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Research paper

Low odor awareness predicts reduced olfactory abilities in women with depressive symptoms, but not with anxiety symptoms

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ABSTRACT

Background: Olfactory disorders and affective symptoms are tightly related. However, the factors underlying this association are not yet understood. One candidate factor is "odor awareness": the degree of attention individuals pays to the odors. However, the association between odor awareness and olfactory abilities in individuals with affective symptoms has not been clarified yet.
Method: The present study examined whether odor awareness may moderate (a) the relation between olfactory dysfunctions and depressive and anxiety symptoms; (b) the relation between the perceptual ratings of the odors and depressive and anxiety symptoms in a sample of healthy women ($n = 214$). Self-report measures of depression and anxiety were collected, whereas the Sniffin' Stick test was employed to measure olfactory abilities.
Results: Linear regression analysis revealed that individuals with higher depressive symptoms presented lower olfactory abilities and that odor awareness was a significant moderator of the association between depressive symptoms and olfactory abilities. Anxiety symptoms were not related to any of the olfactory abilities considered, and this relationship did not change according to odor awareness. The familiarity rating of the odor was significantly predicted by odor awareness. These results were confirmed by Bayesian statistics.
Limitations: The sample was composed only of women.
Conclusions: In a healthy population of women, only the presence of depressive symptoms is related to reduced olfactory performance. Odor awareness may be implicated in the development and maintenance of olfactory dysfunction; hence it could be used as a useful target for specific treatments in clinical settings.

1. Introduction

Olfaction has received less attention compared to the other senses; however, the COVID-19 pandemic has shed light on the crucial role this sense has in human life. Besides the pandemic, olfactory dysfunctions are more common than expected, with an estimated prevalence of approximately 22 % in the general population (Desiato et al., 2020). Indeed, the loss of the sense of smell leads to disturbances in crucial domains, mainly in nutrition, food enjoyment, protection from harmful (e.g., rotten) food and gas leaks or smoke (Croy et al., 2014a; Stevenson, 2010), as well as in social relationships and working life, leading to a general reduction in well-being (Boesveldt and Parma, 2021; Croy et al., 2014a; Mai et al., 2022). Interestingly, olfaction is also closely related to emotion and mood. Indeed, several mental disorders are associated with altered olfactory abilities (Croy and Hummel, 2017; Rochet et al., 2018; Soudry et al., 2011). The tight relationship between olfactory deficits and mental disorders could be explained by the fact that the brain areas involved in the pathophysiology of mental disorders partially overlap with the brain areas implicated in olfactory processing, namely the amygdala, hippocampus, insula, anterior cingulate cortex, and orbitofrontal cortex (Rochet et al., 2018; Soudry et al., 2011). For these reasons, olfaction has been suggested as a possible proxy of the functional integrity of the neural networks implicated in mental disorders. However, the underlying mechanisms leading to this association are not fully understood yet (Croy and Hummel, 2017).

Among mental disorders, the most common are depressive and anxiety disorders, affecting 4.4 % and 3.6 % of the global population in 2015, respectively (World Health Organization, 2017). Individuals with

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depressive symptoms are characterized by diminished olfactory functioning in multiple aspects of olfaction, including threshold, discrimination and identification as shown in several studies (e.g., Athanassi et al., 2021; Croy et al., 2014b; Croy and Hummel, 2017; Kazour et al., 2020; Pabel et al., 2018; Rochet et al., 2018; Sabiniewicz et al., 2022), and meta-analyses (Kim and Bae, 2022; Kohli et al., 2016; Taalman et al., 2017). Furthermore, there is a mutual relationship between olfactory dysfunction and depression, as it has been reported that one-third of patients with olfactory loss present signs of depressive mood (Chen et al., 2021; Croy et al., 2014a). A central feature of odor perception is its hedonic component, however, the relationship between depressive symptoms and the hedonic processing of odorants is not fully understood yet (for a review see Athanassi et al., 2021). Despite most of the studies have reported that depressed patients perceive unpleasant odors as more unpleasant and pleasant odors as less pleasant (e.g., Atanasova et al., 2010; Kazour et al., 2020) than healthy controls, other studies failed to observe this difference (Swiecicki et al., 2009), or even they found an opposite pattern (Lombion-Pouthier et al., 2006; Pause et al., 2001).

Regarding anxiety disorders, to date, very few studies have investigated olfactory functions in this population, reporting conflicting results. In a group of patients with different anxiety disorders, it has been found an impairment in olfactory discrimination, but not in identification and threshold, along with higher intensity and hedonic ratings compared to healthy controls (Clepce et al., 2012), whereas in a group of healthy subjects both state and trait anxiety ratings were significantly associated with reduced odor detection and identification (Takahashi et al., 2015). On the other side, studies focusing specifically on panic disorder reported lower olfactory detection thresholds (i.e., higher sensitivity; Burón et al., 2015, 2018), but intact olfactory identification performance (Kopala and Good, 1996).

