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UPDATE ARTICLE

The impacts of cognitive-behavioral therapy on the treatment of phobic disorders measured by functional neuroimaging techniques: a systematic review

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Objective: Functional neuroimaging techniques represent fundamental tools in the context of translational research integrating neurobiology, psychopathology, neuropsychology, and therapeutics. In addition, cognitive-behavioral therapy (CBT) has proven its efficacy in the treatment of anxiety disorders and may be useful in phobias. The literature has shown that feelings and behaviors are mediated by specific brain circuits, and changes in patterns of interaction should be associated with cerebral alterations. Based on these concepts, a systematic review was conducted aiming to evaluate the impact of CBT on phobic disorders measured by functional neuroimaging techniques.
Methods: A systematic review of the literature was conducted including studies published between January 1980 and April 2012. Studies written in English, Spanish or Portuguese evaluating changes in the pattern of functional neuroimaging before and after CBT in patients with phobic disorders were included.
Results: The initial search strategy retrieved 45 studies. Six of these studies met all inclusion criteria. Significant deactivations in the amygdala, insula, thalamus and hippocampus, as well as activation of the medial orbitofrontal cortex, were observed after CBT in phobic patients when compared with controls.
Conclusion: In spite of their technical limitations, neuroimaging techniques provide neurobiological support for the efficacy of CBT in the treatment of phobic disorders. Further studies are needed to confirm this conclusion.

Keywords: Phobia; cognitive therapy; functional magnetic resonance imaging; positron-emission tomography

Introduction

Functional neuroimaging techniques, such as magnetic resonance imaging (fMRI), single-photon emission-computed tomography (SPECT), spectroscopy, diffusion tensor imaging (DTI), and positron-emission tomography (PET), represent fundamental tools for translational research. These techniques allow the integration of neurobiology, psychopathology, neuropsychology, and therapeutics, contributing significantly to the understanding of the neurobiology of emotional regulation in healthy individuals and the neurocircuitry involved in the pathophysiology of mental disorders.[1] Phobic disorders are characterized by marked and persistent fear prompted by a specific object or situation, and accompanied by the compelling effort to avoid such object or situation.[2] Social phobia, or social anxiety disorder (SAD), has a lifetime prevalence rate of over 10% and is characterized by a relevant fear of social or performance situations involving possible scrutiny by others.[3,4] Specific phobias (SP) are also frequent, with a lifetime prevalence of 7-11%, and are marked by excessive and unreasonable fear of specific objects or situations such as animals (e.g., spiders, snakes, dogs, and mice), flying, driving, enclosed places, heights, and blood/injury. Fear and avoidance cause significant distress and/or impairment in occupational, academic, or social functioning.[4,5] SP and SAD appear to alter different neural circuits,[6] and data from neuroimaging studies and clinical trials suggest that

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pharmacotherapy and cognitive-behavioral therapy (CBT) have positive effects on SAD. In SP, CBT may be one of the few useful interventions.[7,8] A combination of Beck's theoretical model and behavioral techniques, such as exposition and systematic desensitization, synthetizes CBT used in phobic disorders.[1]

Studies involving fMRI in SP patients have demonstrated increased activation of the amygdala, anterior cingulate cortex (ACC), insular cortex, thalamus, and visual areas in patients exposed to or anticipating the presentation of phobic stimulation.[9-11] Such regions are the same as those involved in the pathophysiology of SAD observed in other functional neuroimaging studies.[9] Moreover, a meta-analysis observed hyperactivation of the amygdala and insula in patients with SAD and SPs.[10] Considering the correspondence between changes in brain and behavior, we aimed to systematically review the literature regarding clinical trials using functional neuroimaging techniques to assess the response to CBT in phobic disorders.

Methods

Three investigators (AGA, AB, CT) independently searched the databases of PubMed and ISI Web of Knowledge. Their search included clinical trials evaluating the changes in the pattern of functional neuroimaging methods before and after CBT for phobic disorders, published from January 1980 to April 2012. The keywords used in the search were functional magnetic resonance imaging or positron-emission tomography or single-photon emission-computed tomography or spectroscopy or diffusion tensor imaging and phobic disorders or phobia and cognitive therapy or behavior therapy. An initial searching protocol was prepared considering the following inclusion criteria: 1) studies written in English, Spanish or Portuguese; 2) clinical trials using any cognitive-behavioral technique for phobias; 3) diagnosis of phobia in patients over 18 years of age, and exclusion of any other psychiatric diagnosis based on a structured clinical diagnostic interview or according to the DSM-IV criteria[4]; 4) a functional neuroimaging method used before and after the psychotherapeutic intervention, with a symptom provocation paradigm; 5) presence of a control group.

