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The olfactory deficits of depressed patients are restored after remission with venlafaxine treatment

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Abstract

Background. It is unclear whether olfactory deficits improve after remission in depressed patients. Therefore, we aimed to assess in drug-free patients the olfactory performance of patients with major depressive episodes (MDE) and its change after antidepressant treatment.
Methods. In the DEP-ARREST-CLIN study, 69 drug-free patients with a current MDE in the context of major depressive disorder (MDD) were assessed for their olfactory performances and depression severity, before and after 1 (M1) and 3 (M3) months of venlafaxine antidepressant treatment. They were compared to 32 age- and sex-matched healthy controls (HCs). Olfaction was assessed with a psychophysical test, the Sniffin' Sticks test (*Threshold*: T score; *Discrimination:* D score; *Identification*: I score; total score: $T+D+I=$ TDI score) and *Pleasantness* (pleasantness score: p score; neutral score: N score; unpleasantness score: U score).
Results. As compared to HCs, depressed patients had lower TDI olfactory scores [mean (S.D.) 30.0(4.5) *v.* 33.3(4.2), $p<0.001$], T scores [5.6(2.6) *v.* 7.4(2.6), $p<0.01$], p scores [7.5(3.0) *v.* 9.8(2.8), $p<0.001$)] and higher N scores [3.5(2.6) *v.* 2.1(1.8), $p<0.01$]. T, p and N scores at baseline were independent from depression and anhedonia severity. After venlafaxine treatment, significant increases of T scores [M1: 7.0(2.6) and M3: 6.8(3.1), $p<0.01$] and p scores [M1: 8.1(3.0) and M3: 8.4(3.3), $p<0.05$] were evidenced, in remitters only (T: $p<0.01$; P: $p<0.01$). Olfaction improvement was mediated by depression improvement.
Conclusions. The olfactory signature of MDE is restored after venlafaxine treatment. This olfaction improvement is mediated by depression improvement.

Introduction

Major depression is the second cause of incapacity worldwide (Mokdad et al., 2016). Antidepressant drug treatments are prescribed to 10% of the general population (Pratt, Brody, & Gu, 2011). However, their ability to achieve remission in major depressive episodes (MDE) in patients with major depressive disorder (MDD) is limited to a third of patients (Trivedi et al., 2006).

Some clinical data suggest a potential association between major depression and olfaction impairment (Croy & Hummel, 2017; Kohli, Soler, Nguyen, Muus, & Schlosser, 2016). Phylogenetically, olfaction is the most ancient sense characterized by a unique intimacy with the emotion system. Olfaction enables to detect volatile molecules depending on their concentration, this detection threshold being named olfactory *Threshold* (T) (also called sensitivity) (Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997). Olfaction also enables to discriminate different odorants (Bushdid, Magnasco, Vosshall, & Keller, 2014), called *Discrimination* (D) as well as the identification of odorant, called *Identification* (I) (Hummel et al., 1997).

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Olfactory *Pleasantness* is the pleasure produced by an odorant molecule, described as pleasant (*P*), neutral (*N*) and unpleasant (*U*) (Croy & Hummel, 2017). *Threshold* reflects, to some degree, the peripheral aspects of olfactory function, *Identification* and *Discrimination* reflecting central nervous system cognitive functions (Croy et al., 2014; Hedner, Larsson, Arnold, Zucco, & Hummel, 2010; Horio, Murata, Yoshikawa, Yoshihara, & Touhara, 2019; Lapid et al., 2011). *Pleasantness* is already coded in the periphery (Lapid et al., 2011) and at early stages in the central nervous system, e.g. at the level of the piriform cortex (Bensafi, Sobel, & Khan, 2007). Previously, our group showed that in a mouse model of depression based on chronic corticosterone administration (CORT model), olfactory *Threshold* score was decreased and restored after antidepressant drug treatment with fluoxetine (Siopi et al., 2016), while *Discrimination* score remained unaltered in depressed mice compared to controls.

Previous clinical findings suggest that olfactory functions may be decreased in patients with a current MDE. Sixteen studies have compared olfactory functions between patients suffering from MDE and healthy controls (HCs) (online Supplementary Table S1) (Atanasova et al., 2010; Chen et al., 2019; Clepce, Gossler, Reich, Kornhuber, & Thuerauf, 2010; Croy et al., 2014; Gross-Isseroff et al., 1994; Kamath et al., 2018; Kopala, Good, & Honer, 1994; Lombion-Pouthier, Vandel, Nezelof, Haffen, & Millot, 2006; Naudin et al., 2012; Negoias et al., 2010; Pause, Miranda, Goder, Aldenhoff, & Ferstl, 2001; Pentzek, Grass-Kapanke, & Ihl, 2007; Rossi et al., 2015; Scinska et al., 2008; Serby, Larson, & Kalkstein, 1990; Warner, Peabody, & Csernansky, 1990; Zucco & Bollini, 2011): four studies out of 12 reported a lower *Threshold* score, one study out of six reported lower *Discrimination* score in MDE patients and six studies out of 15 reported a lower *Identification* score in MDE patients. A meta-analysis including 13 of these studies (Kohli et al., 2016), found a lower *Threshold* score, a lower *Discrimination* score and a lower *Identification* score in MDE patients (Kohli et al., 2016). Furthermore, decreased *Pleasantness* score was observed in MDE patients in two studies out of six (Atanasova et al., 2010; Naudin et al., 2012) (online Supplementary Table S1). *Pleasantness* is of particular interest in MDE because anhedonia is a core symptom of major depression.

Preliminary studies suggest that olfactory functions could be improved after antidepressant treatment (Gross-Isseroff et al., 1994). In a study including nine patients suffering from a current MDE and treated with maprotiline ($n = 3$), imipramine ($n = 4$) or fluoxetine ($n = 2$) during 6 weeks, an increased *Threshold* score was shown after treatment (Gross-Isseroff et al., 1994). A study including 18 patients suffering from a current MDE, treated with escitalopram during 6 weeks, found an increase of the *Pleasantness* score after treatment (Naudin et al., 2012).

However, the vast majority of depressed patients included in the previous studies were not antidepressant-free at baseline. Thus, their previous antidepressant treatments may have modulated their olfactory abilities. Only five studies assessing *Threshold and Identification* scores focused on antidepressant-free patients: three with small MDE sample sizes ($n = 9$, $n = 12$ and $n = 6$) (Gross-Isseroff et al., 1994; Serby et al., 1990; Warner et al., 1990), one with only elderly depressed patients ($n = 25$) (Scinska et al., 2008) and two without healthy controls (Scinska et al., 2008; Serby et al., 1990) (online Supplementary Table S1). These studies provided controversial findings (online Supplementary Table S1) and *Pleasantness* has never been assessed in antidepressant-free patients.

Olfactory deficits may be independent therapeutic targets, since they reflect underlying neurobiological abnormalities associated with major depression. Furthermore, identifying treatments able to restore olfactory deficits in depressed patients could impact positively the quality of life of depressed patients.

Thus, we aimed to assess, in drug-free depressed patients, if olfactory impairment could be restored after antidepressant drug treatment, taking into account depression severity.

Material and methods

Participants and design

DEP-ARREST-CLIN is a three-month prospective cohort (ClinicatTrials.gov NCT02051413), including MDE antidepressant-free (one month) patients and HCs matched for age and sex. A subgroup of patients was antidepressant drug naïve (never treated with antidepressant drugs). Patients and HCs provided written informed consent for study participation which was approved by the relevant ethics committee (CPP IDF VI) and the French National Agency for Medicines and Health Products Safety (ANSM). All participants were included between February 2014 and January 2017. They underwent a comprehensive physical and psychiatric assessment by senior physicians at Bicêtre Hospital.

