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ORIGINAL ARTICLE

Improvement of hedonic perception of odors as a marker of treatment response to escitalopram: olfactory changes through an open-label antidepressant trial

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Objectives: To assess olfactory functions (threshold, identification, and hedonic valence) of depressed subjects before and after an 8-week trial of escitalopram and compare the results of responders and nonresponders.
Methods: Fifty-two depressed subjects were recruited. Participants received escitalopram and were evaluated at two visits: baseline (V0) and week 8 (V8). They were categorized as responders (Montgomery-Åsberg Depression Rating Scale [MADRS] score reduction of $>$ 50%) or nonresponders to treatment. Participants were evaluated with the Mini International Neuropsychiatric Interview (MINI) at V0 and, at V0 and V8, completed psychometric and olfactory assessments, including MADRS and the State-Trait Anxiety Inventory (STAI), as well as the Sniffin' Sticks® test (threshold and identification tasks). The hedonic valence of smell was assessed on a 10-cm linear scale after presenting two pleasant and two unpleasant odors. Forty-three participants completed the study (24 responders and 19 nonresponders). The Mann-Whitney, chi-square, and Fisher's exact tests were used to compare olfactory, clinical, and demographic variables between groups and within the same group at V0 and V8. The Spearman coefficient was used to calculate the correlation between clinical characteristics and olfactory variables.
Results: The hedonic score of pleasant odors increased significantly between V0 and V8 only for responders ($V = 61.5$, $p = 0.018$), with no significant change in nonresponders ($V = 90.5$, $p = 0.879$). Comparison of olfactory performances between groups at V0 and V8 separately did not show a significant difference between responders and nonresponders to escitalopram. Olfactory threshold and identification scores were not different between V0 and V8 for responders or nonresponders.
Conclusion: Depressed subjects have olfactory anhedonia, which appears to regress following a positive antidepressant response. Hedonic valence may be an indicator of cognitive changes associated with depression; improvement of this valence may indicate a clinical response to antidepressants.

Keywords: Depression; antidepressant; escitalopram; response; olfactory; marker

Introduction

Major depression is one of the most prevalent psychiatric disorders worldwide.[1] To date, the diagnosis of a major depressive episode (MDE) has relied on clinical criteria reported by patients and observed by clinicians, rather than objective biological or sensory measurements.[2]

Biological and clinical markers, as well as surrogates, are clinical measurement tools that are used to determine the progression of a disease or the effect of a therapeutic approach. Markers and surrogates consist of biological, radiological, or clinical parameters associated with a specific condition or a treatment. They may constitute objective indicators that intend to substitute for a clinical endpoint.[3] Several biological parameters have been identified as biomarkers of MDE.[4] Similarly, sensory characteristics, such as visual, auditory, and gustatory alterations, have also been identified as potential markers of MDE.[5-8] Olfactory dysfunctions can be considered potential markers for psychiatric disorders, and may constitute either a factor of vulnerability or a consequence of the disorder.[9,10] Several studies have found that

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olfactory perception may be affected in patients suffering from MDE, thus serving as a potential indicator of this disorder.[5,11] Olfactory markers can be characteristic of the type of depression (bipolar or unipolar) can be found during the symptomatic phase of the disorder (state markers) or persist after remission (trait markers).[10,12,13]

Among different olfactory variables, identification capacity and hedonic judgment can be altered in depression,[14] and the olfactory threshold can be lower among depressed subjects compared to controls.[15-17] Pollatos et al.[18] observed a negative correlation between olfactory sensitivity and depressive symptoms among non-depressed subjects. Several studies have shown that this olfactory parameter can improve after antidepressant treatment or in remission.[17-19] However, these results are still controversial, since other results show that this olfactory variable is not affected by depression.[20] Several of these studies measured the olfactory threshold using the Sniffin' Sticks® test with 2-phenylethanol (rose-like odor) as a stimulus.[15,18,20] Others used L-carvone (menthol-like odor), tetrahydrothiophene (gas-like odor),[16] eugenol (clove-like odor),[17] isoamyl acetate (banana-like odor), and androstenone (urine-like odor)[19] as different stimuli to measure the threshold.

