders. Considering that smell deficits may precede other symptoms in these disorders, accurate smell evaluation could potentially improve early and correct diagnosis of FTD, which could greatly improve the management and quality of life for many individuals.

1.1. Frontotemporal dementia

Frontotemporal dementia (FTD) is a progressive neurodegenerative disorder affecting primarily the frontal and temporal lobes of the brain. Depending on the location of atrophy, the clinical presentation involves predominantly behavioural changes (behavioural-variant FTD; bvFTD) or takes the form of either fluent (semantic dementia; SD) or nonfluent (progressive nonfluent aphasia; PNFA) language deficits (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). bvFTD is characterised by changes in behaviour and personality, with features including disinhibition, apathy and loss of social conduct (Burrell et al., 2016; Devenney et al., 2015; Garcin et al., 2009; Hodges, 2007; Kipps et al., 2007; Piguet and Kumfor, 2020; Piguet et al., 2017; Rascovsky et al., 2011; Seelaar et al., 2011). SD is characterised by a progressive loss of semantic knowledge which manifests as difficulty naming and recognising objects and comprehending single words (Gorno-Tempini et al., 2011; Hodges, 2007; Kipps et al., 2007; Mesulam, 2013). Finally, PNFA is characterised by disturbance of speech output and/or agrammatism (Gorno-Tempini et al., 2011; Hodges, 2007; Kipps et al., 2007; Mesulam, 2013).

Notably, FTD is unique in that its underlying neuropathology is heterogeneous and unpredictable (Piguet et al., 2017). The FTD variants (and dementia syndromes generally) overlap in pathology and clinical presentation, forming 'mixed' types, particularly with disease progression (Kamath et al., 2018a, Kipps et al., 2007). In this review,

however, the various FTD subtypes have been combined due to the low number of studies to date.

Studies of smell dysfunction in FTD, although limited, have utilised a range of different smell tests and have shown olfactory deficits in FTD patients. It is unclear what the basis for these deficits are; whether they reflect degeneration of brain areas important for olfactory processing or more general impairments in cognitive or executive function.

Olfactory impairment in AD has been extensively studied as a model for smell loss in neurodegenerative diseases generally. Smell impairment is an early sign of AD (Winchester and Martyn, 2020). The possibility that the disease originates in the entorhinal cortex could explain the correlation between smell loss and early AD (Khan et al., 2014). Smell impairment in AD is mainly assessed with identification tests, but many others have also demonstrated a clear impairment in odour discrimination (Jung et al., 2019; Luzzi et al., 2007; Peters et al., 2003; Sohrabi et al., 2012) and odour threshold abnormalities have also been reported (Doty, Hawkes et al., 2015).

1.2. Overlapping symptomatology and brain network abnormalities between FTD and psychiatric disorders

FTD, especially bvFTD, is commonly misdiagnosed with psychiatric disorders due to many overlapping symptoms (Devenney et al., 2018; Gossink et al., 2016; Johnen and Bertoux, 2019; Lanata and Miller, 2016; Vijverberg et al., 2016; Woolley et al., 2011). In particular, it may be challenging to discriminate between the early stages of bvFTD and late-onset depression, bipolar disorder or schizophrenia (Gossink et al., 2019; Pose et al., 2013; Velakoulis et al., 2009; Vijverberg et al., 2017; Woolley et al., 2011). Taken together, over a quarter of patients with a neurodegenerative brain condition – and up to 50 % of bvFTD patients – are initially misdiagnosed with a psychiatric disorder (Woolley et al., 2011). Symptoms of apathy or lack of interest/initiative are often mistakenly diagnosed as a major depressive disorder. In contrast, disinhibition and stereotypical behaviour are often misdiagnosed as bipolar disorder. In addition, because of their psychiatric features, bvFTD patients are also often misdiagnosed as having schizophrenia. Similarly, a quarter of SD patients are also initially misdiagnosed with a psychiatric disorder, usually major depression, due to their emotional blunting and loss of empathy being mistaken for anhedonia and social withdrawal (Woolley et al., 2011).

This shared symptomatology is not entirely surprising. Indeed, the brain structures implicated in FTD and psychiatric disorders show considerable overlap. These include lateral and medial cortical regions (frontal and temporal cortices) as well as subcortical structures (striatum, thalamus, amygdala and hippocampus) (Bora et al., 2012; Chen et al., 2011; Ellison-Wright and Bullmore, 2010; Kempton et al., 2011; Koolschijn et al., 2009; Schroeter et al., 2008; Seelaar et al., 2011; Shenton et al., 2001; Strakowski et al., 2005).

Importantly, many of these regions also overlap with the olfactory system (Fig. 1A and B) (Atanasova et al., 2008; Frasnelli et al., 2010; Jones-Gotman et al., 1997; Negoias et al., 2019; Pardini et al., 2009). Given these close anatomical relationships, investigations of olfactory function across these disorders may improve differential diagnosis early in the disease process (Altshuler et al., 1990; Chen et al., 2018; Davatzikos et al., 2008; Dusi et al., 2015; Frasnelli et al., 2010; Frisoni et al., 1999; Hornberger et al., 2010; Kiparizoska and Ikuta, 2017; Rosen et al., 2002; Seeley et al., 2008; Zatorre et al., 1992).

1.3. Measures of Olfactory Function

Smell deficits are found in ~20 % of the general population (Bramerson et al., 2004; Mullol et al., 2012; Vennemann et al., 2008). The most common smell disturbances include anosmia (complete loss of olfactory ability) and hyposmia (decreased olfactory ability) (Doty et al., 1984a). Hyperosmia (heightened olfactory ability) is less common. Qualitative olfactory dysfunctions also occur, albeit less commonly, and include parosmia (distorted smell perception in the presence of an odour) and phantosmia (odour perception in the absence of an odour) (Landis et al., 2010; Sjolund et al., 2017).

Aspects of smell commonly tested in clinical populations include odour sensitivity/threshold, odour discrimination and odour identification (Cain et al., 1983; Doty et al., 1984b; Hummel et al., 1997; Taalman et al., 2017; Takagi, 1987). Odour threshold refers to the smallest concentration of an odour required to produce the percept of smell. Odour discrimination is the ability to distinguish between two or more different odours. Odour identification, the most commonly used test, is the ability to detect, identify and name a scent (Taalman et al., 2017). Characteristics and advantages/disadvantages of available olfactory tests are reported in Table 1.

It is still controversial whether all the facets of smell are similarly affected in olfactory disorders and whether they are supported by common or distinct neuroanatomical correlates. Some studies show that all three tests measure the same olfactory perceptual attribute (Doty et al., 1994), are similarly affected in patients e.g. epilepsy (Jones-Gotman et al., 1997; Rausch and Serafetinides, 1975; Zatorre et al., 1992) and similarly correlated with neuroanatomical structures such as the olfactory bulb (Chen et al., 2018; Mazal et al., 2016; Negoias et al., 2010). Other studies show preserved olfaction in one component but not in others (e.g. Parkinson's disease) (Hedner et al., 2010; Lotsch et al., 2008) and specific neuroanatomical correlates of particular components (e.g. medial orbitofrontal cortex, insula and superior temporal gyrus for odour identification) (Atanasova et al., 2008; Frasnelli et al., 2010; Kjelvik et al., 2012; Martzke et al., 1997).

In terms of differences between these tests, both odour identification and odour discrimination tests rely more on cognitive functions (specifically semantic memory) than odour threshold tests, given that they require knowledge of a particular scent (Hedner et al., 2010). Furthermore, odour discrimination is more dependent on executive functions such as working memory and attentional capacity than odour threshold tests, as a scent must be held in mind in order to subsequently discriminate it from another (Hedner et al., 2010). Whether threshold tests measure a different aspect of the olfactory system compared with identification and discrimination tests is still debated (Doty et al., 1994; Lotsch et al., 2016).

This review focuses on odour identification and discrimination, as they are the most widely tested aspects of smell in FTD, and they are more likely to reflect central processing than threshold tests (Hedner et al., 2010). It will concentrate on the tests commonly used clinically to measure olfactory function in FTD: University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al., 1984c), Sniffin' Sticks (Hummel et al., 1997), Brief Smell Identification Test (B-SIT) (Doty, 2001) and Odour Perception and Semantics Battery (SPSB).

2. Methods

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Moher et al., 2009) were followed in screening studies for inclusion in this systematic review. The PubMed search criteria for olfaction studies in FTD included a combination of olfaction keywords and FTD keywords which were searched in titles and abstracts ([Title/Abstract]). The olfaction keywords were 'olfactory OR olfaction OR smell'. The FTD keywords were 'frontotemporal dementia OR behavioural variant OR behavioral variant OR primary progressive aphasia OR progressive non-fluent aphasia OR progressive nonfluent aphasia OR semantic dementia OR frontotemporal lobar degeneration', which yielded 37 results as of 7th July 2020.

The same olfaction keywords were then used in conjunction with psychiatric disorder keywords which were 'schizophrenia OR schizophrenic OR psychotic OR psychosis OR schizoaffective OR depression OR depressive OR bipolar'. This search was limited to 'Humans[Mesh] AND English[lang]', which yielded 937 results as of 7th July 2020. The 'Humans[Mesh]' criterion was replaced with 'NOT Humans[Mesh] NOT

Table 1
Characteristics, advantages and disadvantages of currently available psychophysical olfactory tests.

COMPONENT	PSYCHOPHYSICAL TEST	CHARACTERISTICS
Identification	• Sniffin' Sticks • Smell Identification Test • Connecticut Chemosensory Clinical Research Center Test • T&T Olfactometer • Smell Diskettes Test • Cross Cultural Smell Identification Test • Pocket Smell Test • Brief Identification Test • San Diego Odour Identification Test • Scandinavian Odour Identification Test • Barcelona Smell Test (BAST-24) • Open Essence • European Test for Olfactory Capabilities • Odour Perception and Semantics Battery	• Task: Detecting an odour at suprathreshold concentration and *identifying* the corresponding smell among descriptors. • The sum of the correct answers gives an identification score. • The accuracy of the test to discriminate normosmic from hyposmic and anosmic subjects depends on the numbers of items. • Strong cultural/semantic bias – requires familiarity with the odours used in the tests. • Most widely used olfactory test. • Possibility to detect malingering when testing score is below chance.
Threshold	• Sniffin' Sticks • Connecticut Chemosensory Clinical Research Center Test • T&T Olfactometer • Smell Threshold Test • Olfactory Perception Threshold Test • Barcelona Smell Test (BAST-24) • Snap & Sniff Olfactory Test System • European Test for Olfactory Capabilities	• Task: The patient has to detect the *strongest odour* among other stimuli. • Different paradigms are used to determine the threshold (e.g. adaptive staircase threshold). • Score may be biased by inter-individual genetic variability in odorant receptor set (specific anosmia in subjects with intact sense of smell). • Non-semantic.
Discrimination	• Sniffin' Sticks • Odour Perception and Semantics Battery	• Task: The patient has to detect the *different* odour (qualitative) among other stimuli. • Cultural bias - familiarity facilitates odour discrimination. • Non-semantic.

Adapted from Hummel et al. (2016).

Animals[Mesh]' in order to find other studies not associated with the Mesh term of human but not listed as an animal study either, leading to a further 266 results.

All titles and abstracts were reviewed for eligibility, with no limit to the date of the publication. Studies violating any of the following eligibility criteria were excluded:

- Clinical population with frontotemporal dementia, schizophrenia, depressive disorder or bipolar disorder, including any variants
- Human study
- Inclusion of at least one participant > 40 years of age
- Inclusion of a minimum of 3 patients (no case studies)
- Inclusion of a direct comparison of smell function between the clinical population and the control group
- Olfaction as the dependent variable in the study design
- Inclusion of a psychophysical measure of smell (UPSIT, Sniffin' Sticks, B-SIT or SPSB)
- Written in English
- Full-text available
- Original study (no reviews or meta-analyses).