Patients aged 18–65 years with a current MDE diagnosis (MINI interview, Sheehan et al., 1998) and a minimum depression score of 18 on the Hamilton Depression Rating Scale-17 items (HDRS) (Hamilton, 1960) in the context of MDD, as well as free of antidepressant drug use at least one month before the study beginning, were included. Patients suffering from bipolar disorder, psychotic disorder, eating disorder, and addictions, according to the DSM-5 criteria, or from nasal polyposis, chronic or acute sinusitis, chronic or acute rhinitis or pregnancy or breast-feeding, were not included. HCs were included based on the absence of current or past mental disorders or somatic conditions, particularly nasal polyposis and chronic or acute sinusitis or rhinitis and were matched for age and sex with 32 antidepressant drug-naïve patients with MDE.

Patients were treated prospectively with the antidepressant venlafaxine extended release, at flexible doses (dose range: 37.5–375 mg/day) using a naturalistic ecological design, in which the dosage was flexible and chosen by the treating psychiatrist. Other antidepressant treatments, antipsychotic drugs, or mood stabilizers were not allowed during the study. Benzodiazepines were allowed at the minimum effective dose and for the minimum duration.

Olfaction, memory and depression were assessed by independent investigators. They were assessed at baseline, and after 1 and 3 months of venlafaxine treatment for depressed patients. They were assessed once for HCs since olfaction scores are stable over 3 months in healthy subjects (Al Ain et al., 2019; Albrecht et al., 2008; Doty, McKeown, Lee, & Shaman, 1995; Hummel et al., 1997; Sorokowska, Albrecht, Haehner, & Hummel, 2015).

Seven out of 69 patients dropped out before the end of the study because of: adverse effect ($n = 2$) (increased sweating and nausea), lost to follow-up ($n = 2$), consent withdrawal ($n = 2$), and mood switch ($n = 1$).

Olfactory assessment

The Sniffin' Sticks test, which provides a total TDI score and *T*, *D* and *I* scores, is the most used test to assess olfactory performance (Hummel, Kobal, Gudziol, & Mackay-Sim, 2007). It provides a

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validated quantification of *T* score, *D* score, *I* score (Hummel et al., 2007). The total TDI score was the main outcome variable.

- The *T* score was assessed using 16 dilutions prepared from a 4% n-butanol solution (dilution ratio 1:2). Three pens (two containing the solvent and the third the odorant) were presented in a randomized order using a single staircase of increasing concentration [16 (lower concentration) to 1 (higher concentration)]. Subjects had to identify the odor-containing pen. Reversal of the staircase was triggered when the odorant was correctly identified in two successive trials. The *T* score was defined as the mean of the last four of seven staircase reversals, scores ranging from 1 to 16 (the higher, the better). Subjects were blindfolded during this test.
- To assess the *D* score, triplets of pens were presented in a randomized order (two containing the same and one a different odorant). Subjects had to determine which of three pens smelled differently, scores ranging from 1 to 16. Subjects were blindfolded during this test as well.
- The *I* score was assessed for 16 common odors (orange, leather, cinnamon, peppermint, banana, lemon, liquorice, turpentine, garlic, coffee, apple, cloves, pineapple, rose, anise and fish). Using a multiple choice task, the *I* index of individual odors was performed from lists of four descriptors each, scores ranging from 1 to 16.

Moreover, during the Sniffin' Sticks I task, patients and HCs were asked for the *Pleasantness* of the 16 selected odors smelling, as it was previously published (Swiecicki et al., 2009). The number of odors rated as 'pleasant' (*P*), 'unpleasant' (*U*) or 'neutral' (*N*) corresponding to the *P*, *U* and *N* scores range from 0 to 16 and the sum of these scores was equal to 16.

Memory assessment

Since memory impairments are associated with MDE (Gorwood, Corruble, Falissard, & Goodwin, 2008) and olfactory dysfunctions (Yahiaoui-Doktor et al., 2019), the memory immediate recall task from the Wechsler Memory Scale – Revised (Wechsler, 1987) was rated accordingly.

Depression intensity at baseline and improvement after antidepressant treatment

The Hamilton Depression Rating Scale 17 items (HDRS) (Hamilton, 1960) (score range : 0–52) was rated by certified psychiatrists. Remission was assessed after 3 months of venlafaxine treatment. Remission was defined by a HDRS total score of 7 or less at follow-up after 3 months of treatment (Moller, 2008; Rush et al., 2006).

The Snaith-Hamilton Pleasure Scale (SHAPS), a self-rated questionnaire comprising 14 items (score range: 0–14), was used to assess anhedonia severity (Snaith et al., 1995), anhedonia being a symptom of depression.

Statistical analysis

The statistical analyses were performed using R 3.4.2 and STATA v13 MP. Values were expressed in mean (s.d.).

Taking into account the non-normality distribution of olfactory variables and the small sample size, non-parametric tests were chosen.

Socio-demographical variables were compared between MDE patients and HCs. The variables to be explained were the TDI score (the main one) and Pleasantness. The explicative variables were the socio-demographical and clinical characteristics (age, sex, tobacco use, HDRS, SHAPS and memory task scores for depressed patients), the diagnosis group (MDE *v.* HCs). Wilcoxon rank-sum tests, χ^2 tests and Spearman correlations were computed. Mixed-effects regressions were used to assess olfactory score changes after one and three months of antidepressant treatment in MDE patients, looking at a time effect. We fitted the mixed models with patients as a random intercept. No random slopes were considered. An independent covariance structure was used to allow a distinct variance for each random effect within a random-effects equation, assuming all covariances are zero. A likelihood ratio test was also used to test the hypothesis that our random intercept mixed model differed significantly from a fixed effect linear model. Post-hoc analyses were performed in case of significant time effects. Wilcoxon signed-rank tests and Wilcoxon rank-sum tests were used to compare olfactory scores of depressed patients 1 and 3 months after treatment with those of HCs. Linear regressions were performed to control the explicative effect of diagnosis (MDE *v.* HCs) for potential confounders among socio-demographical variables. Covariables of the multivariate models were selected on the basis of a significant association ($p < 0.05$) in bivariate analyses: they comprised age, sex and tobacco use. Furthermore, to exclude a possible confounding effect of tobacco use change during follow-up, repeated measures mixed-effects regressions for olfactory score changes after 1 and 3 months of antidepressant treatment were performed in the subgroup of non-smoker patients (Ajmani, Suh, Wroblewski, & Pinto, 2017). Since corrections for multiple comparisons are controversial (Streiner & Norman, 2011), we used mixed models to take into account the multiple comparisons due to repeated measures and a significant level of $p < 0.05$.

Post-hoc analyses were computed to test whether baseline olfaction scores may predict changes in HDRS scores after 1 and 3 months of treatment and whether olfaction score changes after 1 month of treatment may predict remission after 3 months.

The mediation effects of depression improvement (HDRS score change) and anhedonia improvement (SHAPS score change) on olfactory score improvements were assessed with path analyses.