As for olfactory identification, research has found that patients with depression may exhibit reduced levels of odor identification compared to healthy controls.[21,22] This deficit in olfactory identification is more pronounced in severe depression.[22] Again, other studies showed contradictory results, finding that olfactory identification was not affected by depression.[16,23,24] Atanasova et al.[25] observed that deficits in olfactory identification in depression depend on the hedonic value of the stimulus; depressed subjects tend to identify fewer pleasant smells compared to unpleasant ones.[25]

Concerning hedonic judgment of odors, the literature is also contradictory. Different studies have reported alterations of this parameter in depression. On one hand, Lombion-Pouthier et al.[16] showed that depressed subjects tend to overestimate the pleasantness of positive smells. On the other, Naudin et al.[11,14] demonstrated that depression may be associated to "olfactory anhedonia," whereby subjects in depression may underestimate the hedonicity of pleasant odors. Other studies did not report any difference between depressed subjects and controls regarding odor hedonicity.[20,26]

In a previous study, our team found that subjects diagnosed with MDE have smell identification deficits compared to subjects in remission and controls. Patients in MDE also present with olfactory anhedonia: they tend to assign lower hedonic ratings to pleasant odors compared to controls and patients in remission.[12] As for olfactory sensitivity, this study found it to be significantly lower in depressed subjects than in controls, with a tendency toward progressive improvement in odor sensitivity among subjects with MDE, those in remission, and healthy controls.[12] However, this study, as most studies assessing olfaction in depression, was cross-sectional. Very few studies have evaluated the effect of antidepressant treatment on olfaction.[11] Gross-Isseroff et al.[19] showed that patients with major depression had increased olfactory sensitivity to isoamyl acetate 6 weeks after initiating an antidepressant treatment. Colle et al.[27] showed that responders to venlafaxine improved their olfactory threshold and pleasantness scores. It is still unclear if olfaction is affected by the response to antidepressant.

In this study, we assessed and compared the olfactory characteristics of subjects with MDE, responders and nonresponders to an 8-week escitalopram trial, to detect a potential association between olfaction and antidepressant response. The olfactory variables of interest, assessed at baseline and at week 8, were olfactory threshold, identification, and hedonic judgment.

The primary aim of this study was to detect changes in olfactory parameters related to antidepressant response after 8 weeks of treatment. Our secondary aims were: to compare olfactory performance of subjects who responded to antidepressant medication to the results of those who did not; and to explore correlations between observed olfactory changes and patients' clinical characteristics.

Our main hypothesis was that improvement in olfactory performance could be observed 8 weeks after the initiation of an antidepressant treatment, and that these changes might indicate antidepressant response. The outcome measures for this hypothesis were improvement of olfactory threshold, identification capacity, and hedonic valence.

Methods

Participants and general design

The present study was carried out as part of the Biomarkers of Antidepressant Resistance (BIORESA) project, whose main objective was to identify metabolomic signatures associated with response to antidepressants. Fifty-two outpatients diagnosed with MDE (DSM-IV criteria) and a severity score $>$ 20 on the Montgomery-Åsberg Depression Rating Scale (MADRS) participated in this study. Participants were required to have received no antidepressant treatment for at least 2 weeks before inclusion. Pregnancy, bipolar or schizophrenic disorder, neurological disorders, and being under legal guardianship were criteria for non-inclusion.

Patients were recruited and evaluated at the Clinical Investigation Center (Centre d'Investigation Clinique) of the Tours University Hospital (Bretonneau – Centre hospitalier régional universitaire de Tours). The study consisted of an 8-week open-label trial of escitalopram with two evaluation visits: baseline (V0) and end-of-trial at week 8 (V8).

Psychometric and clinical assessments were carried out by a trained psychiatrist (WEH or TD). After the baseline visit, all participants were prescribed escitalopram to be started within 24 h. The MADRS score was used to classify participants regarding their response status: those with a MADRS score reduction of 50% or more were considered as responders, otherwise they were nonresponders. The same clinical, psychometric, and olfactory assessments were performed at V0 and at V8.

The participants did not receive any antidepressant drug prior to inclusion in this study, and had no treatment resistance for the current MDE. All patients were treated with escitalopram 10 mg daily. In case of nonresponse after 4 weeks of treatment, escitalopram was progressively increased to 20 mg daily. Plasma levels of escitalopram on week 8 were not significantly different between responders and nonresponders (20.89 ng/mL vs. 20.75 ng/mL (U = 198.5, p = 0.874) (Table 1). Psychiatric comorbidity was assessed for both groups using the Mini International Neuropsychiatric Interview (MINI 5.0.0). Concomitant medications used by participants before and during the trial were the following: for responders, bilastine, valproate, ketoprofen, paracetamol, melatonin, levothyroxine, perindopril, zolmitriptan, and desloratadine; for nonresponders, bilastine, valproate, ketoprofen, paracetamol, melatonin, levothyroxine, zolmitriptan, desloratadine, oxazepam, and phloroglucinol.

