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Review Article

The Association Between Olfaction and Depression: A Systematic Review

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Abstract

Previous studies on the relationship between olfaction and depression have revealed mixed results. In addition, few have focused on the reciprocity of this association. The aim of this study is to combine depression and olfactory data in two separate patient populations to further understand their association. A systematic literature review was conducted using 3 online databases to identify studies correlating olfaction and depression in patients presenting with either primary depression or primary olfactory dysfunction. For the depressed population, weighted means and standard deviations for the Sniffin' Sticks Test and the 40-item Smell Identification Test were combined using 10 studies. For the olfactory dysfunction population, weighted means of Beck's Depression Inventory were combined using 3 studies. Independent *t*-tests were used to compare differences between groups. Comparing primary depressed patients with controls, depressed patients showed decreased scores in olfactory threshold (6.31 ± 1.38 vs. 6.78 ± 0.88, $P = 0.0005$), discrimination (12.05 ± 1.44 vs. 12.66 ± 1.36, $P = 0.0073$), identification (12.57 ± 0.74 vs. 12.98 ± 0.90, $P < 0.0001$), and 40-Item Smell Identification Test (35.31 ± 1.91 vs. 37.41 ± 1.45, $P < 0.0001$). In patients with primary olfactory dysfunction, Beck's Depression Inventory scores were significantly different between patients classified as normosmics, hyposmics and anosmics (5.21 ± 4.73 vs. 10.93 ± 9.25 vs. 14.15 ± 5.39, $P \leq 0.0274$ for all 3 comparisons). In conclusion, patients with depression have reduced olfactory performance when compared with the healthy controls and conversely, patients with olfactory dysfunction, have symptoms of depression that worsen with severity of smell loss.

Key words: anosmia, BDI, hyposmia, normosmia, SIT-40, Sniffin' Sticks

Introduction

Depression and olfactory dysfunction are chronic conditions that commonly affect adults in the United States. Major depression is the most common mental health disorder in the United States, and in 2013, 6.7% (an estimated 15.7 million) of adults had at least 1 major depressive episode in the past year (NIMH 2015). Olfactory dysfunction is also a prevalent condition. In 2011–2012, 10.6% (an estimated 15.1 million) of US adults over the age of 40 reported problems with their sense of smell in the past year (Bhattacharyya 2005). Although these disorders often coexist in the same patients, their exact relationship is not entirely clear (Negoias et al. 2010; Burón and Bulbena 2013; Croy et al. 2014a).

Evolutionarily, the olfactory bulb (OB) is the most primitive of brain structures and gave rise to the ancient limbic system that refers to the network of neural structures responsible for emotional processing (Joseph 2013). Human survival once depended on the

hardwiring between the olfactory and limbic systems to run away or attack based upon odor molecules of predators or prey or to feed on the edible instead of poisonous (Croy et al. 2014a). As the neocortex developed, reliance on neural connections between the OB and limbic organs lessened; however, olfactory projections to core limbic structures, such as the amygdala, hippocampus, insula, anterior cingulate cortex, and orbitofrontal cortex, remain (Heimer et al. 2007). The piriform cortex that composes the majority of the primary olfactory cortex sends signals to the higher order orbitofrontal cortex via the amygdala (Soudry et al. 2011). The secondary olfactory cortex is located in the input section of the hippocampus (Soudry et al. 2011). These areas also transmit "top-down" reciprocal axons (Krusemark et al. 2013).

Both the OB and limbic system are highly plastic structures that can change organizational networks based on environmental input and output. For example, in cases of reduced olfactory sensory input such as in post-viral or post-traumatic olfactory loss, OB volumes have been shown to be smaller than a normosmic population (Negoias et al. 2010).

These shared neural connections implicate a bidirectional relationship between olfaction and depression. Deems et al. conducted one of the earliest and largest studies examining this concept, demonstrating variations in depression scores exist among dysosmic patients (Deems et al. 1991). More recent studies on the association between olfaction and depression have used validated methods of classifying olfactory dysfunction and depression but have shown mixed results. This is likely due to differences in patient populations, with some studies using patients with primary olfactory loss and others using patients with primary depression, varying measures of olfactory function, and small patient cohorts. The purpose of this study is to systematically evaluate data from two juxtaposed patient populations—one with primary olfactory loss, the other with primary depression—to more clearly understand the reciprocal relationship between olfaction and depression.

