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No effects of psychosocial stress on memory retrieval in non-treated young students with Generalized Social Phobia

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ABSTRACT

Generalized Social Phobia (GSP) is a common anxiety disorder that produces clear social life disruptions. There is no consensus on the specific processes involved in its development, but the role of the hypothalamic-pituitary-adrenal (HPA) axis has been suggested. This study analyzed the effects of the cortisol response to the Trier Social Stress Test (TSST) on the memory retrieval of pictures with different emotional valences in 45 non-treated young students with GSP and 50 non-anxious (NA) subjects (mean = 19.35 years, SD = 0.18). No differences were found in the cortisol response of GSP and NA subjects to the TSST and control sessions. In addition, psychosocial stress impaired memory retrieval in both the GSP and NA groups, with no differences between them. Regarding the sex factor, no effects were found in the cortisol response to the TSST. However, during the encoding session, GSP men had higher cortisol levels than GSP women and NA subjects. There was also a significant interaction between sex and stress exposure on memory retrieval. Women recognized more unpleasant and neutral pictures than men; however, under stress, the women's advantage disappeared, and the men's performance improved. Sex also interacted with social phobia on positive mood, with GSP women exposed to the TSST showing the lowest positive mood. These results suggest that GSP subjects do not present an HPA axis sensitization to psychosocial stress, and they emphasize the importance of Sex in understanding stress effects on memory.

1. Introduction

Social Phobia (SP) is a common anxiety disorder with high prevalence during adolescence and youth, characterized by intense fear and/or avoidance of situations where an individual is fearful of a negative social evaluation (American Psychiatric Association, 2000; van Peer et al., 2010); when fears are related to most social situations, the specification of Generalized Social Phobia (GSP) is used. Deficits in the associative learning processes have been proposed as the main impaired underlying mechanism of this condition (Stravynski, 2007), although SP may also be considered a stress-related condition. Several studies have examined the hypothalamic-pituitary-adrenal (HPA) axis reactivity in SP subjects, reporting conflicting findings for cortisol levels that support both sensitization (Condren et al., 2002; Roelofs et al., 2009; van West et al., 2008) and reduced activation of the HPA axis to psychosocial stress (e.g. Shirotsuki et al., 2009) in this population. These studies are heterogeneous, not only in terms of the population under study (e.g. inpatients, community samples, children, and elder individuals), but also in the type of stressor and the nature of the tasks employed. In general, stressful events induce an increase in the hypothalamic production of the corticotropin-releasing hormone (CRH), which stimulates pituitary release of the adrenocorticotropin hormone (ACTH) and, as a consequence, cortisol secretion by the adrenal cortex (Suay and Salvador, 2012). Given the relevance of the reaction to social stress in SP and the inconclusive and sparse reports on the HPA axis response to stress in subjects with SP, more research is needed to understand the acute stress response in this population.

In addition to the cortisol response to psychosocial stress, the relationship between social phobia and emotional reactivity to stress has been extensively studied. At the brain circuitry level, it has been suggested that social phobic subjects display enhanced activation of the prefrontal-limbic circuitry, including the amygdala, anterior cingulate, and orbitofrontal cortex, in response to the anticipation of faces displaying pain (Veit et al., 2002). High levels of

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subjective anxiety, but not physiological reactivity, were observed in 12-year-old SP children compared to healthy control subjects (Krämer et al., 2012); by contrast, van West et al. (2008) reported an elevated cortisol response, but no state-anxiety reactivity, in 6–12-year-old children compared to controls, employing the same psychosocial stressor, the Trier Social Stress Test (TSST, Kirschbaum et al., 1993). In older people (Grossman et al., 2001), using a public speaking task and, more recently, in middle-aged people using the TSST (Klumbies et al., 2014), higher subjective anxiety, but not higher cortisol response to the social stressor, has been reported in individuals with social phobia.