Paper titles were scrutinised and selected by SEC. Two other raters, FK and JH, judged the selection for inter-rater reliability. First, titles and abstracts of each paper were reviewed to eliminate studies clearly not meeting one or more criteria. Cohen's κ analysis revealed almost perfect inter-rater reliability (SEC and FK) based on 10 % of these studies ($\kappa = .901$, $p < .001$). Then, full-texts of the articles selected at that stage were reviewed for inclusion with almost perfect agreement as well (SEC and JH) based on 10 % of these studies ($\kappa = .865$, $p < .001$) (Landis and Koch, 1977).

164 eligible studies were then thoroughly assessed to ensure that all of the inclusion criteria were met, resulting in the selection of 74 studies. These included one study (Serby et al., 1990) not found via PubMed but identified from another review (Taalman et al., 2017). The results of the identification, screening, eligibility and inclusion of studies are shown in Fig. 2.

3. Results

3.1. Odour identification in FTD (Table 2)

In 6 out of the 7 studies reviewed, odour identification was impaired in all subtypes of FTD (Fig. 3) (Greenberg et al., 2011; Luzzi et al., 2007; McLaughlin and Westervelt, 2008; Omar et al., 2013; Piwnica-Worms et al., 2010; Rami et al., 2007). The remaining study, however, found no impairments in odour identification in bvFTD (Orasji et al., 2016).

When compared against normative data, FTD patients showed severe odour identification impairments. McLaughlin and Westervelt (2008) tested 28 patients with bvFTD and PNFA on the B-SIT and found that 57 % of FTD patients scored below the 16th percentile. Greenberg et al. (2011) tested smell identification in 5 SD patients using the UPSIT and all patients scored at chance level or in the severely impaired range. Omar et al. (2013) tested 25 FTD patients and found that 67 % of bvFTD, 50 % of SD and 20 % of PNFA patients scored below the 5th percentile on the UPSIT. Piwnica-Worms et al. (2010) tested odour identification in 3 SD patients on the UPSIT; 2 SD patients performed below the 5th percentile, while 1 patient and the healthy controls performed within normal limits. Further, Rami et al. (2007) tested 3 FTD patients, one diagnosed with bvFTD, one with SD and one with PNFA on the UPSIT and found that the two patients with bvFTD and SD scored below the 10th percentile for odour identification. Taken together, these findings indicate significant impairments on odour identification for all subtypes of FTD compared to similarly aged people without dementia.

3.2. Odour discrimination in FTD

Of the two studies that investigated odour discrimination in FTD, both reported normal odour discrimination (Luzzi et al., 2007; Rami et al., 2007).

3.3. Odour identification in schizophrenia (Table 3)

Overall, odour identification was impaired in all types of schizophrenia (46/54 studies reviewed). This finding is consistent with two

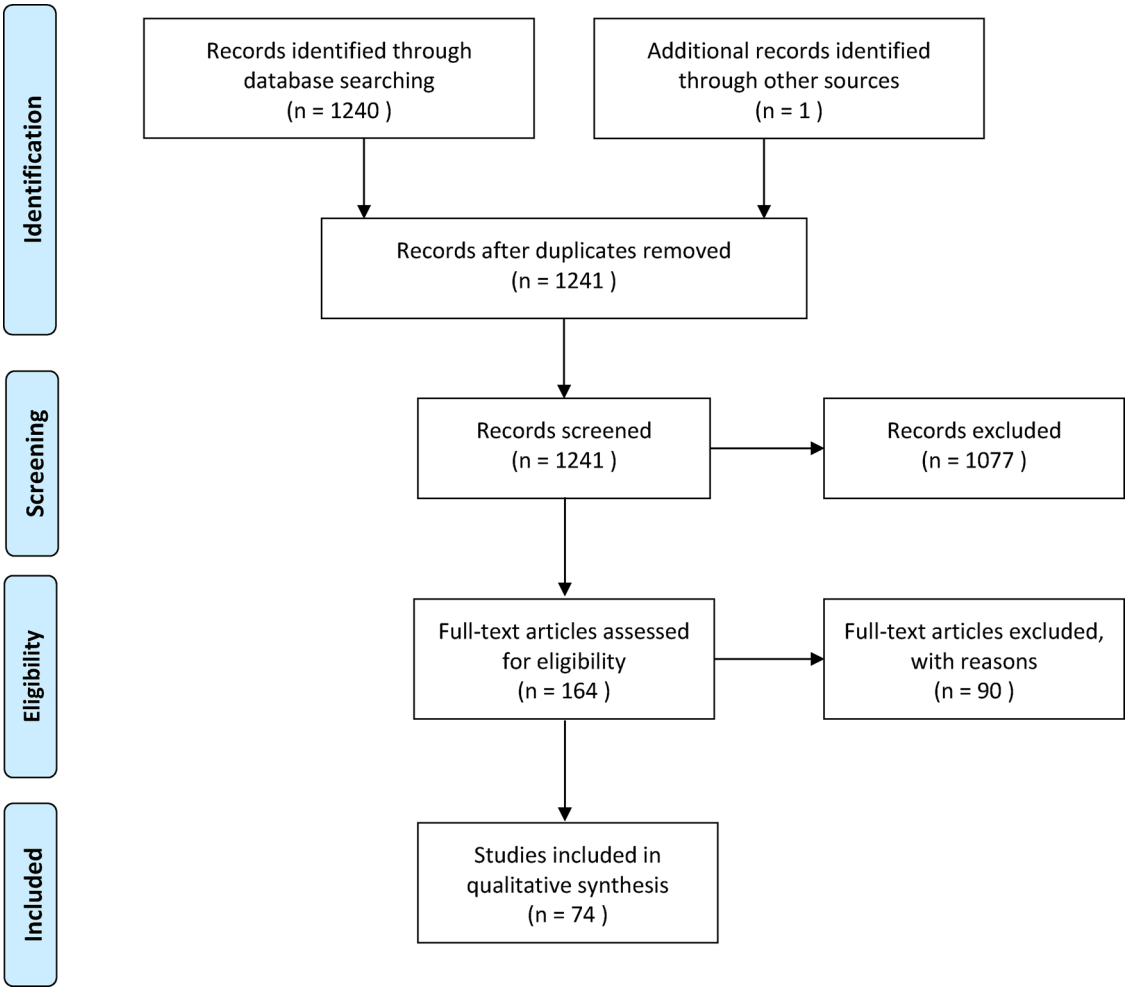

Fig. 2. PRISMA flow diagram including identification, screening, eligibility and inclusion of publications relevant to the systematic review.

meta-analyses on olfaction in schizophrenia, which reported performance in this population of at least 1 standard deviation below that of controls (Cohen et al., 2012; Moberg et al., 1999).

Eight studies, however, found no deficits in odour identification in patients with schizophrenia (Cieslak et al., 2015; Kohler et al., 2007; Malaspina et al., 2012a,b; , Martin et al., 2015; McLean et al., 2004; Minovi et al., 2015; Ugur et al., 2005). This finding may be due to shorter duration of illness, younger age, or milder negative symptomatology in their patient groups. For example, Ugur et al. (2005) found worse odour identification in older schizophrenia patients and those with longer duration of illness, despite patients' odour scores overall being not significantly different from controls. Also, Cieslak et al. (2015) and Malaspina et al., (2012a,b) found a significant correlation between impaired odour identification and severity of negative symptoms, despite, again, odour scores being similar between patients and controls.

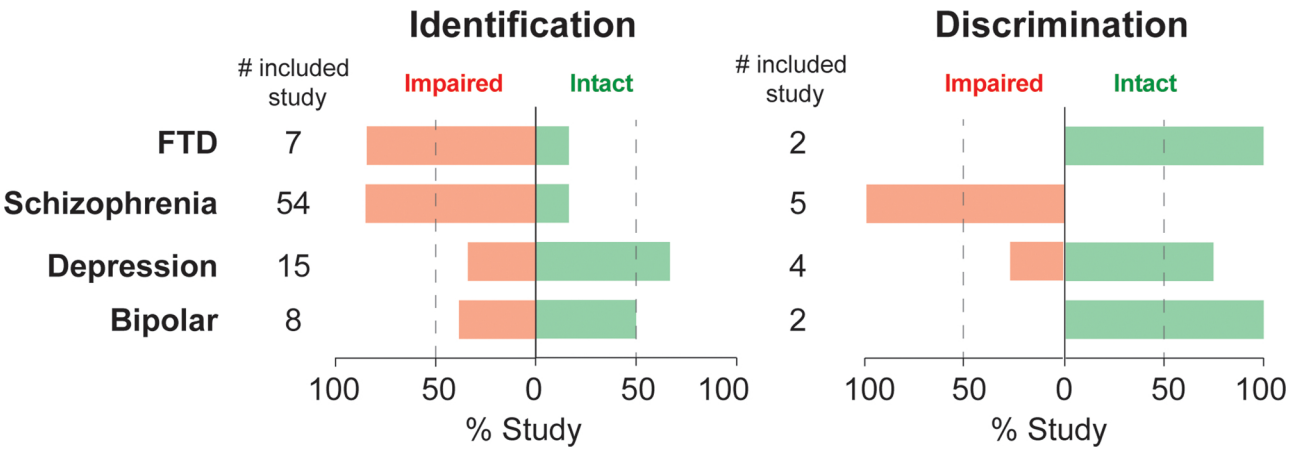

Fig. 3. Odour identification and discrimination in frontotemporal dementia (FTD), schizophrenia, depression and bipolar disorder.

Table 2
Publications on odour identification/discrimination in FTD.

Study	*n* (Patients/ Controls), Diagnosis	Gender *(Male/ Female)*, Mean Age ± SD (years)	Disease Severity	Olfactory Test	Findings
Greenberg et al. (2011)	10 (5/5) SD = 5	SD: *(1/4)*, 61.2 ± 4.5 C: Matched on age and gender	CDR: SD: 0.6 ± 0.2 C: 0 MMSE: SD: 27.6 ± 1.5 C: < 24	UPSIT	**Odour Identification (Verbal = Visual):** SD < C
Luzzi et al. (2007)	60 (40/20) bvFTD = 11 SD = 8 AD = 14 CBD = 7	bvFTD: *(8/3)*, 64 ± 7 SD: *(5/3)*, 68 ± 6 AD: *(7/7)*, 71 ± 8 CBD: *(4/3)*, 64 ± 7 C: *(10/10)*, 65 ± 7	MMSE: bvFTD: 24 ± 6 SD: 21 ± 9 AD: 24 ± 2 CBD: 28 ± 2	SPSB	**Odour Identification:** AD = SD < bvFTD = CBD < C **Odour Discrimination:** AD < C = bvFTD = SD = CBD
McLaughlin and Westervelt (2008)	42 (28/14) bvFTD = 6 PNFA = 8 AD = 14	bvFTD, PNFA: *(6/8)*, 64.9 ± 10.0 AD: *(6/8)*, 68.8 ± 8.9 C: *(6/8)*, 65.9 ± 8.2	MMSE: FTD: 20.7 ± 5.1 AD: 24.1 ± 3.0 C: 29.1 ± 0.7 3MS: FTD: 67.1 ± 17.7 AD: 75.8 ± 10.8 C: 96.8 ± 3.1 CDR Global Score: FTD: 1.2 ± 0.5 AD: 1.0 ± 0 CDR Total Box Score: FTD: 6.1 ± 2.7 AD: 4.6 ± 1.4	B-SIT	**Odour Identification**: bvFTD = PNFA = AD < C
Omar et al. (2013)	42 (25/17) bvFTD = 12 SD = 8 PNFA = 5	bvFTD: *(12/0)*, 66.1 ± 7.6 SD: *(5/3)*, 66.1 ± 6.9 PNFA: *(1/4)*, 62.7 ± 8.2 C: *(8/9)*, 66.2 ± 8.1	MMSE: bvFTD: 23.5 ± 6.0 SD: 22.8 ± 5.6 PNFA: 19.2 ± 10.8 C: 29.9 ± 0.3 NART: bvFTD: 26.5 ± 16.1 SD: 18.7 ± 11.9 PNFA: 17.0 ± 15.3 C: 42.7	UPSIT	**Odour Identification:** bvFTD = SD = PNFA < C
Orasji et al. (2016)	20 (9/11) bvFTD = 9	bvFTD: *(8/1)*, 73.1 ± 10.3 C: *(6/5)*, 71.6 ± 6.1	MMSE: bvFTD: 25 ± 3 C: 28 ± 1 FAB: bvFTD: 15 ± 2 C: 17 ± 2 FDRS: bvFTD: 37 % (13 %–67 %). All patients moderate to severe	B-SIT	**Odour Identification** bvFTD = C
Piwnica-Worms et al. (2010)	10 (4/6) SD = 3 LPA = 1	SD: *(2/1)*, 59 (55–63) LPA: *(1/0)*, 56 C: *(4/2)*, 61.5 (52–67)	2 SD patients had moderately severe disease based on estimated disease duration (both 7 years) and brain MRI findings. 1 SD patient was assessed earlier in the disease course (4 year disease duration).	UPSIT	**Odour Identification:** LPA = SD < C (statistical significance unavailable)
Rami et al. (2007)	7 (3/4) bvFTD = 1 SD = 1 PNFA = 1	bvFTD: *(1/0)*, 72 SD: *(1/0)*, 66 PNFA: *(1/0)*, 72 C: *(4/0)*, 69.5 (69–70)	MMSE: bvFTD: 27 SD: 20 PNFA: 24	UPSIT	**Odour Identification (Verbal):** bvFTD, PNFA, SD < C (statistical significance unavailable) **Odour Identification (Visual):** PNFA, SD < C (statistical significance unavailable) (bvFTD patient declined the test) **Odour Discrimination:** bvFTD = PNFA = SD = C (statistical significance unavailable)

