

## Does Cognitive Behavioral Therapy Change the Brain? A Systematic Review of Neuroimaging in Anxiety Disorders

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*This systematic review aims to investigate neurobiological changes related to cognitive-behavioral therapy (CBT) in anxiety disorders detected through neuroimaging techniques and to identify predictors of response to treatment. Cognitive-behavioral therapy modified the neural circuits involved in the regulation of negative emotions and fear extinction in judged treatment responders. The only study on predictors of response to treatment was regarding obsessive-compulsive disorder and showed higher pretreatment regional metabolic activity in the left orbitofrontal cortex associated with a better response to behavioral therapy. Despite methodological limitations, neuroimaging studies revealed that CBT was able to change dysfunctions of the nervous system.*

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Neuroscience has developed several methods to analyze the cognitive function and potentiate the understanding of the mental functioning of healthy and mentally disordered individuals. The recent advances in neuroimaging techniques have helped to increase the understanding of the neuronal correlates of mental disorders.

Psychological interventions can promote changes in the thoughts, feelings, and behaviors of patients. Can we then say that the psychological treatment promotes brain changes? Unfortunately, the biological mechanisms related to psychotherapy are little known. On the other hand, the arrival of neuroimaging techniques make it possible to investigate the neurobiological consequences of psychological treatment. Such investiga-

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tion is highly important, as a better understanding of the brain mechanisms underlying therapy can promote improvements in the therapeutic interventions as well as increase our knowledge on the formation and maintenance of symptoms.<sup>1,2</sup> Elucidating the neural correlates associated with symptom reductions has been the subject of research aimed at the identification of the biological mechanisms of psychotherapy.<sup>1-5</sup>

Raedt<sup>6</sup> points out in his work that behavioral therapy offers an interesting perspective for integration with the neuroscience field, since any intervention is connected to a support of experimental and empirical research. Cognitive behavioral therapy (CBT) proposes to treat various mental disorders. The literature has reported that CBT has treatment models with high efficacy rates.<sup>7,8</sup>

One of the basic assumptions of CBT is that feelings and behaviors are largely influenced by the way the situations are interpreted. It is believed that individuals respond to the cognitive representations of the events, instead of responding to the events themselves. Consequently, they can process information in a way that does not match their reality, characterizing the cognitive distortions. Thus, the ways in which the facts are construed play an important role in the formation and maintenance of psychiatric disorders.<sup>7</sup>

This systematic review aimed to investigate CBT-related neurobiological changes in anxiety disorders, detected through neuroimaging techniques, and to identify predictors of response to treatment. By gathering results of studies on the new findings in the area, we can eventually contribute with knowledge for the increase of therapy efficacy, either through the improvement of new therapeutic strategies or through the potentialization with drugs that facilitate the basic mechanisms of action. The understanding of the underlying neurobiological mechanism can eventually aid in the choice of the most indicated treatment for a particular patient.

## METHODS

An electronic search was carried out on January 26, 2007, in the following databases: PubMed, PsychInfo, and Web of Science. The search strategies used are available upon request. Searches were also performed from the references of the systematic review articles on neurobiological changes and psychotherapy.

We included studies that evaluated neurobiological changes due to CBT through neuroimaging techniques and studies that involved adult patients with anxiety disorders. We excluded studies that used concomitant treatment besides CBT in the same sample of patients. Moreover, articles that dealt with subclinical anxiety were excluded. The outcome measures studied were the neurobiological changes resulting from CBT, assessed through neuroimaging techniques. Thirteen studies were found: five on patients with obsessive-compulsive disorder (OCD), three on posttraumatic stress disorder (PTSD), two on specific phobia, two on panic disorder, and one on social phobia. No studies were found for generalized anxiety disorder. Three studies were excluded because the patients were treated concomitantly with psychotherapy and medication (one from the OCD group and two from the posttraumatic stress disorder group). Thus, 10 articles met the selection criteria of this systematic review.

## RESULTS AND DISCUSSION

### Changes Related To CBT in Anxiety Disorders

Nine of the 10 studies identified provided data as to the first objective of this work—studies assessing the neurobiological changes of CBT detected through neuroimaging techniques (Table 1).

*Studies with Spider Phobia* Cognitive behavioral therapy has been shown to be effective to reduce symptoms of specific phobia.<sup>9</sup> The neuroimaging studies in CBT were conducted by Paquette *et al.*<sup>10</sup> and Straube *et al.*<sup>11</sup> Both studies used the paradigm of symptom provocation and functional magnetic resonance (fMRI).