Results

Sixty-nine MDE patients and 32 HCs matched with antidepressant-naive patients were included in the current study. MDE patients matched with HCs did not differ regarding age, sex and tobacco use with those who were not matched with HCs. Matched MDE patients and HCs did not differ with respect to age, sex and tobacco use. Patients and HCs did not differ with respect to age [MDE years mean (s.d.): 34.1 (12.5) and HCs: 35.1 (12.9)] and sex [MDE n (%): 46 (66.7%) women and HCs: 21 (65.6%) women]. MDE patients were more frequently tobacco smokers than HCs [MDE *n* (%): 27 (39.1%) smokers *v.* HCs: 4 (12.5%) smokers, $p < 0.01$].

In MDE patients, the mean HDRS score at baseline was 26.4 (5.3). 65 (94.2%) were inpatients at inclusion. The mean (s.d.) venlafaxine doses were 184.1(63.9) mg/day and 196.4 (85.2) mg/day after 1 and 3 months of treatment, respectively. Fifty-three (76.8%) patients received benzodiazepines at baseline, 48 (71.6%) after 1 month, and 25 (42.4%) after 3 months of

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treatment. After 3 months of venlafaxine treatment, 46 (74.2%) patients were remitters and 16 (25.8%) were non-remitters.

Table 1 summarizes associations between olfactory scores and demographic and clinical data in HCs and MDE patients. Among HCs, the *p* score was positively correlated with age ($r = 0.40$, $p < 0.05$) and the *U* score was negatively correlated with age ($r = -0.51$, $p < 0.01$). There was no other significant association between olfactory scores and age, gender, and tobacco use (Table 1).

Among MDE patients, the *p* score was positively correlated with age ($r = 0.36$, $p < 0.01$) and the N score was negatively correlated with age ($r = -0.34$, $p < 0.01$). Women had higher *U* scores than men ($p < 0.01$) (Table 1). In MDE patients, except for the *D* score ($r = -0.28$, $p = 0.019$), olfactory scores were not significantly correlated with HDRS scores (TDI score: $r = -0.19$ $p = 0.21$) or with SHAPS scores (TDI score: $r = 0.07$, $p = 0.59$). In MDE patients, the memory task scores were not correlated with TDI ($r = 0.01$, $p = 0.25$) but were correlated with *D* ($r = 0.38$, $p = 0.0038$) and *I* ($r = 0.28$, $p = 0.036$) scores. Moreover, in HCs, olfactory scores were correlated neither with HDRS and SHAPS, nor with memory task scores.

Figures 1 and 2 illustrate olfactory score changes after antidepressant treatment within the MDE group. As compared to pHCs, MDE patients had lower TDI scores [mean (S.D.): 30.0 (4.5) *v.* 33.3 (4.2), $p < 0.001$], lower olfactory *T* scores [mean (S.D.): 5.6 (2.6) *v.* 7.4 (2.6), $p < 0.01$]. Olfactory deficit was observed even after adjustment for age, sex and tobacco use [TDI score: estimate = −3.4, CI 95% (−5.3 to −1.4), $p < 0.001$, *T* score estimate = −1.9, CI 95% (−3.1 to −0.8)]. TDI total score did not change significantly after antidepressant treatment (Fig. 1). However, *T* scores increased significantly after antidepressant treatment [M0:5.6 (2.6), M1: 6.9(2.6), and M3: 6.7 (2.9), $\beta = 0.32$, 95%CI (0.04–0.59), $p < 0.05$], with a return to normal scores (Fig. 1). In the subgroup of non-smoker patients ($n = 42$), this T score increase was almost significant [$\beta = 0.34$, 95%CI (−0.03 to 0.73), $p = 0.08$]. D and I scores did not change significantly (Fig. 1).

Regarding Pleasantness, MDE patients had lower *p* scores [mean (S.D.): 7.5(3.0) *v.* 9.8(2.8), $p < 0.001$] and higher *N* scores [mean (S.D.): 3.5(2.7) *v.* 2.1(1.8), $p < 0.05$] (Figs 1 and 2). This olfactory deficit was observed even after adjustment for age, sex and tobacco use [*p* score: estimate = −2.2, CI 95% (−3.5 to −1.0), $p < 0.001$; *N* score: estimate = 1.4, CI95% (0.3–2.4), $p < 0.01$]. *p* scores increased significantly after antidepressant treatment [M0: 7.5(3.0), M1: 8.1(3.0) and M3: 8.4(3.3), $\beta = 0.39$, 95%CI (0.16–0.62), $p < 0.001$] whereas *N* scores were unchanged (Fig. 2). In the subgroup of non-smoker patients ($n = 42$), these *p* scores increase [*p* score: $\beta = 0.32$, 95%CI (0.11–0.53), $p < 0.01$] remained significant.

Data were analyzed by subgroups according to clinical remission status after 3 months of treatment (Fig. 3). *T* scores increased significantly after antidepressant treatment [$\beta = 0.39$, 95%CI (0.09–0.69), $p < 0.05$] with a return to normal scores in remitters ($n = 46$) but not in non-remitters (Fig. 3). *p* scores increased significantly after antidepressant treatment [$\beta = 0.39$, 95%CI (0.16–0.62), $p < 0.001$] in remitters but not in non-remitters (Fig. 3). No significant change of *N* scores was shown. In the subgroup of non-smoker remitters ($n = 30$), a significant increase of *p* scores [$\beta = 0.34$, 95%CI (0.11–0.57), $p < 0.01$] was confirmed.

Baseline olfactory scores were not associated with HDRS score changes after 1 and 3 months of venlafaxine treatment (data not shown).

T score changes after 1 month of treatment were not associated with 3-month remission [remitters = 1.3 (3.0) *v.* non-remitters = 0.9 (3.7), $p = 0.86$].

The estimated mediating effects of HDRS score change on the association between venlafaxine treatment and *T* and *p* score changes were 0.43 [95% CI (0.1–0.75)] and 0.32 [95% CI (0.01–0.64)] respectively (online Supplementary Fig. S1). The estimated mediating effects of HDRS score change on the association between venlafaxine treatment and *T* and *p* score changes were 0.43 [95% CI (0.1–0.75)] and 0.32 [95% CI (0.01–0.64)], respectively (online Supplementary Fig. S1). There was no mediation effect of anhedonia change on the association between venlafaxine treatment and *T* and *p* score changes (except for *p* score change), which was, as expected, mediated by anhedonia score change [estimated mediating effect = 0.15, (95% CI (0.04–0.28))] (online Supplementary Fig. S2).

Discussion

This study shows that antidepressant-free patients exhibit some olfactory deficits during a major depressive episode. These deficits are characterized by lower TDI, *Threshold*, *Pleasantness* and *Neutral* scores, and are independent from the severity of depression and anhedonia. *Threshold* and *Pleasantness* scores are restored after remission with venlafaxine treatment. Path analyses show that this recovery of olfaction (*Threshold* and *Pleasantness*) is mediated by depression improvement.

By showing lower olfactory TDI and *Threshold* scores in the largest cohort of antidepressant drug-free depressed patients, our study supports the results from a recent meta-analysis (Kohli et al., 2016), in which antidepressant drug status was not taken into account. The size effect disclosed in our study (24% lower in MDE than in HCs) is higher than the one observed in the meta-analysis (7% lower in MDE than in HCs), possibly because patients of our sample are antidepressant drug-free and more severely depressed (online Supplementary Table S1). It could be hypothesized that, in the meta-analysis, antidepressant drug treatment had positive effects on olfactory *Threshold* scores and minimized the difference between MDE patients and controls.