Besides the objective measure of olfactory abilities, other cognitive factors can shape the olfactory experience, such as "odor awareness": the degree of attention individuals pay to the odors in the environment (Smeets et al., 2008). Indeed, in contrast with other sensory modalities, olfactory stimuli are characterized by poor spatial and temporal resolution, making them difficult to detect in the olfactory environment (Sela and Sobel, 2010). Nonetheless, we are constantly exposed to several olfactory stimuli that are processed mainly unconsciously (Sela and Sobel, 2010). However, some people suddenly notice the aroma of the food or the stench coming from the bathroom, while others detect them only when it is brought to their attention (Keller, 2011). Indeed, it has been shown that higher interest and higher attention to odors are related to higher familiarity ratings of odorous stimuli (Bensafi and Rouby, 2007), more affective experiences when smelling odors (Wrzesniewski et al., 1999), higher odor-related memories (Arshamian et al., 2011), better abilities to form olfactory images in our mind (Arshamian and Larsson, 2014; Stevenson and Case, 2005), but also better olfactory abilities (Nováková et al., 2014; Smeets et al., 2008). Due to the characteristics of olfactory stimuli, specifically for the related literature, the concepts of "awareness" and "attention" are often overlapping (see Stevenson, 2009; Sela and Sobel, 2010; but note that the same debate is also present in the visual domain, see van Gaal and Fahrenfort, 2008). Accordingly, the Odor Awareness Scale (OAS, Smeets et al., 2008), a tool specifically developed to measure this metacognitive ability, refers to odor awareness in terms of "paying attention to", "noticing" or "giving importance", not allowing a proper distinction between "awareness" and "attention". Hence, even though the term odor awareness is privileged, the term "paying attention to" is used interchangeably.

Following this line of reasoning, olfactory attention has been suggested as one of the factors involved in the development of olfactory dysfunction in depression. Indeed, Croy and Hummel (2017) have proposed that at least two mechanisms participate in explaining the link between olfaction and depression. A first possible mechanism is the presence of structural alterations in the olfactory bulb that make people vulnerable to depression, showing, for example, a reduction in olfactory bulb size as depression severity increases (Negoias et al., 2010). A second mechanism seems to be activated during depressive episodes: here, the reduction of olfactory attention leads to a decreased olfactory receptor turnover rate. For instance, animal studies report that depressed rats exhibit a thinner olfactory epithelium as well as a reduction of olfactory receptor neurons (Li et al., 2015) which may be linked to olfactory attention. Despite the proposed theory, very few studies investigated odor awareness in affective disorders. These studies reported higher odor awareness traits in individuals with general anxiety and with panic disorder (Burón et al., 2015, 2018; Dal Bò et al., 2022), however, no relation has been found with depressive symptoms (Dal Bò et al., 2022). Moreover, to our knowledge, the association between odor awareness and olfactory abilities in individuals with affective disorders has not been investigated yet. This is particularly surprising since a deeper understanding of the development and course of olfactory dysfunction as well as the possible initial mechanisms that cause it may represent potential clinical targets in the prevention and treatment of depressive and anxiety symptoms. Elucidating these aspects could improve our understanding of complex phenomena, such as affective disorders and olfaction, allowing us to identify potential predictive biomarkers of affective disorders and develop more specialized treatments.

Therefore, the aim of the present study was twofold: first, to test the hypothesis that odor awareness would represent a moderator underlying the relationship between depressive and anxiety symptoms and olfactory abilities and, second, to explore the association between odor awareness and hedonic perception of the odors, and in general odor ratings, in individuals with depressive and anxiety symptoms.

2. Methods

2.1. Participants and procedure

Through an online survey conducted on the platform Qualtrics, 467 subjects were screened with the following inclusion criteria: female gender, age between 18 and 35, being a non-smoker. Only women were included to avoid gender-related effects, considering that it is documented that women present higher olfactory abilities (Doty and Cameron, 2009), higher odor awareness (Ferdenzi et al., 2008), higher interest in the sense of smell (Seo et al., 2011), and higher importance of olfaction (Croy et al., 2010; Havlicek et al., 2008) than men. During the online survey, participants answered questions regarding demographic information, health status, including the presence of neurological or psychiatric conditions, the use of psychotropic drugs, drugs, alcohol and nicotine consumption, olfactory dysfunction, and then completed the following questionnaires: Beck Depression Inventory-II (BDI-II; Beck et al., 1996; Italian version by Ghisi et al., 2006), Beck Anxiety Inventory (BAI; Steer and Beck, 1997; Italian version by Sica and Ghisi, 2007), and Odor Awareness Scale (OAS; Smeets et al., 2008). After participants completed the online survey, they underwent an ad-hoc anamnestic interview conducted by phone in order to ensure that they were medically healthy and free from psychotropic medication. Specifically, exclusion criteria were being pregnant, having a cardiovascular, neurological, or psychiatric disease, diagnosis of COVID-19 (Parma et al., 2020) during the three months before the experiment, drug and nicotine consumption, olfactory dysfunction, previous head trauma leading to unconsciousness, chronic rhinitis or other conditions that may affect the ability of perceiving odors, being younger than 18 years or older than 35 years. After this screening, 214 participants were included in the study and were invited to the lab for the experimental procedure. During the experimental procedure, participants completed the Sniffin' Sticks test and the perceptual ratings of the identification subtest's odorants. All participants were told not to eat or drink anything except water for up to 1 h before participating in the test. The entire procedure lasted approximately 60 min. Participants accepted informed consent before starting the online survey and provided written informed consent before the experimental procedure.

Data were collected during the screening session of a larger protocol held at the University of Padova between November 2019 and April 2022. The present study was conducted with the adequate understanding and written consent of the participants in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee, University of Padua (prot. no. 3667).

