Symptoms of Depression Change With Olfactory Functions

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Abstract

Olfactory loss is associated with symptoms of depression. The present study, conducted on a large cohort of mostly dysosmic patients, aimed to investigate whether improvement in olfactory performance would correspond with a decrease in depression severity and, if so, to what extent. In 171 participants, we assessed olfactory function and severity of depression before and after an average interval of 11 months, with many patients improving in function. Separate analyses were conducted for a) the whole group of patients and b) the group of dysosmic patients in both classic and Bayesian ways. Student t-test demonstrates that the whole sample improved consistently, especially within the group of dysosmic patients in terms of odor identification, and the dysosmic group also improved in terms of odor threshold and olfactory functions in general. Pearson correlation showed that the increase in olfactory functions corresponded with the decrease in depression severity, particularly in dysosmic patients. To conclude, the present study results indicate that symptoms of depression change with olfactory functions in general and odor identification in particular.

Introduction

Olfactory dysfunctions are mutually related to depression [1–11]. For example, Deems and colleagues [12] demonstrated on 750 dysosmic patients variations in depression scores. A more recent study showed that about one-fourth to one-third of patients who lost their sense of smell showed depressive symptoms [13]. Also, among older adults, impairment in olfaction was related to depression [14]. Interestingly, overall healthy older adults were more likely to develop depressive symptoms 5 or 10 years after losing their sense of smell [15]. On the other hand, depressed patients express impaired olfactory functions, mainly for odor identification [16–20] but also at the level of odor thresholds [9;21–23] and, even though there is limited evidence, for odor discrimination [3;16].

The reciprocal relationship between olfaction and depression may result from the neuroanatomical connections between regions in the brain that are involved in these processes [2;4]. Sensory areas play an essential role in affective experience [24]. Olfactory information passes through the first central-nervous relay, the olfactory bulb, and is further conducted to the primary olfactory cortex, which then projects to the amygdala, hippocampus, anterior cingulate cortex, insula and orbitofrontal cortex [2;25]. These areas are at the same time involved in many affective functions such as emotional processing and modulation, autonomic regulation included [25]. The volume of the olfactory bulb, a highly plastic structure that sends inhibitory projections to the amygdala, was demonstrated to be reduced in the case of depressed patients [22] and can be generally treated as a biological vulnerability factor for the occurrence and/or maintenance of depression [7]. Likewise, both the amygdala, a structure responsible for processing aversive stimuli and detection of emotional signals [25] and the hippocampus, a neuroplastic temporal lobe structure responsible for both consolidating and providing an emotional context to memories [25], are identified as primary neurobiological structures involved in the pathophysiology of depression [26–28].

Recent studies demonstrated that mood benefits from improving olfaction via regular olfactory exposure, so-called “olfactory training, " leading to decreased depression severity [29–30]. The question remains open whether this effect is caused by the well-established positive impact of exposure to odors on mood [31–34] during olfactory training or whether improvement in olfaction, even without olfactory training, is directly related to the improvement in mood, presumably via neuroanatomical changes. Thus, in the present study, conducted on a large cohort of mostly dysosmic patients we aimed to investigate whether improvement in olfactory performance would correspond with a decrease in depression severity and if so, to what extent. We hypothesized that improvement in olfactory functions and especially in odor identification (because it has been shown to be strongly affected in depression [16;18] is directly related to the decrease of depression severity.

Materials And Methods

Participants

A total of 171 participants aged from 14 to 87 years of age took part in the study. Their detailed characteristics are presented in Table 1. Please, note that 44% of participants were 60 years old or older.

All participants visited the Smell and Taste Clinic of the Department of Otorhinolaryngology at the TU Dresden because of an olfactory disorder. The duration of treatment varied from 1 up to 16 months (10.9±3.22) and consisted of different medical strategies presented in Table 1. Different etiologies of olfactory loss were present (Table 1).

The retrospective study was performed according to the principles of the Declaration of Helsinki on biomedical research involving human subjects. It was approved by the Ethics Committee at the Medical Faculty of the TU Dresden (EK number 251112006) covering anonymized retrospective and pooled analyses. Informed consent was obtained from all subjects.

Olfactory testing

Detailed results of olfactory testing are presented in Table 2. The testing was conducted twice, during the first and the second visit in the Clinic. 39-40 patients were not included in the second measure as they did not return for the second measure. They were instead followed up by a phone interview.

