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Original article

New evidence of heterogeneity in social anxiety disorder: Defining two qualitatively different personality profiles taking into account clinical, environmental and genetic factors

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ABSTRACT

Purpose: To study qualitatively different subgroups of social anxiety disorder (SAD) based on harm avoidance (HA) and novelty seeking (NS) dimensions.
Method: One hundred and forty-two university students with SAD (SCID-DSM-IV) were included in the study. The temperament dimensions HA and NS from the Cloninger's Temperament and Character Inventory were subjected to cluster analysis to identify meaningful subgroups. The identified subgroups were compared for sociodemographics, SAD severity, substance use, history of suicide and self-harm attempts, early life events, and two serotonin transporter gene polymorphisms (5-HTTLPR and STin2.VNTR).
Results: Two subgroups of SAD were identified by cluster analysis: a larger (61% of the sample) inhibited subgroup of subjects with "high-HA/low-NS", and a smaller (39%) atypical impulsive subgroup with high–moderate HA and NS. The two groups did not differ in social anxiety severity, but did differ in history of lifetime impulsive-related-problems. History of suicide attempts and self-harm were as twice as frequent in the impulsive subgroup. Significant differences were observed in the pattern of substance misuse. Whereas subjects in the inhibited subgroup showed a greater use of alcohol ($P = 0.002$), subjects in the impulsive subgroup showed a greater use of substances with a high-sensation-seeking profile ($P < 0.001$). The STin2.VNTR genotype frequency showed an inverse distribution between subgroups ($P = 0.005$).
Conclusions: Our study provides further evidence for the presence of qualitatively different SAD subgroups and the propensity of a subset of people with SAD to exhibit impulsive, high-risk behaviors.

1. Introduction

Social anxiety disorder (SAD) is a highly prevalent [1] psychiatric disorder characterized by fear and avoidance of interpersonal situations, which exceeds the adaptive threshold and interferes with daily life [2]. SAD is associated with significant psychosocial impairment and high rates of comorbidity [3], early life events [4] and has been reported to be a risk factor for subsequent depressive and substance abuse disorders [5].

The majority of people with SAD is shy, avoid meeting new people, and are withdrawn in unfamiliar social settings, with frequent avoidant behaviors associated [2,5]. Available evidence suggest that a great number of patients with SAD show dysfunctional personality traits and high rates of comorbidity with certain personality disorders, in particular with avoidant and dependent personality disorders [6,7]. Of particular interest in the study of SAD have been two temperamental dimensions from Cloninger's psychobiological model of personality: harm avoidance (HA) and novelty seeking (NS) [8]. It should be noted that both dimensions assess differences in automatic emotional responses to stimuli defining personality style, and have their corresponding neurobiological substrate [9]. HA is defined as a heritable bias in the inhibition of behaviors and the tendency to respond fearfully to

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stimuli, and is believed to be regulated by the serotonin system. NS is defined as a tendency to respond actively to novel stimuli with frequent exploratory and impulsive activity in response to novelty, and is believed to be regulated by the dopamine system [9]. Numerous studies indicate that SAD is associated with an increase in HA [10–17] and a decrease in NS [10,16,17]. In addition, a recent meta-analysis of temperament in anxiety disorder confirms that increases in the HA dimension has been the most consistent and replicated finding across SAD studies, followed by decreases of the NS dimension [6]. The combination of both high-HA and low-NS might well represent the prototypical SAD pattern characterized by shyness, behavioral inhibition, and avoidance patterns. However, there is increasing evidence of an atypical subgroup of SAD subjects with impulsive rather than inhibited traits that use alternative strategies, such as impulsive, risky and exploratory behaviors [18–22].

