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Research Report

Cortical thinning of the right anterior cingulate cortex in spider phobia: A magnetic resonance imaging and spectroscopy study

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ABSTRACT

There a lack of consistent neuroimaging data on specific phobia (SP) and a need to assess volumetric and metabolic differences in structures implicated in this condition. The aim of this study is investigate possible metabolic (via ^{1}H MRS) and cortical thickness abnormalities in spider-phobic patients compared to healthy volunteers. Participants were recruited via public advertisement and underwent clinical evaluations and MRI scans. The study started in 2010 and the investigators involved were not blind in respect to patient groupings. The study was conducted at the Ribeirão Preto Medical School University Hospital of the University of São Paulo, Brazil. Patients with spider phobia (n=19) were matched to 17 healthy volunteers with respect to age, education and socioeconomic status. The spider SP group fulfilled the diagnostic criteria for spider phobia according to the Structured Clinical Interview for DSM-IV. None of the participants had a history of neurological, psychiatric or other relevant organic diseases, use of prescribed psychotropic medication or substance abuse. All imaging and spectroscopy data were collected with a 3 T MRI scanner equipped with 25 mT gradient coils in 30-minute scans. The *Freesurfer* image analysis package and LC Model software were used to analyze data. The hypothesis being tested was formulated before the data collection (neural correlates of SP would include the amygdala, insula, anterior cingulate gyrus and others). The results indicated the absence of metabolic alterations, but thinning of the right anterior cingulate

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cortex (ACC) in the SP group when compared to the healthy control group (mean cortical thickness ± SD: SP = 2.11 ± 0.45 mm; HC = 2.16 ± 0.42 mm; t (34) = 3.19, $p = 0.001$ [−35.45, 71.00, −23.82]). In spectroscopy, the ratios between N-acetylaspartate and creatine and choline levels were measured. No significant effect or correlation was found between MRS metabolites and scores in the Spider Phobia Questionnaire and Beck Anxiety Inventory ($p > 0.05$). The ACC is known to be related to the cognitive processing of fear and anxiety and to be linked with the conditioning circuit. The MRS findings are preliminary and need more studies. The finding of reduced ACC thickness in SP is in agreement with evidence from previous functional neuroimaging studies and highlights the importance of this brain area in the pathophysiology of SP.

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1. Introduction

Specific phobia (SP) is characterized by unreasonable, excessive, and persistent fear in the presence or anticipation of feared situations or objects. SP is considered to be one of the most prevalent anxiety disorders and is subdivided into five subtypes (animal, blood-injection-injury, situational, natural events, and others) (Kessler et al., 2005). The most common subtype of SP is the animal subtype, which has a prevalence of 12.1% in women and 3.3% in men (Fredrikson et al., 1996).

The etiology of animal SP remains uncertain, but available evidence suggests that constitutional and environmental factors may contribute to its etiology (Fyer, 1998). Environmental factors are related to specific events and to the conditioning process. Fear conditioning is essential for danger detection; however, in some cases it may also influence the emergence of disorders related to anxiety and fear (Sehlmeyer et al., 2009). It is important to mention that the outcomes of conditioning processes are dependent on vulnerability factors including differences in life experiences, perceived controllability, direct or vicarious experience, type and intensity of experience, and information transmission (Mineka and Zinbarg, 2006).

Constitutional factors refer to genetic components and ensuing neural alterations. Some studies have supported the notion that genetic risk factors play a role in the etiology of SP (Kendler et al., 2001). Moreover, there are hypotheses that animal SP can be related to abnormalities in the encephalic aversion system (EAS), although the specific neural networks of the EAS involved in the physiopathology of SP are not completely understood. Several original articles and some reviews (Shin and Liberzon, 2001) pointed to the involvement of the amygdaloid complex (Morris et al., 1988; Phelps, 2005), the dorsal hippocampus (Zelikowsky et al., 2012), the nucleus accumbens (Luckett et al., 2001), the ventromedial hypothalamus (Wilent et al., 1994; Biagioni and Coimbra, 2012), the periaqueductal gray matter (Carrive et al., 1997; Vianna and Brandao, 2003), the corpora quadrigemina (Castellan-Baldan et al., 2006; Coimbra et al., 2006; Eichenberger et al., 2002), the insular cortex (van Well et al., 2012) thalamic nuclei, and some prefrontal neocortical regions (Mobbs et al., 2007) in both unconditioned and conditioned fear-related behaviors studied in laboratory animal- and human-based models of fear and panic. Therefore, patients with animal SP would be expected to have abnormalities in this network.

To assess brain responses and better comprehend animal SP, most studies have used functional neuroimaging techniques (fMRI, PET, and SPECT) to measure the effects of exposure to phobia-related images (Linares et al., 2012). The results are not totally homogeneous; however, many studies that investigated spider phobia identified neural correlates of autonomic (amygdala) and direct evaluation (e.g. insula, anterior cingulate gyrus, and left dorsomedial prefrontal cortex) of threatening stimuli (Straube and Miltner, 2006; Schienle et al., 2005; Dilger et al., 2003). In spite of that, little is known about other neuroimaging techniques and their possible contributions to the understanding of the neurobiology of animal SP.

Newer structural, metabolic and functional neuroimaging techniques might contribute to a better understanding of the etiology and pathophysiology of SP. Magnetic resonance spectroscopy (MRS) and structural MRI provide in vivo neuroanatomical information and neurochemical quantification and, in association with functional neuroimaging techniques, can help uncover the neural substrates of SP. To the best of our knowledge, no study has investigated possible metabolite changes using proton magnetic resonance spectroscopy (^{1}H MRS) in SP, and only two studies have used structural measures of cortical thickness (Rauch et al., 2004; Rosso et al., 2010) in this population.

The insufficiency of consistent data and the need to assess volumetric differences in structures implicated in SP make the continuation of complementary studies in the area an issue of paramount importance. Thus, the aim of the present study was to investigate possible cortical thickness and metabolic abnormalities in spider-phobic patients compared to healthy volunteers.

2. Results

2.1. Cortical thickness

Cortical thickness measurements indicated thinning of the right ACC in the group with spider phobia compared to the HC group (mean cortical thickness ± SD: SP = 2.11 ± 0.45 mm, HC = 2.16 ± 0.42 mm; t (34) = 3.19, $p = 0.001$ [−35.45, 71.00, −23.82]). There were

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