This study provides the largest antidepressant drug-free MDE patients sample assessed for olfactory *Pleasantness*. Lower *Pleasantness* scores and higher *Neutral* scores in depressed patients than in HCs are disclosed confirming results of two previous studies (Atanasova et al., 2010; Naudin et al., 2012). In contrast, four others did not, but these studies included smaller sample sizes which underpowered them (Pause et al., 2001; Swiecicki et al., 2009) and non-antidepressant drug-free patients, which may have biased the results (Clepce et al., 2010; Lombion-Pouthier et al., 2006; Pause et al., 2001).

We report for the first time that the olfactory signature of MDE is restored after venlafaxine treatment and that this olfaction improvement is mediated by depression improvement.

After venlafaxine treatment, remitters returned to normal *Threshold* and *Pleasantness* scores. The olfactory changes after antidepressant treatment are also observed in the subgroup of non-smoker patients. This sub-analysis rules out the potential confounding effect of tobacco use decrease because of antidepressant treatment. Our results are in line with findings in a mouse model of depression, in which *Threshold* is increased after fluoxetine treatment (Siopi et al., 2016). The olfactory *Threshold* score improvement after venlafaxine treatment, observed in this study,

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Table 1. Association of olfaction and baseline characteristics in controls and MDE patients

	Threshold	Discrimination	Identification	TDI score	Pleasant	Neutral	Unpleasant
Healthy controls ($n = 32$)							
Age (r)	−0.11	−0.08	0.24	−0.03	**0.40***	−0.11	**−0.51***
Sex (m(s.d.)							
Women ($n = 21$)	7.1 (3.0)	12.5 (1.7)	13.2 (2.2)	32.8 (4.7)	9.9 (2.6)	1.8 (1.4)	4.3 (1.9)
Men ($n = 11$)	8.0 (1.8)	12.5 (1.2)	13.7 (1.5)	34.2 (2.9)	9.7 (3.4)	2.8 (2.2)	3.5 (1.9)
Tobacco (m(s.d.)							
Yes ($n = 4$)	8.9 (3.5)	11.8 (2.2)	14.3 (0.5)	33.6 (4.2)	11.8 (4.0)	1.5 (2.4)	4.2 (1.9)
No ($n = 28$)	7.6 (2.4)	12.6 (1.4)	13.3 (2.0)	33.3 (4.2)	9.6 (2.6)	2.2 (1.7)	2.8 (1.7)
Depressed patients ($n = 69$)							
Age (r)	−0.12	−0.07	0.01	−0.11	**0.36***	**−0.34***	−0.10
Sex m(s.d.)							
Women (n = 46)	5.6 (2.4)	11.7 (2.2)	12.6 (1.7)	29.9 (4.5)	7.3 (2.8)	3.2 (2.4)	**5.6 (2.6)***
Men (n = 23)	5.7 (3.0)	12.0 (1.9)	12.7 (1.9)	30.3 (4.5)	8.0 (3.2)	4.3 (3.1)	**3.7 (2.3)***
Tobacco m(s.d.)							
Yes ($n = 27$)	5.8 (2.5)	11.3 (2.4)	13.0 (1.5)	30.0 (4.7)	7.5 (3.0)	3.6 (3.0)	5.0 (2.6)
No ($n = 42$)	5.5 (2.7)	12.0 (1.9)	12.4 (1.9)	30.0 (4.4)	7.5 (3.0)	3.5 (2.4)	5.0 (2.7)

Means are presented with standard deviations; MDE, major depressive episode; in bold ***: $p < 0.05$.**

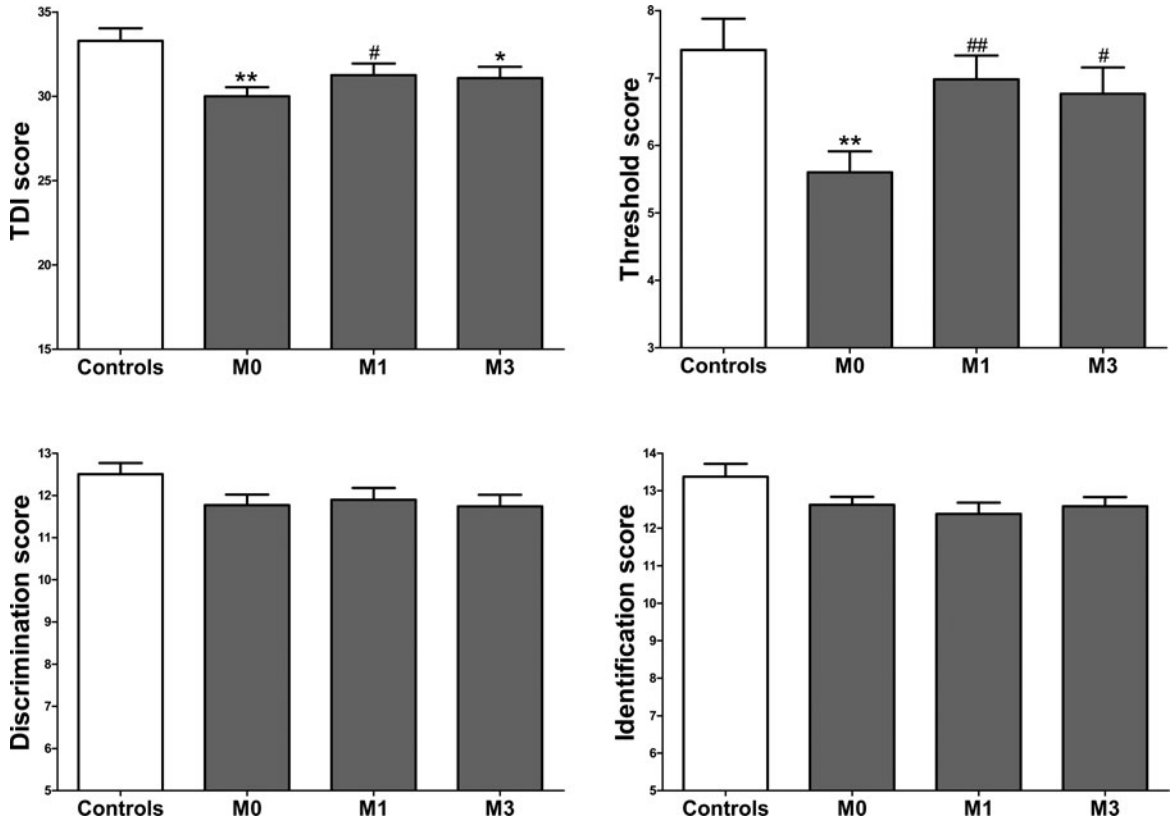

Fig. 1. *Threshold, Discrimination, Identification* and TDI olfactory scores before and after venlafaxine treatment in MDE patients and controls. Means are presented with standard errors; TDI, total score = T (olfactory threshold score) + D (olfactory discrimination score) + I (olfactory identification scores); MDE, Patients with a current major depressive episode in a context of major depressive disorder (in gray); M0, patients before venlafaxine treatment; M1, patients one month after venlafaxine treatment; M3, patients three months after venlafaxine treatment; * $p < 0.05$ and ** $p < 0.01$ for MDE (M0, M1 or M3) v. controls; # $p < 0.05$ and ## $p < 0.01$ for MDE (M1 or M3) v. MDE M0.