Previous studies, using cluster analysis and latent class approaches performed in both clinical [18–20,22] and non-clinical [21] samples, found evidence for qualitatively different subgroups of SAD subjects. In 2008, Kashdan and Hoffman [19] used cluster analysis and found evidence for two qualitatively different SAD subgroups based on high- or low-NS, as a measure reflecting risk-prone and disinhibited behavior tendencies. The two groups did not differ in terms of social anxiety severity; but clinicians' severity ratings for comorbid substance use disorders were greater in the high-NS group. Kashdan et al. [20] explored risk-prone and impulsive behaviors among 679 people with current diagnoses of SAD and 1143 people with lifetime diagnoses of SAD. The authors found again evidence for two SAD subgroups, one characterized by a pattern of behavioral inhibition and risk aversion, and another one by an atypical pattern of aggression, moderate/high sexual impulsivity and substance use problems. This atypical pattern of risk-prone behaviors was associated with greater functional impairment, less education and income, younger age, and comorbidity for impulse control and bipolar disorders [19,22]. Recently, Mörtberg et al. [22] studied subgroups of SAD in a clinical sample based on HA and NS temperament dimensions and social anxiety severity. The study identified different subgroups, including a typically inhibited subgroup of generalized SAD with "high-HA and low-NS", as well as an atypical subgroup of generalized SAD with coexisting anxiety and impulsivity traits (high-HA, high-NS), with both clusters being associated to greater depressive symptoms. In non-clinical samples [21], evidence of an impulsive, risk-prone subgroup of socially anxious individuals has also been reported. Compared to a more inhibited group, the risk-prone subgroup reported more frequent unsafe sexual practices, aggression, and substance abuse over the course of a 3-months period, and greater difficulties on several indices of psychological and social well-being [21]. Taken together, these studies contribute to growing evidence of the existence of heterogeneity in SAD and the notion that high-NS, and impulsive risk-prone behaviors may be a characteristic feature of a distinct subgroup of SAD subjects.

The biological differences between inhibited and impulsive subgroups of SAD have not been examined to date, but some authors have suggested that they may be based in the functioning of executive attention brain networks required for inhibitory control [23]. Moreover, since HA and NS are temperamental dimensions which are believed to be highly hereditable and have their corresponding neurobiological substrate, dopamine and serotonin function respectively [9], one might expect that genetic differences may also partially account for the behavioral differences of these two qualitatively different subgroups. Genes related to the serotonin or dopamine pathways may contribute to the genetic liability to both temperamental dimensions and psychiatric disorders, such as SAD [24,25]. Of particular interest have been two polymorphisms on the human serotonin transporter gene (*SLC6A4*), the 5-HTTLPR, a 44-base pair insertion/deletion in the promoter region, and the STin2, a multi-allelic 17-base pair variable number of tandem repeats (VNTR) within intron 2, which are thought to regulate variations in transcriptional activity [26–28]. Several studies suggest that these variants might modulate a wide range emotional and behavioral disturbances [25]. In the field of SAD, studies with clinical samples have reported an association between the 5-HTTLPR with increased levels of anxiety-related traits, SAD severity and greater amygdala excitability in response symptom provocation [29], to amygdala hyper-responsivness in response to threat faces [30], and to alterations in insula activation to threat [31]. However, to our knowledge, differences in functional variant of the serotonin transporter have not been previously studied in the impulsive-inhibited subtypes of SAD.

On this basis, the aims of the present study were:

- to study whether qualitative different subgroups based on HA and NS temperament dimensions could be identified using cluster analysis;
- to explore differences between the potential different subgroups of SAD subjects in terms of clinical and sociodemographic variables and 5-HTTLPR and STin2.VNTR functional variants of the serotonin transporter.

We expected that at least two qualitative different subgroups based on these temperament dimensions would characterize individuals with SAD: a larger subgroup representing the prototypical inhibited SAD profile (HAns: high-HA and low-NS), and a smaller subgroup representing fearful individuals who show atypical impulsive tendencies (HANS: high-HA and high-NS).

2. Material and methods

2.1. Sample and procedure

One hundred and forty-two Caucasian university students (both genders, aged over 18) with DSM-IV criteria for SAD [2] and a Liebowitz Social Anxiety Scale (LSAS) score greater than 60 [32,33] and for whom social anxiety was the primary mental health problem were included in the study. Participants were recruited by advertisements distributed throughout the campus of the Autonomous University of Barcelona, Spain. Exclusion criteria included lifetime diagnoses of psychotic disorders and mental disorders due to a medical condition. Written informed consent was obtained from all the participants. The study was approved by the local Ethics Committee (CEIC-IMAS and CEIC-UAB).

2.2. Measures

An ad hoc categorical questionnaire designed by the team was administered to all participants. It included sociodemographic data, first-degree family psychiatric history, as well as personal history of medical and psychiatric conditions and drug-use. The questionnaire also included the assessment of history of self-harm and suicide attempts, and early negative life events (loss of someone close, family violence, and emotional, physical and sexual abuse).

Social anxiety was assessed by the validated self-reported Spanish version of the LSAS [34], comprising 24 items, each describing different social situations. The LSAS evaluates the severity of anxiety and/or social avoidance in a wide range of social situations using a Likert scale.