Results

The initial search strategy yielded 45 studies. Forty-one of them (91.1%) were published in English, Spanish or Portuguese, which were screened for relevance related to the topic. Thirty-five studies (85.4%) were excluded for the following reasons: 21 were review studies; four consisted of reports on meeting presentations; five focused on other disorders (two on generalized anxiety disorder, one on panic disorder, one on posttraumatic stress disorder, and one on irritable bowel syndrome); finally, five studies did not perform CBT as an intervention. The systematic literature review search process and final results are shown in Figure 1. Six studies met all inclusion criteria. All of those studies were prospective and had a control group of non-phobic patients. Phobic patients were allocated in two groups: those submitted to CBT and a waiting list group. Patients and controls were submitted to a functional neuroimaging method before treatment, and all phobic patients (including those in the waiting lists) were submitted to a functional neuroimaging method after CBT. Comparisons were made between phobic patients and controls before treatment, and between patients who were submitted to CBT vs. waiting list patients. Blindness of imaging analysis was not declared in none of the studies. Overall, phobic patients presented higher activations of the amygdala, insula, thalamus and hippocampus, as well as lower activation of the medial orbitofrontal cortex (OFC) compared with a healthy control group. In addition, significant deactivations of the amygdala, insula, thalamus and hippocampus, as well as activation of the medial OFC, were observed in phobic patients after CBT when compared with controls (waiting list group). Those changes in brain activity were correlated with improvements of phobic symptoms. Table 1 summarizes the main characteristics and results of these studies included in the review.

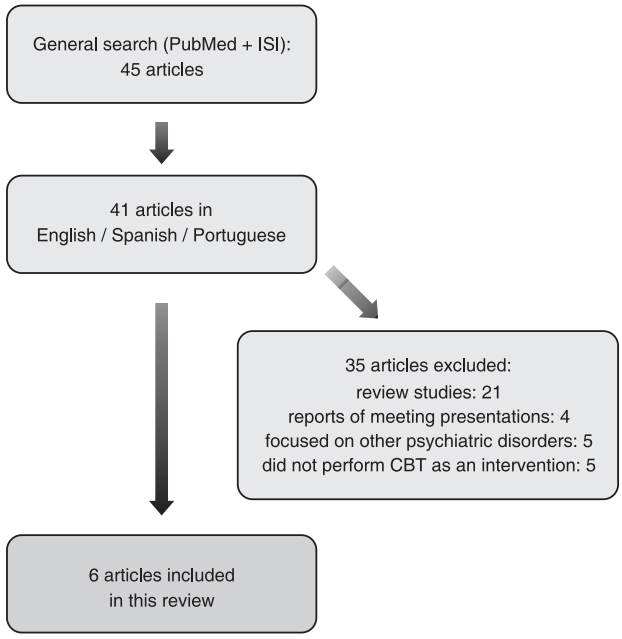


Figure 1 Systematic literature review search process and final results

Discussion

Previous studies have suggested that the mental functions and processes involved in CBT exert a significant influence on brain functioning and plasticity. Furthermore, functional neuroimaging studies have contributed to the understanding of the pathophysiological mechanisms underlying phobic disorders, thus providing an objective parameter to evaluate the impact of psychotherapeutic approaches and other non-pharmacological interven-

Table 1 Main characteristics and results of the studies included in the review

Study	Disorder	Subjects, n (M/F)	Subjects' age, mean ± SD (years)	Controls, n (M/F)	Controls' age, mean ± SD (years)	Therapy type, interval	Scales	Response to psychotherapy	Functional neuroimaging method	Paradigm	Posttreatment $p < 0.05$
Furmark et al., 2002[12]	Social phobia	6 (3/3)	35.2±7.3	SoP patients given citalopram: 6 (3/3); WL: 6 (4/2)	Not available	Group CBT, eight weekly 3-hour sessions, for 9 weeks	STAI-S1, SPS18, SIAS18, PRCS19, SPSQ10, GAF20	66%	Oxygen 15-labeled water PET	Public speaking task	↓ amygdala, hippocampus, and anterior and medial temporal cortices
Paquette et al., 2003[13]	Spider phobia	12 (0/12)	24.8±4.5	H: 13 (0/13)	28.6±7.8	Group CBT, four 3-hour sessions, for 4 weeks	AAS	100%	fMRI	Neutral images and images of living spiders	↓ R parahippocampal gyrus and R DLPFC, L inferior occipital gyrus, L fusiform gyrus and R inferior frontal gyrus
Straube et al., 2006[9]	Spider phobia	14 (0/14)	21.92±2.02	WL: 14 (0/14); H: 14 (0/14)	WL: 21.33±2.46 H: 22.07±1.98	Group CBT, two 4-5-hour sessions, in 2 days	SPQ	100%	fMRI	Video clips with a moving spider and neutral image	↓ L insula, L thalamus and ACC
Goossens et al., 2007[14]	Spider phobia	16 (0/16)	24±3.02	H: 14 (2/12)	23±1.0	Group CBT, one 4-5-hour session, in 1 day	SPQ, VAAS	100%†	fMRI	Spider, snake, and neutral stimuli	↓ L amygdala, ACC and insula
Schienle et al., 2007[15]*	Spider phobia	14 (0/14)	27.2±9.2	WL: 12 (0/12) H: 25 (0/25)	WL: 24.3±2.0 H: 24.6±6.3	Group CBT, one 4-hour session, in 1 day	SPQ	100%	fMRI	Spider, Fear, Disgust, and Neutral	↑ medial OFC
Schienle et al., 2009[16]*	Spider phobia	10 (0/10)	29.1±11.5	H: 8 (0/8)	24.0±3.7	Group CBT, one 4-hour session, in 1 day	SPQ, BAT	100%	fMRI	Spider, Fear, Disgust, and Neutral	↓ insula and the lateral OFC, medial OFC