Olfactory testing was performed by means of "Sniffin' Sticks” [35-36] and consisted of tests for odor threshold (rose-like odor, phenylethylalcohol; PEA), odor discrimination, and odor identification. Results of the 3 subtests were presented both separately for threshold (T), with a range between 1 and 16, discrimination (D), with a range between 0 and 16 and identification (I) score, with a range between 0 and 16, and finally as a sum of the results (TDI), with the final score ranging between 1 and 48 points [36]. If the TDI score was 31 or higher, the patient was regarded as normosmic (n = 14); with a score below 31, the patient was regarded as dysosmic (n = 157).

Neuropsychological testing

Detailed results of the depression scale are presented in Table 3 and Figure 1. Like olfactory testing, also depression test was conducted twice, during the first and the second visit to the Clinic. In case of patients were not able to come for the second visit, the measure was conducted via phone.

The General Depression Scale – long form [37-38] (“Allgemeine Depressionsskala” - Langform; ADSL) was employed to gauge the severity of depression. The scale is a self-assessment tool that consists of 20 questions about emotional, motivational, cognitive, somatic and motor/interactional complaints, such as, e.g. 'During the last week I hardly had an appetite; 'During the last week I felt as good as others'; 'During the last week I was scared'. Due to its time-saving and cost-effective applicability, the ADSL is a practical method [37]. Patients are considered depressed when scoring 16 or more [38]. According to this cutoff point, 62 participants (36%) of the present sample was considered depressed.

Statistics

Separate analyses were conducted for a) the whole group of patients and b) the group of dysosmic patients.

Possible differences between the first and the second measure in a) olfaction and b) depression were investigated by means of paired samples two-way t-test. Additionally, independent samples t-test was used to examine possible differences in depression scores between the normosmic and the dysosmic patients.

One-way Pearson correlation was employed to investigate the relationship between the improvement in the odor functions and depression severity. Improvement in the odor functions was measured so that the first olfactory measure, separate for T, D, I and TDI was subtracted from the second olfactory measure. Improvement in depression was measured oppositely: the second depression measure was subtracted from the first one. This was done so that positive differences indicate improvement in olfaction and depression corresponded to larger numbers.

All the analyses were conducted twice, firstly with classical p-values and secondly with Bayesian statistics [39]. The Bayes Factor (B) is a method that weighs evidence and shows which out of two hypotheses is better supported and to what extent. Adopting the B in statistical inference, it can be shown whether data provided robust support for the null hypothesis, the alternative hypothesis or whether it is inconclusive and more data needs to be collected to provide more decisive evidence [40]. Furthermore, Bayesian statistics are resistant to multiple comparisons.

Data are presented as mean values (±standard deviation). Statistical analyses were performed using JASP v. 0.11.1 (Univ. of Amsterdam, The Netherlands: www.jasp-stats.org), with $p < .05$ set as the significance level. The effect sizes are accompanied by their 95% confidence intervals.

Results

Olfactory tests and depression outcome

The whole group of patients

For the whole group of patients, the classical t-test indicated that the patients improved in terms of almost all olfactory components: odor threshold (T: t = 2.35, p = .021), identification (I: t = 3.9, p < .001) and general olfactory functions (TDI: t = 2.7, p = .008), while in case of odor discrimination no change was noticed (D: t = 1.42, p = .16) (Figure 2).

Bayesian t-test demonstrated slightly different results (Figure 3). While Bayes factor supported very strongly the presumption about change in odor identification performance (I: B10 = 112.77), neither odor threshold (T: B10 = 1.36) nor discrimination (D: B10 = 0.26) was shown to change, and in these cases Bayes factor supported H0. Instead, general olfactory functions were demonstrated to change very slightly (TDI: B10 = 3.1), which was probably driven by the big change in odor identification.

In terms of depression score, for the whole group classical t-test indicated no evidence supporting the difference between the first and the second measure in depression (t = 0.07, p = .94). Bayesian t-test results provided further strong evidence for the null hypothesis stating that both measures did not, indeed, differ from each other (B01 = 11.69).