2.1.1. Self-report questionnaires

Depressive symptoms were assessed using the Beck Depression Inventory-II (BDI-II; Beck et al., 1996 Italian version by Ghisi et al., 2006). The BDI-II is a reliable and valid self-report questionnaire that is used to assess the severity of current depressive symptoms in the past two weeks. Specifically, the BDI-II is composed of 21 items, each based on a four-point Likert scale and scores range from 0 to 63, with the higher scores indicating greater depressive symptoms.

Anxiety symptoms were assessed using the Beck Anxiety Inventory (BAI; Steer and Beck, 1997; Italian version by Sica and Ghisi, 2007). The BAI is a self-report questionnaire composed of 21 anxiety symptoms. Respondents have to rate how much each of these symptoms bothered them in the past week, from 0 ("not at all") to 3 ("severely, I could barely stand it") and the score ranges from 0 to 63, with the higher scores indicating greater anxiety symptoms.

To assess the person's tendency to pay attention to the odors in the environment, the Odor Awareness Scale (OAS; Smeets et al., 2008) was presented. This measure refers to a metacognitive ability, that is the knowledge of one's knowledge. Specifically, the OAS was developed to investigate a trait-like feature that can explain how humans process olfactory information and react to those stimuli. The OAS is a 34-item questionnaire that covers topics such as food and drink (e.g., "When someone is busy in the kitchen, do you notice the odor of the food being prepared?"), civilization (e.g., "When you are studying, or concentrated in general, do you get distracted by odors in the environment?"), nature (e.g., "When you walk through the woods, do you pay attention to the odors surrounding you?"), and man (e.g., "Do you pay attention to the perfume, the aftershave, or deodorant other people use?"). The OAS total score is calculated by the addition of the items (ranging from 32 to 158), with higher scores indicating higher odor awareness.

2.1.2. Olfactory assessment and odor rating

Olfactory function was assessed using the Sniffin' Sticks test, a validated and widely used paradigm (Burghart GmbH, see Hummel et al., 1997). This test allows the study of the olfactory function in terms of three distinct olfactory abilities: odor identification, threshold, and discrimination. The Sniffin' Sticks are felt-tips pens filled with an odorant solution, presented to the participant for approximately 3 s with a 2 cm distance in front of both nostrils. Olfactory identification was assessed with 16 common odors (Hummel et al., 1997). Participants were asked to identify the odor from a list of four verbal and visual descriptors. The number of correct answers was summated as identification score. Olfactory discrimination was assessed using a three alternative force choice (3AFC) task across 16 trials. For each trial, three pens were presented to the blindfolded participants in random order, two containing the same odor and the third containing the target odor. Finally, n-butanol diluted in propylene glycol with 16 available dilution steps was used to assess olfactory threshold. Blindfolded participants were presented with a 3AFC task with two pens containing an odorless solvent (propylene glycol) whereas one was filled with n-butanol in a certain concentration. The participants' task was to detect the pen containing the odor. A staircase procedure was used to measure the odor threshold: if the odor had not been detected, the concentration was increased, if the odor was detected twice in a row, the concentration was decreased. The odor threshold was defined as the mean of the last four of seven staircase reversals. Hence, a higher threshold score means a higher ability to detect the target odorant. Each sub-test was scored between 1 and 16. A total TDI (Threshold Discrimination Identification) score below 16.5 is considered to be within the anosmic range, between 16.5 and 30 within the hyposmic range, whereas above 30 is in the normosmic range (Hummel et al., 2007).

Specifically for the present study, during the identification test, participants, after having answered the identification question, were asked to rate each odor for intensity, pleasantness, and familiarity. Ratings were collected on a 10-point computerized Visual Analogue Scale (VAS), ranging from "not at all" to "very much".

Since February 2020, due to the SARS-CoV-2 pandemic and to avoid the spread of the disease, the procedure slightly changed, and a single-use smell test system was adopted. The only difference was that, instead of presenting the pens to the nostrils of the participants, each odor was presented on a single-use paper strip, which was then handed over to the participant. Specifically, the experimenter was instructed to write some curves with the odorous pen on a paper strip. Then, the participant smelled the paper and answered the question. The paper strip was then discarded, and the procedure was repeated for the next stick (Besser et al., 2020; Mueller et al., 2006; Wirkner et al., 2021). Moreover, the experimenter was required to wear gloves and the FFP2 face mask during the entire procedure, while participants were wearing a face shield to be able to smell the paper strips. The entire procedure took place in a well-ventilated room. In addition, to reduce the time the experimenter and the participant spent together in the laboratory, a shorter version of the threshold test was used, which involved the ascending methods of limits (Besser et al., 2020; Pössel et al., 2020). With this method, the triplets were presented in ascending order, from the weakest to the strongest concentration. The threshold score was calculated by computing the mean between the last wrong and the first correct answer, from which five odor-corrected detections were made in a row (Pössel et al., 2020). This test has been shown to be effective in reducing the timing of the test (time reduction of 51 %) but maintaining a high correlation ($r = 0.76$) with the original Sniffin' Sticks threshold test and a retest-reliability of $r = 0.68$ within one week (Pössel et al., 2020).

2.2. Statistical analyses

First, four *t*-tests were performed to control for possible differences between the two testing procedures (classical procedure vs. single-use paper strips) used to administer the Sniffin' Sticks test, one for each olfactory function measured (TDI, threshold, discrimination, identification), using the *t.test* function (*stats* package; R Core Team, 2017).