Materials and methods

Literature search strategy

A comprehensive literature search of the PubMed, Scopus, and PsycINFO online databases was performed on 22 September 2015. Search terms included and related to "olfaction," "smell," and "depression." The full search strategy can be found in the Supplemental Section. Language or date filters were not applied with the intention of generating a broad list of potential studies. Two authors (P.K. and J.S.M.) independently conducted the searches. The resulting studies were reviewed first using titles and abstracts and then using full manuscripts. Articles were categorized into those using a primary depression or primary olfactory dysfunction patient population. References from reviewed manuscripts were also scanned for studies of relevance. Each included study was evaluated for quality using the Oxford Center for Evidence-Based Medicine (OCEBM) criteria (OCEBM Levels of Evidence Working Group 2011).

Inclusion and exclusion criteria

For inclusion in the primary depression portion of the study, patients had to have been diagnosed with depression by a physician or by way of a validated instrument to measure symptoms of depression. Studies had to include associated data on quantitative olfactory loss in depressed patients and healthy controls. Articles were excluded if they used patient self-report to assess depression, included patients with neurocognitive or neuropsychiatric disorders other than depression, reported only subjective olfactory data, or utilized ≤2 odors for olfactory testing. For inclusion in the primary olfactory dysfunction portion of the study, patients had to have existing olfactory dysfunction as defined by patient-reported or objective measures, with no restriction on the etiology of olfactory loss. Each included study had to report measured depressive symptoms using a validated depression instrument. Reviews and individual case reports were excluded from all analyses.

Data extraction and statistical analysis

Data were extracted from studies meeting inclusion criteria by 2 authors (P.K. and J.S.M.). Extracted information included demographic characteristics, number of cases and controls, mean and standard deviations of any reported depression or olfaction data, any data on prevalence estimates, and correlations and conclusions on the relationship between olfaction and depression. All data analyses were performed with MedCal 16.2.0 (MedCalc Software bvba). Pooled n, means, and standard deviations were calculated for depressed populations if two or more studies reported olfactory data using a validated scale. Pooled n, means, and standard deviations were calculated for patients with olfactory dysfunction if two or more studies reported depression data using a validated scale. Correlation coefficients were weighted by sample size and combined for primary olfactory dysfunction studies reporting this data point. Heterogeneity across studies was assessed using the I^2 statistic. If the heterogeneity test was significant, P value for a random effects model was used. If the heterogeneity test was nonsignificant, P value for fixed effects model was used. Independent t-tests were used to compare differences between groups. A P value of <0.05 was considered statistically significant for all statistical tests.

Results

Primary depression

Search characteristics and prevalence

The database search yielded 2716 articles of which 30 full manuscripts were reviewed and 13 fulfilled inclusion/exclusion criteria. A total of 10 studies presented data that was amenable to quantitative analysis of olfactory data (Figure 1). Other studies reported mean olfactory metrics but did not report the prevalence of olfactory loss or data in such a way that would allow combined analysis. Included studies were either prospective cohorts or cross-sectional (level of evidence 3; OCEBM Levels of Evidence Working Group 2011). A summary of all included articles can be found in Table 1. Only one study reported the prevalence of olfactory impairment in a population of depressed patients: 8 of the 29 major depressive disorder patients (28%) showed olfactory impairment as assessed by total Sniffin' Sticks test scores and appropriate cut points to define normal and olfactory impairment (Rossi et al. 2015).

Olfactory impairment in depressed patients versus controls

Six studies presented data on olfactory *threshold* in a depressed and control population (Lombion-Pouthier et al. 2006; Scinska et al. 2008; Swiecicki et al. 2009; Negoias et al. 2010; Croy et al. 2014b; Rossi et al. 2015). Five of these studies tested olfactory threshold using The Sniffin' Sticks Test, which when pooled together, yielded 122 depressed patients and 169 controls (Table 2). Threshold scores were significantly lower in depressed patients when compared with the controls (6.31 ± 1.38 vs. 6.78 ± 0.88; $P = 0.0005$).