In this study, the clinical assessment was carried out first, using psychometric and clinical scales. This was followed by an olfactory testing session. Prior to this session, all sensory tasks (evaluation of the olfactory threshold, odor identification, and odor hedonic assessment) were explained to the participants. Clinical evaluation sessions lasted an average of 25-30 min. The different tests were presented in the same order for all participants.

Clinical assessment

The MINI 5.0.0[28,29] was administered at V0 and used for the diagnosis of current and past psychiatric disorders. The severity of depressive symptoms was evaluated with the MADRS.[30] The State-Trait Anxiety Inventory (STAI) was used to evaluate the intensity of anxiety symptoms.[31]

Olfactory assessment

Olfactory evaluation included olfactory threshold, olfactory identification, and rating of the odors' hedonic aspect.

The Sniffin' Sticks® threshold test (Burghardt, Wedel, Germany) with 2-phenylethanol (rose-like odor) was used to determine the olfactory threshold through the so-called staircase procedure.[32] Using a triple-forced-choice

Table 1 Demographic and clinical characteristics of participants

	Responders (n=24)	Nonresponders (n=19)	Group comparison
Female/male ratio	18/6	15/4	χ^2, p = 0.761
Mean age, years	31.7 (12.3)	31.0 (15.7)	U = 263.5, p = 0.384
Age range, years	19-57	19-56	
Educational attainment, years	14.0 (2.9)	13.2 (2.3)	U = 263.5, p = 0.252
BMI (kg/m^2) at V0	25.7 (5.9)	23.0 (3.4)	U = 294.0, p = 0.117
BMI (kg/m^2) at V8	26.0 (6.0)	23.0 (3.2)	U = 295.0, p = 0.105
Escitalopram, plasma, ng/mL[†]	20.89 (18.1)	20.75 (17.3)	U = 198.5, p = 0.874
Duration of MDE, weeks	21.9 (33.0)	19.9 (14.7)	U = 162.5, p = 0.116
Number of previous MDEs	2.1 (0.9)	1.7 (0.5)	U = 71.5, p = 0.499
MADRS score at V0	30.0 (4.4)	29.3 (3.7)	U = 248.5, p = 0.628
MADRS score at V8	7.7 (4.6)	23.3 (5.8)	U = 4.0, p < 0.001
STAI score at V0	60.5 (10.5)	58.5 (10.6)	U = 238.5, p = 0.375
STAI score at V8	41.3 (13.5)	55.0 (11.1)	U = 75.0, p < 0.001
MINI 5.0.0			Fisher test, p = 0.021
			Significance by cell:
MDE, current episode	24	19	
Suicidal risk, last month	14	9	p = 0.749
Manic episode	0	0	
Hypomania	0	0	
Bipolar I and bipolar II disorder	0	0	
Bipolar disorder not otherwise specified	0	0	
Panic disorder	1	0	p = 1.000
Agoraphobia	2	0	p = 0.535
Social anxiety disorder	0	1	p = 0.349
OCD	0	0	
PTSD	6	0	p = 0.076
Alcohol use disorder	1	0	p = 1.000
Alcohol abuse	1	0	p = 1.000
Substance use disorder	0	0	
Abuse of one substance	2	0	p = 0.535
Psychotic disorder	0	0	
Anorexia nervosa	0	0	
Bulimia	0	0	
GAD	1	5	p = 0.015
Medical, organic, induced cause	0	0	
Personality disorder	0	0	

BMI = body mass index; GAD = generalized anxiety disorder; MADRS = Montgomery-Åsberg Depression Rating Scale; MDE = major depressive episode; MINI 5.0.0 = Mini-International Neuropsychiatric Interview version 5.0.0; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; STAI = State-Trait Anxiety Inventory; V0 = at baseline; V8 = at week 8.
[†] Escitalopram blood test performed once at the 2-month follow-up visit.

paradigm, three sticks were presented to the subject in a randomized order: two contained the solvent and the other the odorant at a specific dilution. The task of the subject was to indicate the stick with the odorant. Presentation of stick-triplets to participants occurred every 15-20 s, until they had correctly discerned the odorant in two successive trials, which triggered a reversal of the staircase. The mean of the last four staircase reversal points of a total of seven reversals was used as the threshold estimate. The duration of this procedure varied between 15 and 20 min according to the subject.