In addition, partial Pearson's correlations (*rcorr* function, *Hmisc* package) were performed to investigate the association between BDI-II, BAI scores, and the OAS scores.

Then, to investigate whether the depressive and anxiety symptoms were related to altered olfactory function, and if this link was moderated by the level of attention to the odors, four stepwise linear regression models were conducted, one for each olfactory function measure (TDI, threshold, discrimination, identification), using the *lm* function (*stats* package; R Core Team, 2017).

The initial model for each dependent variable was:

$$\sim (\mathrm{BDI}-\mathrm{II}+\mathrm{BAI})\times(\mathrm{OAS})$$

Odor ratings (intensity, pleasantness, and familiarity) were analyzed to evaluate whether the depressive and anxiety symptoms may modulate the perceptual qualities of odors, and if this effect was moderated by the level of attention to the odors. The odorants used for the perceptual rating were classified into three main categories (pleasant, neutral, and unpleasant) based on the results of the database Hedos-F (Clepce et al., 2014; Markovic et al., 2007; Thuerauf et al., 2009): unpleasant odorants were turpentine, garlic, and fish; neutral odorants were shoe leather, liquorice, coffee, and clove; pleasant odorants were orange, cinnamon, peppermint, banana, lemon, apple, pineapple, rose, and anise.

Three Linear Mixed Models (LMM) were performed with the main effects of BDI-II and BAI, and their interactions with the OAS scores, using the *lmer* function (*stats* package; R Core Team, 2017). In addition, we explored the interaction between each of these predictors with a categorical variable, called *odor category* indicating whether the odor rated was pleasant, neutral or unpleasant. The participant's ID and the individual TDI score were included as random factors:

$$\sim (\mathrm{BDI-II} + \mathrm{BAI}) \times \mathrm{OAS} \times \text{odor category} + (1 \mid \mathrm{ID}) + (1 \mid \mathrm{TDI})$$

All continuous variables were centered and scaled, and collinearity was tested by calculating the Variance Inflation Factors (VIF) with the *vif* function of the *car* package (Fox et al., 2018). All factors showed low collinearity with values below 3.5. For all regression models, to ensure that each predictor improved the models' fit, the function *step* (*stats* package; R Core Team, 2017) was used to perform automatic backward elimination, which relies on the AIC criterion (Bolker et al., 2009). AIC values of the initial and final models were calculated using the *anova* function (*stats* package, R Core Team, 2017). Initial and final AIC values and complete information of the final models are reported in Tables 1s and 2s in the Supplementary material. Simple slope analysis was conducted to interpret the interactions using the *interactions* package (Long, 2019).

All analyses were repeated with Bayesian statistics, performed with JASP software (JASP Team, 2022; Wagenmakers et al., 2018). Bayes factors (BF) were interpreted following standard recommendations (Jarosz and Wiley, 2014; Jeffreys, 1998): BF between 1 and 3 implies indecisive to anecdotal evidence, 3–10 substantial, and 10–30 strong evidence. Separate Bayesian linear regression analyses were performed for each continuous variable and included as covariate OAS and BDI-II or OAS and BAI scores. For the odor ratings, separate analyses were also performed for neutral, pleasant and unpleasant odors.

3. Results

3.1. Descriptive statistics

The final sample consisted of 214 participants (see Table 1 for sample characteristics). Of these, 37 performed the "Sniffin' Sticks" test with the classical procedure, 177 with single-use paper strips. No significant differences were found between these two types of testing for TDI score [t(212) = −1.59, p = 0.11], identification score [t(212) = −1.1, p = 0.27], discrimination score [t(212) = −0.03, p = 0.97], or threshold score [t(212) = −1.52, p = 0.13], thus it was not included as a control variable in the multivariate models. The lack of differences between the two types of testing was also confirmed by Bayesian statistics showing all $BF_{10} < 1$.

Table 1
Characteristics of the sample.

	Mean (SD)	Range (min-max)
Age (years)	22.5 (2.3)	18–31
Education (years)	15.9 (2.2)	12–22
BDI-II	11.3 (8.4)	0–47
% mild depression (14–19)	18 %	
% moderate depression (20–28)	11 %	
% severe depression (>28)	4 %	
BAI	12.6 (9.0)	0–39
% mild anxiety (7–15)	34 %	
% moderate anxiety (16–25)	20 %	
% severe anxiety (>25)	26 %	
OAS	115.7 (14.4)	48–152
TDI	34.3 (3.9)	22.5–46
% normosmic	89 %	
Threshold	7.3 (2.9)	0-16
Discrimination	13.1 (1.6)	8-16
Identification	13.8 (1.4)	6-16

Notes: BDI-II = Beck Depression Inventory-II; BAI = Beck Anxiety Inventory; OAS = Odor Awareness Scale; TDI = Sniffin' Sticks Threshold Discrimination Identification total score.

The correlation analysis between the OAS score and the BDI-II score did not yield a significant relationship (r = 0.05), as well as between the OAS score and the BAI score (r = 0.08).