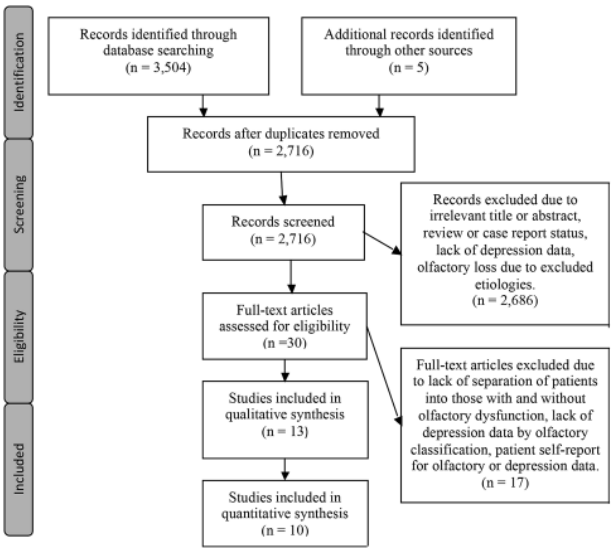


Figure 1. PRISMA flowchart outlining primary depression search strategy.

Three studies reported olfactory *discrimination* scores for depressed patients and controls using The Sniffin' Sticks Test (Negoias et al. 2010; Croy et al. 2014b; Rossi et al. 2015). Combined analysis generated 77 depressed patients and 79 controls (Table 2). Discrimination scores were significantly lower in depressed patients in comparison with the controls (12.05 ± 1.44 vs 12.66 ± 1.36; $P = 0.0073$).

Eleven studies presented data on olfactory *identification* in depressed and control populations (Serby et al. 1990; Warner et al. 1990; Kopala et al. 1994; Lombion-Pouthier et al. 2006; Pentzek et al. 2007; Scinska et al. 2008; Swiecicki et al. 2009; Clepce et al. 2010; Negoias et al. 2010; Croy et al. 2014b; Rossi et al. 2015). Six of these studies used the standard Sniffin' Sticks Test (Pentzek et al. 2007; Scinska et al. 2008; Swiecicki et al. 2009; Clepce et al. 2010; Negoias et al. 2010; Rossi et al. 2015), and 3 of these used the 40-Item Smell Identification Test (SIT-40; Serby et al. 1990; Warner et al. 1990; Kopala et al. 1994). After pooling data, a total of 152 depressed patients and 208 controls were assessed by Sniffin' Sticks, and 36 depressed patients and 94 controls were testing using SIT-40 (Table 2). Identification scores using Sniffin Sticks were significantly lower in depressed patients compared with the controls (12.57 ± 0.74 vs. 12.98 ± 0.90; $P < 0.0001$). Additionally, SIT-40 identification scores were significantly lower in depressed patients compared with the controls (35.31 ± 1.91 vs. 37.41 ± 1.45; $P < 0.0001$).

Primary olfactory dysfunction

Search characteristics and prevalence

The database search yielded 2716 articles of which 18 full-length manuscripts were reviewed and 3 fulfilled inclusion/exclusion criteria (Figure 2). All included studies were either prospective cohorts or cross-sectional (level of evidence 3). A summary of all included articles can be found in Table 3. One study reported the prevalence of depression in a population of patients with olfactory impairment: 10 of the 25 patients with chronic rhinosinusitis (40%) and 19 of the 25 patients with post-upper respiratory infection olfactory dysfunction (76%) were depressed as measured by Beck's Depression Inventory (BDI; Jung et al. 2014).

