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Both anxiety and joint laxity determine the olfactory features in panic disorder

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ABSTRACT

Previous research showed a high sensitivity in sensorial modalities in panic disorder (PD). This disorder has been consistently associated to the joint hypermobility syndrome (JHS). In non-clinical samples, this collagen alteration has been also related to an enhanced sensitivity in some sensorial modalities. The main aim of this study is to explore the olfactory functioning in PD in relation to JHS. Sixty patients with PD and sixty healthy controls performed the Sniffin' Sticks Test (SST) (threshold subtest), and completed the Affective Impact of Odors scale (AIO), the Relational Scale of Olfaction (EROL), and the Odor Awareness Scale (OAS). Clinical symptom rating scales and JHS assessment were also obtained. PD patients showed enhanced odor acuity, greater reactivity to smells and also increased odor awareness compared to the healthy controls. Within the patients group, those suffering from JHS displayed higher functioning in all olfactory domains compared to the non-JHS ones. The JHS and anxiety measures emerged as predictor variables of the olfactory function. The present findings highlight the importance of the olfactory function in PD and underline that both, JHS and anxiety, determine the olfactory characteristics in this disorder.

1. Introduction

The diagnosis of panic disorder (PD) is based on the existence of three major clinical syndromes: recurrent and unexpected panic attacks, anticipatory anxiety and phobic avoidance (APA, 2013). In the last decades, a significant amount of research has been conducted regarding the sensory characteristics of patients with anxiety disorders and most specifically, in patients with PD. Although the data are limited, several studies have provided evidence of an increased sensitivity to internal and external sensory cues in this type of patients. PD patients have lower thresholds and greater reactivity to somatic sensations (Domschke et al., 2010), visual peripheral stimulation (Caldirola et al., 2011), light (Bossini et al., 2009, 2013), sounds (J uris et al., 2013), taste stimuli (DeMet et al., 1989), and also to meteorological phenomena (Bulbena et al., 2005). In the area of olfaction, our group recently evaluated the olfactory function in PD and found that PD patients appeared to be highly sensitive, reactive and aware of odors compared to controls (Bur on et al., 2015). The study of this sensory modality in PD is especially significant given the great neuroanatomical overlap between olfactory and fear structures (Gorman et al., 2000; Zald and

Pardo, 2000). Despite research in this area is limited, it may provide more fine grained information about the pathophysiological and neurobiological mechanisms of PD and may help develop more specific treatments. Additionally, it can help to a better understanding of this clinical phenomenon.

Anxiety disorders and most specifically PD are strongly associated with the joint hypermobility syndrome (JHS) (Bulbena et al., 2015, 2017; Smith et al., 2014), a benign heritable collagen condition that is characterized by increased laxity of the joints, resulting in enhanced joint distensibility in passive movements and hypermobility in active movements. This collagen condition also comprises other articular and extra-articular features including arthralgias, dislocation of joints, tendinitis, abnormalities of the skin, easy bruising and myopia among others (Ross and Grahame, 2011). Individuals suffering from JHS frequently report symptoms associated with autonomic nervous system abnormalities and stress-sensitive illnesses (Bulbena et al., 2015; Gazit et al., 2003). Some studies showed that comorbidity rates between PD and JHS are substantial, with rates as high as 67.7% (Garc a-Campayo et al., 2011; Mart ın-Santos et al., 1998). Bulbena et al. (2011) conducted a 15-year follow-up study and reported that JHS was a risk

Abbreviations: PD, Panic disorder; JHS, Joint hypermobility syndrome; SST, Sniffin' Sticks Test (SST); AIO, Affective Impact of Odors scale; EROL, Relational Scale of Olfaction (EROL); OAS, Odor Awareness Scale; OFC, Orbitofrontal cortex; and PEA, Phenyl ethyl alcohol

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factor trait for developing PD, highlighting the importance of evaluating JHS among patients with anxiety disorders.

Research on sensory modalities in JHS is scarce and all the studies have been conducted in non-psychiatric samples so no data on comorbid anxiety is available. Except for joint proprioception, which is reduced in these individuals (Smith et al., 2013), research on other sensory areas such as interoception, nociception and emotional visual stimuli have shown that these subjects have lower thresholds and a higher reactivity respectively to these sensory modalities (Eccles et al., 2012; Grahame, 2000; Mallorquí-Bagué et al., 2014, 2015).