3MS: Modified Mini Mental State Examination; AD: Alzheimer's Disease; B-SIT: Brief Smell Identification Test; bvFTD: Behavioural Variant Frontotemporal Dementia; C: Controls; CBD: Corticobasal Degeneration; CDR: Clinical Dementia Rating Scale; FAB: Frontal Assessment Battery; FDRS: Frontal Dementia Rating Scale; FTD: Frontotemporal Dementia; LPA: Logopenic Progressive Aphasia; MMSE: Mini Mental Status Exam; NART: National Adult Reading Test ; PNFA: Progressive Non-Fluent Aphasia; SD: Semantic Dementia; SPSB: Odour Perception and Semantics Battery; UPSIT: University of Pennsylvania Smell Identification Test.

Table 3
Publications on odour identification/discrimination in schizophrenia.

Study	*n* (Patients/ Controls), Diagnosis	Gender *(Male/Female)*, Mean Age ± SD (years)	Disease Severity	Olfactory Test	Findings
Brewer et al. (1996)	46 (27/19) SZ = 27	SZ: *(27/0)*, 31.8 ± 8.5 C: *(19/0)*, 34.8 ± 12.5	DSM-III-R PANSS Positive: 17.5 ± 5.6 PANSS Negative: 20.7 ± 5.4 PANSS General Psychopathology: 32.9 ± 9.5 HRSD: 7.6 ± 5.3 NART: SZ: 106.8 ± 9.7 C: 105.1 ± 8.7	UPSIT	**Odour Identification:** SZ < C Impaired odour identification associated with: Depression rating (HRDS) (SZ) Negative symptom severity (PANSS) (SZ) Executive Dysfunction (SZ) Impaired Verbal Memory Index (controls)
Brewer et al. (2007)	87 (63/24) SZ = 32 FEP = 31	SZ: *(28/4)*, 33.13 ± 8.4 FEP: *(23/8)*, 22.94 ± 3.9 C: *(19/5)*, 20.21 ± 4.19	NART: SZ: 107.58 ± 12.88 FEP: 101.98 ± 12.45 C: 109.81 ± 8.50 MS Reality Distortion: SZ: 3.95 ± 2.2 FEP: 2.5 ± 2.1 MS Disorganisation: SZ: 2.26 ± 1.8 FEP: 4.0 ± 0.5 MS Psychomotor Poverty: SZ: 3.97 ± 2.3 FEP: 3.0 ± 0.8	UPSIT	**Odour Identification:** SZ < FEP < C
Chen et al. (2019)	326 (127,199) SZ = 32 FEP = 20 MDD = 38 MDE = 37	SZ/FEP: (*22/30)*, 32.7 ± 9.4 MDD/MDE: (*23/52)*, 36.6 ± 10.0 C: (*90/109)*, 34.1 ± 11.9	DSM-IV PANSS Positive: SZ:14.7 ± 2.4 PANSS Negative: SZ: 17.3 ± 3.6 PANSS General: SZ: 31.0 ± 5.8 PANSS Total Score: SZ: 62.2 ± 9.2 HAM-D: MDD/MDE: 23.8 ± 4.5	Sniffin' Sticks	**Odour Identification:** SZ, MDD, MDE < FEP, C Impaired odour identification associated with severity of psychopathological symptoms (PANSS total score) (SZ/FEP) **Odour Discrimination:** MDD, SZ, MDE < FEP, C; MDD < MDE
Cieslak et al. (2015)	93 (56/37) SZ = 56 (includes 7 SZA(Dep) and 6 SZA(Bip))	SZ: *(29/27)*, M: 32.2 ± 10.3; F: 33.0 ± 8.3 C: *(18/19)*, M: 29.5 ± 8.3; F: 35.8 ± 14.5	DSM-IV PANSS Positive: SZ (M): 12.0 ± 5.3 SZ (F): 12.2 ± 7.9 PANSS Negative: SZ (M): 13.7 ± 5.5 SZ (F): 13.2 ± 5.6 PANSS General Psychopathology: SZ (M): 25.5 ± 5.9 SZ (F): 25.6 ± 9.3 HAM-D: SZ (M): 7.6 ± 6.0 SZ (F): 9.2 ± 7.3	UPSIT	**Odour Identification:** SZ = C Impaired odour identification associated with: Greater physical anhedonia (SZ) Lower social fear (independently of greater physical anhedonia) (SZ males)
Clepce et al. (2013)	68 (34/34) SZ = 34	SZ: *(24/10)*, M: 33.50 ± 10.27; F: 38.70 ± 12.08 C: *(24/10)*, M: 33.58 ± 10.26; F: 38.80 ± 12.14	DSM-IV PANSS Positive: 16.23 (SEM = 0.99) PANSS Negative: 14.97 (SEM = 0.91) SHAPS: 1.79 ± 0.37	Sniffin' Sticks	**Odour Identification:** SZ < C **Odour Discrimination:** SZ < C
Coleman et al. (2002)	138 (70/ 68) SZ = 53 SZA(Bip) = 13 SZA(Dep) = 4	SZ, SZA: *(44/26)*, 33.2 ± 9.8 C: *(43/25)*, 40.3 ± 15.7	DSM-IV	UPSIT	**Odour Identification:** SZ = SZA(Dep) = SZA(Bip) < C

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Table 3 (*continued*)

Study	*n* (Patients/ Controls), Diagnosis	Gender *(Male/Female)*, Mean Age ± SD (years)	Disease Severity	Olfactory Test	Findings
Cumming et al. (2011)	69 (47/22) SZ = 27 BP = 20	SZ: *(15/12)*, 37.1 ± 8.4 BP: *(10/10)*, 34.6 ± 11.3 C: *(11/11)*, 35.5 ± 9.8	DSM-IV BPRS: SZ: 20.6 ± 15.0 BP: 16.3 ± 9.5 SAPS: SZ: 21.9 ± 20.7 SANS: SZ: 23.7 ± 15.9 YMRS: BP: 9.9 ± 8.0 HRSD: BP: 11.2 ± 5.7	UPSIT	**Odour Identification:** SZ < BP < C Impaired odour identification associated with lower social competence (all)
Good et al. (1998)	124 (65/59) SZ = 65	SZ: *(65/0)*, 28.1 ± 8.4 C: *(59/0)*, 32.2 ± 7.8	DSM-IV PANSS Positive: 17.3 ± 6.3 PANSS Negative: 25.1 ± 9.2	UPSIT	**Odour Identification:** SZ < C
Goudsmit et al. (2003)	152 (83/69) SZ = 60 SZA, SZNA = 23	SZ, SZA, SZNA: *(52/31)*, 33.90 ± 10.70 C: *Matched on age and gender*	DSM-IV	UPSIT	**Odour Identification:** SZ = SZA = SZNA < C Impaired odour identification associated with: Greater deficit syndrome (DS) symptomatology Restricted affect Diminished emotional range Poverty of speech
Houlihan et al. (1994)	83 (47/36) SZ = 47	SZ: *(25/22)*, M: 32.7 ± 5.8; F: 33.8 ± 7.9 C: *(21/15)*, M: 30.3 ± 6.3; F: 32.9 ± 8.7	DSM-III-R	UPSIT	**Odour Identification:** SZ < C
Ishizuka et al. (2010)	34 (15/19) SZ = 15	SZ: *(9/6)*, 27.47 ± 10.67 C: *(14/5)* 36.00 ± 10.89	DSM-IV SAPS: 4.40 ± 2.90 SANS: 7.40 ± 3.44	UPSIT	**Odour Identification:** SZ < C Impaired odour identification associated with: Negative symptom severity (SANS) Apathy (SANS) Anhedonia (SANS) Affective flattening (SANS)
Kamath et al. (2012)	72 (42/30) SZ = 42	SZ: *(23/19)*, 35.43 ± 10.82 C: *(18/12)*, 30.83 ± 12.14	DSM-IV BPRS: 29.33 ± 9.14 SAPS: 14.83 ± 15.58 SANS: 26.12 ± 17.11	UPSIT	**Odour Identification:** SZ < C
Kamath et al., 2013a	145 (64/54) SZ = 64 + 1° Relatives (27)	SZ: *(36/28)*, 36.97 ± 10.82 C: *(30/24)*, 33.20 ± 10.87 Rel: *(9/18)*, 36.30 ± 16.33	DSM-IV SAPS: 18.25 ± 16.66 SANS: 27.70 ± 17.05	Sniffin' Sticks	**Odour Identification:** SZ = Rel < C Impaired odour identification associated with negative symptom severity (SANS) (SZ)
Kamath et al., 2013b	32 (16/16) SZ = 16	SZ: *(12/4)*, 34.3 ± 7.95 C: *(13/3)*, 30.7 ± 7.06	DSM-IV BPRS: 33.7 ± 12.8 SAPS: 23.2 ± 20.9 SANS: 26.7 ± 13.8	UPSIT	**Odour Identification (Standard UPSIT):** SZ < C **Odour Identification (Free-response UPSIT):** SZ = C
Kamath et al. (2014)	155 (65/66) SZ = 65 + 1° Relatives (24)	SZ: *(36/29)*, 37.3 ± 10.4 C: *(34/32)*, 33.9 ± 11.4 Rel: *(8/16)*, 36.7 ± 16.9	BPRS: 32.1 ± 8.8 SAPS: 14.5 ± 14.3 SANS: 25.9 ± 16.9	Sniffin' Sticks	**Odour Identification:** SZ = Rel < C Impaired odour identification associated with impaired odour discrimination **Odour Discrimination:** SZ < C = Rel Impaired odour discrimination associated with: Negative symptom severity (SANS) (SZ) Impaired odour identification (SZ)
Kamath et al., 2011a)	44 (23/21)SZ = 23	SZ: *(19/4)*, 42.8 ± 10.7 C: *(13/8)*, 43.9 ± 12.8	DSM-IV PANSS Positive: 29.8 ± 3.5 PANSS Negative: 27.5 ± 5.9 PANSS Composite: 2.3 ± 7.6 PANSS General Psychopathology: 54.9 ± 9.3	B-SIT	**Odour Identification:** SZ < C Impaired odour identification associated with negative and positive symptoms combined severity (PANSS composite)

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Table 3 (*continued*)