Depressive symptoms in patients with olfactory loss

Two studies were combined to yield a total of 74 normosmics, 87 hyposmics, and 49 anosmics (Katotomichelakis et al. 2013; Simopoulos et al. 2012). The weighted mean and standard deviation of BDI scores for normosmics, hyposmics, and anosmics are 5.21 ± 4.73, 10.93 ± 9.25, 14.15 ± 5.39, respectively (Figure 3). Normosmics had higher BDI scores than hyposmics ($P < 0.0001$) and anosmics ($P < 0.0001$). Hyposmics also had higher BDI scores than anosmics ($P = 0.0274$). Three studies reported correlation coefficients between BDI and TDI total scores, yielding a total of 260 patients. The weighted correlation coefficient is –0.349 ($P < 0.001$; Figure 4).

Discussion

Prior studies of depressed patients have shown varied results on olfactory function depending upon which aspects of olfaction are measured. The main objective of the primary depression segment of this study was to report the prevalence of olfactory dysfunction in a population with depression and analyze differences in olfactory performance between depressed patients and controls. We found depressed individuals to have diminished olfactory functioning when compared with nondepressed controls in multiple aspects of olfaction, including threshold, discrimination, and identification. Olfactory threshold is a test of basic acuity and measures the minimum stimulus strength needed to detect odors (Sanders and Gillig 2009). On the other hand, identification and discrimination testing involves the presentation of odorants at suprathreshold levels and necessitates higher order cognitive processing. Primary depression affects all aspects of olfaction; however, further neuroimaging and neurochemical evidence is needed to elucidate the pathophysiological mechanism as so how and the degree to which each individual dimension is affected. Additional related comorbidities could play a role. Depression is known to cause sleep disturbances (Lacruz et al. 2016). The resulting sleep dysfunction could impair cognitive function and negatively impact higher order olfactory processing required for odor identification and discrimination.

In patients with primary depression, potential physiologic mechanisms for the secondary development of olfactory dysfunction center around the release of biochemical stress molecules during depressive episodes (Negoias et al. 2010; Yuan et al. 2015). Inflammatory cytokines, particularly interleukin (IL) 6, tumor necrosis factor α (TNF-α), IL-1β, and glucocorticoids, that are elevated in depressed patients (Furtado and Katzman 2015) can limit hippocampal neurogenesis, which in turn limits the proliferation of central and peripheral olfactory neurons (Yuan and Slotnick 2014). Furthermore, depression is associated with a dysfunctional amygdala and subsequent inhibitory projections to the OB, disrupting regular olfactory function (Negoias et al. 2010). Recent studies demonstrating decreased OB volumes in depressed patients compared with the controls and a negative correlation between OB volume and olfactory sensitivity provide support to this hypothesis (Negoias et al. 2010).

The primary objective of the olfactory dysfunction segment of the study was to report the prevalence of depression in a population with olfactory dysfunction and determine whether depression scores differ depending upon the degree of olfactory dysfunction. Our results show that individuals with olfactory dysfunction often have symptoms of depression. In patients with olfactory dysfunction, the prevalence of depression ranged from 40% to 76% (Jung et al. 2014). Prior studies have found similar estimates (Temmel et al. 2002; Frasnelli and Hummel 2005). In contrast, an estimated 6.7% of the general US population had an episode of depression in the past year (NIMH 2015). Our study also illustrates that BDI scores increase with severity of olfactory impairment, with anosmics demonstrating the highest depression scores.

