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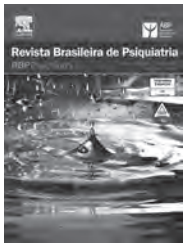

REVIEW ARTICLE

Neuroimaging in specific phobia disorder: a systematic review of the literature

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DESCRIPTORS
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Abstract
Objective: Specific phobia (SP) is characterized by irrational fear associated with avoidance of specific stimuli. In recent years, neuroimaging techniques have been used in an attempt to better understand the neurobiology of anxiety disorders. The objective of this study was to perform a systematic review of articles that used neuroimaging techniques to study SP. *Method:* A literature search was conducted through electronic databases, using the keywords: imaging, neuroimaging, PET, spectroscopy, functional magnetic resonance, structural magnetic resonance, SPECT, MRI, DTI, and tractography, combined with simple phobia and specific phobia. One-hundred fifteen articles were found, of which 38 were selected for the present review. From these, 24 used fMRI, 11 used PET, 1 used SPECT, 2 used structural MRI, and none used spectroscopy. *Result*: The search showed that studies in this area were published recently and that the neuroanatomic substrate of SP has not yet been consolidated. *Conclusion:* In spite of methodological differences among studies, results converge to a greater activation in the insula, anterior cingulate cortex, amygdala, and prefrontal and orbitofrontal cortex of patients exposed to phobia-related situations compared to controls. These findings support the hypotheses of the hyperactivation of a neuroanatomic structural network involved in SP.

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DESCRITORES:
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Neuroimagem do transtorno de fobia específica: uma revisão sistemática da literatura

Resumo
A Fobia Específica (SP do inglês) é caracterizada por medos irracionais associados à evitação de estímulos específicos. Nos últimos anos, técnicas de neuroimagem vêm sendo empregadas na tentativa de melhor compreender a neurobiologia dos transtornos de ansiedade. O objetivo do presente estudo é realizar uma revisão sistemática dos artigos que utilizaram neuroimagem para estudar a SP. A busca na literatura foi realizada por intermédio de indexadores eletrônicos, utilizando-se as palavras-chave: *imaging*, *neuroimaging*, PET, *spectroscopy*, *functional magnetic ressonance*, *structural magnetic ressonance*, SPECT, MRI, DTI e *tractography*, cruzadas individualmente com os termos *simple phobia* e *specific phobia*. Foram encontrados 115 artigos, sendo 38 deles selecionados para a presente revisão. Desses, 24 usaram fMRI, 11 usaram PET, 1 usou SPECT, 2 usaram MRI estrutural e nenhum artigo de espectroscopia. Verifica-se que os estudos na área foram publicados recentemente e que, até o momento, o substrato neuroanatômico deste transtorno não está consolidado. Apesar das diferenças metodológicas entre os estudos, os resultados convergem para maior ativação na ínsula, cíngulo anterior, amídala e córtex pré-frontal e orbitofrontal dos pacientes expostos a situações *phobia related* quando comparados aos controles. Esses achados reforçam hipóteses a respeito da hiperativação de uma determinada rede de estruturas neuroanatômicas envolvidas no transtorno de SP.

Introduction

Specific phobia (SP), or simple phobia, is an anxiety disorder characterized by increased and persistent excessive or irrational fear in the presence or anticipation of an object or phobic situation causing, almost invariably, an immediate anxiety response (DSM-IVR – APA, 2000).[1] DSM-IV defined five subtypes of SP: animal, natural environment, blood-injection-injury (BII), situational, and others. Specific phobias are considered the most frequent anxiety disorders and are among the most common psychiatric disorders in general population, with a prevalence of about 12.5%.[2]

Although environmental, constitutional, and genetic factors are believed to contribute to the pathogenesis of the disorder,[3-5] little attention had been dedicated to the study of SP neurobiology and etiology. The neuroimaging techniques, in particular, have helped to deepen the understanding of the neural circuitry underlying SP. Since its advent, neuroimaging has enabled the *in vivo* analysis of anatomical and functional structures, as well as analyses of regional metabolism in different psychiatric disorders. Methods like magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) have been used in the investigation of biological processes involved in the neurocircuitry of SP.

In order to expose a panoramic view to the readers, this article presents a systematic qualitative review of published studies on neuroimaging of patients with SP. The qualitative approach was chosen because quantitative methods, such as meta-analysis, show that: (a) the information necessary to calculate result size is not always available, and may limit this analysis to a small subset of studies;[6] (b) methods and extent of detailed information to define regions of interest vary greatly among studies, hindering accurate comparisons; (c) there are great differences regarding secondary variables in studies (for instance, gender, medication, co-morbidity, SP subsets); (d) studies used different functional (PET, SPECT, fMRI, relaxometry) and structural (MRI) neuroimaging methods, which precludes comparative statistical analyses; (e) different methods are used to analyze images (automatic vs. ROI) in different forms of investigation, and (f) meta-analyses have intrinsic limitations in estimating negative results which are not published (the file drawer problem;[7]). Thus, a quantitative analysis is not adequate for a review with large amplitude (with no time limit set). Finally, it is relevant to point out that although animal research is valuable to understanding anxiety disorders, the current study will focus only on research performed with humans, as the analysis of animal research is beyond the scope proposed.

Method

Searches were performed in LILACS, SciElo and Web of Science databases, using the following key words: imaging, neuroimaging, PET, spectroscopy, functional magnetic resonance, structural magnetic resonance', SPECT, MRI, DTI e tractography, individually crossed with the terms simple phobia and specific phobia. Additional articles were sought manually in references from previously selected material.

The inclusion criteria for the articles used in the current study were: complete and original articles; in English; with samples of patients whose main diagnosis was SP and who had undergone investigation using neuroimaging techniques. No time limit was established, having the last search been performed in April, 2011. The search found 115 articles, of which 38 were selected to compose the present review (Figure 1).