Dysosmic patients

For the group of dysosmic patients, the classical t-test indicated that the dysosmic patients improved in terms of three out of four olfactory components: odor threshold (T: t = 3.42, p < .001), identification (I: t = 4.35, p < .001) and general olfactory functions (TDI: t = 3.24, p = .002), while odor discrimination value did not change (D: t = 1.55, p = .12) (see: Figure 2).

Bayesian t-test demonstrated further that the hypothesis about change in odor identification, threshold and general olfactory functions were respectively very strongly and strongly supported (for I: B10 =535.09, for T: B10 = 23.505, for TDI: B10 = 14.02). At the same time, odor discrimination data indicate the null hypothesis (D: B10 = 0.329).

Like in the case of the whole group, also here depression severity did not change significantly, which was indicated by the classic t-test (t = .47, p = .64). Bayesian test, additionally, provided strong evidence for the lack of difference between the first and the second measure (BF01 = 10.11)

Furthermore, no difference was found between the dysosmic and normosmic group in terms of depression severity neither for the first measure (t = 1.49, p = .14) nor the second one (t = 0.4, p = .69). Bayesian factor indicated that the severity of depression in the second measure was the same in both groups (B01 for the first measure = 1.44; for the second measure = 3.35).

Pearson Correlations

The whole group of patients

For the whole group of patients, change in depression severity correlated positively with the change in general olfactory functions (TDI: r = .25, p = .004) and in olfactory identification performance (I: r = .22, p = .011) (Table 4). This finding was respectively strongly and moderately confirmed by the Bayesian factor (for “TDI score” B10 =12.8, for I score: 5.51 (Supplemental Table 1).

Dysosmic patients

For the group of dysosmic patients change in depression severity correlated positively with the change in general olfactory functions (r = .28, p < .001) and in olfactory identification performance (r = .25, p = .003) (Table 5 and Figure 4), what was confirmed by Bayesian factor, strongly for general olfactory functions (B10 = 28.5) and moderately for odor identification (B10 = 8.8) (Supplemental Table 2).

Discussion

Exploring further the idea that depression can benefit from improving olfaction via regular exposition to odors, we examined whether olfaction improvement is directly related to a decrease in depression severity. Specifically, in a large sample of primarily dysosmic patients, we sought evidence for the change in depression severity, measured by ADSL scale [38] to be related to the variation in olfactory functions, namely odor threshold (T), discrimination (D), identification (I), and general olfactory functions (TDI) as measured by the Sniffin’Sticks test battery (35;36]. In accordance with our assumption, the present results show that the increase in several olfactory functions corresponded moderately to firmly with the decrease in depression severity, which was particularly notable in the group of dysosmic patients. Furthermore, the whole sample improved consistently, especially within the group of dysosmic patients in terms of I, and the dysosmic group also improved in terms of T and TDI.

The majority of the participants in the present study was dysosmic due to viral infections, sinonasal disease, and traumatic brain injury, the most typical causes of olfactory dysfunction [12;41–43]. Sinonasal disease may lead to a slow loss of olfactory function generated by nasal obstruction blocking the access of odor stimuli to the olfactory cleft via, for example, nasal polyposis, and inflammation of the olfactory epithelium [44]. In turn, infections have been demonstrated to result in damage of the olfactory mucosa, thereby disabling the function and regeneration of olfactory receptor neurons [45–46]. Finally, head trauma occurrence may disrupt olfactory pathways [47].

Previous studies demonstrated that dysosmic patients can benefit from olfactory training to improve their olfactory abilities and reduce their depression severity [29–30]. Odor identification is an olfactory dimension with a solid cognitive association [48] that has been consistently reported to be impaired in depression [16–20] probably because of the cognitive impairment in recurrent depression [18]. The present finding indicating a relationship between odor identification and depression severity in dysosmic patients may also be linked to the large improvement in odor identification in this group, which was five times bigger than in the whole sample. We presume that better general olfactory and odor identification performance may lead to cognitive and affective improvement.

Notably, the majority of the sample in the present study was not clinically depressed, as indicated by the results of the ADSL scale [38]. However, according to the previously mentioned scale, a significant percentage of the present sample (one-third of the entire sample) was classified as depressed. That could probably explain why the depression severity before and after the medical treatment focused on olfaction remained the same, contrary to previous olfactory training work [29–30]. In this context, solid and moderate relationships obtained between change in TDI, I, and depression severity suggest that olfaction is related even to very subtle changes in mood.