In their 2003 study, Paquette *et al.*<sup>10</sup> evaluated the subjects with fMRI before and after CBT treatment. The participants of the study comprised of 12 women with spider phobia and a comparison group of 13 women without history of neurological or psychiatric disease and absence of anxiety response to spider exposure. The treatment with CBT consisted of the gradual exposure to spiders and cognitive restructuring. All subjects responded successfully to the therapy.

The neuroimaging findings showed that before the treatment, phobic patients presented significantly activated dorsolateral prefrontal cortex and parahippocampal gyrus. The findings after CBT treatment showed that there was no significant activation of these struc-

tures in the phobic subjects. The absence of activation of the dorsolateral prefrontal cortex and parahippocampal gyrus after CBT demonstrated for the authors strong support to the hypothesis that CBT reduces phobic avoidance through the extinction of the contextual fear learned in the hippocampal/parahippocampal region and reduces the dysfunctional and catastrophic thoughts in the prefrontal cortex. Therefore, the process of extinction would be able to prevent reactivation of traumatic memories, allowing the phobic subject to modify his or her perception of stimuli which evoked fear before the treatment. With the modification of stimulus perception, it ceases to be a threat, and this cognitive restructuring could inhibit the activation of brain regions previously associated with a phobic reaction.<sup>10</sup>

Straube et al.<sup>11</sup> performed another study of symptom provocation using fMRI. They also investigated the neurobiological effect of a successful therapeutic intervention with CBT. The study included healthy as well

as phobic individuals on a waiting list. The phobic subjects were scanned before and after CBT treatment.

Twenty-eight women with spider phobia and 14 healthy women took part in the study. The subjects with spider phobia were randomly assigned to the therapy group and comparison group on a waiting list. The groups did not differ in phobia severity, age, or educational level. The CBT treatment consisted of gradual exposure to spiders and cognitive restructuring. All of the subjects in the therapy group responded successfully to the treatment.

The neuroimaging findings before the treatment showed that only the phobic subjects displayed activation of the insula and anterior cingulate cortex, while the activation of the amygdala was restricted to the healthy control subjects. No activation of other areas was found among the phobic groups.

The neuroimaging findings after the treatment showed significant differences between the waiting list

TABLE 1. Neurobiological Changes Associated with CBT

| Study                  | Mental Disorder | Neuroimaging Technique | Neuroimaging Findings  |
|------------------------|-----------------|------------------------|--|
| Paquette et al. (2003) | Spider phobia   | fMRI                   | After CBT there was significant activation of the dorsolateral prefrontal cortex and parahippocampal gyrus regions.  |
| Straube et al. (2006)  | Spider phobia   | fMRI                   | After treatment the CBT group displayed absence of activation of the anterior ventral insula and failed to show any difference from the healthy control subjects.  |
| Furmark et al. (2002)  | Social phobia   | PET                    | After treatment with CBT and citalopram, there was reduction of activities at the temporal lobe regions, mainly at the right hemisphere. Decreased activity at the right amygdala, hippocampus, rhinal activity, and periamygdaloid.   |
| Farrow et al. (2005)   | PTSD            | fMRI                   | In the social cognition of empathy there was significant activation of the left posterior and anterior medial temporal gyrus and posterior cingulate gyrus. As for the forgiveness-related cognition, there was activation of the posterior cingulate, medial frontal gyrus, posterior cingulate activation, medial frontal gyrus, and left posterior medial temporal gyrus. |
| Baxter et al. (1992)   | OCD             | PET                    | After treatment the CBT and medication groups showed decreased activation of the head of the right caudate nucleus.  |
| Schwartz et al. (1996) | OCD             | PET                    | After treatment the patients presented significant decrease of activation of the right caudate nucleus. When the subjects of this study were combined with those of the previous study (Baxter et al., 1992), they showed as well reduced activation of the left caudate nucleus.  |
| Brody et al. (1998)    | OCD             | PET                    | The higher metabolism of the left frontal orbital cortex before treatment was associated with a better response to BT  |
| Nakao et al. (2005)    | OCD             | fMRI                   | After treatment there was a decrease in the activation of the frontal orbital cortex.  |
| Prasko et al. (2004)   | Panic           | PET                    | The increase of activity in the left hemisphere was mainly in the prefrontal, temporoparietal and occipital regions. In the right hemisphere, in the posterior cingulate. The decrease was predominant at the left hemisphere in the frontal region, and at the right hemisphere in the frontal, temporal, and parietal region.  |
| Sakai et al. (2006)    | Panic           | PET                    | After treatment there was decrease in the metabolism at the right hippocampus, left ventral anterior cingulate cortex, uvula, and pyramid of the left cerebellum and pons. The increased metabolism was found in the bilateral medial prefrontal region.   |

fMRI=functional magnetic resonance imaging; PET=positron emission tomography; CBT=cognitive behavior therapy; PTSD=posttraumatic stress disorder; OCD=obsessive-compulsive disorder

group and the therapy group. The therapy group showed absence of activation during symptom elicitation in the anterior cingulate cortex and only a small area of activation of the anterior ventral insula, while the waiting group displayed marked responses bilaterally in the insula and anterior cingulate cortex. The therapy group did not show any significant difference from the healthy comparison subjects, while the waiting list patients showed more activation of the right insula and anterior cingulate cortex.