Odor identification was evaluated using the Sniffin' Sticks® Identification Test 16 (Burghardt, Wedel, Germany).[32] A series of 16 odor sticks (orange, leather, cinnamon, peppermint, banana, lemon, liquorice, turpentine, garlic, coffee, apple, clove, pineapple, rose, anise, and fish) was presented to the subject. Each time, the subject had to identify the odorant from a list of four descriptors (multiple choice paradigm). A score of 1 or 0 was attributed when the odor was identified correctly or incorrectly, respectively. The maximum identification score was 16. The duration of the odor identification test was approximately 10 min.

The hedonic perception of participants was studied using four odorants presented at supra-threshold concentrations: two with pleasant valence (2-phenylethanol, smell of roses [1 mL/L]; benzaldehyde, smell of bitter almonds [0.5 mL/L]) and two with unpleasant valance (hexanoic acid, smell of goat [0.12 mL/L]; butyric acid, smell of rancid butter [1.6 ml/l]). All odorant compounds were supplied by Sigma (Illkirch, France) and diluted with purified water to isointense concentrations. The odorous solutions were poured into 60-mL brown glass flasks (10 mL per flask), each coded with a three-digit random number. The presentation order of the different stimuli was balanced across stimuli and was identical for all participants. Participants were asked to evaluate the pleasantness (hedonic aspect) of the perceived odor on a 10-cm linear scale labeled at each end (highly pleasant/highly unpleasant). The resulting response was expressed on a score ranging from 0 to 10. The duration of hedonic olfactory testing was approximately 5 min.

Statistical analysis

Statistical analyses were performed with nonparametric tests, because the Levene test for homogeneity of variances revealed unequal variance for the majority of the variables and the assumption of normal data distribution was not always validated by the Kolmogorov-Smirnov test.

To study the hedonic responses, we pooled the odorants according to their hedonic valence (positive or pleasant [POS] odors and negative or unpleasant [NEG] odors) to enhance statistical reliability. The Wilcoxon signed test for paired measures within groups was used to compare the hedonic responses, the olfactory threshold, and the odor identification scores. Comparison of these parameters between responders and nonresponders at each time (V0 and V8) was carried out with the unpaired Mann-Whitney test. The Mann-Whitney test was also used to compare the demographic and clinical characteristics of the two groups (responders and nonresponders). The chi-square test was used to compare proportions of qualitative variables of the two groups of subjects (gender). Fisher's exact test was applied to compare proportions of qualitative variables in analysis of small samples (MINI psychiatric diagnoses). When the p-value of this test was significant, significance by cell was observed.

The Spearman correlation coefficient was used to study the relationship between the clinical subjects' characteristics and their olfactory performances. The Spearman coefficient was calculated for the responders group, for the nonresponders group by using the change (delta) for the responders group, and for the nonresponders group. Only the olfactory parameters demonstrating significant results were considered.

All statistical analyses were performed at alpha = 5%, in XLSTAT-Pro software.

Ethics statement

The present study was approved by the French National Research Agency (2016-A01757-44) and an independent national research ethics committee (16/45-1043). The BIORESA project was registered on the ClinicalTrials.gov website (NCT03118193) and was supervised by a clinical investigation monitoring committee (Institut National de la Santé et de la Recherche Médicale [Inserm] CIC1415). The experimental procedure was clearly explained to all participants. The subjects were informed that they were free to stop their participation to the study at any time. All participants signed informed-consent forms prior to the start of the trial.

Results

Demographic and clinical characteristics

Full olfactory data were available for 43 participants: one subject committed suicide, two subjects were lost to follow-up, and six subjects were not able to carry out the olfactory tests at V8 because of COVID-19 pandemic restrictions (mask mandates and social distancing requirements). Based on the change in MADRS score (reduction of 50% or more at V8), the participants were separated into two groups: 24 (55.8%) responders and 19 (44.2%) nonresponders to antidepressant treatment. As shown in Table 1, no significant difference between the two groups was found concerning age, gender, educational level, body mass index (BMI) (at V0 and at V8), duration of MDE, number of previous MDEs, MADRS score at V0, and STAI score at V0. Compared to the responders, the nonresponders had a significantly higher STAI score at V8. As expected, the responders had significant lower MADRS scores at V8. Regarding MINI psychiatric diagnoses, a significant difference between responders and nonresponders was found only for generalized anxiety disorder (GAD) (Fisher test: p = 0.015), although a trend toward a difference in frequency

of comorbid posttraumatic stress disorder (PTSD) was observed (Fisher test: p = 0.076). For all other parameters, the p-values obtained with Fisher's exact test were greater than 5%.