The relationship between olfaction and mood changes is also underlined by the difference between correlations results in both groups. It is worth noting that in the group of dysosmic patients, both improvements of general olfactory functions (TDI) and odor identification score (I) corresponded with the decrease of depression severity to a higher degree than in the whole sample of patients that included several normosmic participants.

Olfactory impairment was demonstrated to coexist with depression both in the general population [1;6;10] and in specific groups, such as older adults [14–15;49–50; but see also: 51]. This age group might be particularly prone to experience a decrease in olfaction [52]. Hence, this group appears to be specifically exposed to the consequences of olfactory dysfunction. Qazi and colleagues [50], in a very recent study, demonstrated that olfactory impairment allowed to predict the occurrence of depressive symptoms in a group of American older adults. In line with this evidence, the present study results, where almost half of the participants were older than 65 years old, show that controlling for olfactory functions might be an efficient tool to monitor mood changes.

To conclude, the present study results conducted on a large cohort of mostly dysosmic patients indicate that olfactory function in general (TDI), and odor identification (I) in particular, may be used as an indicator of very subtle mood changes. Further, the results indicate an improvement of symptoms of depression with the improvement of the sense of smell.

Declarations

Authors contributions:

AS: data analysis - writing – critical review

LH: conceptualization – data collection – critical review

AH: data collection –supervision – critical review

TH: conceptualization – data collection – supervision – critical review

Competing interests: The authors declare no competing interests.

Data Availability: The datasets analysed during the current study are not publicly available due to the privacy of the participants but are available from the corresponding author on reasonable request.

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Tables

Table 1 Descriptive characteristics of the participants

	Total
Number of participants	171
Age (M±SD)	57.1±14
Men	45
Cause of olfactory disorder	Idiopathic: 34%; postviral: 33%; sinunasal: 15%; posttraumatic: 12%; toxic: 1%; radio-chemo: 2%; postsurgery: 1%; neurodegenerative: 1%
Additional information potentially related to olfaction	Skull surgery: 2%; sinunasal surgery: 11%; polypectomy: 5%; tonsilectomy: 2%; septoplasty: 7%; polyposis: 4%; OSAS: 2%; asthma: 8%; allergy: 20%; sinusitis: 11%
Parkinson disease family history %	3%
Alzheimer disease family history %	3%
Medical treatment	Olfactory training: 80%; vitamin A nasal drops: 53%; mometasone nasal spray: 28%; prednisolone: 5%; azelastine plus fluticasone nasal spray: 1%; nasal douche: 5%; zinc gluconate: 10%; acupuncture: 5%; alpha lipoic acid: 2%; nasal sodium citrate: 1%

Table 2 Results of Sniffin' Sticks testing conducted during the first (before) and the second (after) visit to the Clinic.

	Time	n	Mean	SD
Threshold	Before	170	2.84	2.56
	After	131	3.27	2.55
Identification	Before	171	8.23	3.79
	After	130	9.3	3.77
Discrimination	Before	170	8.44	3.27
	After	130	9.15	3.2
TDI	Before	171	19.45	8.1
	After	132	21.42	8.55

Table 3 Results of ADSL scale conducted during the first (before) and the second (after) visit.

	Time	n	Mean	SD
ADSL	Before	171	14.32	9.89
	After	171	14.36	10.45

Table 4 Classical Pearson one-way correlation between the change in olfactory functions and depression severity (ADSL) score for the whole group of patients

	Change in ADSL
TDI change	.25*
I change	.22*
D change	.09
T change	.17

*p < .05

Table 5 Classical Pearson one-way correlation between the change in olfactory functions and depression severity (ADSL) score for the group of dysosmic patients.