Following the accumulated evidence of the co-occurrence between anxiety and JHS over the past 30 years, Bulbena et al. (2015) recently described the “Neuroconnective phenotype” of anxiety disorders, which is built around the core association between these two variables. This model has five dimensions including somatosensory, psychopathological, somatic illnesses, behavioural patterns, and the somatic symptoms domains. Among those areas, the somatosensory dimension implies that patients with this phenotype, suffering from both JHS and anxiety, have greater sensitivity to the inner and external sensory stimuli which is especially relevant for this study. The consideration of sensory modalities in patients with PD and JHS is significant for two reasons: first, PD patients with this collagen condition have shown greater clinical severity (Martín-Santos et al., 1998) which may be related to sensory perception and processing; and secondly, the study of the olfactory functioning in patients with this phenotype may help to shed light into the neurobiological mechanisms behind this association.

Based on this background, it is reasonable to consider that both, PD and JHS, might be associated with a higher sensitivity to the sensory cues. However, while some sensory modalities have been evaluated separately in anxiety disorders and JHS respectively, to date, no data is available about olfaction in patients with PD and comorbid JHS. In this novel study, we evaluated olfactory functioning among patients with both PD and JHS and since these variables have never been evaluated together, the relationship among them will be studied for the first time.

The specific aims of this study are the following: (1) to determine whether JHS and non-JHS subjects with PD have different olfactory features in odor acuity (i.e. detection threshold), reactivity to smells and odor awareness, (2) to investigate whether the olfactory characteristics in PD might be explained by anxiety and/or JHS, and (3) to test if previous findings of increased olfactory function in PD patients were supported in a higher sample size.

We hypothesized that both, anxiety and JHS, would determine the olfactory function. Following this rationale, PD patients would have an increased olfactory functioning compared to the healthy controls. Taking into account that several studies showed that both patients with PD and healthy individuals with JHS showed a higher sensitivity to the sensory cues, the presence of the two conditions (PD and JHS) may lead to an additive effect on the sensory response. Therefore, we also hypothesized that amongst patients, those bearing the JHS diagnosis would display more pronounced olfactory characteristics in comparison to the non-JHS ones.

2. Methods

2.1. Participants

This study was carried out at the Parc de Salut Mar in Barcelona (Spain) between 2011 and 2015. Individuals who attended the outpatient anxiety clinic that fulfilled DSM-IV-R criteria for PD (APA, 2000) were selected as eligible patients. Psychiatric diagnoses were established by two trained clinicians using The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) along with a review of medical records. The control subjects were healthy individuals with no history of mental illness that were matched for age and sex with PD patients and also underwent a diagnostic interview using the MINI to rule out any psychiatric diagnosis. These individuals

were recruited through word of mouth from families of the researchers and local community.

The exclusion criteria included the presence of neurological disorders, history of head injury with loss of consciousness, systemic disturbances of metabolism (i.e. active thyroid disorders, diabetes, and liver or kidney diseases) and medications that could affect the olfactory function such as some antihypertensives and medications for cardiac diseases, age less than 18 or greater than 50 years old, current toxic chemical or industrial agent exposure, being pregnant or currently breastfeeding, anosmia, smoking 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 (Doty et al., 2008). Conditions that could hamper a full joint examination and any other psychiatric diagnosis on Axis I other than PD were also exclusion factors. We did not screen participants for any comorbid Axis II disorder.

All subjects gave informed consent after study procedures were fully explained. The study was reviewed and approved by the Ethics Committee of Clinical Investigation (CEIC) of the hospital. This investigation was conducted according to the Declaration of Helsinki and there was no financial reward for the participants.

2.2. Measures

2.2.1. Sociodemographic and clinical measures

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

The severity of PD with and without agoraphobia was assessed using “The Panic and Agoraphobia Scale” (PAS) (Bandelow, 1995). Depression and anxiety symptoms were measured with the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). The Liebowitz Social Anxiety Scale (LSAS) (Liebowitz, 1987) was used for the evaluation of social anxiety. The extent of state and trait anxiety was assessed with the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983).

2.2.2. Olfactory measures

The Affective Impact of Odors scale (AIO) (Wrzesniewski et al., 1999) and the Relational Scale of Olfaction (EROL) (Burón et al., 2013) were used to assess the reactivity to odors. 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 scale score is calculated taking the mean of all the items, in which higher scores indicate greater impact of odors on liking the aforementioned topics (range from 0 to 3). The EROL scale is an 11-item questionnaire that evaluates the influence of odors on several emotional, cognitive and behavioural domains such as mating behaviour, safety and attractiveness of odors, and the influence of the smell on space perception. The scale is scored by adding the ratings of the 11 items (ranging from 0 to 36), in which higher scores show greater influence of odors on the mentioned topics.

Olfactory awareness was evaluated with the Odor Awareness Scale (OAS) (Smeets et al., 2008). This 32-item questionnaire captures 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 as the addition of all the items, ranging from 32 to 158, and higher scores indicate greater odor awareness.

The Sniffin' Sticks Test (Hummel et al., 1997), specifically the detection threshold subtest, was used to perform the psychophysical assessment of the olfactory acuity. 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

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