Study	*n* (Patients/ Controls), Diagnosis	Gender *(Male/Female)*, Mean Age ± SD (years)	Disease Severity	Olfactory Test	Findings
Kamath et al., 2011b	64 (33/31) SZ = 33	SZ: *(21/12)*, 34.9 ± 10.2 C: *(20/11)*, 30.7 ± 10.3	DSM-IV SAPS: 23.2 ± 21.3 SANS: 39.4 ± 21.9 BPRS: 35.4 ± 12.4 HAM-D: 11.2 ± 7.7	UPSIT	**Odour Identification:** SZ < C Impaired odour identification (for unpleasant odours) associated with: Lower levels of anhedonia (SANS) Lower depression ratings (HAM-D)
Kastner et al. (2013)	983 (881/102) SZ = 881	SZ: *(590/291)*, 39.5 ± 13, (17–78) C: *(69/33)*, 38.8 ± 14, (18–71)	PANSS Positive: Median 12.0, (7.0–38.0) PANSS Negative: Median 17.0,(7.0–44.0)	UPSIT	**Odour Identification (Naming):** SZ < C Impaired odour identification associated with: Negative symptom severity (PANSS) Impaired cognition
Kohler et al. (2007)	33 (19/14) SZ = 19	SZ: *(13/6)*, 34.3 ± 8.4 C: *(8/6)*, 27.4 ± 6.9	No data available	UPSIT	**Odour Identification:** SZ = C
Kopala et al., 1995a	95 (65/30) SZ = 65 All patients neuroleptically medicated	SZ: *(49/16)*, M: 26.9 ± 8.0, (16–48); F: 32.7 ± 8.4, (21–47) C: *(14/16)*, M: 31.5 ± 7.7, (21–43); F: 37.0 ± 8.6, (20–48)	DSM-III-R	UPSIT	**Odour Identification:** SZ < C
Kopala et al., 1998b	27 (18/9) SZ = 18	SZ: *(18/0)*, 39.6 ± 5.45 C: *(9/0)*, 39.2 ± 8.5	DSM-III-R and/or DSM-IV Folstein Mini-Mental State: SZ range 25–30	UPSIT	**Odour Identification:** SZ < C
Kopala et al., 1998a	36 (12/24) SZ = 12 Unaffected twin of SZ = 12 Control twins = 12	SZ: (*No gender data available*), 36.8 ± 4.9 C: Unaffected twin of SZ: 36.8 ± 5.0 Control twins: (*Matched on gender*), 37.5 ± 4.6	No data available	UPSIT	**Odour Identification:** SZ = Unaffected twin < C
Kopala et al. (2001)	89 (19/43) SZ = 19 (includes 5 SZA and 3 NOS) + 1° or 2° Relatives (27)	SZ: *(11/8)*, 43.4 ± 9.9, (20–64) C: *(18/25)*, 42.5 ± 10.9 Rel: *(10/17)*, 43.6 ± 11.9	DSM-III-R	UPSIT	**Odour Identification:** SZ < Rel < C
Kopala et al. (1993)	98 (40/58) SZ = 40 (includes some SZP) All patients neuroleptic-naïve	SZ: *(30/10)*, M: 25.9 ± 7.1, F: 27.3 ± 8.3; (18–45) C: *(28/30)*, M: 28 ± 7.5, F: 29 ± 8.1; (18–45)	DSM-III-R GAS: SZ (M): 41.5 SZ (F): 40.4	UPSIT	**Odour Identification:** SZ (M) < SZ (F) = C
Kopala et al. (1994)	260 (183/77) SZ = 131 MDD = 21 ED = 31	SZ: *(92/38)*, 27.3 ± 7.8, (16–52) MDD: *(8/13)*, 37.0 ± 9.6, (21–56) ED: *(0/31)*, 20.9 ± 5.0, (14–40) C: *(30/47)*, 32.5 ± 11.1, (19–64)	DSM-III-R	UPSIT	**Odour Identification:** SZ < ED = MDD = C
Kopala et al., 1995b	52 (27/25) SZ = 27: Pre-Menopausal SZ = 15 Post-Menopausal SZ = 12	SZ: *(0/27)*, 42.9 ± 7.1; Pre-SZ: 33.7 ± 8.6, Post-SZ: 54.3 ± 5.1 C: *(0/25)*, 42.8 ± 9.0; Pre-C: 36.8 ± 10.1, Post-C: 55.6 ± 6.4	DSM-III-R PANSS Positive: Pre-SZ: 19.1 ± 7.6, Post-SZ: 23.3 ± 9.0 PANSS Negative: Pre-SZ: 20.3 ± 6.6, Post-SZ: 20.9 ± 6.2 GAS: Pre-SZ: 29.5 ± 11.7, Post-SZ: 34.0 ± 14.2	UPSIT	**Odour Identification:** Post-SZ < Pre-SZ < C

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Table 3 (*continued*)

Study	*n* (Patients/ Controls), Diagnosis	Gender *(Male/Female)*, Mean Age ± SD (years)	Disease Severity	Olfactory Test	Findings
Lui et al. (2020)	90 (60/30) SZ(PN) = 30 SZ(NPN) = 30	SZ(PN): (*11/19*), 37.4 ± 11.06 SZ(NPN) : (*13/17*), 40.07 ± 10.24 C: (*11/19*), 38.33 ± 11.96	DSM-IV PANSS Positive: SZ(PN): 7.5 ± 1.72 SZ(NPN): 7.17 ± 0.59 PANSS Negative: SZ(PN): 26.7 ± 6.07 SZ(NPN): 8.77 ± 2.70 PANSS General Psychopathology: SZ(PN): 18.27 ± 2.83 SZ(NPN): 16.37 ± 1.19	UPSIT	**Odour Identification:** SZ(PN) < SZ(NPN) < C Impaired odour identification associated with negative symptom severity (SANS, all 5 subscales) (SZ)
Malaspina et al. (1994)	40 (20/20) SZ = 20	SZ: *(15/5)*, 32.70 ± 7.98, C: *(15/5)*, 33.25 ± 5.9,	DSM-III-R PANSS Positive: 18.20 ± 7.44 PANSS Negative: 21.20 ± 6.65	UPSIT	**Odour Identification:** SZ < C
Malaspina et al., 2012ab	87 (55/32) SZ = 55 (includes some SZA)	SZ: *(30/25)*, M: 32.3 ± 10.2; F: 33.2 ± 8.3 C: *(17/15)*, M: 28.6 ± 7.7; F: 38.9 ± 14.5	DSM-IV Working Memory (WAIS-III): SZ (M): 94.8 ± 13.2 SZ (F): 97.1 ± 9.8 C (M): 110.7 ± 16.2 C (F): 101.0 ± 9.3 Processing Speed (WAIS-III): SZ (M): 88.2 ± 13.7 SZ (F): 91.1 ± 14.0 C (M): 103.7 ± 10.7 C (F): 104.4 ± 12.2 NART Errors: SZ (M): 31.4 ± 14.1 SZ (F): 25.8 ± 15.1 C (M): 29.9 ± 10.3 C (F): 24.1 ± 11.1	UPSIT	**Odour Identification**: SZ = C Impaired odour identification associated with: Higher executive function (WCST) (SZ females) Better memory and attention (WMS-R General Index) (female controls)
Malaspina et al., 2012a	100 (58/42) SZ = 58 (includes some SZA)	SZ: *(31/27)*, M: 32.3 ± 10.0; F: 33.0 ± 11.0 C: *(18/24)*, M: 29.5 ± 8.3; F: 34.5 ± 13.2	DSM-IV PANSS Positive: SZ (M): 12.7 ± 6.2 SZ (F): 12.2 ± 7.9 PANSS Negative: SZ (M): 14.3 ± 6.1 SZ (F): 13.2 ± 5.6 PANSS General Psychopathology: SZ (M): 27.2 ± 11.2 SZ (F): 25.6 ± 9.3 Verbal IQ (WAIS-III): SZ (M): 99.8 ± 16.2 SZ (F): 103.7 ± 13.6 C (M): 110.4 ± 13.1 C (F): 106.4 ± 12.9	UPSIT	**Odour Identification:** SZ = C Impaired odour identification associated with: Negative symptom severity (PANSS) (SZ males) Blunted affect (PANSS) (SZ males)
Martin et al. (2015)	100 (50/50) SZ = 50	SZ: *(34/16)*, 45.48 ± 10.44 C: *(Gender matched)*, 46.48 ± 9.64	DSM-IV Stroop Test: SZ: 49.17 ± 13.29 C: 65.72 ± 11.09 Phonemic Word Fluency: SZ: 12.14 ± 4.07 C: 15.76 ± 5.21 Semantic Word Fluency: SZ: 16.82 ± 4.67 C: 22.78 ± 5.27	UPSIT	**Odour Identification:** SZ = C
McLean et al. (2004)	59 (38/21) SZNA = 22 (includes 18 SZ, 2 DD and 2 AP); SZA = 16 (includes 12 BP^+ and 4 MDD^+)	SZNA: *(14/8)*, 37.3 ± 9.0 SZA: *(8/8)*, 38.6 ± 10.2 C: *(14/7)*, 34.8 ± 11.1	No data available	UPSIT	**Odour Identification**: SZA = SZNA = C

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Table 3 (*continued*)

Study	*n* (Patients/ Controls), Diagnosis	Gender *(Male/Female)*, Mean Age ± SD (years)	Disease Severity	Olfactory Test	Findings
Minor et al. (2004)	187 (54/133) SZ = 54	SZ: *(43/11)*, M: 32.7 ± 9.6; F: 40.0 ± 10.9 C: *(64/69)*, 25.8 ± 7.8	DSM-IV	UPSIT	**Odour Identification:** SZ < C
Minovi et al. (2015)	31 (18/13) SZ = 18	SZ: *(8/10)*, 34.2 (19–58) C: *(2/11)*, 29.5 (23–37)	DSM-IV	Sniffin' Sticks	**Odour Identification**: SZ = C **Odour Discrimination**: SZ < C
Moberg et al., 1997a	78 (38/40) SZ = 38	SZ: *(18/20)*, 50.6 ± 25.5 C: *(18/22)*, 49.6 ± 24.6	DSM-III-R	UPSIT	**Odour Identification**: SZ < C
Moberg et al., 1997b	56 (36/20) SZ = 16 AD = 20	SZ: *(4/12)*, 77.9 ± 6.5 AD: *(4/16)*, 73.9 ± 9.4 C: *(6/14)*, 72.5 ± 6.4	DSM-III-R (SZ) NINCDS-ADRDA (AD) MMSE: SZ: 19.1 ± 6.6 AD: 19.5 ± 5.5 C: 29.8 ± 0.5	UPSIT	**Odour Identification**: SZ = AD < C
Mossaheb et al. (2018)	130 (51/79) SZ = 51 (includes 12 SZP and 17 SZA)	SZ: *(30/21)*, M: 30.67 ± 8.59, F: 33.33 ± 9.4; (18–49) C: *(31/48)*, M: 26.65 ± 6.04; F: 27.81 ± 8.86	DSM-IV-TR PANSS Positive: SZ (M): 14.0 ± 5.14 SZ (F): 11.90 ± 4.15 PANSS Negative: SZ (M): 18.03 ± 4.34 SZ (F): 15.8 ± 7.8 PANSS Global Score: SZ (M): 32.43 ± 6.8 SZ (F): 30.30 ± 10.19 PANSS Total Score: SZ (M): 64.57 ± 11.89 SZ (F): 58 ± 18.91 WMS-R: SZ (M): 17.39 ± 4.77 SZ (F): 16 ± 4.48 C (M): 21.29 ± 2.48 C (F): 20.06 ± 2.98	UPSIT	**Odour Identification**: SZ < C Impaired odour identification associated with impaired visuospatial working memory (WMS-R) (SZ males)
Nguyen et al. (2011)	25 (14/11) SZ = 14	SZ: *(14/0)*, 47.89 C: *(11/0)*, 44.18	DSM-IV PANSS Total Score: SZ: 79.29 ± 26.72 WRAT-III Scaled Reading: SZ: 97.27 ± 11.59 C: 104.50 ± 10.22 WAIS-III Overall IQ: SZ: 94.25 ± 11.96 C: 111.21 ± 15.09	UPSIT	**Odour Identification**: SZ < C
de Nijs et al. (2018)	260 (132/128) SZ = 132	SZ: *(107/25)*, 30.68 ± 7.03 C: *(71/57)*, 32.41 ± 9.50	DSM-IV PANSS Positive: 11.55 ± 4.62 PANSS Negative: 12.53 ± 4.96 PANSS General Psychopathology: 24.91 ± 6.99	Sniffin' Sticks	**Odour Identification**: SZ < C Impaired odour identification associated with: Impaired cognition Impaired memory Impaired attention Impaired executive functioning
Roalf et al. (2006)	97 (22/45) SZ = 22 + 1° Relatives (30)	SZ: *(10/12)*, 34.9 ± 12.5 C: *(21/24)*, 34.2 ± 12.7 Rel: *(16/14)*, 39.5 ± 18.9	DSM-IV BPRS: 30.9 ± 7.7 SAPS: 13.9 ± 15.9 SANS: 31.1 ± 15.6	UPSIT	**Odour Identification**: SZ = Rel < C
Seidman et al. (1992)	33 (16/17) SZ = 16	SZ: *(15/1)*, 36.5 ± 8.1 C: *(16/1)*, 31.7 ± 8.9	DSM-III WAIS-R Vocabulary: SZ: 8.9 ± 3.1 C: 12.7 ± 2.8 WAIS-R IQ Estimate: SZ: 91.4 ± 18.0 C: 116.1 ± 17.5	UPSIT	**Odour Identification**: SZ < C Impaired odour identification associated with impaired working memory (WCST) (controls)