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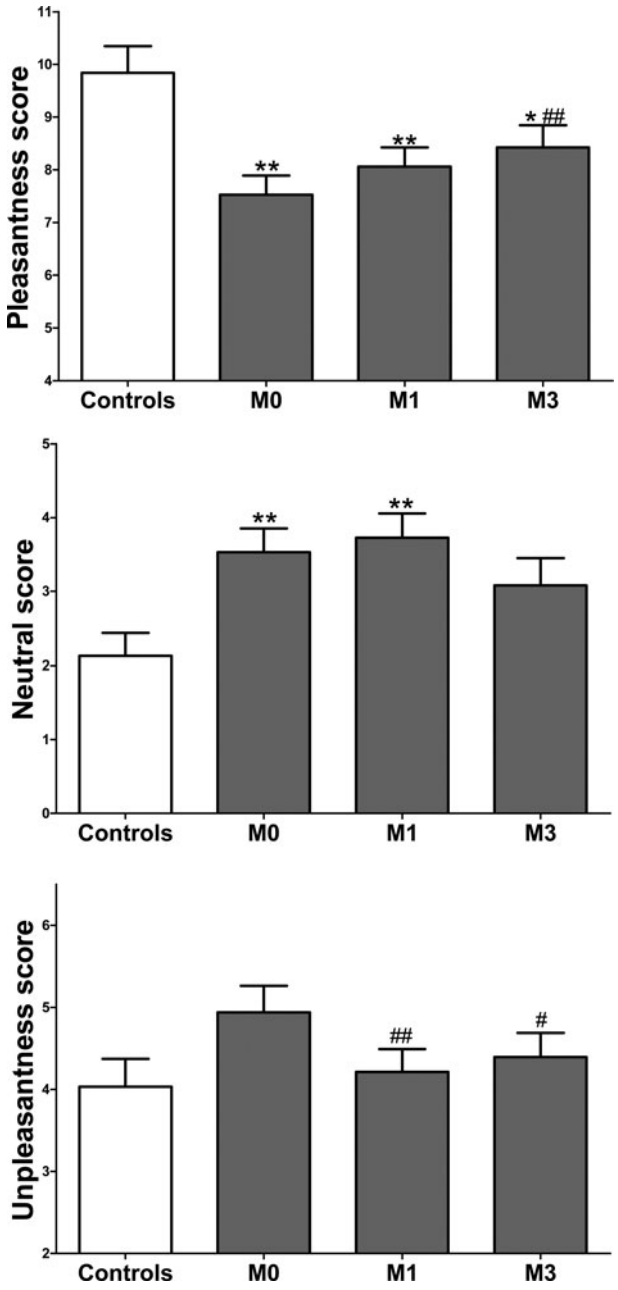

Fig. 2. *Pleasantness*, *Neutral* and *Unpleasantness* olfactory scores before and after venlafaxine treatment in MDE patients and controls. Means are presented with standard errors; MDE, patients with a current major depressive episode in a context of major depressive disorder (in gray); M0, patients before venlafaxine treatment; M1, patients one month after venlafaxine treatment; M3, patients three months after venlafaxine treatment; * $p < 0.05$ and ** $p < 0.01$ for MDE (M0, M1 or M3) v. controls; # $p < 0.05$ and ## $p < 0.01$ for MDE (M1 or M3) v. MDE patients M0

is in line with previous results in a small sample of patients treated with other antidepressant drugs [maprotiline ($n = 3$), imipramine ($n = 4$) or fluoxetine ($n = 2$)] (Gross-Isseroff et al., 1994). The olfactory *Pleasantness* score increase shown in our sample is in accordance with the results from a small study with benzaldehyde (Naudin et al., 2012). But our results go beyond those of Naudin et al., since we show that recovery of olfactory Pleasantness is mediated by depression improvement and anhedonia (a symptom of depression) improvement. This result should be confirmed with other antidepressant drugs.

The mechanisms underlying olfactory *Threshold* and *Pleasantness* decreases in MDE patients are unknown. It is striking that only olfactory dimensions that rely more on early stages of olfactory information processing (i.e. *Threshold* and *Pleasantness*) are decreased whereas those from higher cognitive levels (*Discrimination* and *Identification*) remain unaltered (Croy et al., 2014; Horio et al., 2019; Lapid et al., 2011). Thus, the assessment of olfactory neuroepithelial cells from MDE patients could be a promising approach to further explore the mechanisms of olfactory impairment in MDE patients (Borgmann-Winter et al., 2009). Of note, in rodent models of depression, decreased olfactory receptor turnover has been observed (Li et al., 2015) and olfactory bulb dysfunctions were reported (Cheng et al., 2016; Siopi et al., 2016). Interestingly, lower olfactory bulb volumes were observed in MDE patients compared to HCs (Negoias et al., 2010; Rottstadt et al., 2018) with a possible association with severity. In a rodent model of depression, lower cellular plasticity and energy metabolism were observed in the olfactory bulb (Cheng et al., 2016; Siopi et al., 2016). Since altered brain plasticity (Miller & Hen, 2015) and energy metabolism are both involved in MDE (Miller & Hen, 2015; Zuccoli, Saia-Cereda, Nascimento, & Martins-de-Souza, 2017), antidepressant drug treatments could improve olfaction by acting on these two targets (Miller et al., 2015; Villa et al., 2017).

This study has several strengths. This is the first study with a prospective comprehensive assessment of olfaction in MDE patients, before and after venlafaxine treatment and in HCs. And it provides the largest sample of antidepressant drug-free MDE patients assessed for olfaction (including *Pleasantness*).

However, this study also has several limitations. First, olfactory tests are performed before and after 1 and 3 months of antidepressant treatment in MDE patients. A test–retest bias cannot be excluded even though no major difference between mean results were observed in seven consecutive measurements (during 4 months) with Sniffin' Sticks in six subjects (Hummel et al., 1997). Second, the remission rates after antidepressant treatment in this study are higher than the one reported from a previous cohort of MDE patients (Trivedi et al., 2006). This may be explained by the fact that only antidepressant drug-free, mainly hospitalized patients, were included (Berlim & Turecki, 2007) and that venlafaxine has a high efficacy especially at high dosages (Hennings et al., 2009; Kienke & Rosenbaum, 2000). Third, this study could be underpowered to detect some olfactory differences. Indeed, unlike Kohli et al. (2016) and Kamath et al. (2018), olfactory *Discrimination* and *Identification* scores are not statistically different between MDE patients and HCs. Fourth, tobacco use was higher in MDE patients than in HCs. Taking into account the relevance of tobacco consumption in olfactory function, some studies showing an association between tobacco use and worse olfactory function (Ajmani et al., 2017), this point has been considered carefully in our analyses. We have shown that there were no associations in our sample between olfactory variables and tobacco use, neither in MDE patients nor in HCs. Furthermore, to control for a potential confounding effect of tobacco use, we have added tobacco use as a covariable into multivariate models comparing olfactory variables between MDE patients and HCs. Moreover, regarding prospective olfactory assessment in MDE patients, we have provided analyses within the sub-group of non-tobacco users. Finally, even if *Threshold* score recovery is mediated by depression improvement, the non-significant result in *Threshold* score change in the non-remitter subgroup could be due to the small sample size ($n = 16$). Indeed, with this sample size, the statistical power to detect a