Table 1. Characteristics of primary depression studies

Source	# Cases	Depression metric	Olfactory test(s)	Conclusion
Clepce et al. (2010)[a]	37 depressed; 37 controls	DSM-IV BDI	Sniffin' Sticks: I VAS—intensity	Identification reduced in depressed patients compared to controls (12.081 ± 0.327 vs. 13.014 ± 0.277, $P = 0.034$). Intensity not significantly different between depressed patients and controls.
Croy et al. (2014b)[a]	27 Depressed; 28 controls	BDI HDS	Sniffin' Sticks: T, D 32-Item identification	Discrimination reduced in depressed patients compared with controls (12.5 ± 1.7 vs. 13.3 ± 1.7, $P = 0.037$). Threshold and identification not significantly different between depressed patients and controls.
Gross-Isseroff et al. (1994)	9 Depressed; 9 controls	DSM-III HDS	Threshold calculated by an ascending series of solvent concentrations.	Threshold not significantly different between depressed patients and controls.
Kopala et al. (1994)[a]	21 depressed; 77 controls	DSM-III	SIT-40	SIT-40 not significantly different between depressed patients and controls.
Lombion-Poutheir et al. (2006)	49 Depressed; 58 controls	DSM-IV BDI	Test Olfactif[b]	Sensitivity reduced in depressed patients compared with controls (4.2 ± 1.38 vs. 3.66 ± 1.36, $P < 0.035$). Identification, detection, intensity not significantly different between depressed patients and controls.
Negoias et al. (2010)[a]	21 Depressed; 21 controls	DSM-IV	Sniffin' Sticks: T, D, I	Threshold reduced in depressed patients compared with controls (7.56 ± 2.67 vs. 9.14 ± 1.89, $P = 0.032$). Discrimination and identification not significantly different between depressed patients and controls. Correlation coefficient between BDI and olfactory threshold is $r = -0.34$, $P = 0.04$
Pentzek et al. (2007)[a]	20 Depressed; 30 controls	ICD-10 HDS	Sniffin' Sticks: I	Identification not significantly different between depressed patients and controls.
Rossi et al. (2015)[a]	29 Depressed; 30 controls	DSM-V	Sniffin' Sticks: T, D, I, total Hyposmia Rating Scale (HRS)[c]	Threshold, discrimination, identification, total Sniffin' Sticks score or HRS not significantly different between depressed patients and controls.
Scinska et al. (2008)[a]	25 Depressed; 60 controls	GDS	Sniffin' Sticks: T, I	Threshold and identification not significantly different between depressed patients and controls.
Serby et al. (1990)[a]	9 Depressed; 9 controls	DSM-III	SIT-40 Threshold evaluated by using successive concentrations of geraniol.	SIT-40 scores reduced in depressed patients compared with controls (29.8 ± 2.1 vs. 37.0 ± 1.3, $P < 0.01$). Threshold not significantly different between depressed patients and controls.
Swiecicki et al. (2009)[a]	20 Depressed; 30 controls	ICD-10 HDS BDI	Sniffin' Sticks: T, I	Threshold and identification not significantly different between depressed patients and controls.
Warner et al. (1990)[a]	6 Depressed; 8 controls	RDC	SIT-40	SIT-40 not significantly different between between depressed patients and controls
Zucco et al. (2011)	12 Mildly depressed; 12 severely depressed; 12 controls	DSM-IV	10 Odorant identification and recognition[d]	Identification and recognition reduced in severely depressed patients compared with mildly depressed patients (Identification: 8.21 ± 1.05 vs. 9.33 ± 0.65, $P < 0.01$; Recognition: 7.3 ± 1.08 vs. 8.91 ± 0.66, $P < 0.01$) and compared with controls (Identification: 8.21 ± 1.05 vs. 9.58 ± 0.51, $P < 0.01$; Recognition: 7.3 ± 1.08 vs. 9.33 ± 0.77, $P < 0.01$).[e] Identification or recognition not significantly different between mildly depressed patients and controls.

T, threshold; D, discrimination; I, identification; VAS, Visual Analogue Scale; MDD, major depressive disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; BDI, Beck's Depression Inventory; HDS, Hamilton Depression Scale; ICD-10, International Classification of Mental and Behavioral Disorders; GDS, Geriatric Depression Scale; RDC, Research Diagnostic Criteria.

[a]Included in combined data analysis.

[b]Test Olfactif measures: sensitivity using forced choice procedure for 5 successive concentrations of 2 different odors; scores range from 2 (high sensitivity) to 10 (low sensitivity). Odors detection: subject chooses odorant from 4 bottles, 3 of which contain solvents. 16-odor identification test: subject picks correct label from 4 multiple choice answers. Self-rating of intensity from 0 (low intensity) to 10 (high intensity) for each of the 16 odors.

[c]HRS contains 6 Likert-type self-administered questions on recognizability of common odors.

[d]10 odorant identification—subject picks presented odor from 4 verbally presented choices. Recognition—subject smells target odorant and identifies the same odor from 4 test tubes. Scores range from 0 (lowest) to 10 (highest) for both tasks.