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Table 3 (*continued*)

Study	*n* (Patients/ Controls), Diagnosis	Gender *(Male/Female)*, Mean Age ± SD (years)	Disease Severity	Olfactory Test	Findings
Seidman et al. (1997)	72 (40/32) SZ = 40	SZ: *(24/16)*, 38.5 ± 6.5 C: *(15/17)*, 36.4 ± 9.3	DSM-III-R WAIS-R Vocabulary: SZ: 9.8 ± 3.0 C: 12.9 ± 2.9 WAIS-R IQ Estimate: SZ: 98.7 ± 14.2 C: 112.6 ± 14.3	UPSIT	**Odour Identification**: SZ < C
Serby et al. (1990)	46 (23/23) SZ = 14 MDD = 9	SZ: *(14/0)*, Age range 40–49 MDD: *(9/0)*, Age range 50–59 C: *(23/0)*, Age range 40–59	DSM-III-R HAM-D: MDD: 19.9 ± 1.6 (SEM)	UPSIT	**Odour Identification:** MDD, SZ < C
Strauss et al. (2010)	63 (41/22) SZ(DS) = 15 SZ(ND) = 26	SZ: *(28/13)*, 41.85 ± 11.8 C: *(4/18)*, 40.05 ± 12.13	DSM-IV-TR BPRS: 40.95 ± 7.62	B-SIT	**Odour Identification**: SZ(DS) < SZ(ND) = C Impaired odour identification associated with: Negative symptom severity (SZ) Restricted affect (SZ) Poverty of speech (SZ)
Strauss et al. (2015)	60 (39/21) SZ = 39	SZ: *(28/11)*, 43.9 ± 11.7 C: *(14/7)*, 42.6 ± 9.3	DSM-IV BNSS Total: 24.8 ± 17.5 BPRS Total: 38.1 ± 9.6 BPRS Positive: 2.4 ± 1.1 BPRS Negative: 2.2 ± 1.1 BPRS Disorganised: 1.5 ± 0.5	UPSIT	**Odour Identification**: SZ < C
Striebel et al. (1999)	71 (55/16) SZ = 16 BP^+ = 18 MDD^+ = 1 BP– = 12 MDD– = 8 All SZ patients treatment-refractory	SZ: *(14/2)*, 34.75 ± 9.53, (20–57) BP^+/MDD^+: *(10/9)*, 45.05 ± 11.43, (23–66) BP–/MDD–: *(11/9)*, 45.45 ± 11.39, (23–65) C: *(13/3)*, 33.56 ± 9.23, (23–48)	DSM-III-R	UPSIT	**Odour Identification**: BP^+/MDD^+ < BP–/MDD– < C; SZ = BP^+/MDD^+, BP–/MDD–
Turetsky et al., 2003a,b	90 (52/38) SZ = 52	SZ: *(27/25)*, M: 28.5 ± 7.2, F: 36.3 ± 9.3; (19–53) C: *(21/17)*, 28.2 ± 9.4, (18–56)	DSM-IV BPRS: SZ (M): 35.2 ± 16.3 SZ (F): 32.8 ± 15.9 SAPS: SZ (M): 19.2 ± 17.0 SZ (F): 15.0 ± 16.4 SANS: SZ (M): 30.0 ± 24.4 SZ (F): 22.8 ± 17.1	UPSIT	**Odour Identification**: SZ < C
Ugur et al. (2005)	40 (10/30) SZ = 10 (includes 3 SZA) Unaffected twin of SZ = 10 Control twins = 20	SZ: (*No gender data available*), 34.5 ± 11.4 C: Unaffected twin of SZ: 34.5 ± 11.4 Control twins: (*Matched on gender*), 35.3 ± 11.1	ICD-10 BPRS: SZ: 32.4 ± 6.4 Unaffected twin: 19.4 ± 1.6 C: 18.5 ± 0.5 SAPS: SZ: 18.4 ± 14.8 Unaffected twin: 1.1 ± 2.3 SANS: SZ: 27.1 ± 14.2 Unaffected twin: 0.9 ± 1.2	Sniffin' Sticks	**Odour Identification:** SZ = C **Odour Discrimination:** SZ < Unaffected twin = C

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Table 3 (*continued*)

Study	*n* (Patients/ Controls), Diagnosis	Gender *(Male/Female)*, Mean Age ± SD (years)	Disease Severity	Olfactory Test	Findings
Urban-Kowalczyk et al. (2018)	69 (48/21) SZ(PP) = 25 SZ(PN) = 23	SZ(PP): *(11/14)*, 32.36 ± 7.78 SZ(PN): *(10/13)*, 34.68 ± 7.18 C: *(10/11)*, 35.30 ± 8.68	ICD-10 PANSS Positive: SZ(PP): 7.00 ± 5.65 SZ(PN): 10.36 ± 4.36 PANSS Negative: SZ(PP): 12.44 ± 4.99 SZ(PN): 26.76 ± 3.14 PANSS General Psychopathology: SZ(PP): 14.96 ± 8.57 SZ(PN): 20.64 ± 6.78 PANSS Total Score: SZ(PP): 34.40 ± 15.95 SZ(PN): 57.52 ± 10.56	UPSIT	**Odour Identification**: SZ(PN) < SN(PP) < C Impaired odour identification associated with having predominantly negative symptomatology SZ(PN)
Urban-Kowalczyk et al. (2017)	100 (50/50)SZ = 50	SZ: *(22/28)*, 35.4 ± 10.69 C: *(22/28)*, 35.12 ± 7.88	ICD-10 PANSS Positive: 8.18 ± 5.134 PANSS Negative: 17.6 ± 6.82 PANSS General Psychopathology: 17.8 ± 8.172	UPSIT	**Odour Identification**: SZ < C Impaired odour identification (overall) associated with severity of negative symptoms (PANSS)
Urban-Kowalczyk et al. (2019)	76 (47/29) SZ = 27 FEP = 20	SZ: *(12/15)*, 33.7 ± 5.11 FEP: *(8/12)*, 27.2 ± 4.6 C: *(13/16)*, 33.14 ± 4.85	ICD-10 PANSS Positive SZ: 10.77 ± 5.20 FEP: 8.85 ± 5.32 PANSS Negative SZ: 21.47 ± 8.39 FEP: 14.90 ± 7.98 PANSS General Psychopathology SZ: 17.63 ± 7.47 FEP: 18.00 ± 9.18 PANSS Total Score: SZ: 48.3 ± 15.71 FEP: 44.7 ± 19.83	UPSIT	**Odour Identification:** SZ < FEP < C Impaired odour identification (overall) associated with: Severity of psychopathological symptoms (PANSS General; PANSS Total Score) (SZ) Severity of negative symptoms (PANSS Negative) (SZ)
Walsh-Messinger et al. (2018)	53 (26/27) SZ = 26 (includes 4 SZA)	SZ: *(16/10)*, 45.42 ± 7.92 C: *(16/11)*, 37.30 ± 12.28	DSM-IV PANSS Positive: 14.75 ± 6.23 PANSS Negative: 13.92 ± 4.32 PANSS General Psychopathology: 29.04 ± 8.12 HAM-D: 11.20 ± 10.23 HAM-A: 8.06 ± 7.28 YMRS: 7.14 ± 6.52	Sniffin' Sticks	**Odour Identification:** SZ < C
Warner et al. (1990)	26 (18/8) SZ = 12 MDD = 6	SZ: *(12/0)*, 34 (20–42) MDD: *(6/0)*, 37 (28–50) C: *(8/0)*, 32 (20–44)	RDC	UPSIT	**Odour Identification:** SZ < MDD = C
Wu et al. (1993)	44 (20/24) SZ = 20 All patients unmedicated	SZ: *(19/1)*, 32.1 ± 9.3 C: *(23/1)*, 27.7 ± 7.2	DSM-III-R	UPSIT	**Odour Identification:** SZ < C

AD: Alzheimer's Disease; AP: Atypical Psychosis; BP: Bipolar Disorder; BP+: Bipolar Disorder with psychosis; BP–: Bipolar Disorder without psychosis; BNSS: Brief Negative Symptom Scale; BPRS: Brief Psychiatric Rating Scale; B-SIT: Brief Smell Identification Test; C: Controls; DD: Delusional Disorder; DSM-III: Diagnostic and Statistical Manual of Mental Disorders, Third Edition; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revision; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV -TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; ED: Eating Disorder; FEP: First Episode Psychosis; GAS: Global Assessment Scale; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; HRSD: Hamilton Rating Scale for Depression; ICD-10: International Classification of Diseases – Tenth Edition; MDD: Major Depressive Disorder; MDD+: Major Depressive Disorder with psychosis; MDD–: Major Depressive Disorder without psychosis; MDE: Major Depressive Episode; MS: Manchester Scale; NART: National Adult Reading Test; NINCDS-ADRDA: National Institute of Neurological and Communicative Diseases and Stroke/Alzh'imer's Disease and Related Disorders Association; NOS: Psychosis Not Otherwise Specified; PANSS: Positive and Negative Syndrome Scale; RDC: Research Diagnostic Criteria; Rel: Relatives; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; SHAPS: Snaith-Hamilton Pleasure Scale; SZ: Schizophrenia; SZ(DS): Deficit Syndrome Schizophrenia; SZ(ND): Non-Deficit Schizophrenia; SZ(NPN): Schizophrenia with Not Predominantly Negative Symptoms; SZ(PN): Schizophrenia with Predominantly Negative symptoms; SZ(PP): Schizophrenia with Predominantly Positive symptoms; SZA: Schizoaffective Disorder; SZA(Bip): Schizoaffective Disorder, Bipolar type; SZA(Dep): Schizoaffective Disorder, Depressed type; SZNA: Non-Affective Psychotic Disorders (includes DD, SZP and NOS); SZP: Schizophreniform Disorder; UPSIT: University of Pennsylvania Smell Identification Test; WAIS-III: Wechsler Adult Intelligence Scale, Third Edition; WAIS-R: Wechsler Adult Intelligence Scale, Revised Edition; WMS-R: Wechsler Memory Scale, Revised Edition; WRAT-III: Wide Range Achievement Test, Third Edition; YMRS: Young Mania Rating Scale.

3.4. Odour discrimination in schizophrenia

Odour discrimination was also impaired in schizophrenia patients, although only a handful of studies investigated odour discrimination (5/5 studies reviewed) (Clepce et al., 2013; Kamath et al., 2014; Minovi et al., 2015; Ugur et al., 2005; Urban-Kowalczyk et al., 2019).