Olfactory threshold, identification, and hedonic evaluation

Comparing the olfactory threshold scores obtained at V0 and V8, no significant difference was found for responders (V = 146, p = 0.814) and for nonresponders (V = 79.5, p = 0.884). No significant prospective change in identification scores between V0 and V8 in either group was observed (responders: V = 96, p = 0.640; nonresponders: V = 22, p = 0.985) (Figure 1A and B).

Regarding the hedonic evaluation of NEG odors, no significant difference was found between V0 and V8 for responders (V = 64.5, p = 0.375) or for nonresponders (V = 50.5, p = 0.214). However, the hedonic score of POS odors increased significantly between V0 and V8 among responders only (V = 61.5, p = 0.018), with no significant change in nonresponders (V = 90.5, p = 0.879) (Figure 1C and D).

As for the between-group comparison at each time point, the results obtained at V0 did not show a significant difference between groups concerning olfactory threshold (U = 177.5, p = 0.227), odor identification (U = 235.5, p = 0.850), or hedonic evaluation of negative (U = 230.0, p = 0.811) and positive (U = 297.5, p = 0.210) odors (Figure 2). No significant difference between responders and nonresponders at V8 was observed for olfactory threshold (U = 194.0, p = 0.417), odor identification (U = 235.5, p = 0.850), or hedonic evaluation of negative (U = 251.0, p = 0.574) and positive (U = 248.5, p = 0.625) odors (Figure 2).

Correlation between variables

Among the studied olfactory parameters, a significant difference was found only for hedonic perception. Therefore, this parameter was used to study potential correlations between the clinical subjects' characteristics and their olfactory perception.

For responders and nonresponders alike, no significant correlation was found between any clinical characteristics and the hedonic perception of positive and negative odors (Table 2).

Discussion

The study described herein involved a prospective, open-label, 8-week trial of escitalopram. We evaluated the olfactory perception and characteristics of participants at baseline and at the end of the trial, and compared the results of responders and nonresponders to the antidepressant.

The main finding of our study was improvement of the hedonic value of pleasant (POS) odors, observed among responders after 8 weeks of treatment with escitalopram. It must be noted that a trend toward a higher frequency of comorbid PTSD was observed in the responders' group (six responders with comorbid PTSD versus zero nonresponders). Indeed, a previous study found that a

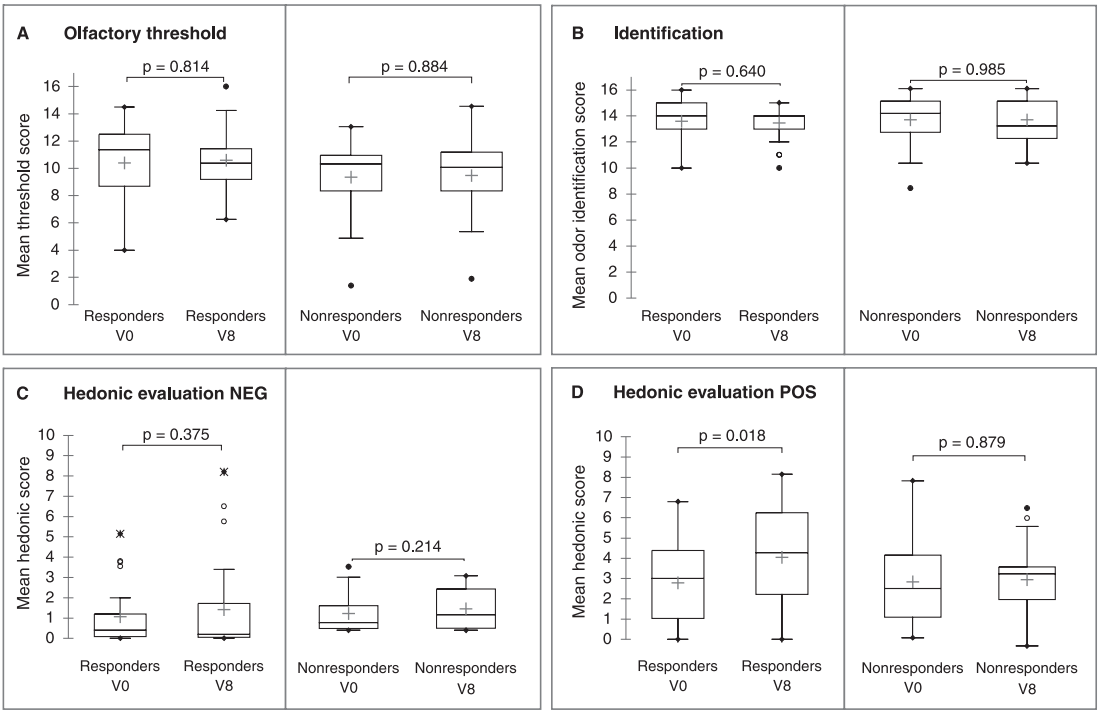

Figure 1 Comparison of olfactory performances at baseline (V0) and at week 8 (V8) for responders and nonresponders separately. NEG = negative/unpleasant odors; POS = positive/pleasant odors.