[e]Significance determined using pair-wise post hoc comparison using Tukey's test.

In patients with primary olfactory dysfunction, mechanisms for the development of secondary depression focus upon how abnormal olfactory functioning affects daily life. Olfaction serves to alert us to imminent dangers such as fires, gas leaks, or poisonous fumes. Patients with olfactory dysfunction experience anxiety over their ability to protect themselves and family members from such hazards (Croy et al. 2014a). Olfaction also has a prominent role in food behavior. Sense of smell not only plays a key role in cooking and enjoying meals but also in detecting spoiled or inedible food (Croy et al. 2014a). As a result, patients with olfactory dysfunction may develop decreased appetites and are less inclined to socialize over meals (Rolls 2015). Lack of awareness for personal hygiene can also have psychosocial consequences resulting in isolation and vulnerability (Croy et al. 2014a). On a neurological level, the olfactory bulbectomy animal model, in which removing the OB leads to chemical and behavioral pathology characteristic of a depressed state, is well described (Yuan and Slotnick 2014; Song and Leonard 2005). Moreover, olfactory loss may decrease the intensity of stimulus going from the OB to the limbic system, limiting effective management of emotions and enhancing feelings of fear and sadness.(Croy et al. 2014a; Negoias et al. 2010) Lastly, it is also possible that the pro-inflammatory cytokine dysfunction occurring in several conditions causing olfactory loss, such as CRS, cross the blood–brain barrier to affect the hippocampus, limiting neurogenesis, and amygdala, promoting emotional instability (Yuan and Slotnick 2014). IL-6 and TNF-α have been particularly implicated (Yuan and Slotnick 2014; DeConde et al. 2015; Soler et al. 2015)

Table 2. Combined measures of olfaction in depressed patients and nondepressed controls

	Patients (*n*)	Score (Mean, SD)	*P* value
Sniffin' Sticks Test			
Threshold			
Depressed	122	6.31 (1.38)	0.0005
Controls	169	6.78 (0.88)	
Discrimination			
Depressed	77	12.05 (1.44)	0.0073
Controls	79	12.66 (1.36)	
Identification			
Depressed	152	12.57 (0.74)	<0.0001
Controls	208	12.98 (0.90)	
SIT-40			
Depressed	36	35.31 (1.91)	<0.0001
Controls	94	37.41 (1.45)	

SIT-40: 40-Item Smell Identification Test.

The data support the concept of a reciprocal relationship between olfaction and depression in two distinct populations—those with primary depression and those with primary olfactory dysfunction. This complementary relationship involves psychosocial aspects of depression and olfactory dysfunction as well as anatomical overlap and communication between the olfactory and limbic systems. The clinical impact of this association is currently unknown. However in theory, symptoms of olfactory impairment in depressed patients may serve as an objective marker in diagnosis. Similarly, enhanced screening for depression in patients with olfactory impairment may improve global health outcomes by allowing introduction of timely mental health services or medication.

The strengths of this study include the power and precision gained by combining individual studies to yield relatively large sample sizes. A comparison with a control population was achieved for the primary depression population, and in the olfactory dysfunction population, normosmics served the purpose of controls. Olfaction was also comprehensively assessed by examining threshold, discrimination, and identification instead of solely relying on one measure. Inherent to systematic reviews is potential for publication bias that can skew results toward significance and heterogeneity between studies. Moreover, our results likely underestimate olfactory dysfunction in those with primary depression and depression in those