3.5. Odour identification in depressive disorders (Table 4)

Overall, two thirds (10/15) of the studies reviewed on depressive disorders reported intact odour identification, including in Major Depressive Disorder (MDD), Major Depressive Episode (MDE), Late-Life Depression (LLD), Recurrent Depressive Disorder (RDD) and first episode depression (Amsterdam et al., 1987; Chen et al., 2019; Croy et al., 2014; Khil et al., 2016; Kopala et al., 1994; Negoias et al., 2010; Pentzek et al., 2007; Rottstaedt et al., 2018; Swiecicki et al., 2009; Warner et al., 1990). In particular, a large study by Khil et al. (2016) found no differences in odour identification between MDD patients (n = 728) and controls (n = 555). The proportion of individuals exhibiting olfactory deficits was equivalent between the groups (15.0 % for MDD and 15.3 % for controls). Similarly, a study by Rottstaedt et al. (2018) of 68 patients with MDD found no differences in odour identification compared to healthy controls.

Five studies did report odour identification deficits (Chen et al., 2018; Clepce et al., 2010; Kamath et al., 2018a,b; Serby et al., 1990; Striebel et al., 1999). One study in MDD patients showed that odour identification impairments deficits disappeared in the remitted (i.e. symptom-free) phase of the disorder (Clepce et al., 2010). This implies that odour identification impairments could represent a state (rather than trait) marker of depression, attributable to decreased attention/mood during the depressed state. Indeed, such impairments are significantly correlated with depression severity ratings (Kamath et al., 2018ab; Khil et al., 2016) and impaired executive function (Chen et al., 2018).

3.6. Odour discrimination in Depressive Disorders

Three out of four studies reported intact odour discrimination in depression (Chen et al., 2019; Kamath et al., 2018a,b; Negoias et al., 2010). The fourth study found impaired odour discrimination in their sample of MDD patients (n = 27) prior to psychotherapy; following psychotherapy, however, ability to discriminate odours returned (Croy et al., 2014). This further suggests that odour impairments might represent a state marker of depression that can be alleviated with therapy or remission.

3.7. Odour identification in bipolar disorder (Table 5)

The literature is mixed with regards to the presence of odour identification disturbance in bipolar disorder (BP). Among the 8 studies identified, 3 studies reported deficits (Cumming et al., 2011; Lahera et al., 2016; Striebel et al., 1999), 4 found no difference from controls (Amsterdam et al., 1987; Hardy et al., 2012; Negoias et al., 2019; Swiecicki et al., 2009), and 1 study reported equivocal results (Kamath et al., 2018a,b).

The largest study, which included 43 BP type I and 48 BP type II patients, reported deficits in odour identification in patients diagnosed with BP type I with psychosis but not in those with BP type II or BP type I without psychosis (Kamath et al., 2018a,b). Preserved odour identification was also reported in a sample of 51 BP type II patients (Amsterdam et al., 1987), in 21 patients with BP type I or BP type II (Swiecicki et al., 2009) and was also found in 27 euthymic BP patients (type I or II) (Negoias et al., 2019). Hardy et al. (2012) also showed preserved odour identification in their sample of 20 unspecified-subtype BP patients.

Most studies showing impairments in odour identification were not classified into subtypes I or II. Lahera et al. (2016) found odour identification impairments in their study of 39 euthymic BP patients; Striebel et al. (1999) found impairments in their study of 30 patients with BP, both with and without psychosis; and Cumming et al. (2011) found impairments in 20 BP patients.

3.8. Odour discrimination in bipolar disorder

Only two papers studied odour discrimination in bipolar disorder, and both found that patients performed similarly to controls (Kamath et al., 2018a,b; Negoias et al., 2019).

4. Discussion

This review suggests that administration of both an odour discrimination and an odour identification test may contribute to the differential diagnosis of FTD with schizophrenia and depression. While patients with FTD showed odour identification deficits but preserved odour discrimination, a finding already highlighted in previous reviews (Kamath et al., 2018a,b; Silva et al., 2019; Tonacci and Billeci, 2018), individuals with schizophrenia showed deficits in both odour identification and discrimination, and patients with depression performed similarly to controls on both measures. The results for bipolar disorder are ambiguous.

It is important, however, to make a strong caveat here: most studies simply look at odour identification without comparison to odour detection or discrimination. As such, more evidence (i.e. studies comparing odour detection, discrimination and identification directly across disease groups) are required to strengthen this conclusion.

4.1. Differential diagnosis of FTD and schizophrenia based on Odour Discrimination

The first finding of this review revealed that odour discrimination dissociated FTD from schizophrenia patients. Patients with schizophrenia were globally impaired on all odour tests whereas only odour identification was impaired in FTD. Olfactory testing – more specifically, odour discrimination testing – could prove useful when considering a differential diagnosis between schizophrenia and FTD. Again, more studies directly comparing odour detection, discrimination and identification between FTD and schizophrenia would be required to strengthen this conclusion.

4.2. Differential diagnosis of FTD and depression based on odour identification

The second finding of this review revealed that odour identification dissociated FTD and depression, whereby patients diagnosed with depression had overall better olfactory function than FTD patients. Although odour discrimination was preserved in FTD, odour identification was not. These findings align with a previous study that demonstrated worse performance in FTD than in MDD on an odour identification test (the Alberta Smell test) (Heyanka et al., 2014) and with recent reviews on olfaction in FTD (Silva et al., 2019) and in depressive disorders (Burón and Bulbena, 2013). This finding is also in line with studies showing that odour identification testing distinguished depression from other neurodegenerative disorders including Alzheimer's disease (Duff et al., 2002). In sum, olfactory testing – more specifically, odour identification testing – appears useful to distinguish between depression and FTD.

4.3. Odour Identification and discrimination in FTD vs bipolar disorder

Odour identification and discrimination testing yielded mixed results and did not clearly dissociate FTD from bipolar disorder. This is in alignment with recent reviews by Kazour et al. (2017) and Henry et al.

Table 4
Publications on odour identification/discrimination in depressive disorders.

Study	*n* (Patients/Controls) and Diagnosis	Gender *(Male/Female)*, Mean Age ± SD (years)	Disease Severity	Olfactory Test	Findings
Amsterdam et al. (1987)	102 (51/51) MDD, BP(II) = 51	MDD, BP(II): *(17/34)*, M: 49 ± 14; F: 43 ± 13 C: *Matched on age and gender*	DSM-III	UPSIT	**Odour Identification**: MDD = BP(II) = C
Chen et al. (2018)	235 (175/60) LLD = 125 AD = 50	LLD: *(29/96)*, 66.7 ± 6.2 AD: *(22/28)*, 71.9 ± 9.9 C: *(24/36)*, 65.4 ± 7.3	MMSE: LLD: 22.7 ± 5.3 AD: 12.4 ± 5.1 C: 26.8 ± 1.9	Sniffin' Sticks	**Odour Identification:** AD < LLD < C Impaired odour identification associated with: Cognitive impairment (MMSE) Impaired immediate and delayed recall Impaired naming Impaired verbal fluency Impaired attention Impaired executive function (LLD)
Chen et al. (2019)	326 (127,199) SZ = 32 FEP = 20 MDD = 38 MDE = 37	SZ/FEP: *(22/30)*, 32.7 ± 9.4 MDD/MDE: *(23/52)*, 36.6 ± 10.0 C: *(90/109)*, 34.1 ± 11.9	DSM-IV PANSS Positive: SZ:14.7 ± 2.4 PANSS Negative: SZ: 17.3 ± 3.6 PANSS General: SZ: 31.0 ± 5.8 PANSS Total Score: SZ: 62.2 ± 9.2 HAM-D: MDD/MDE: 23.8 ± 4.5	Sniffin' Sticks	**Odour Identification:** SZ, MDD, MDE < FEP, C Impaired odour identification associated with severity of psychopathological symptoms (PANSS total score) (SZ/FEP) **Odour Discrimination:** MDD, SZ, MDE < FEP, C; MDD < MDE
Clepce et al. (2010)	91 (37/37) MDD = 37 All patients tested in the acute phase of depression	MDD: *(16/21)*, M: 48.31 ± 11.95, (23–71); F: 47.52 ± 11.33, (29–66) C: *Matched on age and gender*	DSM-IV BDI: 24.73 SHAPS: 4.68	Sniffin' Sticks	**Odour Identification:** MDD < C 17 out of 37 patients were tested again during a remitted state; these patients performed similarly to controls on all odour tests
Croy et al. (2014)	55 (27/28) MDD = 27 Patients were tested before and after psychotherapy	MDD: *(0/27)*, 38.5 ± 10.6, (22–59) C: *(0/28)*, 35.3 ± 10.3, (22–56)	BDI: Before therapy: 31.2 ± 9.3 After therapy: 27.8 ± 11.7 HAM-D: Before therapy: 25.4 ± 8.7 After therapy: 22.2 ± 9.7	Sniffin' Sticks	**Odour Identification:** Before therapy: MDD = C After therapy: MDD = C **Odour Discrimination** Before therapy: MDD < C After therapy: MDD = C
Kamath et al., 2018a,b	345 (273/72) BP(I) = 43 BP(II) = 48 MDD = 134 ANX = 48	BP(I): *(15/28)*, 43.66 ± 12.61 BP(II): *(19/29)*, 44.85 ± 15.60 MDD: *(37/97)*, 50.31 ± 14.87 ANX: *(12/36)*, 48.78 ± 17.12 C: *(42/30)*, 50.50 ± 18.09	Disorder severity: BP(I): Mild = 2.3 % Moderate = 23.3 % Severe = 74.4 % BP(II): Mild = 10.4 % Moderate = 56.3 % Severe = 33.3 % MDD: Mild = 7.9 % Moderate = 66.9 % Severe = 25.2 % ANX: Mild = 8.7 % Moderate = 71.7 % Severe = 19.6 %	UPSIT Sniffin' Sticks	**Odour Identification (UPSIT):** MDD, BP(I)$^{+}$ < BP(I)– = BP(II) = ANX = C Impaired odour identification associated with: Disorder severity (BP(I), MDD) Impaired lifetime global functioning (GAF) (BP(I)) **Odour Discrimination (Sniffin' Sticks):** BP(I) = BP(II) = ANX = MDD = C

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Table 4 (*continued*)