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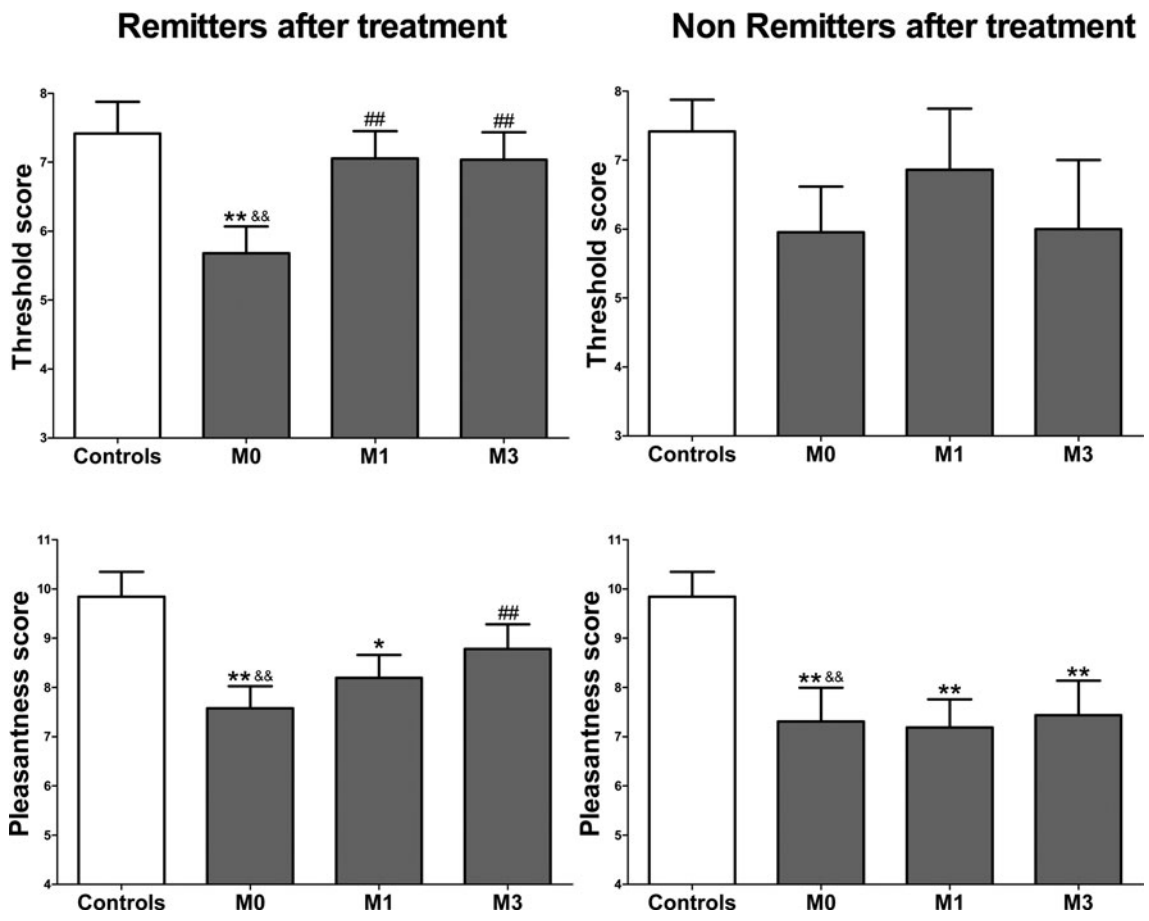

Fig. 3. *Threshold* and *Pleasantness* olfactory scores before and after venlafaxine treatment in remitters and non-remitter patients. Mean were presented with standard error; MDE, patients with current major depressive episode in a context of major depressive disorder (in gray); M0, patients before venlafaxine treatment; M1, patients one month after venlafaxine treatment; M3, patients three months after venlafaxine treatment; * $p < 0.05$ and ** $p < 0.01$ for MDE (M0, M1 or M3) v. controls; # $p < 0.05$ and ## $p < 0.01$ for MDE (M1 or M3) v. MDE M0.; & $p < 0.05$ and && $p < 0.01$ for MDE (M0) v. controls after adjustment for age, sex and tobacco use.

significant increase of *Threshold* score was moderate (55% for an effect size similar to remitters).

Our results call for a special attention on the deficits of the sense of smell that may accompany MDE. These olfactory deficits might require special olfactory training to alleviate the patients' quality of life and depressive symptoms. Indeed, olfactory training improves olfactory functions (Sorokowska, Drechsler, Karwowski, & Hummel, 2017) and also have been reported to improve depressive symptoms in older people with mild subclinical depression (Birte-Antina, Ilona, Antje, & Thomas, 2018). Along these lines, aromatherapy has shown some beneficial effects on mild MDE patients ($n = 5$) (Okamoto et al., 2005), this effect could be mediated by olfactory stimulation. Moreover, the impact of venlafaxine treatment on olfactory function should be assessed in patients with smell disorders and particularly those experiencing depressive symptoms (Kohli et al., 2016). This is of particular interest because there is no pharmacological treatment for olfactory dysfunction (Gaines, 2013; Harless & Liang, 2016) and MDE are frequent in patients with olfactory dysfunctions (Kohli et al., 2016).

Conclusions

The olfactory signature of MDE is restored after venlafaxine treatment. This olfaction improvement is mediated by depression improvement. Altogether, our results suggest an alteration of the early stages of olfactory information processing in the olfactory system of MDE patients. The biological mechanisms underlying these results should be further investigated. New therapeutic strategies focusing on olfaction should be developed for MDE patients and antidepressants should be tested in patients with smell disorders.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291720003918

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Conflict of interest. RC, KEA, CV, KEA, PML, ED, AEKAT, KC, FL, ED, SR, JFCL, FG, AMG, TH, EC, have no conflict of interest to disclose. BF has been consultant, expert or has given talks for E. Lilly, BMS, Servier, Sanofi, GlaxoSmithKline, HRA, Roche, Boeringer Ingelheim, Bayer, Almirall, Allergan, Stallergene, Genzyme, Pierre Fabre, Astra Zeneca, Novartis, Janssen, Astellas, Biotronik, Daiichi-Sankyo, Gilead, MSD, Lundbeck. DJD currently receives investigator-initiated research support from Lundbeck and served as a consultant in the areas of target identification and validation and new compound development to Lundbeck Inc., Roche and Servier. LB: investigator for Antisense Therapeutics, Alnylam Pharmaceuticals, Alexion, Actelion, Auris Medical, Gilead Sciences, Ionis Pharmaceuticals, MedDay

Pharma, Novartis, PregLem SA, Ultragenix pharmaceutical. Received consulting fees from Sanofi-Aventis, Pfizer, Kyowa Kirin and Servier; lecture fees from Genzyme, GlaxoSmithKline, Bristol-Myers Squibb, Merck Sharp and Dohme; a close family member works at Sanofi France.