	Change in ADSL
TDI change	.28*
I change	.25*
D change	.09
T change	.05

*p < .05

Figures

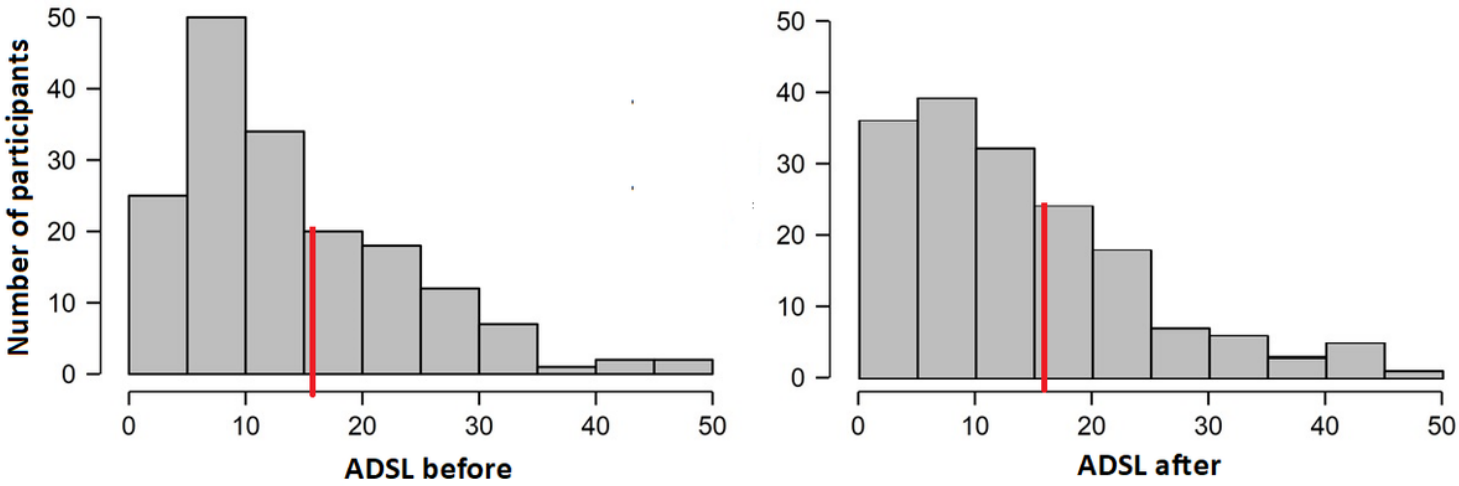

Figure 1

Density of results in ADSL scale in the first (before) and the second (after) measure. The red line indicates a turning point for depression [38].

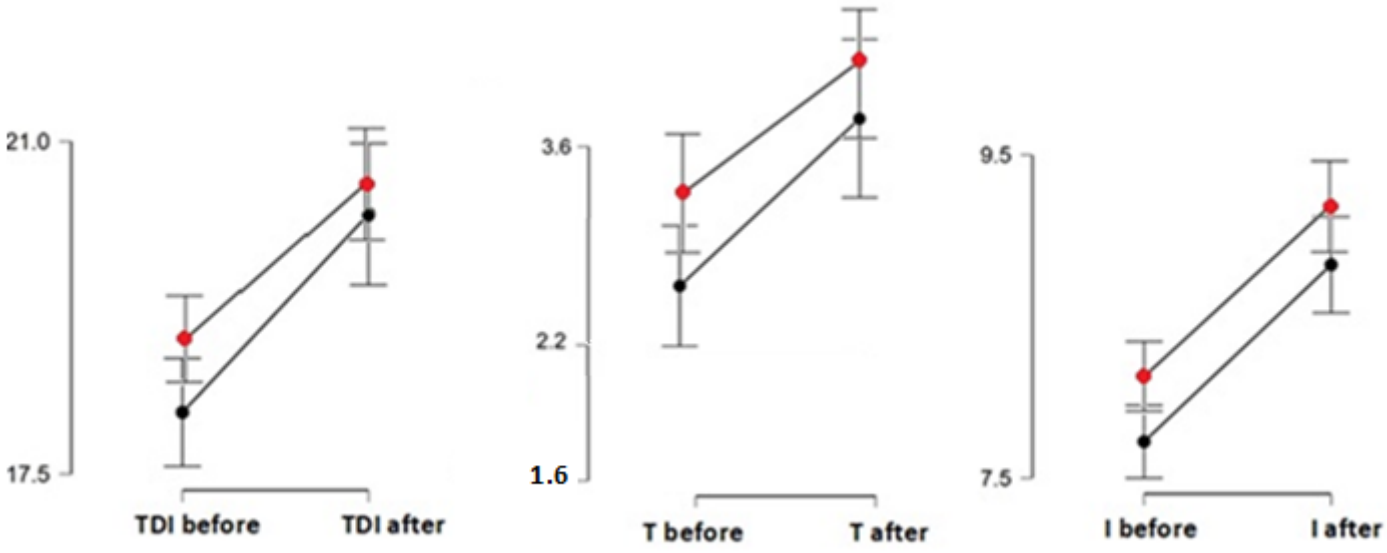

Figure 2

Improvement in general olfactory functions (TDI), odor threshold (T) and odor identification (I) score in the whole group of patients (marked with red color) and in the group of dysosmic patients (means, standard errors of means). Please, note the range of the Y-axes has been adjusted.