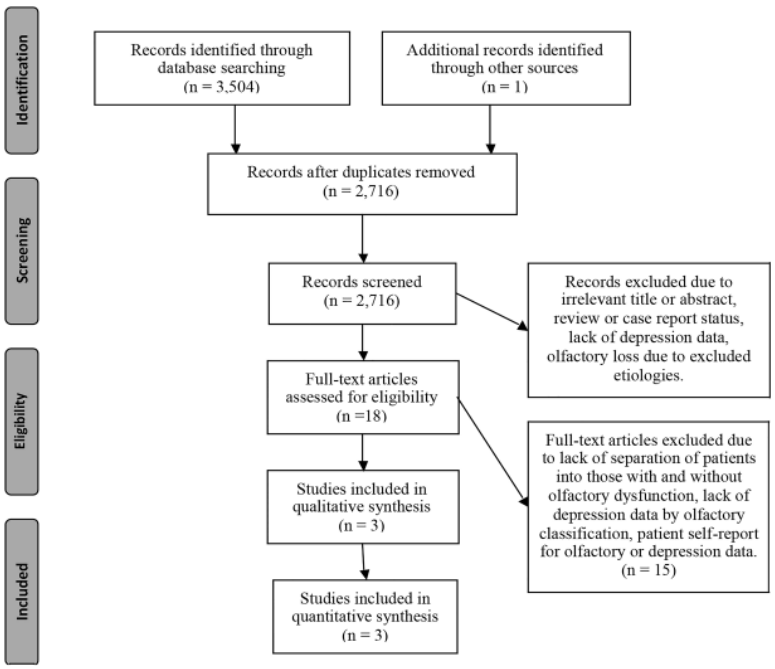


Figure 2. PRISMA flowchart outlining primary olfactory dysfunction search strategy

Table 3. Characteristics of primary olfactory dysfunction studies

Source	Cause of olfactory dysfunction	Olfactory test	Case # by olfactory status	Depression metric	Conclusion
Jung et al. (2014)[a]	CRS	Sniffin' Sticks	25 hyposmics or anosmics	BDI	Correlation coefficient between BDI and T, D, I total score in CRS group is –0.423, $P = 0.035$.
	Post-URI		25 hyposmics or anosmics	BDI	Correlation coefficient between BDI and T, D, I total in post-URI group is –0.092, p=0.663.
Katotomichelakis et al. (2013)[a]	CRS and AR	Sniffin' Sticks	40 Normosmics, 42 hyposmics, 26 anosmics	BDI; ZDS	Anosmics scored worse than hyposmics on BDI (14.54 ± 6.32 vs. 10.69 ± 9.31, $P = 0.025$) and ZDS (44.62 ± 8.42 vs. 35.60 ± 6.08, $P < 0.001$). Anosmics scored worse than normosmics on BDI (14.54 ± 6.32 vs. 5.23 ± 4.12, $P < 0.001$) and ZDS (44.62 ± 8.42 vs. 35.35 ± 8.64, $P < 0.001$). Hyposmics scored worse than normosmics on BDI ($P = 0.004$). Correlation coefficient between BDI and T, D, I total score is $r = -0.395$, $P < 0.001$. Correlation coefficient between ZDS and T, D, I total score is $r = -0.321$, $P < 0.001$.
Simopoulos et al. (2012)[a]	CRS	Sniffin' Sticks	34 Normosmics, 45 hyposmics, 23 anosmics	BDI	Anosmics scored worse than normosmics on BDI (13.70 ± 4.33 vs. 5.18 ± 5.44, $P < 0.001$). Hyposmics scored worse than normosmics on BDI (11.16 ± 9.20 vs. 5.18 ± 5.44, $P < 0.001$) Anosmics and hyposmics were not significantly different in BDI scores. Correlation coefficient between BDI and T, D, I total score is $r = -0.336$, $P < 0.001$

CRS, chronic rhinosinusitis; AR, allergic rhinitis; URI, upper respiratory infection; BDI, Beck's Depression Inventory; ZDS, Zung Depression Scale; T, threshold; D, discrimination; I, identification.

[a]Included in combined data analysis.

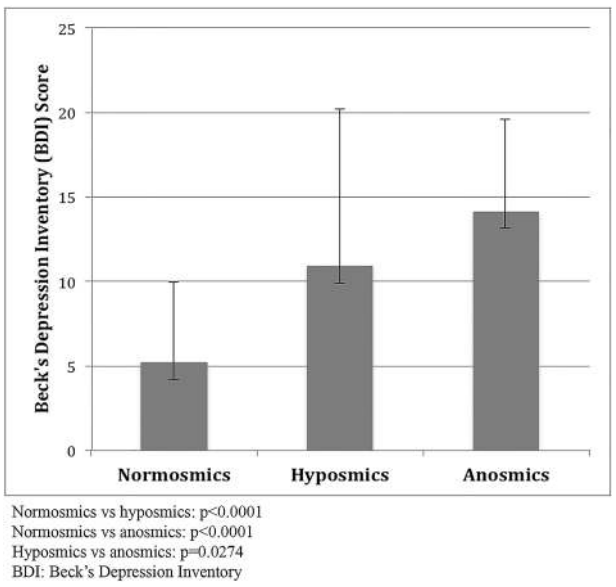


Figure 3. BDI scores by olfactory classification.