References

Ajmani, G. S., Suh, H. H., Wroblewski, K. E., & Pinto, J. M. (2017). Smoking and olfactory dysfunction: A systematic literature review and meta-analysis. *The Laryngoscope*, *127*, 1753–1761. doi: 10.1002/lary.26558

Al Ain, S., Poupon, D., Hetu, S., Mercier, N., Steffener, J., & Frasnelli, J. (2019). Smell training improves olfactory function and alters brain structure. *NeuroImage*, *189*, 45–54. doi: 10.1016/j.neuroimage.2019.01.008

Albrecht, J., Anzinger, A., Kopietz, R., Schopf, V., Kleemann, A. M., Pollatos, O., & Wiesmann, M. (2008). Test-retest reliability of the olfactory detection threshold test of the Sniffin' sticks. *Chemical Senses*, *33*, 461–7. doi: 10.1093/chemse/bjn013

Atanasova, B., El-Hage, W., Chabanet, C., Gaillard, P., Belzung, C., & Camus, V. (2010). Olfactory anhedonia and negative olfactory alliesthesia in depressed patients. *Psychiatry Research*, *176*, 190–6. doi: 10.1016/j.psychres.2008.11.016

Bensafi, M., Sobel, N., & Khan, R. M. (2007). Hedonic-specific activity in piriform cortex during odor imagery mimics that during odor perception. *Journal of Neurophysiology*, *98*, 3254–62. doi: 10.1152/jn.00349.2007

Berlim, M. T., & Turecki, G. (2007). Definition, assessment, and staging of treatment-resistant refractory major depression: A review of current concepts and methods. *Canadian Journal of Psychiatry. Revue canadienne de Psychiatrie*, *52*, 46–54. doi: 10.1177/070674370705200108

Birte-Antina, W., Ilona, C., Antje, H., & Thomas, H. (2018). Olfactory training with older people. *International Journal of Geriatric Psychiatry*, *33*, 212–220. doi: 10.1002/gps.4725

Borgmann-Winter, K. E., Rawson, N. E., Wang, H. Y., Wang, H., Macdonald, M. L., Ozdener, M. H., … Hahn, C. G. (2009). Human olfactory epithelial cells generated in vitro express diverse neuronal characteristics. *Neuroscience*, *158*, 642–53. doi: 10.1016/j.neuroscience.2008.09.059

Bushdid, C., Magnasco, M. O., Vosshall, L. B., & Keller, A. (2014). Humans can discriminate more than 1 trillion olfactory stimuli. *Science*, *343*, 1370–2. doi: 10.1126/science.1249168

Chen, B., Klarmann, R., Israel, M., Ning, Y., Colle, R., & Hummel, T. (2019). Difference of olfactory deficit in patients with acute episode of schizophrenia and major depressive episode. *Schizophrenia Research*, *212*, 99–106.

Cheng, K., Li, J., Yang, D., Yang, Y., Rao, C., Zhang, S., … Xie, P. (2016). 2D-gel based proteomics unravels neurogenesis and energetic metabolism dysfunction of the olfactory bulb in CUMS rat model. *Behavioural Brain Research*, *313*, 302–309. doi: 10.1016/j.bbr.2016.05.026

Clepce, M., Gossler, A., Reich, K., Kornhuber, J., & Thuerauf, N. (2010). The relation between depression, anhedonia and olfactory hedonic estimates—a pilot study in major depression. *Neuroscience Letters*, *471*, 139–43. doi: 10.1016/j.neulet.2010.01.027

Croy, I., & Hummel, T. (2017). Olfaction as a marker for depression. *Journal of Neurology*, *264*, 631–638. doi: 10.1007/s00415-016-8227-8.

Croy, I., Symmank, A., Schellong, J., Hummel, C., Gerber, J., Joraschky, P., & Hummel, T. (2014). Olfaction as a marker for depression in humans. *Journal of Affective Disorders*, *160*, 80–6. doi: 10.1016/j.jad.2013.12.026

Doty, R. L., McKeown, D. A., Lee, W. W., & Shaman, P. (1995). A study of the test-retest reliability of ten olfactory tests. *Chemical Senses*, *20*, 645–56. doi: 10.1093/chemse/20.6.645

Gaines, A. (2013). Chapter 13: Olfactory disorders. *American Journal of Rhinology & Allergy*, *27*(Suppl 1), S45–7. doi: 10.2500/ajra.2013.27.3898

Gorwood, P., Corruble, E., Falissard, B., & Goodwin, G. M. (2008). Toxic effects of depression on brain function: Impairment of delayed recall and the cumulative length of depressive disorder in a large sample of depressed outpatients. *The American Journal of Psychiatry*, *165*, 731–9. doi: 10.1176/appi.ajp.2008.07040574

Gross-Isseroff, R., Luca-Haimovici, K., Sasson, Y., Kindler, S., Kotler, M., & Zohar, J. (1994). Olfactory sensitivity in major depressive disorder and obsessive compulsive disorder. *Biological Psychiatry*, *35*, 798–802.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, *23*, 56–62.

Harless, L., & Liang, J. (2016). Pharmacologic treatment for postviral olfactory dysfunction: A systematic review. *International Forum of Allergy & Rhinology*, *6*, 760–7. doi: 10.1002/alr.21727

Hedner, M., Larsson, M., Arnold, N., Zucco, G. M., & Hummel, T. (2010). Cognitive factors in odor detection, odor discrimination, and odor identification tasks. *Journal of Clinical and Experimental Neuropsychology*, *32*, 1062–7. doi: 10.1080/13803391003683070

Hennings, J. M., Owashi, T., Binder, E. B., Horstmann, S., Menke, A., Kloiber, S., … Lucae, S. (2009). Clinical characteristics and treatment outcome in a representative sample of depressed inpatients – findings from the Munich Antidepressant Response Signature (MARS) project. *Journal of Psychiatric Research*, *43*, 215–29. doi: 10.1016/j.jpsychires.2008.05.002

Horio, N., Murata, K., Yoshikawa, K., Yoshihara, Y., & Touhara, K. (2019). Contribution of individual olfactory receptors to odor-induced attractive or aversive behavior in mice. *Nature Communications*, *10*, 209. doi: 10.1038/s41467-018-07940-1

Hummel, T., Kobal, G., Gudziol, H., & Mackay-Sim, A. (2007). Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: An upgrade based on a group of more than 3000 subjects. *European Archives of Oto-Rhino-Laryngology : Official Journal of the European Federation of Oto-Rhino-Laryngological Societies*, *264*, 237–43. doi: 10.1007/s00405-006-0173-0

Hummel, T., Sekinger, B., Wolf, S. R., Pauli, E., & Kobal, G. (1997). 'Sniffin' sticks': Olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chemical Senses*, *22*, 39–52.

Kamath, V., Paksarian, D., Cui, L., Moberg, P. J., Turetsky, B. I., & Merikangas, K. R. (2018). Olfactory processing in bipolar disorder, major depression, and anxiety. *Bipolar Disorders*, *20*, 547–555. doi: 10.1111/bdi.12625

Kienke, A. S., & Rosenbaum, J. F. (2000). Efficacy of venlafaxine in the treatment of severe depression. *Depression and Anxiety*, *12*(Suppl 1), 50–4. doi: 10.1002/1520-6394(2000)12:1+<50::AID-DA6>3.0.CO;2-4

Kohli, P., Soler, Z. M., Nguyen, S. A., Muus, J. S., & Schlosser, R. J. (2016). The association between olfaction and depression: A systematic review. *Chemical Senses*, *41*, 479–86. doi: 10.1093/chemse/bjw061

Kopala, L. C., Good, K. P., & Honer, W. G. (1994). Olfactory hallucinations and olfactory identification ability in patients with schizophrenia and other psychiatric disorders. *Schizophrenia Research*, *12*, 205–11.

