A meta-analytic review of neuroimaging studies of specific phobia to small animals

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Received 23 May 2016; accepted 9 November 2016

KEYWORDS
Specific phobias; Neuroimaging; fMRI; Meta-analysis

Abstract
Introduction: Neuroimaging techniques have been used to identify the neurological bases of phobias.
Objective: This meta-review examines functional magnetic resonance imaging studies of individuals with specific animal phobia compared to healthy controls.
Method: Searches on Medline, PsycINFO, Academic Search Complete, PubMed, PsycARTICLES, Redalyc, Scopus, and Cochrane databases were conducted. Twenty high quality studies were selected. The effect size estimation was calculated.
Results: The random-effects model showed a high overall effect size for both limbic and frontal sites. Data analyses showed greater brain activity in the left amygdala and insular cortex in phobic individuals. We also observed an activation of the fusiform gyrus, the dorsolateral prefrontal cortex left, and the left cingulate cortex, although these areas were less frequently involved. Healthy controls showed high heterogeneity in the brain areas activated by phobic stimuli.
Conclusions: These findings suggest the possible existence of a double processing pathway in phobic stimuli: a rapid processing pathway involving limbic areas and a slow pathway involving both limbic and frontal areas.

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Introduction
The use of neuroimaging techniques has contributed to a better understanding of the neural circuitry involved in mental illness. Neuroimaging scans have delimited not only the anatomical and functional brain structures of many psychopathological disorders but also the regional metabolism of such disorders. As a consequence, neuroimaging has helped to increase our knowledge about the processes that underlie psychopathological disorders. This knowledge has had practical clinical implications, facilitating the diagnosis of mental disorders and the development of new treatments, especially those derived from psychiatric drugs.

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http://dx.doi.org/10.1016/j.ejpsy.2016.12.003
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Phobias, a special case of anxiety disorders, are one of those mental disorders. Phobia disorder refers to a high persistent anxiety response that people usually (but not always) consider excessive or irrational to the presence or anticipation of a threatening object or situation. There are three groups of phobias: agoraphobia, social phobia, and specific phobias.5 Phobias are one of the most frequent mental disorders, with specific phobias (SP) reaching the highest prevalence rates (from 7.7% to 12.1%).3,4

The etiology of phobias involves both environmental and constitutional/biological factors.3 Environmental factors refer to learning/instructional processes in the acquisition of an anxiety response. Biological factors justify the concept of preparedness: some people are biologically vulnerable to developing phobia disorders. Yet, although there is some consensus about the learning/instructional processes associated to phobia acquisition,6 no agreement has been reached so far on the neurological bases of phobias, including biochemical markers.7

Functional neuroimaging studies have been conducted with the aim of providing evidence of those neurological bases. Most of these studies have dealt with specific phobias (insects, spiders, blood-injury). Systematic reviews have found a group of similar brain areas and circuits related to brain responses to phobic stimuli.8,9 The areas most often found are those associated with limbic and paralimbic structures (insula, amygdala, thalamus). The cingulate gyrus, the medial prefrontal cortex, and the orbitofrontal cortex have also been found to be activated by those stimuli. However, several other areas have been found in various studies. These disparities hamper research on the specific biological bases of phobias.

Because of the many methodological differences between studies (i.e., age, gender, type of phobia, absence of a control group), a more restrictive review and meta-analysis were carried out in an attempt to select more comparable and comparable studies.10 In 10 of the 13 studies selected, the amygdala (especially the left amygdala) was the brain structure found to be most closely associated with specific phobia, followed by the globus pallidus, the pulvinar thalamus, the left insula, and the right cerebellum. The left insula was found to have the highest activation level (effect size data were not provided). Yet, depending on the study, several other areas (e.g., the anterior cingulate cortex, the hippocampus, the cingulate gyrus) were also found to be associated with phobias. Given that methodological disparities did not disappear (there were descriptive studies and experimental/treatment studies, designs with and without a control/healthy group, different subtypes of specific phobia), differences between studies may also be due to those discrepancies.

Considering the above, the aim of this meta-analysis was to provide an update of the neurological bases of specific phobias by applying more refined inclusion criteria in order to find more combinable studies. As regards techniques, we only included studies in which functional magnetic resonance imaging (fMRI) was used because the variability found in the brain activation areas may be mediated by the analysis technique used. There are few studies on specific phobias to small animals that used other neuroimaging techniques than fMRI. Techniques as Loretta and EEG as PET are not incorporated in our analysis because while LORETA provides high-resolution temporal EEG in comparison with fMRI, it is worse in 3D, especially in subcortical brain spatial resolution. Recently published studies combining both techniques.11 In addition, PET implies some advantages in eliminating artifacts due to the mobility of participants during data recording and facilitates the study of brain biochemistry with several isotopes. But, it also provides both less spatial resolution and statistical significance results comparatively to fMRI.12,13 Given these arguments it was decided to include studies with a similar level of comparison. However, studies tested with these different techniques showed similar functional results to fMRI in specific phobias.14-16 As regards methodologies, we only considered descriptive studies with a control/healthy group and a group of individuals with animal phobia because results suggest that there are partially different neurobiological substrates between animal and blood-injection-injury phobic subtypes.17,18

Methods

This study was performed according to the PRISMA statement on the information that should be included in a systematic review.19

Identification and selection of studies

We identified eligible studies by searching the Medline, PsycINFO, Academic Search Complete, PubMed, PsycARTICLES, Redalyc, Scopus, and Cochrane databases. We included studies published from inception of the database until September 2015 using combinations of database-specific index and free-text terms to identify studies of subjects diagnosed with specific phobia who were scanned using functional magnetic resonance imaging. ‘Specific phobia,’ OR ‘simple phobia,’ OR ‘phobia’ AND ‘imaging,’ OR ‘neuroimaging,’ OR ‘functional magnetic resonance,’ or ‘fMRI’ were used as syntax. No search period was specified, as this is a recent area of clinical psychology.

Inclusion criteria

The scientific papers included in this review were studies dealing with functional magnetic resonance imaging in specific phobia that were published in peer-reviewed journals. To be eligible for inclusion, studies had to include at least two groups: one in which participants had been diagnosed with specific phobia to small animals according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V)2 or the International Statistical Classification and Related Health Problems of Diseases (ICD-10),20 and a control group.

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 specific phobia and who had undergone fMRI scanning.

Exclusion criteria

We excluded studies about participants with blood-injection-injury specific phobia and functional magnetic

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