3.2. Basic olfactory abilities

The model for the TDI score included the main effects of the BDI-II and the OAS and their interaction.

$$\mathrm{TDI} \sim \mathrm{BDI-II} + \mathrm{OAS} + \mathrm{BDI-II} \times \mathrm{OAS}$$

The TDI score was significantly predicted by the BDI-II [F(1,210) = 7.35, p = 0.007], showing that participants with higher depressive symptoms presented lower olfactory abilities, and by the OAS [F(1, 210) = 6.37, p = 0.012], indicating that higher attention to the odors predicted higher olfactory abilities. Moreover, a significant interaction between depressive symptoms and OAS scores emerged [F(1, 210) = 6.36, p = 0.012]. Simple slope analysis revealed that the effect of depressive symptoms in predicting olfactory abilities was only significant for OAS scores 1 SD below or equal to the mean ($p < 0.001$ and p = 0.01 respectively, Fig. 1A), but not for scores 1 SD above (p = 0.95).

The model for the threshold subtest score included the main effects of the BDI-II, the OAS and their interaction.

$$\text{Threshold} \sim \mathrm{BDI-II} + \mathrm{OAS} + \mathrm{BDI-II} \times \mathrm{OAS}$$

The threshold score was significantly predicted by the BDI-II [F(1, 210) = 7.82, p = 0.006], indicating that participants with higher depressive symptoms presented a lower olfactory threshold. Moreover, a significant interaction between depressive symptoms and OAS scores emerged [F(1, 210) = 5.80, p = 0.017]. Simple slope analysis revealed that higher depressive symptoms predicted lower olfactory threshold in individuals with low (− 1 SD) odor awareness (simple slope = −0.30, t = −2.73, p = 0.01) but not average (p = 0.09) and high (+1 SD, p = 0.67) odor awareness (Fig. 1B).

The model for the discrimination subtest score included only the main effects of the OAS.

$$\text{Discrimination} \sim \mathrm{OAS}$$

However, for the discrimination subtest, no significant results emerged from the model.

Also, the model for the identification subtest score included only the main effects of the OAS.

$$\text{Identification} \sim \mathrm{OAS}$$

The identification score was significantly predicted by the OAS score [F(1,212) = 4.28, p = 0.04], showing that individuals with higher odor awareness presented higher identification scores.

The Bayesian Linear regressions showed that only the TDI score changed in function of the interaction BDI-II × OAS (B_{10} = 4.19). However, for the subtests the Bayes Factor supported H0 both for BDI-II and BAI ($B_{10} < 1$).

3.3. Perceptual ratings of the odors

The model for Pleasantness rating included the main effects of the BDI-II, the OAS and their interaction, the main effect of the odor category, and participants' ID as a random factor.

$$\text{Pleasantness} \sim \mathrm{BDI-II} + \mathrm{OAS} + \text{odor category} + (1 \mid \mathrm{ID}) + \mathrm{BDI-II} \times \mathrm{OAS}$$

The final model investigating the pleasantness rating revealed a significant main effect of the category of the odors [$\chi^2(2) = 1533.58$, $p < 0.001$]. Specifically, unpleasant odors were rated as less pleasant than pleasant and neutral odors ($p < 0.001$), whereas pleasant odors were rated as more pleasant than neutral ones ($p < 0.001$). Moreover, a significant interaction between the BDI-II score and the OAS score [$\chi^2(1) = 5.29$, p = 0.021] emerged. In particular, simple slope analysis revealed

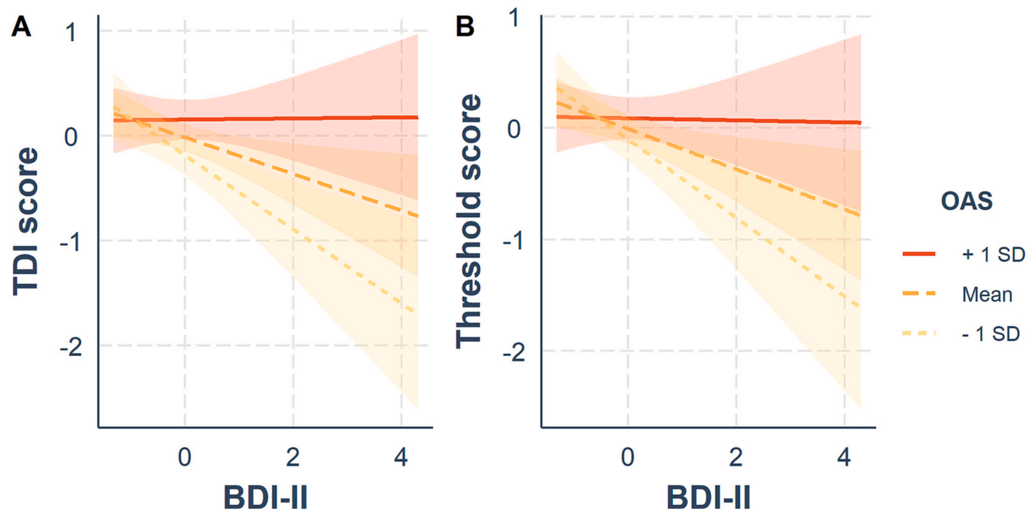

Fig. 1. (A) Interaction effects of depressive symptoms and odor awareness on TDI score. A higher TDI score indicates higher olfactory abilities. (B) Interaction effects of depressive symptoms and odor awareness on threshold score. A higher threshold score indicates higher abilities in detecting odorants. *Notes*. Ninety-five % confidence bands for mean, +1 SD, − 1 SD values of odor awareness are presented in different colors.

that higher depressive symptoms predicted higher pleasantness ratings in individuals with low (−1 SD) odor awareness ($p = 0.05$) but not average ($p = 0.56$) and high (+1 SD, $p = 0.18$) odor awareness (Fig. 2).