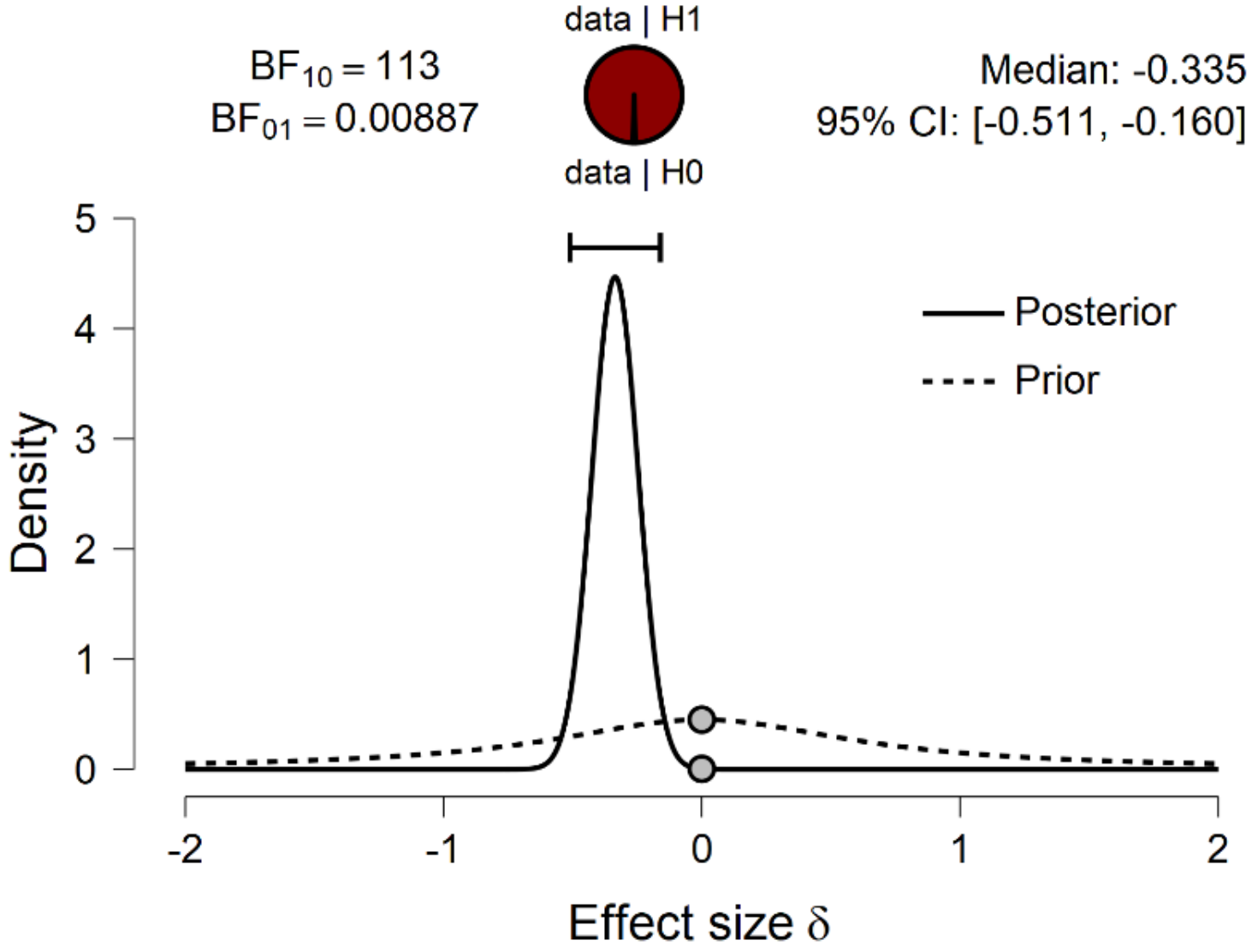

Figure 3

Two tailed t-test results for odor identification (I) change in the whole group. The probability wheel on top demonstrates the evidence that the data provide for the two rival hypotheses. The two gray dots specify the prior and posterior density at the test value. The median and the 95% central credible interval of the posterior distribution are presented in the top right corner (van Doorn et al., 2020)