↓ = decrease; ↑ = increase; AAS = anxiety analog scale; ACC = anterior cingulate cortex; BAT = behavioral approach test; CBT = cognitive-behavioral therapy; DLPFC = dorsolateral-prefrontal cortex; F = female; fMRI = functional magnetic resonance imaging; GAF20 = global assessment of functioning scale; H = healthy; L = left; M = male; OFC = orbitofrontal cortex; PET = positron-emission tomography; PRCS19 = personal report on confidence as a speaker; R = right; SD = standard deviation; SIAS18 = social interaction anxiety scale; SoP = social phobia; SpP = spider phobia; SPQ = spider phobia questionnaire; SPS18 = social phobia scale; SPSQ10 = social phobia screening questionnaire; STAI-S1 = Spielberger state anxiety inventory; VAAS = visual analogue anxiety scale; WL = waiting list.

* Same sample evaluated in a 6-month follow-up investigation.

† Data provided by Dr. Schruers, co-author of the article.

tions.[1,11-13,15-18] Over the past decades, CBT has demonstrated good efficacy in treating most anxiety disorders, including phobias.[7,8] Individuals with phobias exposed to phobic stimuli showed increased amygdala, ACC, and insular cortex activation in functional neuroimaging studies when compared with healthy controls.[5] Reduced amygdala and insula and increased medial OFC activations after a successful CBT treatment are in agreement with expected cognitive and emotional changes. Amygdala activity modulates vigilance, which, in turn, facilitates an increased attentional interest in environmental factors in order to acquire information to resolve the ambiguity.[14,16,19,20] As the amygdala has been related to the pathophysiology of phobias, a reduction in the symptoms of autonomic arousal could be represented by reduced amygdala activity measured by functional neuroimaging methods.[14,19,20] Moreover, the insular cortex has been shown to be generally involved in the recognition and experience of aversive states, such as disgust, fear, and pain, and it is possible that successful CBT reduces the need to decode unpleasant emotional states usually related to exposure to phobic stimuli.[14] In addition, since the medial prefrontal cortex (MPFC) is involved in processes associated with extinction of conditioned fear, an increased activity in these areas could result in remission of emotion-related neural responses.[21]

We found that all clinical trials using functional neuroimaging techniques to assess the CBT response in phobic disorders found significant deactivation of the amygdala, insula, thalamus, and hippocampus, as well as activation of the medial OFC, after CBT in phobic patients when compared with controls. As these regions have been associated with the pathophysiology of either SP or SAD, deactivations of such areas after CBT would be a possible marker of improvement.[14,19,20] Such findings, which are similar to those observed in functional neuroimaging studies of phobic patients treated with antidepressants,[22,23] could support the efficacy of CBT in the treatment of phobias.[6,12-21] Moreover, recent studies have observed that functional brain imaging may detect biomarkers that substantially improve predictions for the success of cognitive-behavioral interventions, suggesting that such biomarkers could offer personalized approaches for optimally selecting among treatment options for a patient.[24]

Finally, a number of important limitations need to be considered, such as the reduced number of studies found in the literature and their small sample size. Moreover, differences across the studies precluded a direct comparison between them. Such heterogeneities were related to the phobic disorders examined, neuroimaging techniques used, data analysis methods, number of subjects, nature of volunteer controls, condition of data acquisition (resting state, activation task), and timing of the second imaging study during treatment. Although anxiety disorders are more prevalent in women, the studies had a gender limitation because all simple phobia patients were women, thus preventing generalization of results. In addition, the studies included in the present review did not allow determining whether the brain changes measured after psychotherapy were the cause or the effect of symptom reduction.

Nevertheless, despite such technical limitations, current literature data provide a possible neurobiological support for the efficacy of CBT in phobic disorders measured by functional neuroimaging studies.[12-21] Further complementary and longitudinal studies with larger and homogeneous samples, comparing different functional neuroimaging techniques in the same sample, are needed to better understand the underlying pathogenesis of phobic disorders and the efficacy of CBT in this context.[6]

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Disclosure

The authors report no conflicts of interest.

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