Study	*n* (Patients/Controls) and Diagnosis	Gender *(Male/Female)*, Mean Age ± SD (years)	Disease Severity	Olfactory Test	Findings
Khil et al. (2016)	1283 (728/555) MDD = 728	MDD: *(311/417)*, 49.9 ± 7.3 C: *(281/274)*, 53.1 ± 8.0	ICD-10 HAM-D: 13.4 ± 6.5	Sniffin' Sticks	**Odour Identification:** MDD = C Impaired odour identification associated with: Prevalence of recurrent MDD Higher depression ratings (HAM-D) (first diagnosis MDD patients only)
Kopala et al. (1994)	260 (183/77) SZ = 131 MDD = 21 ED = 31	SZ: *(92/38)*, 27.3 ± 7.8, (16–52) MDD: *(8/13)*, 37.0 ± 9.6, (21–56) ED: *(0/31)*, 20.9 ± 5.0, (14–40) C: *(30/47)*, 32.5 ± 11.1, (19–64)	DSM-III-R	UPSIT	**Odour Identification:** SZ < ED = MDD = C
Negoias et al. (2010)	42 (21/21) MDD = 21	MDD: *(4/17)*, 36.86 ± 10.13, (21–55) C: *(6/15)*, 39.62 ± 11.39, (20–52)	DSM-IV BDI: 29.67 ± 10.84, (11–51)	Sniffin' Sticks	**Odour Identification:** MDD = C **Odour Discrimination:** MDD = C
Pentzek et al. (2007)	70 (40/30) AD = 20 MDD = 20	AD: *(5/15)*, 75.95 ± 9.09 MDD: *(5/15)*, 73.45 ± 5.61 C: *(6/24)*, 77.07 ± 6.81	ICD-10 (MDD) NINCDS-ADRDA (AD) ADAS – cognitive subscale: AD: 25.05 ± 7.57 MDD: 9.40 ± 3.22 C: 8.83 ± 3.02 HAM-D AD: 5.10 ± 4.72 MDD: 19.05 ± 7.57 C: 13.00 ± 3.61	Sniffin' Sticks	**Odour Identification:** AD < MDD = C
Rottstaedt et al. (2018)	135 (84/51) All patients had 1 − 6 comorbidities: MDD = 68 ANX = 50 SOM = 17 PTSD = 44 SUBS = 9 ED = 14	P: *(19/65)*, 40.2 ± 12.0, (19–62) C: *(25/26)*, 39.2 ± 13.0, (20–69)	BDI-II: P: 31.4 ± 12.2 C: 2.8 ± 2.8	Sniffin' Sticks	**Odour Identification:** P = C
Serby et al. (1990)	46 (23/23) SZ = 14 MDD = 9	SZ: *(14/0)*, Age range 40–49 MDD: *(9/0)*, Age range 50–59 C: *(23/0)*, Age range 40–59	DSM-III-R HAM-D: MDD: 19.9 ± 1.6 (SEM)	UPSIT	**Odour Identification:** MDD, SZ < C
Striebel et al. (1999)	71 (55/16) SZ = 16 BP^+ = 18 MDD^+ = 1 BP– = 12 MDD– = 8 All SZ patients treatment-refractory	SZ: *(14/2)*, 34.75 ± 9.53, (20–57) \BP^+/MDD^+: *(10/9)*, 45.05 ± 11.43, (23–66) BP–/MDD–: *(11/9)*, 45.45 ± 11.39, (23–65) C: *(13/3)*, 33.56 ± 9.23, (23–48)	DSM-III-R	UPSIT	**Odour Identification**: BP^+/MDD^+ < BP–/MDD– < C; SZ = BP^+/MDD^+, BP–/MDD–
Swiecicki et al. (2009)	76 (46/30) RDD = 20 BP(I) = 10 BP(II) = 11 FE = 5	RDD: *(3/17)*, 35.7 ± 2.3 BP: *(8/13)*, 39.6 ± 2.5 C: *(9/21)*, 35.4 ± 2.1	DSM-IV MMSE: RDD: 27.9 ± 0.4 BP: 28.5 ± 0.5 C: 28.6 ± 0.2 HAM-D: RDD: 15.2 ± 1.6 BP: 14.1 ± 1.0 C: 0.5 ± 0.3 BDI: RDD: 27.2 ± 2.8 BP: 23.2 ± 1.8 C: 1.9 ± 0.5	Sniffin' Sticks	**Odour Identification:** RDD = BP = C

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Table 4 (*continued*)

Study	*n* (Patients/Controls) and Diagnosis	Gender *(Male/Female)*, Mean Age ± SD (years)	Disease Severity	Olfactory Test	Findings
Warner et al. (1990)	26 (18/8) SZ = 12 MDD = 6	SZ: *(12/0)*, 34 (20–42) MDD: *(6/0)*, 37 (28–50) C: *(8/0)*, 32 (20–44)	RDC	UPSIT	**Odour Identification:** SZ < MDD = C

AD: Alzheimer's Disease; ADAS: Alzheimer's Disease Assessment Scale; ANX: Anxiety Disorder; BDI: Beck Depression Inventory; BDI-II: Beck Depression Inventory, Second Edition; BP: Bipolar Disorder; BP+: Bipolar Disorder with psychosis; BP–: Bipolar Disorder without psychosis; BP(I): Bipolar Disorder Type I; BP(II): Bipolar Disorder Type II; C: Controls; DSM-III: Diagnostic and Statistical Manual of Mental Disorders, Third Edition; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revision; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ED: Eating Disorder; FE: First Lifetime Episode of Depression; HAM-D: Hamilton Depression Scale; ICD-10: International Classification of Diseases – Tenth Edition; LLD: Late-Life Depression; MDD: Major Depressive Disorder; MDD+: Major Depressive Disorder with psychosis; MDD–: Major Depressive Disorder without psychosis; MDE: Major Depressive Episode; MMSE: Mini Mental Status Exam; NINCDS-ADARDA: National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; P: Patients; PTSD: Post-Traumatic Stress Disorder; RDC: Research Diagnostic Criteria; RDD: Recurrent Depressive Disorder; SHAPS: Snaith-Hamilton Pleasure Scale; SOM: Somatoform Disorders; SUBS: Substance Abuse; SZ: Schizophrenia; UPSIT: University of Pennsylvania Smell Identification Test.

(2020). Discrepancies in odour identification ability across studies in bipolar patients cannot be easily explained. It is possible that the deficits are associated with the severity of psychotic or manic symptoms (Kamath et al., 2018a,b). Future studies on olfaction in bipolar disorder will need to report the subtype of bipolar disorder in their patient populations and to include measures of psychotic, manic and depressive symptoms as well as medication usage. This may help elucidate the pattern of olfactory deficits in this disease and inform how this may be used to discriminate bipolar disorder from FTD.

4.4. Cognitive and neuroanatomical correlates of odour identification and odour discrimination impairments (Table 6)

Disease-specific profiles of olfactory function may rest upon differences in cognitive or neuroanatomical processes underlying odour identification and discrimination. Specifically, to successfully identify odours on odour identification tasks, higher cognitive skills including verbal and semantic skills are required (Fagundo et al., 2015; Frasnelli et al., 2010). Studies in healthy older individuals have shown correlations between general semantic memory, verbal fluency and odour identification ability (Larsson et al., 2000, 2004). These complex cognitive skills have been found to be deficient in FTD (Johnen and Bertoux, 2019; Possin et al., 2013; Stopford et al., 2012). In contrast, odour discrimination is non-verbal, does not require semantic recognition of the odour, and is relatively more reliant on perceptual clarity (Hummel et al., 1997) which is not specifically impaired in FTD (Johnen and Bertoux, 2019; Possin et al., 2013; Stopford et al., 2012).

Odour identification ability in healthy young adults has been correlated with grey matter volume of a number of brain regions extending from the right insular cortex to the right superior temporal gyrus (Frasnelli et al., 2010). Although there is no direct evidence to date of neuroanatomical correlates of odour identification impairments in FTD, odour identification impairments in AD are significantly correlated with loss of grey matter in the right entorhinal cortex and right parahippocampal gyrus (Witoonpanich et al., 2013). Interestingly, both regions are implicated in FTD (including bvFTD and SD) and schizophrenia, and both disorders are associated with odour identification impairments. On the other hand, in depressive and bipolar disorders, the extent to which the right parahippocampal and entorhinal cortices remain integrous is in alignment with the relative preservation of odour identification ability in these disorders. More direct correlative evidence is required however, to confirm the association between these brain regions and odour identification ability in these populations.

Evidence regarding the neural correlates of odour discrimination is scarce. However, structural and/or functional damage to the olfactory bulb observed in schizophrenia may contribute to the odour discrimination deficits observed in this population (Kamath et al., 2018a,b). Studies have shown that schizophrenia patients have reduced posterior nasal cavity and olfactory bulb volumes, as well as smaller depth of the olfactory sulcus (Nguyen et al., 2011). Smaller olfactory bulb volume has also been reported in first-degree relatives of schizophrenia patients (Turetsky et al., 2003a). The same goes for Alzheimer's disease: odour discrimination impairments are common (as are those of identification and threshold) (Doty et al., 2015) and the olfactory bulb is heavily affected (Attems et al., 2014; Mundinano et al., 2011). As such, the olfactory bulb appears to be involved in multiple facets of olfactory deficits. The odour discrimination deficits found in patients diagnosed with schizophrenia patients may also arise from the additional demands on already depleted attentional and working memory capacities in this population (Hedner et al., 2010)

4.5. Limitations and future directions of smell testing in patients with neurodegenerative disorders

Currently, it is difficult to establish whether patients have decreased olfactory testing results due to ageing, genetic variability in odorant receptors, differences in odour knowledge, abnormalities in semantic processing, cognitive dysfunction, or lengthy testing procedures that require more concentration. Solving these issues is the first step towards the development of more accurate olfactory tests for neurodegenerative diseases.

It is yet not possible to distinguish healthy age-related smell loss from neurodegenerative disorders based on smell testing only. Thus, interpreting smell test results remains a problem in the elderly. Of note, even if the FTD patients in this review were considerably older than the psychiatric patients, we don't expect age to be a confound, as patient groups of different ages were not directly compared (e.g. 60-year old FTD group vs. 35-year old schizophrenia group). Rather, all comparisons were made between groups of age-matched patients and controls. During the ageing process, there is a decreased number of olfactory receptors and axons reaching the olfactory bulb (Kalmey et al., 1998; Paik et al., 1992). The olfactory epithelium is progressively replaced by respiratory epithelium. Therefore, a single molecule entering the nasal cavity has a decreased probability of activating olfactory receptors compared to younger subjects. As a consequence, olfactory threshold scores assessed by a single molecule are lower in age-related smell loss, but also in neurodegenerative disorders (e.g. Parkinson's Disease) (Griep et al., 1997; Lotsch et al., 2008). An important step in assessing olfaction in this field is to discriminate both conditions, possibly with a threshold test that is not affected by decreased number of functional olfactory receptors in the epithelium. This issue could be solved by using threshold tests based on odour-mixtures of many molecules that increase the probability of encountering a suitable receptor. This approach has been shown effective in addressing a similar problem: subjects with an intact sense of smell that have a low score in olfactory threshold because they genetically lack a set of specific receptors sensitive to the tested single molecule (Amoore, 1967; Hsieh et al., 2017). In theory, assuming that patients with age-related smell loss do not

Table 5
Publications on odour identification/discrimination in bipolar disorder.

Study	*n* (Patients/Controls) and Diagnosis	Gender *(Male/Female)*, Mean Age ± SD (years)	Disease Severity	Olfactory Test	Findings
Amsterdam et al. (1987)	102 (51/51) MDD, BP(II) = 51	MDD, BP(II): *(17/34)*, M: 49 ± 14; F: 43 ± 13 C: *Matched on age and gender*	DSM-III	UPSIT	Odour Identification: MDD = BP(II) = C
Cumming et al. (2011)	69 (47/22) SZ = 27 BP = 20	SZ: *(15/12)*, 37.1 ± 8.4 BP: *(10/10)*, 34.6 ± 11.3 C: *(11/11)*, 35.5 ± 9.8	DSM-IV BPRS: SZ: 20.6 ± 15.0 BP: 16.3 ± 9.5 SAPS: SZ: 21.9 ± 20.7 SANS: SZ: 23.7 ± 15.9 YMRS: BP: 9.9 ± 8.0 HRSD: BP: 11.2 ± 5.7	UPSIT	Odour Identification: SZ < BP < C
Hardy et al. (2012)	64 (20/44) BP = 20	BP: *(5/15)*, M: 31.1 ± 5.7, F: 35.6 ± 9.7; (20–53) C: *(18/26)*, M: 29.5 ± 8.3, F: 34.7 ± 13.4; (18–61)	DSM-IV YMRS: 4.3 ± 3.1 (0–9)	UPSIT	Odour Identification: BP = C
Kamath et al., 2018a,b	345 (273/72) BP(I) = 43 BP(II) = 48 MDD = 134 ANX = 48	BP(I): *(15/28)*, 43.66 ± 12.61 BP(II): *(19/29)*, 44.85 ± 15.60 MDD: *(37/97)*, 50.31 ± 14.87 ANX: *(12/36)*, 48.78 ± 17.12 C: *(42/30)*, 50.50 ± 18.09	Disorder severity: BP(I): Mild = 2.3 % Moderate = 23.3 % Severe = 74.4 % BP(II): Mild = 10.4 % Moderate = 56.3 % Severe = 33.3 % MDD: Mild = 7.9 % Moderate = 66.9 % Severe = 25.2 % ANX: Mild = 8.7 % Moderate = 71.7 % Severe = 19.6 %	UPSIT Sniffin' Sticks	Odour Identification (UPSIT): MDD, BP(I)$^+$ < BP(I)– = BP(II) = ANX = C Impaired odour identification associated with: Disorder severity (BP(I), MDD) Impaired lifetime global functioning (GAF) (BP(I)) Odour Discrimination (Sniffin' Sticks): BP(I) = BP(II) = ANX = MDD = C
Lahera et al. (2016)	79 (39/40) BP = 39 All patients had euthymic bipolar	BP: *(17/22)*, 46.82 ± 14.8 C: *(27/19)*, 9.78 ± 18.8	DSM-IV-TR HAM-D: 2.51 ± 2.9 YMRS: 1.31 ± 1.9 GAF: 72.3 ± 16.9 FAST: 21.49 ± 18.8	UPSIT	Odour Identification: BP < C Impaired odour identification associated with: Impaired working memory Impaired sustained attention
Negoias et al. (2019)	49 (27/22) BP(I) = 25 BP(II) = 2 All patients had euthymic bipolar	BP: *(11/16)*, 35.63 ± 8.23 C: *(10/12)*, 34.5 ± 8/26	DSM-IV	Sniffin' Sticks	Odour Identification: BP = C Odour Discrimination: BP = C
Striebel et al. (1999)	71 (55/16) SZ = 16 BP$^+$ = 18 MDD$^+$ = 1 BP– = 12 MDD– = 8 All SZ patients treatment-refractory	SZ: *(14/2)*, 34.75 ± 9.53, (20–57) BP$^+$/MDD$^+$: *(10/9)*, 45.05 ± 11.43, (23–66) BP–/MDD–: *(11/9)*, 45.45 ± 11.39, (23–65) C: *(13/3)*, 33.56 ± 9.23, (23–48)	DSM-III-R	UPSIT	Odour Identification: BP$^+$/MDD$^+$ < BP–/MDD– < C; SZ = BP$^+$/MDD$^+$, BP–/MDD–