Lapid, H., Shushan, S., Plotkin, A., Voet, H., Roth, Y., Hummel, T., … Sobel, N. (2011). Neural activity at the human olfactory epithelium reflects olfactory perception. *Nature Neuroscience*, *14*, 1455–61. doi: 10.1038/nn.2926

Li, Q., Yang, D., Wang, J., Liu, L., Feng, G., Li, J., … Li, Z. (2015). Reduced amount of olfactory receptor neurons in the rat model of depression. *Neuroscience Letters*, *603*, 48–54. doi: 10.1016/j.neulet.2015.07.007

Lombion-Pouthier, S., Vandel, P., Nezelof, S., Haffen, E., & Millot, J. L. (2006). Odor perception in patients with mood disorders. *Journal of Affective Disorders*, *90*, 187–91. doi: 10.1016/j.jad.2005.11.012

Miller, B. R., & Hen, R. (2015). The current state of the neurogenic theory of depression and anxiety. *Current Opinion in Neurobiology*, *30C*, 51–58. doi: 10.1016/j.conb.2014.08.012

Mokdad, A. H., Forouzanfar, M. H., Daoud, F., Mokdad, A. A., El Bcheraoui, C., Moradi-Lakeh, M., … Murray, C. J. (2016). Global burden of diseases, injuries, and risk factors for young people's health during 1990-2013: A systematic analysis for the global burden of disease study 2013. *Lancet*, *387*, 2383–401. doi: 10.1016/S0140-6736(16)00648-6

Moller, H. J. (2008). Outcomes in major depressive disorder: The evolving concept of remission and its implications for treatment. *The World Journal of Biological Psychiatry: the Official Journal of the World Federation of Societies of Biological Psychiatry*, *9*, 102–14. doi: 10.1080/15622970801981606

Naudin, M., El-Hage, W., Gomes, M., Gaillard, P., Belzung, C., & Atanasova, B. (2012). State and trait olfactory markers of major depression. *PloS One*, *7*, e46938. doi: 10.1371/journal.pone.0046938

Negoias, S., Croy, I., Gerber, J., Puschmann, S., Petrowski, K., Joraschky, P., & Hummel, T. (2010). Reduced olfactory bulb volume and olfactory sensitivity in patients with acute major depression. *Neuroscience*, *169*, 415–21. doi: 10.1016/j.neuroscience.2010.05.012

https://doi.org/10.1017/S0033291720003918 Published online by Cambridge University Press

Okamoto, A., Kuriyama, H., Watanabe, S., Aihara, Y., Tadai, T., Imanishi, J., & Fukui, K. (2005). The effect of aromatherapy massage on mild depression: A pilot study. *Psychiatry and Clinical Neurosciences*, *59*, 363. doi: 10.1111/j.1440-1819.2005.01385.x

Pause, B. M., Miranda, A., Goder, R., Aldenhoff, J. B., & Ferstl, R. (2001). Reduced olfactory performance in patients with major depression. *Journal of Psychiatric Research*, *35*, 271–7.

Pentzek, M., Grass-Kapanke, B., & Ihl, R. (2007). Odor identification in Alzheimer's disease and depression. *Aging Clinical and Experimental Research*, *19*, 255–8.

Pratt, L. A., Brody, D. J., & Gu, Q. (2011). Antidepressant use in persons aged 12 and over: United States, 2005-2008. *NCHS Data Brief*, *283*, 1–8.

Rossi, M., Perez-Lloret, S., Millar Vernetti, P., Drucaroff, L., Costanzo, E., Ballesteros, D., … Merello, M. (2015). Olfactory dysfunction evaluation is not affected by comorbid depression in Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, *30*, 1275–9. doi: 10.1002/mds.26276

Rottstadt, F., Han, P., Weidner, K., Schellong, J., Wolff-Stephan, S., Strauss, T., … Croy, I. (2018). Reduced olfactory bulb volume in depression—A structural moderator analysis. *Human Brain Mapping*, *39*, 2573–2582. doi: 10.1002/hbm.24024.

Rush, A. J., Kraemer, H. C., Sackeim, H. A., Fava, M., Trivedi, M. H., Frank, E., … Force, A. T. (2006). Report by the ACNP task force on response and remission in major depressive disorder. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *31*, 1841–53. doi: 10.1038/sj.npp.1301131.

Scinska, A., Wrobel, E., Korkosz, A., Zatorski, P., Sienkiewicz-Jarosz, H., Lojkowska, W., … Kukwa, W. (2008). Depressive symptoms and olfactory function in older adults. *Psychiatry and Clinical Neurosciences*, *62*, 450–6. doi: 10.1111/j.1440-1819.2008.01824.x

Serby, M., Larson, P., & Kalkstein, D. (1990). Olfactory sense in psychoses. *Biological Psychiatry*, *28*, 830.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59*(Suppl 20), 22–33, quiz 34–57.

Siopi, E., Denizet, M., Gabellec, M. M., de Chaumont, F., Olivo-Marin, J. C., Guilloux, J. P., … Lazarini, F. (2016). Anxiety- and depression-like states lead to pronounced olfactory deficits and impaired adult neurogenesis in mice. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*, *36*, 518–31. doi: 10.1523/JNEUROSCI.2817-15.2016

Snaith, R. P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., & Trigwell, P. (1995). A scale for the assessment of hedonic tone the Snaith-Hamilton pleasure scale. *The British Journal of Psychiatry: the Journal of Mental Science*, *167*, 99–103.

Sorokowska, A., Albrecht, E., Haehner, A., & Hummel, T. (2015). Extended version of the "Sniffin' Sticks" identification test: Test-retest reliability and validity. *Journal of Neuroscience Methods*, *243*, 111–4. doi: 10.1016/j.jneumeth.2015.01.034

Sorokowska, A., Drechsler, E., Karwowski, M., & Hummel, T. (2017). Effects of olfactory training: A meta-analysis. *Rhinology*, *55*, 17–26. doi: 10.4193/Rhin16.195.

Streiner, D. L., & Norman, G. R. (2011). Correction for multiple testing: Is there a resolution? *Chest*, *140*, 16–18. doi: 10.1378/chest.11-0523

Swiecicki, L., Zatorski, P., Bzinkowska, D., Sienkiewicz-Jarosz, H., Szyndler, J., & Scinska, A. (2009). Gustatory and olfactory function in patients with unipolar and bipolar depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *33*, 827–34. doi: 10.1016/j.pnpbp.2009.03.030

Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., … Team, S. D. S. (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *The American Journal of Psychiatry*, *163*, 28–40. doi: 10.1176/appi.ajp.163.1.28

Villa, R. F., Ferrari, F., Bagini, L., Gorini, A., Brunello, N., & Tascedda, F. (2017). Mitochondrial energy metabolism of rat hippocampus after treatment with the antidepressants desipramine and fluoxetine. *Neuropharmacology*, *121*, 30–38. doi: 10.1016/j.neuropharm.2017.04.025

Warner, M. D., Peabody, C. A., & Csernansky, J. G. (1990). Olfactory functioning in schizophrenia and depression. *Biological Psychiatry*, *27*, 457–8.

Wechsler, D. (1987). Wechsler memory scale–revised. *New York, Psychological Corp*.

Yahiaoui-Doktor, M., Luck, T., Riedel-Heller, S. G., Loeffler, M., Wirkner, K., & Engel, C. (2019). Olfactory function is associated with cognitive performance: Results from the population-based LIFE-adult-study. *Alzheimer's Research & Therapy*, *11*, 43. doi: 10.1186/s13195-019-0494-z

Zucco, G. M., & Bollini, F. (2011). Odour recognition memory and odour identification in patients with mild and severe major depressive disorders. *Psychiatry Research*, *190*, 217–20. doi: 10.1016/j.psychres.2011.08.025

Zuccoli, G. S., Saia-Cereda, V. M., Nascimento, J. M., & Martins-de-Souza, D. (2017). The energy metabolism dysfunction in psychiatric disorders postmortem brains: Focus on proteomic evidence. *Frontiers in Neuroscience*, *11*, 493. doi: 10.3389/fnins.2017.00493