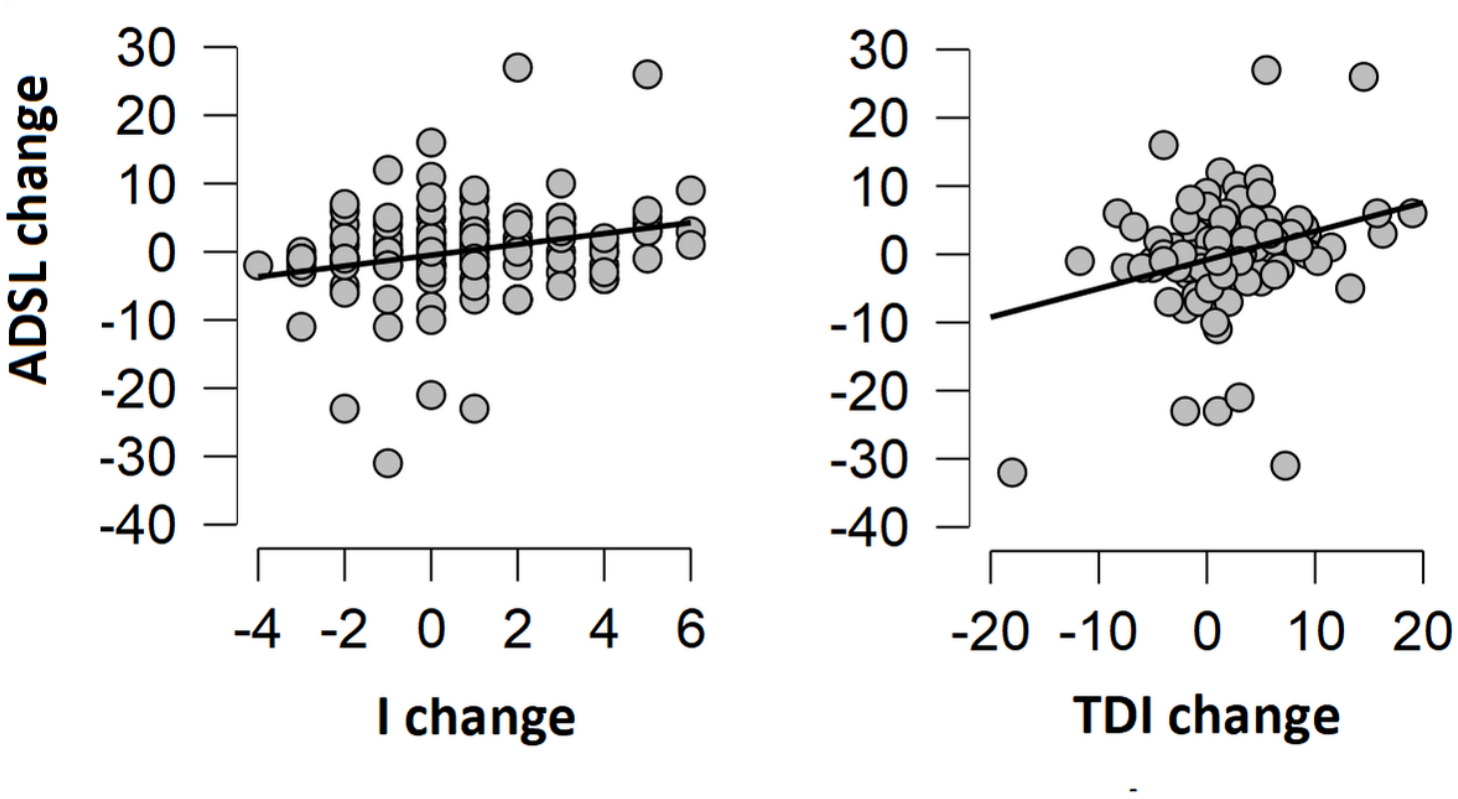

Figure 4

Classical Pearson one-way correlation between, respectively, the change in I and TDI score and depression severity (ADSL) score for the group of dysosmic patients.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.pdf