Straube *et al.*<sup>11</sup> showed that the processing of phobic threat is associated with increased activation of the insula and anterior cingulate cortex in subjects with specific phobia. It is important to highlight that successful CBT led to reduction of hyperactivity in these regions. Consequently, the subjects in the therapy group, as compared to those of the waiting list, showed attenuation of phobic symptoms and reduction of the activity of the insula and anterior cingulate cortex during the second neuroimaging scan.

The neuroanatomic functioning associated with the symptoms of spider phobia is not clear. While Paquette *et al.*<sup>10</sup> pointed to the participation of the dorsolateral prefrontal cortex and parahippocampal gyrus in the processing of phobic fear, Straube *et al.*<sup>11</sup> do not support this hypothesis. This discrepancy between the findings merits further investigation. Both studies did not find evidence of the involvement of the amygdala in the processing of fear stimulus of the subjects with phobia, but in the research by Straube *et al.*<sup>11</sup> the healthy comparison subjects presented activation of the amygdala. Although Paquette and Straube obtained distinct results for the brain areas involved before the treatment, the CBT in both studies proved to be capable of reducing the symptoms and modifying the possible dysfunctional neuronal circuits after the treatment.

*Studies with Social Phobia* The neurofunctional changes associated with the reduction of social anxiety in patients submitted to CBT treatment were investigated by Furmark *et al.*<sup>12</sup> through PET. The only existing study on social phobia used the paradigm of emotional activation. The research also had the aim of exploring whether the brain change was associated with the long-term results of the treatment.

Eighteen individuals who fulfilled the criteria for diagnosis of social phobia according to DSM-IV participated in the study. The participants were sorted according to symptom severity, age, and gender, and then

randomized for treatment with citalopram, CBT, and waiting list; each group comprised six participants. The CBT group used techniques of exposure, cognitive restructuring, and homework.

The gravity of the symptoms of social phobia was significantly reduced after 9 weeks, both in the CBT and citalopram groups, while the waiting-list group did not show any improvement. There was no statistical difference between the CBT and citalopram groups concerning treatment outcome.

The therapeutic effect on regional blood flow was assessed by contrasting the task of speaking in public before and after the treatment in each group. Thus, the improvement of social anxiety was associated with significant reduction of the response of regional blood flow bilaterally in the amygdala, hippocampus, and median and anterior temporal cortex, including the entorhinal, perirhinal, parahippocampal, and periamygdaloid areas both for the CBT and citalopram groups. There was no significant alteration in the regional blood flow in the waiting-list group. The CBT and citalopram groups differed only in the perfusion of the right thalamus, which presented a greater increase in the citalopram group.

The study showed that the degree of reduction of the limbic response with the treatment is associated with the long-term clinical outcome. The decrease in the response of the brain blood flow in the amygdala, periaqueductal gray matter, and left thalamus can indicate which patients show greater improvement in an interval of 1 year. Thus, favorable results at 1-year follow-up were associated with greater attenuation of the subcortical blood flow response while speaking in public.

In their discussion, Furmark *et al.*<sup>12</sup> reported that the amygdala and the hippocampus are structures related to the conditioning of aversive stimuli in individuals with social phobia. These structures, together with the rhinal, parahippocampal, and periamygdaloid would form an alarm system that can be activated by threatening stimuli. The reduction of the activity in the amygdala-hippocampal region and adjacent cortex can be important mechanisms through which both pharmacological and psychotherapeutic treatments could exert an anxiolytic effect.

The study concluded that the neural sites of activation for the treatment with citalopram and CBT in social anxiety converge to the amygdala, hippocampus, and adjacent cortical areas, possibly representing a common way in the successful treatment of anxiety. The attenu-

ation of the activity in the amygdalar and limbic region with the treatment was associated with a favorable long-term result and can be a prerequisite for clinical improvement.

*Studies with Posttraumatic Stress Disorder* No neuroimaging studies were found with a focus on CBT in isolation evaluating the correlation between improvement of posttraumatic stress disorder (PTSD) symptoms and the brain areas involved in this disorder. Nevertheless, Farrow et al.<sup>13</sup> investigated the effects of PTSD, unrelated to combat, on the physiology of social cognition. According to them, PTSD symptoms could affect the processing of social and emotional cognition. These changes could attenuate brain activation in the areas related to social cognition, specifically the ability to forgive and empathize, and for the authors CBT could regularize this brain activation. In a previous study, Farrow et al.<sup>14</sup> showed that the ability to forgive and empathize in healthy subjects was related to activation of the following areas: left medial prefrontal cortex, left anterior medial temporal gyrus, left inferior frontal gyrus, orbital frontal gyrus, and posterior cingulate gyrus/precuneus.