The model for Intensity rating was the following:

$$\text{Intensity} \sim \text{BAI} + \text{OAS} + \text{odor category} + (1 \mid \text{ID}) + \text{BAI} \times \text{OAS} + \text{BAI} \times \text{odor category} + \text{OAS} \times \text{odor category} + \text{BAI} \times \text{OAS} \times \text{odor category}$$

The intensity rating was significantly predicted by the category of the odors [$\chi^2(2) = 421.26$, $p < 0.001$]: Tuckey post-hoc analysis revealed that unpleasant odors were rated as more intense than pleasant and neutral odors ($p < 0.001$), whereas pleasant odors were rated as more intense than neutral ones ($p < 0.001$). The model also revealed a significant interaction between OAS and the category of the odors [$\chi^2(2) = 7.78$, $p = 0.020$]. Enhanced attention to the odors predicted higher intensity ratings only for the unpleasant ($p < 0.001$) and pleasant odors ($p = 0.03$), but not for the neutral ones ($p = 0.61$). In addition, the intensity rating was significantly predicted by the triple interaction between the BAI score, the OAS score and the category of the odors [$\chi^2(2) = 6.18$, $p = 0.045$]. However, no significant results were found in the post-hoc tests.

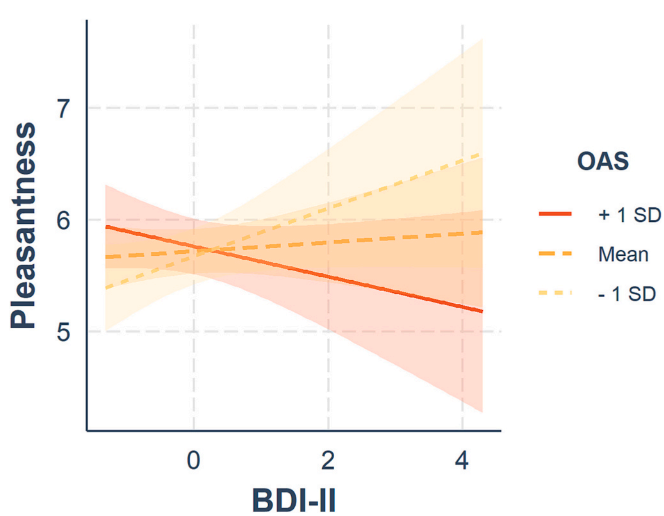

Fig. 2. Interaction effects of depressive symptoms and odor awareness on pleasantness ratings. Notes. Ninety-five % confidence bands for mean, +1 SD, − 1 SD values of odor awareness are presented in different colors.

The model for Familiarity rating included the main effects of the BDI-II, the OAS and their interaction, the main effect of the odor category, and the participants' ID as a random factor.

$$\text{Familiarity} \sim \text{BDI} - \text{II} + \text{OAS} + \text{odor category} + (1 \mid \text{ID}) + \text{BDI} - \text{II} \times \text{OAS}$$

The familiarity rating was significantly predicted by the OAS [(1) = 7.04, $p = 0.008$], indicating that higher attention to the odors predicted higher familiarity ratings, and by the category of the odors [$\chi^2(2) = 149.46$, $p < 0.001$]. Specifically, Tuckey post-hoc analysis showed that pleasant odors were rated as more familiar than unpleasant and neutral odors ($p < 0.001$), whereas unpleasant odors were rated as more familiar than neutral ones ($p < 0.001$). Finally, the model was also predicted by an interaction between BDI-II and OAS [$\chi^2(1) = 4.06$, $p = 0.044$]. Subsequent simple slope analysis showed that low, medium or high levels of odor awareness did not affect the relation between familiarity rating and depressive symptoms (all *ps* > 0.14).

The Bayesian Linear regressions of intensity ratings for unpleasant odors support the hypothesis of the modulation by the interaction between OAS and BDI-II ($B_{10} = 7.56$) and between OAS and BAI ($B_{10} = 7.76$). Moreover, Bayesian Linear regression of intensity for unpleasant odors and familiarity ratings for both pleasant and unpleasant odors support the hypothesis of the modulation by OAS score (intensity unpleasant odors: $B_{10} = 38.41$; familiarity pleasant odors: $B_{10} = 3.70$; familiarity unpleasant odors: $B_{10} = 4.38$). All the other results showed $B_{10} < 1$.

4. Discussion

The attention that individuals pay to the odors in the environment, i.e., *odor awareness*, has been proposed to be one of the factors leading to olfactory disturbances. Indeed, in animal studies, reduced attention to odors has been shown to decrease the olfactory receptor turnover rate which leads to a thinner olfactory epithelium which in turn causes reduced olfactory abilities (Croy and Hummel, 2017).