with primary olfactory dysfunction since we are missing data from populations who did not seek medical care. We were also unable to adjust for patient comorbidities, such as fibromyalgia, anxiety, asthma, and allergies, nor was it possible to control for antidepressant medication use. This allows for unaccounted confounders to weaken associations. The study design is also cross-sectional in nature, and thus, causality is unable to be determined. However, in humans, olfactory loss due to trauma or viral etiologies leads to depression, thus causality in these cases is strongly supported (Jung et al. 2014; Doty et al. 1997).

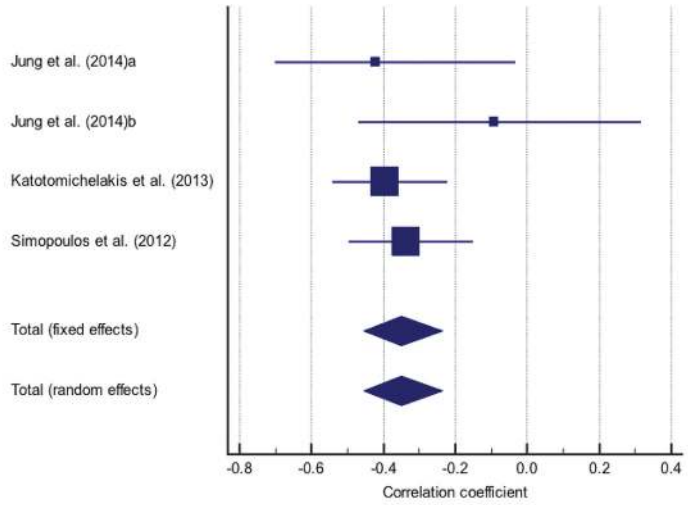
The current paper demonstrates statistical differences in olfaction and depression scores among patient populations. However, whether a clinically meaningful difference exists for individual patients is yet to be determined. Future studies should investigate whether olfactory impairment can effectively be used to enhance depression screening. In addition, it is currently unknown whether comorbid depression and olfaction leads to poorer health outcomes than either condition on its own. The mechanisms underlying the bidirectional relationship between olfaction and depression are also understudied and require further analysis.

Conclusion

There is a reciprocal relationship between olfaction and depression. Patients with primary depression have reduced objective olfactory performance when compared with the healthy controls. In patients with primary olfactory dysfunction, symptoms of depression worsen with severity of olfactory dysfunction. It is critical to be aware of the development of olfactory loss in primary depression patients and of depression in patients with primarily olfactory dysfunction in order to allow for early intervention and prevent greater disease burden.

Supplementary material

Supplementary material can be found at http://www.chemse.oxfordjournals.org/



Study	Sample size	Correlation coefficient	95% CI	P	Weight (%)
Jung et al. (2014)a	25	-0.423	-0.701 to -0.0335		8.87
Jung et al. (2014)b	25	-0.0920	-0.470 to 0.315		8.87
Katotomichelakis et al. (2013)	108	-0.395	-0.543 to -0.223		42.34
Simopoulos et al. (2012)	102	-0.336	-0.498 to -0.151		39.92
Total (fixed effects)	**260**	**-0.349***	**-0.453 to -0.236**	**<0.001**	**100.00**
Total (random effects)	260	-0.349	-0.453 to -0.236	<0.001	100.00

* Negative correlation signifies as BDI increased, TDI decreases
CI: Confidence interval

Figure 4. Combined weighted BDI and TDI total score correlation coefficients for primary olfactory dysfunction studies.

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Conflict of interest statement

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