Journal of Affective Disorders 175 (2015) 292–298

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Olfactory functioning in panic disorder

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ARTICLE INFO

Article history:
Received 17 September 2014
Received in revised form
19 January 2015
Accepted 19 January 2015
Available online 29 January 2015

Keywords:
Panic disorder
Olfactory threshold
Olfactory reactivity
Odor awareness

ABSTRACT

Background: The olfactory function in panic disorder (PD) has been scarcely approached in the literature. The purpose of this paper is to study this question by focusing on the olfactory sensitivity (i.e. detection threshold), the reactivity to odors, and the odor awareness in patients suffering from PD.
Methods: 41 patients with PD and 41 healthy controls performed Sniffin' Sticks Test (threshold subtest) and completed the Affective Impact of Odors scale (AIO), the Relational Scale of Olfaction (EROL) and the Odor Awareness Scale (OAS). Clinical symptoms rating scales were concurrently obtained.
Results: PD patients showed lower olfactory detection thresholds (i.e. higher sensitivity) along with an enhanced reactivity to odors as well as a greater olfactory awareness compared to the healthy controls. The severity of PD was significantly associated with the olfactory questionnaires ratings, but not with the detection ability. Olfactory measures were intercorrelated in most cases.
Limitations: i) The results of the olfactory sensitivity are limited to one odorant (phenyl ethyl alcohol) and thus may not be generalizable to other odorants. ii) As comorbid Axis II disorders were not screened, it is not possible to exclude the influence of personality traits in our results. iii) The involvement of the medications in some olfactory outcomes cannot be ruled out.
Conclusion: The current findings highlight the importance of the olfactory function in PD as patients appeared to be highly sensitive, reactive and aware of odors. These results are discussed in the light of the common neural substrates involved in the olfactory processing and in the pathophysiology of PD, and also related to the clinical features of this disorder.

1. Introduction

Panic disorder (PD) is a prevalent and debilitating condition characterized by sudden and repeated panic attacks that include severe somatic and psychic anxiety symptoms. Agoraphobia may be present from the beginning or it can develop throughout the course of the disorder along with anticipatory anxiety (American Psychiatric Association, 1994). Gorman et al. (2000) hypothesized a neuroanatomical model of PD in which panic derives from an abnormally sensitive fear network that includes the amygdala, the thalamic and brainstem nuclei, the hypothalamus, the hippocampus, and cortical areas such as the cingulate cortex, the medial prefrontal cortex and the insula. Interestingly enough, a number of regions implicated in the pathophysiology of PD such as the frontal and the temporal limbic circuits are at the same time involved in the olfactory processing (Gorman et al., 2000; Zald and Pardo, 2000; Savic, 2002). Given this neuroanatomical overlap between olfactory and fear structures, the study of olfactory function in PD may provide information regarding the pathophysiological mechanisms of PD and can help to a better understanding of this clinical phenomena. However, a review of the literature shows that research on this topic is sparse. Kopala and Good (1996) reported intact olfactory identification performance in PD patients. A recent fMRI study by Wintermann et al. (2013) showed an altered neuronal processing of the olfactory stimuli in PD patients that was associated with an increased severity of the psychopathology. In this study, intensity and valence ratings were comparable to the control group (Wintermann et al., 2013). Locatelli et al. (1993) conducted an EEG study in PD patients under olfactory stimulation and they found a disrupted activity pattern in the temporal lobe. Finally, Clepce et al. (2012) found olfactory abnormalities in a sample of patients suffering from anxiety disorders, including PD. Specifically, they reported a reduced performance in the discrimination domain in the anxiety group while intensity ratings and the range of hedonic estimates were higher in the cases group. Olfactory thresholds and the identification ability were undisturbed. However, clear conclusions

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http://dx.doi.org/10.1016/j.jad.2015.01.049
0165-0327/

could not be drawn since authors did not perform a separate analysis on each anxiety diagnostic category.

To date, no study has addressed the olfactory sensitivity (i.e. detection threshold) and the reactivity to odors in PD. Interestingly, several reports on other sensorial modalities have found a hypersensitivity and a high reactivity in patients suffering from PD to somatic sensations (Domschke et al., 2010; Ogawa et al., 2010), visual peripheral stimulation (Caldirola et al., 2011), light (Bossini et al., 2009, 2013), sounds (Jüris et al., 2013), taste (DeMet et al., 1989), and also to meteorological phenomena (Bulbena et al., 2005). These findings are consistent with the heightened arousal and hypervigilance often seen in these types of patients (Brown and McNiff, 2009). Considering this background, one may wonder if the olfactory functioning in PD patients is in line with the other sensory systems.

Earlier reports in healthy individuals demonstrated that better olfactory abilities and higher reactivity to smells are associated with odor awareness. For example, Smeets et al. (2008) found that people who are extremely aware of odors in their environment are also better at perceiving smells in the odor perception test battery. In the same line, Arshamian et al. (2011) reported that individuals with high odor awareness excelled in several olfactory tasks such as odor memory and identification, but not in detection measurements. Our research group have found odor awareness positively associated with the impact of odors on emotions, cognition and behavior (Burón et al., 2011, 2013). Of interest, a positive association emerged between the reactivity to odors and anxiety ratings (Burón et al., 2013). To our knowledge, odor awareness and its relationship with other olfactory measures have not been previously assessed in PD.