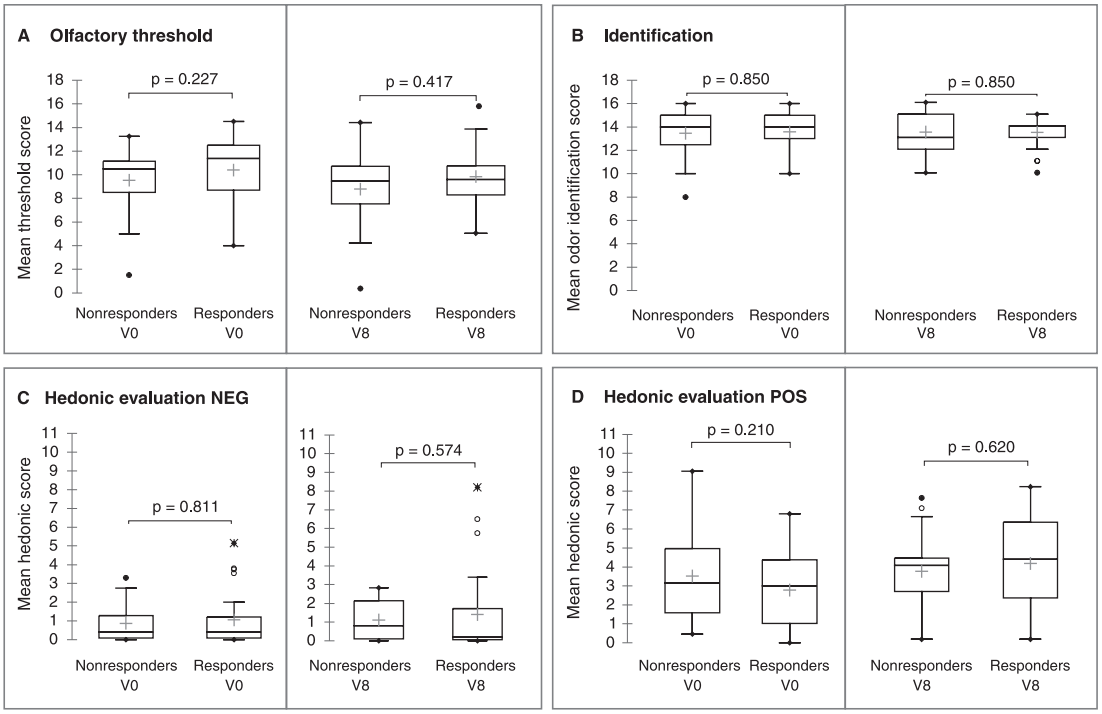

Figure 2 Comparison of olfactory performances between responders and nonresponders at baseline (V0) and at week 8 (V8) separately. NEG = negative/unpleasant odors; POS = positive/pleasant odors.

Table 2 Spearman correlation of change (delta between V0 and V8) in clinical characteristics and hedonic olfactory perception, calculated for responders and nonresponders

	Responders (n=24)		Nonresponders (n=19)	
Variable	NEG	POS	NEG	POS
MADRS score	r = -0.190	r = 0.146	r = -0.398	r = -0.314
	p = 0.371	p = 0.493	p = 0.093	p = 0.190
STAI score	r = 0.041	r = 0.303	r = -0.370	r = -0.032
	p = 0.850	p = 0.150	p = 0.119	p = 0.899
Duration of MDE	r = -0.148	r = 0.063	r = 0.157	r = -0.275
	p = 0.488	p = 0.771	p = 0.521	p = 0.253
BMI	r = -0.194	r = -0.030	r = -0.032	r = 0.314
	p = 0.363	p = 0.890	p = 0.898	p = 0.190

Values in bold are significant at 5%.
BMI = body mass index; MADRS = Montgomery-Åsberg Depression Rating Scale; MDE = major depressive episode; NEG = negative/unpleasant odors; POS = positive/pleasant odors; STAI = State-Trait Anxiety Inventory; V0 = at baseline; V8 = at week 8.