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Table 5 (*continued*)

Study	*n* (Patients/Controls) and Diagnosis	Gender *(Male/Female)*, Mean Age ± SD (years)	Disease Severity	Olfactory Test	Findings
Swiecicki et al. (2009)	76 (46/30) RDD = 20 BP(I) = 10 BP(II) = 11 FE = 5	RDD: *(3/17)*, 35.7 ± 2.3 BP: *(8/13)*, 39.6 ± 2.5 C: *(9/21)*, 35.4 ± 2.1	DSM-IV MMSE: RDD: 27.9 ± 0.4 BP: 28.5 ± 0.5 C: 28.6 ± 0.2 HAM-D: RDD: 15.2 ± 1.6 BP: 14.1 ± 1.0 C: 0.5 ± 0.3 BDI: RDD: 27.2 ± 2.8 BP: 23.2 ± 1.8 C: 1.9 ± 0.5	Sniffin' Sticks	Odour Identification: RDD = BP = C

ANX: Anxiety Disorder; BDI: Beck Depression Inventory; BP: Bipolar Disorder; BP+: Bipolar Disorder with psychosis; BP–: Bipolar Disorder without psychosis; BP(I): Bipolar Disorder Type I; BP(II): Bipolar Disorder Type II; BPRS: Brief Psychiatric Rating Scale; C: Controls; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revision; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; FAST: Functioning Assessment Short Test; FE: First Lifetime Episode of Depression; GAF: Global Assessment of Functioning (taken from DSM-IV); HAM-D: Hamilton Depression Scale; HRSD: Hamilton Rating Scale for Depression; MDD: Major Depressive Disorder; MDD+: Major Depressive Disorder with psychosis; MDD–: Major Depressive Disorder without psychosis; MMSE: Mini Mental Status Exam; RDD: Recurrent Depressive Disorder; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; SZ: Schizophrenia; UPSIT: University of Pennsylvania Smell Identification Test; YMRS: Young Mania Rating Scale.

Table 6
Possible neuroanatomical correlates of odour identification in FTD, Alzheimer's disease and psychiatric disorders.

Anatomical region involved in odour identification	AD	bvFTD	SD	SZ	Dep	BP	References
Right parahippocampal gyrus	X	X	X	X	X	X / ✓	AD: Chan et al. (2001); Chen et al. (2018); Witoonpanich et al. (2013) bvFTD: Seeley et al. (2008) SD: Chan et al. (2001); Galton et al. (2001), SZ: Rimol et al. (2010); Shenton et al. (2001); Turetsky et al., 2003a Dep: Bora et al. (2012); Chen et al. (2018) BP: Impaired: Chen et al. (2011); Negoias et al. (2019); Rimol et al. (2010); Intact: Nenadic et al. (2017)
Right entorhinal cortex	X	X	X	X	✓	X	AD: Chan et al. (2001); Chen et al. (2018); Witoonpanich et al. (2013) bvFTD: Frisoni et al. (1999) SD: Chan et al. (2001); Galton et al. (2001) SZ: Atanasova et al. (2008); Rimol et al. (2010); Shenton et al. (2001); Turetsky et al., 2003a,b Dep: Chen et al. (2018) BP: Nenadic et al. (2017)
Right anterior transverse temporal gyrus (superior temporal gyrus)	X / ✓	X	X	X	X / ✓	X / ✓	AD: Impaired: Chen et al. (2018); Intact: Chan et al. (2001) bvFTD: Seelaar et al. (2011) SD: Chan et al. (2001) SZ: Ellison-Wright and Bullmore (2010); Rimol et al. (2010) Dep: Impaired: Bora et al. (2012); Chen et al. (2018); Intact: Koolschijn et al. (2009) BP: Impaired: Negoias et al. (2019); Intact: Nenadic et al. (2017); Rimol et al. (2010)
Right insula	X	X	?	X / ✓	X	X	AD: Chen et al. (2018) bvFTD: Schroeter et al. (2008); Seelaar et al. (2011); Seeley et al. (2008) SZ: Impaired: Ellison-Wright and Bullmore (2010); Intact: Atanasova et al. (2008) Dep: Impaired: Chen et al. (2018), Intact: Bora et al. (2012) BP: Blond et al. (2012); Ellison-Wright and Bullmore (2010); Negoias et al. (2019)
Right medial orbitofrontal cortex	X	X	X	X	X / ✓	✓	AD: Kumfor et al. (2016); Palmqvist et al. (2017) bvFTD: Schroeter et al. (2008); Seelaar et al. (2011) SD: Kumfor et al. (2016) SZ: Rimol et al. (2010); Shenton et al. (2001) Dep: Impaired: Koolschijn et al. (2009); Intact: Kempton et al. (2011) BP: Nenadic et al. (2017); Rimol et al. (2010)
Left & right olfactory bulbs	X	?	?	X	X	?	AD: Witoonpanich et al. (2013) SZ: Atanasova et al. (2008); Chen et al. (2018) Dep: Asal et al. (2018); Chen et al. (2018); Negoias et al. (2019), 2010

X = affected; ✓= preserved; ? = mixed findings. AD: Alzheimer's disease; bvFTD: behavioural variant frontotemporal dementia, SD: semantic dementia; SZ: schizophrenia; Dep: depressive disorders; BP: bipolar disorder. Brain regions were selected based on neuroanatomical correlates of odour identification in healthy young adults from Frasnelli et al. (2010) and in Alzheimer's disease patients from Witoonpanich et al. (2013).

have abnormalities in central olfactory brain regions, they would have a decreased sensitivity measured by single molecules (e.g. phenyl-ethyl alcohol) and a normal general sensitivity measured by odour-mixtures. On the other hand, patients with central deficits may have a low score for both measures indicating a general loss of smell. Therefore, both conditions could be distinguished, in theory, by combining odour-mixtures and single-molecule-based threshold test results, which rely less on executive function compared to discrimination and identification tests.

It is unlikely that these two later tests, if based on single molecules, will contribute to this differentiation process because their scores are known to be affected in age-related smell loss. Indeed, olfactory sensory neurons are not only decreased in number with age, but they also lose their specificity to odorants and become less responsive to heavier molecules (Sinding et al., 2014), which leads to impairment in discrimination and identification capabilities.

Unlike the olfactory epithelium, the glomerular organisation of the olfactory bulb in healthy ageing may not differ from younger human subjects (Maresh et al., 2008). This observation supports the idea that assessment of central processing for odour discrimination remains possible if the subjects are minimally affected by the above-mentioned age-related changes in the olfactory epithelium (periphery).

Another issue to be solved is the inter-individual variability in familiarity with the tested odours and semantic capability of all patients, especially children and the elderly, undergoing identification and discrimination tests (Doty et al., 1984a; Jiang et al., 2010; Rabin, 1988). For example, it would be unsuitable to diagnose olfactory dysfunction using an identification test alone in patients from different cultures and/or suffering from semantic dementia. This pathological result would be currently difficult to interpret and may reflect cultural differences or semantic dysfunction rather than a true dysfunction in the olfactory system. On the other hand, normal identification and threshold test results may signify intact peripheral and fronto-temporal functioning.

Some efforts have been made to overcome the semantic limitations of olfactory tests in FTD and other dementia populations. For instance, Rami et al. (2007); Piwnica-Worms et al. (2010) and Omar et al. (2013) used a modified UPSIT including both word and pictures for each odour option, to reduce the effect of impaired single-word comprehension on the results. In each study, all FTD subtypes (bvFTD, SD, PNFA) were impaired despite the non-verbal option. In particular, the patients of Rami et al. (2007) performed normally on a picture-word matching test, but struggled to match odours to words or pictures in the modified UPSIT. Luzzi et al. (2007) and Greenberg et al. (2011) further looked at the difference between verbal and visual versions of the UPSIT and found no significant difference between them for any disease subgroup (bvFTD, SD, AD or CBD). Taken together, these findings suggest the odour identification impairments do not reflect general language/verbal or cross-modal matching (semantic) deficits, but are specific to the modality of olfaction.

Odour identification tests also represent an operational burden on translational research and healthcare because many countries lack a validated identification test, which needs to be adapted to every country/culture. International efforts have focused on identifying odours that are cross-cultural but only a handful have been identified. This limited number of universally recognisable odours is insufficient to accurately quantify the degree of smell loss which will be important to monitor disease progression. This issue can be solved by using tests composed of unfamiliar smells, which can be generated by using complex odour-mixtures named “white smells” (Weiss et al., 2012). Based on these “white smells”, it is possible to create non-semantic olfactory sensitivity and fine discrimination acuity (or resolution) tests that are free of these biases (Hsieh et al., 2017) and perhaps better probe the olfactory system in these specific cases.

Finally, regardless of the field, psychophysical measures depend on patients’ collaboration, which requires a certain level of executive functioning. For neurodegenerative disorders, effort should be made to create tests that are less cognitively demanding by decreasing the testing time, reducing the number of stimuli that patients need to remember, and by decreasing the number of trials. Towards these goals, effective testing paradigms exist but remain to be adapted (Höchenberger and Ohla, 2019). An alternative solution would be to use objective tests such as functional MRI or olfactory-event-related potential, but they have limitations such as the cost, inability to quantify olfactory function on an individual level, and they are mostly used for research purposes (Han et al., 2018; Lötsch and Hummel, 2006).

In any case, we recommend to first rule out other etiologies of smell loss (e.g. sinonasal disease that frequently affects the general population) and to test cognitive/executive functioning before interpreting smell test results. Determining a cut-off score below which a smell test cannot be reliably interpreted could be useful.

With our colleagues at the Rockefeller University, we are currently implementing all these changes for the development of SMELL-RS, a universal olfactory resolution (R) and olfactory sensitivity (S) test. In combination with existing cognitive, smell, and imaging assessments, we hope that this new technology will improve the management of patients with FTD and other neurodegenerative disorders. These tests would also be useful in future large-scale cohort studies of populations at genetic risk for FTD to determine whether olfactory testing can predict progression to FTD as shown for AD (Devanand et al., 2015, 2008).

5. Conclusions

This review indicates that two olfactory tests, namely odour identification and odour discrimination, have the potential to differentiate FTD from depression and schizophrenia. Studies comparing odour detection, discrimination and identification directly across these different disease groups would be required to strengthen this conclusion. Distinction between FTD and late-onset bipolar disorder, however, appears challenging based solely on olfactory testing. Commercially-available smell tests have to be improved and integrated into a framework comprising clinical examination (e.g. nasal endoscopy) and a combination of diverse smell, cognitive, imaging tests to accurately measure olfactory function and interpret testing results in this population.

Declaration of Competing Interest

JWH is the inventor of SMELL-RS described in the international patent WO2019010172, published on the 10th of January 2019.

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