The first aim of this study was to explore whether the degree of odor awareness, as measured through the self-report scale OAS, moderated the relationship between depressive and anxiety symptoms and olfactory abilities. Results showed that individuals with higher depressive symptoms present lower olfactory abilities in general, and specifically lower olfactory sensitivity. Moreover, self-reported odor awareness is a significant moderator of the association between depressive symptoms and olfactory abilities (specifically for olfactory threshold). The present findings, confirmed by the Bayesian framework, support the hypothesis that attention is a central mechanism in explaining the presence of reduced olfactory functions in depression. Consistently, Croy and Hummel (2017) proposed that the presence of reduced attention toward odors in the environment may affect the peripheral function of olfaction, as measured by the olfactory threshold test. Moreover, this is also consistent with the neurophysiology of olfaction. The olfactory bulb is the first structure from which olfactory information spreads out to a number of structures, particularly to the amygdala (but also to the piriform cortex and the entorhinal cortex) (Freiherr, 2017). It is well known that the amygdala is involved in emotional processing and its functioning is impaired in affective disorders (Davidson, 2001; Drevets et al., 2008). The aforementioned reduced olfactory input in affective disorders, conceptualized here as reduced attention that individuals pay to the odors in their everyday life, may induce a reduction in receptor turnover rate, changing the functioning of the amygdala, ultimately reducing its ability to encode olfactory information as well as their response to emotional stimuli (Pause et al., 2001; Pollatos et al., 2007). Finally, our result of a reduction in olfactory sensitivity as depressive symptoms increase is also consistent with previous studies showing reduced olfactory sensitivity in patients with depression (e.g., Kazour et al., 2020; Lombion-Pouthier et al., 2006; Negoias et al., 2010; Pabel et al., 2018; Pause et al., 2001; confirmed also by systematic reviews Athanassi et al., 2021; Taalman et al., 2017) and in healthy individuals with depressive symptoms (Pollatos et al., 2007). Interestingly, no relation has been found between depressive symptoms and higher olfactory functions, namely odor identification and discrimination. This result is only partially in line with the literature (e.g., Hardy et al., 2012; Lombion-Pouthier et al., 2006; Naudin et al., 2012; Swiecicki et al., 2009, but see Kazour et al., 2020; Pabel et al., 2018). These mixed findings can be explained mainly by the tests used and by the fact that previous studies examined individuals that presented clinical depression as well as an older age than the present sample. To our knowledge, this is the first study investigating olfactory abilities in young healthy individuals with different degrees of depressive and anxiety symptoms. Despite this approach does not allow us to compare the present results with previous studies, it provides a better understanding of the initial mechanisms related to alteration in olfactory abilities that might be used as a possible future marker of vulnerability, without confounding factors related to medications or the chronicity of the disorder.

Contrary to our hypotheses, we did not find any relationship between anxiety symptoms and olfactory abilities. Our hypotheses were based on the significant overlap between the brain areas involved in olfactory processing and the areas implicated in anxiety disorders, such as the limbic system and the prefrontal structures (Atanasova et al., 2008). In addition, individuals with anxiety symptoms are characterized by heightened hypervigilance in order to suddenly detect danger in the environment which leads them to an increased sensitivity toward visual and acoustic stimuli (for a review see Robinson et al., 2013), that may be extended to the olfactory domain. However, there is still a wide discrepancy within the literature, with studies including medicated patients with different diagnoses, such as generalized anxiety disorder, social anxiety and panic disorder, reporting a reduced olfactory discrimination ability (Clepce et al., 2012), while studies focusing only on panic disorder reported higher olfactory abilities (Burón et al., 2015, 2018) or intact identification abilities in these patients (Kopala and Good, 1996). Interestingly, the only study, to our knowledge, investigating olfactory abilities in a healthy sample reported that both state and trait anxiety ratings were significantly associated with reduced olfactory ability, especially for the identification of rose odor (Takahashi et al., 2015). However, it is worth mentioning that in this study the depression level was not measured, possibly being a confounding factor in the interpretation of the results. All in all, these conflicting findings highlight the need for further studies to better understand the role of olfactory functions in anxiety disorders.

Our study suggests that olfactory disturbances in depression may be a vulnerability factor for the development of the disorder, reflecting both brain abnormalities and cognitive dysfunctions, whereas for anxiety disorders the underlying mechanisms may be more complex. Only a longitudinal assessment can shed light on this complex phenomenon, allowing a better comprehension of the time course of the development of olfactory disturbances in affective disorders. In addition, understanding the processes leading to olfactory deficits in depression, but not in anxiety, may serve as a marker in the clinical setting to make differential diagnoses and hence select the most appropriate treatment.

The second aim of the present study was to explore the association between self-reported levels of odor awareness and the perceptual ratings of odors in individuals with affective disorders. Given that one of the key aspects of depression is anhedonia, we could expect a reduced hedonic evaluation of the odors in individuals with depressive symptoms. Our results partially confirmed our hypothesis. Even though no association has been found between depressive symptoms and the category of the odors (pleasant, neutral, and unpleasant), a significant relationship between depressive symptoms and pleasantness rating emerged, moderated by the attention that individuals pay to the odors: in individuals with low odor awareness, higher depressive symptoms led to higher pleasantness rating, whereas the opposite relation emerged for individuals with higher odor awareness. A possible explanation of the present finding could be found in the cognitive theories of depression, stating that a key characteristic of depressive disorders is the presence of a preferential processing bias for mood-congruent information (Clark and Beck, 2010). This bias potentiates like-valenced or matching emotions, leading to enhanced emotional responding to negative stimuli (Rottenberg et al., 2005). In this view, only individuals that in their everyday life pay attention to the surrounding odors are prone to judge them as more unpleasant as depressive symptoms increase. On the other side, individuals that usually do not pay attention to the odors, when forced to consciously smell the odors, evaluated them as more pleasant, possibly because of a novelty effect. However, this result should be interpreted with caution since this finding is not confirmed by Bayesian statistics.