pleasant odor (vanilla) had a positive (reducing) effect on distress, heart rate, and dissociative response in subjects with PTSD[33]; the authors also reported a significant positive correlation between hedonic tone and behavioral assessments (PTSD symptoms, emotional symptoms, dissociation) among subjects diagnosed with PTSD. These observations suggest that the improvement of the hedonic perception of pleasant odors observed in the responders' group only could be related to the presence of comorbid PTSD. This change in hedonic valence of odors was not observed with unpleasant (NEG) odors. Previous cross-sectional studies have showed that patients with depression may experience olfactory anhedonia, since they have lower ability to appreciate pleasant odorants than patients in remission. This study showed that subjects in remission may recover their hedonic capacity when compared to healthy controls.[12] Using the Sniffin' Sticks® test to assess hedonic valence, the authors found that depressed subjects had lower hedonic valence compared to other groups, but that remitted subjects could not be differentiated from healthy controls in this respect. This change in olfactory performance was also confirmed by Colle et al.,[27] who found that, after antidepressant treatment, only those patients who achieved remission restored their pleasantness score to levels comparable to those of healthy controls.

Lack of pleasure or anhedonia is a cardinal symptom of depression. Accordingly, improvement in this symptom may indicate clinical remission.[2] Previous studies have linked clinical and sensory anhedonia.[25,34] The judgment

of pleasantness is processed in the orbitofrontal cortex, depending also on the integrative function of the prefrontal cortex, and is affected by the emotional state of the subject.[35,36] Previous studies have found that hedonic rating of pleasant odors can be a potential indicator of depression.[12] Atanasova et al.[25] showed that depressed subjects have olfactory anhedonia and negative olfactory alliesthesia, perceiving unpleasant odorants as significantly more unpleasant than did controls. Similarly, Clepce et al.[26] confirmed the presence of olfactory anhedonia in depressed subjects compared to remitted patients and healthy controls. According to Naudin & Atanasova,[37] olfactory anhedonia may constitute a potential state marker of depression. These alterations in olfactory hedonic valence may be the result of depression-associated cognitive biases seen among depressed subjects, associating a negative attributional style and a selective attention oriented toward negative olfactory stimuli.[25,37] In a pilot study, Naudin et al.[11] showed that patients with depression increased the hedonic valence ascribed to pleasant odorants after a 6-week trial of escitalopram. The results of this study show us that this effect on hedonic valence is related to the clinical response to the antidepressant rather than to a direct pharmacological effect of escitalopram on olfaction. Indeed, our results show that this effect was observed only among responders to the escitalopram trial. Therefore, we may consider the hedonic valence of pleasant odors as a potential indicator of treatment response in MDE.

Our results did not show a significant difference between responders and nonresponders regarding olfactory identification capacity. Moreover, the identification scores obtained in the two patient groups at V0 (responders: mean, 13.583±1.6; min, 10; max, 16; nonresponders: mean, 13.474±2.1; min, 8; max, 16) and at V8 (responders: mean, 13.458±1.4; min, 10; max, 15; nonresponders: mean, 13.474±1.8; min, 10; max, 16) seems to be close to normative olfactory function.[38] Nevertheless, in a previous cross-sectional study, our team found that odor identification capacity may be lower in patients with depression compared to those in remission.[12] In a systematic review, Kohli et al.[39] found that depression is associated with deficits in olfactory identification. However, other studies have reported contradictory results regarding this variable.[16,20,40] In a 6-week antidepressant trial, Naudin et al.[11] did not find any change in odor identification among depressed subjects. Similarly, Colle et al.[27] did not find a significant difference in smell identification between healthy controls and patients with depression, before and after antidepressant treatment. Olfactory identification is a variable that depends on different factors, such as cognition, memory, and cultural variables of the population.[14,41,42] Deficits in smell identification in depression may be associated with changes in cognitive functions such as attention or working memory. Our results show that the observed identification scores were near ceiling values and close to normative function. The lack of a significant change in odor identification after an 8-week trial of antidepressant may have been due to our small sample size, resulting in lack of statistical power to detect some olfactory differences.