Considering this background, the present study aims to examine the olfactory sensitivity, the reactivity to odors and the olfactory awareness in panic disorder. The relationship between these olfactory measurements will be also assessed. Olfactory data will be analyzed in regard to psychiatric symptoms, drug intake and smoking habits. We expect that panic disorder patients would be more sensitive, reactive and aware of odors compared to the control group.

2. Methods

2.1. Subjects

Forty-one patients who met DSM-IV (American Psychiatric Association, 1994) criteria for panic disorder with or without agoraphobia and forty-one healthy controls were included in the study. If DSM-5 criteria were adopted, the inclusion criteria would be suffering from panic disorder with or without the additional diagnostic of agoraphobia (American Psychiatric Association, 2013). Patients were recruited from the outpatient anxiety clinic at Parc de Salut Mar in Barcelona, between 2011 and 2013. Psychiatric diagnosis was established by two trained clinicians using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) along with a review of medical records. The MINI is a structured interview with good psychometric properties that allows the clinician to perform a standardized categorical assessment of the main psychiatric disorders according to Axis I of the DSM-IV. When the study started, 20 patients were receiving pharmacological treatment: 14 were on SSRI (selective serotonin reuptake inhibitor), one on TCA (tricyclic antidepressant), one on NaSSA (noradrenergic and specific serotonergic antidepressant), one on SNRI (serotonin and norepinephrine reuptake inhibitor), and three on benzodiazepines as needed. Twelve patients were both on antidepressants and benzodiazepines. All these medications remained unchanged for at least four weeks prior to the beginning of the study for all the patients.

The control group was healthy subjects with no history of mental illness and they were matched for age and gender with PD patients. They were recruited voluntarily from local community.

The exclusion criteria of the study included neurological disorders; head injury with loss of consciousness; systemic disturbances of metabolism and medications that could affect the olfactory function; age less than 18 or greater than 50; current toxic chemical or industrial agent exposure; pregnancy or breastfeeding; anosmia; current smoking habit of more than 10 cigarettes per day; and other conditions known to affect the olfactory functioning such as common cold, influenza, nasal allergies, nasal injury or sinus disease. Another concomitant psychiatric diagnosis on Axis I other than PD was also an exclusion factor. Written informed consent was obtained from each subject after study procedures had been fully explained. The study was reviewed and approved by the Ethics Committee of Clinical Investigation (CEIC) of the hospital. The participants did not receive any financial reward.

2.2. Sociodemographic and clinical measures

Sociodemographic variables such as gender, age, and educational level were collected through direct interview. Smoking habit was assessed in terms of the mean of cigarettes smoked per day.

Concerning clinical variables, the severity of PD with and without agoraphobia was assessed using the Panic and Agoraphobia Scale (PAS) (Bandelow, 1995; Bobes et al., 2004). Depressive and anxious symptoms were measured with the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983; Herrero et al, 2003). For the social anxiety evaluation, the Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987; Bobes et al., 1999) was used. The extent of state and trait anxiety was assessed using the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983, 2008).

2.3. Olfactory measures

2.3.1. Questionnaires

The reactivity to odors was measured with the Affective Impact of Odors scale (AIO) (Wrzesniewski et al., 1999; Burón et al., 2011) and the Relational Scale of Olfaction (EROL) (Burón et al., 2013). The AIO is an 8-item questionnaire that measures the impact of liked and disliked smells in determining liking new foods, places, cosmetic/health products and people. The AIO score is calculated taking the mean of all the items where higher scores indicate more impact of odors on liking the aforementioned topics (ranging from 0 to 3). The EROL questionnaire evaluates the influence of odors on several emotional, cognitive and behavioral issues such as mating behavior, safety and attractiveness of odors, and the influence of the smell on space perception. The score is obtained by adding the ratings of the 11 items (range from 0 to 36), with higher scores showing more influence of odors on the mentioned topics.

The Odor Awareness Scale (OAS) (Smeets et al., 2008; Burón et al., 2011) was used to assess the olfactory awareness. The OAS is a 32-item scale designed to capture a person's tendency to notice, pay attention to or attach importance to odors in the environment, covering topics such as food and drink, civilization, nature, and man. The OAS is calculated by the addition of the items (range from 32 to 158). Higher scores indicate higher odor awareness.

2.3.2. Psychophysical testing

The olfactory sensitivity was tested using the extended version of Sniffin' Sticks Test (Hummel et al., 1997). This is a widely used research and clinical tool based on pen-like odor dispensing devices. Each subject was required to wear a sleeping mask to prevent visual identification of the pens. Detection threshold for phenyl ethyl alcohol (PEA) was assessed using a single staircase, and three odor dispensing pens were presented in a randomized order, 2 cm below each nostril. Two pens contained deionized water and the third pen, one of the 16 concentrations of PEA. Each