Notably, both LMM and Bayesian analyses showed that odor awareness is a significant predictor of the familiarity ratings of the odor: the higher the attention that individuals pay to the odors, the higher the odor familiarity. This result highlights how this metacognitive ability affects not only the level of objective olfactory perception (Nováková et al., 2014; Smeets et al., 2008) but also the perceptual ratings of the odors. Odor familiarity is an important characteristic in odor perception, representing prior knowledge of the odor without the semantic association that is characteristic of odor identification (Larsson et al., 2006; Lehrner et al., 1999). Hence, it is possible that individuals that pay more attention to the odors in the environment become also more familiar with them.

In addition, given the limited literature on affective disorders and olfactory metacognitive abilities, such as odor awareness, a correlational analysis investigating the direct relationship between odor awareness and depressive and anxiety symptoms has been performed. In line with the previous study on depressive symptoms (Dal Bò et al., 2022), we did not find a significant relationship between the BDI-II score and the OAS score. However, despite in this study a direct relation has not been found, we believe that this trait-like feature may be a key factor in moderating the relationship between affective disorders and olfactory disturbances. On the other side, contrary to previous studies (Burón et al., 2015, 2018; Dal Bò et al., 2022), no relationship has been found between anxiety symptoms and odor awareness levels. This inconsistency may be due to the sample characteristics (i.e., two of these studies focused on participants with a diagnosis of panic disorder, Burón et al., 2015, 2018), the modality (Dal Bò et al., 2022 was an online study) or the sample size (Dal Bò et al., 2022 included 429 participants). Specifically, the online procedure of the previous study allowed the inclusion of a rather bigger and more heterogenous group of individuals, making it easier to detect an effect that is probably small in a sub-threshold sample.

Our results also provide some insights to develop future treatments. Considering that odor awareness proved to have a key role in determining the presence of olfactory dysfunctions in individuals with depressive symptoms, it could be a potential target in the clinical setting. Accordingly, daily olfactory training improves the olfactory function, the olfactory bulb volume and the number of olfactory receptor neurons, but also the depressive symptoms and the general well-being in individuals experiencing subclinical depression (Birte-Antina et al., 2018; Negoias et al., 2017; Wang et al., 2004; but see Pabel et al., 2020; Pieniak et al., 2022). New training are emerging, mainly focusing on odor-based cognitive interventions (for example including a smell memory game; Olofsson et al., 2020). However, future treatments should be aimed to strengthen not only the cognitive, but also the emotional functions. In addition, they should specifically take into account the characteristics of individuals with depressive symptoms, to increase compliance and motivation to follow the treatment.

The current findings ought to be interpreted in light of some methodological limitations. First, all participants included in the present study were females, thus making it impossible to generalize the current results to a male population. Second, whether the participants presented a family history of depression or anxiety was not investigated. Whether olfactory dysfunction is a vulnerability factor present in at-risk populations (as first-degree relatives of patients with mood disorders) is unknown. While further studies need to clarify this aspect, in the present study, we were specifically interested in the effect of current symptoms of depression or anxiety. Third, part of the data collection was carried out during the COVID-19 pandemic. The continuous screening of COVID-19 symptoms, including paying particular attention to possible reduction and/or modification of the olfactory abilities in daily life, may lead individuals to become more aware of odors in the surroundings or, on the contrary, less aware as a habituation phenomenon. Even though our analysis revealed that olfactory abilities did not differ between the participants tested before and during the pandemic, future studies are needed to replicate these findings in a non-emergency situation to overcome these issues. Related to this point, a modification of the protocol was necessary to contain the spread of the contagion. However, again the collected data did not significantly differ between the two methods, suggesting that the potential confounding effect of having used a slightly different procedure was limited in the present study. In addition, although the recruitment of participants during the pandemic period has been carried out after the acute phase of the pandemic when people were allowed to use the university facilities, this particular emergency situation may have introduced some selection bias in our sample. Fourth, participants did not perform any cognitive tests to assess their cognitive abilities. However, the recruited participants were young university students who reported being medically healthy and free from medications, therefore confounding factors related to the cognitive abilities of the participants are most likely not present. Moreover, odor awareness was analyzed only by a self-report questionnaire, and future studies should implement lab-based tasks to specifically investigate odor attention. Finally, the study was not pre-registered since it was part of a screening procedure within an extensive research project. However, hypotheses were based on the review of the literature.

To conclude, while with the present study it is not possible to state if the reduced olfactory abilities are the cause or the consequence of the development of depressive symptoms, the evidence that odor awareness is a moderator of this relationship is an important step forward in the understanding of the disorder and in the development of useful treatments. Moreover, the current study has several implications for vulnerability to and early identification of depression, identifying olfactory dysfunction and odor awareness as potential risk factors in the development of clinical depression. Indeed, the concomitant evaluation of depressive and anxiety symptoms has allowed us to better disentangle the different roles of these two disorders in olfaction. With the present findings we provide evidence that in a healthy population, only the presence of depressive symptoms is related to a reduced olfactory performance, whereas anxiety symptoms are not. In addition, odor awareness may be involved in the development and maintenance of olfactory dysfunction.

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CRediT authorship contribution statement

E.D.B, C.C., C.G. development of the study concept and the study design; E.D.B, C.C., L.N. data collection; E.D.B and C.C. data analysis under the supervision of C.G.; E.D.B and C.C. data interpretation and manuscript writing; C.G. and L.N. review and editing. All authors approved the final version of the manuscript.

Declaration of competing interest

There are no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.06.009.

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