As for olfactory threshold, our results did not show a significant difference between responders and nonresponders. While a previous study showed a lack of difference in olfactory acuity between subjects in depression and in remission,[12] others observed significant changes in olfactory threshold as a result of antidepressant treatment.[27] Moreover, as for the identification scores presented above, the threshold scores obtained in the two patient groups at V0 (responders: mean, 10.396±3.2; min, 4; max, 14.5; nonresponders: mean, 9.526±2.9; min, 1.5; max, 13.25) and at V8 (responders: mean, 10.60±2.2; min, 6.25; max, 16; nonresponders: mean, 9.632±2.9; min, 2; max, 14.75) seem to be close to normative olfactory function.[38] Differences in olfactory acuity are seen between depressed subjects, on one hand, and healthy controls and remitted patients on the other.[15,27] Moreover, Negoias et al.[43] showed that olfactory bulb volume correlates with change in depression severity and may be a anatomic predictor of therapeutic response. These findings suggest that, among other variables, smell acuity may be a potential state-indicator of depression that warrants further study. A recent study with healthy subjects demonstrated that, for pleasant odors (apple and jasmine), the higher the concentration, the more pleasant the odorant.[44] Moreover, the authors revealed a significant correlation between the olfactory detection threshold steps and hedonic evaluation of the odor (i.e., the more sensitive the subject to an odor, the more this odor was evaluated as pleasant). In the present study, 2-phenylethanol (rose-like odor) was used to evaluate the olfactory threshold and study hedonic perception. There is the possibility that individuals with high sensitivity to this odorant obtain a greater subjective experience with the odorant during the threshold test, which could subsequently impact the perceived intensity of the odor and participant judgements during hedonic evaluation. In this context, we calculated the Spearman correlation coefficient between the threshold scores and hedonic scores of 2-pheylethanol for each group. The analysis was carried out using the change (delta) in the scores. Our results are partly in line with the previous study carried out with healthy subjects,[44] because a significant correlation was found only for nonresponders: $r = 0.474$, $p = 0.042$ (for responders: $r = -0.167$, $p = 0.433$). These observations suggest that, in our population, the relationship between hedonic perception and odor threshold depend on factors other than age, gender, and BMI (the parameters for which the two groups were matched). Several studies have shown great flexibility in hedonic perception of odors. Differences have been observed in relation to subjects' general experience towards odorants,[45] physiological state,[46] and level of hunger.[47] Future studies are needed to confirm our observations. A better understanding of the relationship between sensitivity and hedonic rating may be needed because of the close relationship between hedonic perception and quality of life.

The present study also found no significant difference between responders and nonresponders at V0 regarding

the three tested olfactory variables. Therefore, we can assume that these three variables cannot be used to differentiate responders from nonresponders before the onset of treatment and cannot be associated with a "trait" of antidepressant response profile.

Our study has several limitations that need to be addressed. First, olfactory assessment was done at baseline and 8 weeks after initiation of treatment. However, some changes in olfactory measures may only be detected several months after remission, and thus could have been missed by this study. Second, this study did not include healthy controls, and therefore we cannot detect possible baseline olfactory dysfunctions associated with vulnerability for depression, which may constitute possible olfactory trait-markers of depression. Third, our sample was largely composed of young adults, and conclusions cannot be drawn for different forms of clinical depression observed in different age groups. Fourth, only 43 subjects completed the study. This small sample size could have underpowered our results to detect otherwise significant olfactory differences. A study with a larger population would allow use of parametric tests with greater statistical power compared to nonparametric ones; if an effect actually exists, a parametric analysis is more likely to detect it. Our results showed a significant difference between both groups on the MINI assessment regarding comorbid GAD, and a trend toward a significant difference regarding PTSD. This was the only difference between groups regarding comorbidity profiles, perhaps due to the relatively small sample size. Studies with larger populations may be needed to evaluate the possible effect of comorbid GAD or PTSD on olfactory perception. Finally, our evaluation did not include specific cognitive assessments of attention and memory. We assume that observed sensory alterations may be related to cognitive biases, even though specific cognitive assessment was not performed.

To conclude, this was one of the first studies to assess olfactory function before and after an 8-week antidepressant trial. Our findings characterize the olfactory profile of responders, before and after antidepressant treatment, compared to nonresponders. We were able to observe significant olfactory changes associated with clinical improvement. Depressed subjects presented olfactory anhedonia to pleasant odors, and this alteration of hedonic valence improved after a positive antidepressant response.

Our results suggest that improvement of odor hedonic valence may be associated with clinical response to antidepressants and that this variable may thus be a potential indicator of cognitive or emotional impairments associated with depression. Sensory indicators such as olfactory performance may be an alternative way to objectify emotional and cognitive changes associated with depression and clinical response to treatment. However, the conclusions of this study remain speculative, and should not be overinterpreted. A larger cohort evaluating how depression-associated cognitive changes modulate olfactory perception may bring more insight to this subject.

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Disclosure

The authors report no conflicts of interest.

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