Among the main consequences of exposure to stress, cognitive effects, particularly on memory, have attracted considerable attention. Many studies have assessed the acute effects of increased levels of glucocorticoids (GCs) on memory performance, although the precise direction of these effects is dependent on several factors. When the HPA axis is activated, cortisol secretion takes place and crosses the blood-brain barrier, binding to GC receptors located in the hippocampus, amygdala, and prefrontal cortex (Ulrich-Lay and Herman, 2009), which play an essential role in memory. The type of process (acquisition, consolidation or retrieval) and memory (e.g. declarative, priming, working memory, and so on), as well as the nature of the material (neutral vs emotional) to be recalled, are important factors to be considered. Studies employing declarative memory tasks based on the repetition of a neutral word list have shown that stress (Wolf et al., 2001) or cortisol administration (de Quervain et al., 2000) leads to poorer memory retrieval in humans. However, material with emotional content improves consolidation (Cahill and McGaugh, 1998) and appears to interact with some effects of stress or cortisol administration on memory retrieval (Jelici et al., 2004). Specifically, there is evidence for a negative effect of cortisol on memory retrieval in healthy young adults for negative material, but with no effects on neutral material (de Quervain et al., 2007; Smeets et al., 2007; Marin et al., 2010). However, in other studies, stress and cortisol treatment impaired memory retrieval, especially of emotionally arousing material, regardless of its valence (Buchanan and Tranel, 2008; Smeets et al., 2008; Tollenaar et al., 2008). People with SP have been described as remembering more negative stimuli, both emotional facial expressions (Foa et al., 2000) and specific negative aspects of social events (Hertel et al., 2008). Together, these results point to the anticipation of negative emotional aspects of social events as the trigger for the social fear experienced (Veit et al., 2002). However, how controlled stressful social events affect the memory retrieval of emotionally arousing material in SP subjects remains unknown. Individuals with GSP have been described as having differential working memory and short-term memory capacities compared to healthy controls (Amir and Bomyea, 2011). Specifically, they displayed better performance on negative material and poorer performance on neutral material. This becomes particularly important when studying the effect of stress on delayed memory processes, as these effects may be driven not by the social stress, but by specific deficits in the early acquisition phases. Thus, it is fundamental to measure both immediate and delayed memory in order to properly assess the stress effects on memory retrieval in GSP subjects.

Sex is a fundamental factor when studying the hormonal response to stress, as sex differences in both the cortisol response to stress (Kudielka and Kirschbaum, 2005) and stress effects on learning and memory (Andreano and Cahill, 2009; Wolf, 2006) are often reported. Men tend to show a greater cortisol stress response than women in laboratory studies (Kirschbaum et al., 1999; Kudielka et al., 2009), and they are more affected by stress on declarative memory retrieval (Wolf et al., 2001). There is also evidence that women outperform men on episodic memory tasks of verbal material, faces and pictures (Herlitz et al., 2013; Spalek et al., 2015). When recalling pictures with different emotional valences, women outperformed men on free recall of positive, negative, and neutral pictures, with a particular advantage for positive pictures. However, these sex-related differences disappeared on the recognition task (Spalek et al., 2015). Little is known about whether these sex differences remain after exposure to stress. For instance, in a pre-learning stress study, we found that in the group exposed to the psychosocial stressor, men's performance on the memory test improved and matched the level displayed by women (Espín et al., 2013). The potential beneficial effects of female sex hormones (Wolf, 2006) and sex differences in the cortisol response to stress (Kudielka and Kirschbaum, 2005) may explain this pattern of results.

To shed light on the different results reported in the literature and examine a period of the life span that is particularly important due to the potential negative effects of social phobia, we conducted a multi-measure study of GSP young people, exposing them to the most widely used social stressor in the aforementioned studies, the TSST, and comparing them with controls. Our aim was to investigate the effects of the stressor on the HPA axis and the subjective state, and find out how stress affects the memory retrieval of pictures with different emotional valences in young GSP and non-anxious (NA) subjects. We expected to find a higher stress-induced cortisol response in GSP subjects during the stressor, and we hypothesized that an elevation in cortisol levels may cause impairing effects on the retrieval process of emotional material (specifically for positive pictures). Finally, we explored whether these stress effects are modulated by sex.

2. Materials and methods

2.1. Participants

The final sample was composed of ninety-five undergraduate students of Psychology (60%) and Computer Engineering (40%), with ages between 18 and 25 years old (mean age: 19.4 years old; S.D. = 0.18), who participated in the study for one class credit.

The recruitment of the sample was performed in two steps. In the first step, 675 students filled out the Social Phobia and Anxiety Inventory (SPAI; Turner et al., 1989), but 580 were excluded from the study based on one or more of the following criteria: they scored between 50 and 97 on the SPAI; they displayed a history of alcohol or other drug abuse; they had cardiovascular, endocrine, neurological or psychiatric diseases; they had visual or hearing problems; they had experienced a stressful life event during the past year; they were using any medication directly related to emotional or cognitive function, or one that was able to influence hormonal levels, such as glucocorticoids, oral contraceptives, beta-blockers, antidepressants, benzodiazepines, asthma medication, thyroid therapies, and psychotropic substances. Vitamins, sporadic use of painkillers, and natural therapies were allowed. None of the participants were habitual smokers (more than 10 cigarettes a week). The SPAI has shown good internal consistency coefficients (Cronbach's alpha = 0.96 for the subscale of Social Phobia) and high test-retest reliability (0.89) in young Spanish adults and college students (Olivares et al., 2010). The remaining 95 students were classified as the GSP group if they obtained a score >97, and as the non-anxious group (NA) if their score was <50 on the Social Phobia subscale, based on available normative data for the Spanish population (Olivares et al., 2010), with the following distribution: GSP group (N = 45) and NA group (N = 50). In the second step, subjects identified as GSP participated in an individual clinical interview with a clinician who was blind to the previous classification. All participants included in the GSP group met all the clinical criteria for Generalized Social Phobia from the Anxiety Disorders interview Schedule (DSM-IV-TR), which confirmed the distribution. There-