In the 2005 study,<sup>13</sup> Farrow et al. evaluated whether CBT could regularize the activation of these areas involved with the physiology of social cognition (the ability to forgive and empathy) in individuals with PTSD, as described in the 2001<sup>14</sup> report. The participants underwent fMRI before and after treatment with the paradigm of evaluation for social cognition of empathy and forgiveness. Thirteen subjects who fulfilled the criteria of the DSM-IV for PTSD participated in the trial. The patients presented significant reduction of PTSD symptoms.

The main finding was that after the treatment, the PTSD patients experienced symptom improvement accompanied by increased brain activity in areas which were previously related to social cognition.<sup>14</sup> Specifically, there was an increase in the activation of the left medial temporal gyrus in response to the paradigm of empathy. The same process occurred with the posterior cingulate gyrus, which had its activation increased in response to the condition of forgiveness after the treatment. From this study Farrow et al.<sup>13</sup> concluded that CBT can promote changes in the brain area.

*Studies with Obsessive-Compulsive Disorder* Three studies were identified evaluating the neurobiological ef-

fects of CBT in patients with OCD. Baxter et al.<sup>15</sup> and Schwartz et al.<sup>16</sup> used PET, and Nakao et al.<sup>17</sup> examined the patients through fMRI.

Baxter et al.<sup>15</sup> investigated the changes in brain metabolism resulting from the treatment with behavioral therapy and fluoxetine in OCD through FDG-PET. Eighteen OCD patients took part in the study, with each treatment group containing nine participants, and the method of allocation was based on the preference of subjects. The group of healthy control subjects was composed of four participants. All patients were scanned at rest.

In the fluoxetine group there were comorbidities with cyclothymic disorder, panic disorder, Tourette's disorder, and social phobia. In the behavioral therapy group there were comorbidities with cyclothymic disorder, panic disorder, and agoraphobia.

The behavioral therapy utilized techniques of exposure with prediction of response which was individualized for each patient. The exposures and predictions of response were facilitated by cognitive techniques. None of the patients in the therapy group took medication during the study, but six patients participated in group therapy for OCD.

The participants presented improvement of symptoms both in the fluoxetine and in the behavioral therapy group. The neuroimaging findings after treatment showed decrease of the right anterior cingulate and left thalamus in the fluoxetine group who responded to the treatment. The head of the right caudate nucleus presented a significant decrease in both treatments.

Baxter et al.<sup>15</sup> concluded that the glucose metabolism of the head of the right caudate nucleus was changed in the patients treated successfully with both behavioral therapy and fluoxetine. There was a significant correlation of activity of the orbital cortex with the caudate nucleus and the thalamus before the treatment in patients who responded. This correlation disappeared after the success of the treatment.

In a subsequent study, the same research group<sup>16</sup> investigated through PET neurobiological changes in patients with OCD before and after behavioral therapy. The aim of that study was to replicate the previous findings with an independent sample and increase the sample of subjects whose results could be combined with those treated with behavioral therapy in the first study.<sup>15</sup>

The results of the first study<sup>15</sup> corroborate the idea that the pathological activity of the cortical-striate-tha-

lamic circuit could be responsible for the brain mediation of both fixed, repetitive thoughts and the behaviors observed in OCD. Also, the effective treatment could reestablish the functioning of the head of the caudate nucleus of selecting if a particular stimulus will activate the psychopathology-related circuit.

The nine participants of the subsequent study were analyzed separately and with the nine subjects of the first study by Baxter *et al.*<sup>15</sup> The patients did not have comorbidities with other axis I pathologies, which differed from the sample from the first study;<sup>15</sup> however, the treatment with behavioral therapy was similar to the first study. Six patients responded to the treatment.

Schwartz *et al.*<sup>16</sup> replicated the previous findings of significant decrease of the activity of the right caudate nucleus in those who responded to therapy. When the patients of the subsequent study were combined with the patients of the first study, including those with good or little response to therapy, the right caudate nucleus presented a statistically significant decrease after the treatment. The information of the new patients combined with those of the old patients shows that the left caudate nucleus also displayed a significant change after treatment in those who responded to the therapy. It is important to highlight that in the first study, with a smaller sample, the left caudate nucleus did not show any significant difference between responders and nonresponders.

Schwartz *et al.*<sup>16</sup> concluded that the results of this study replicated those of the first study,<sup>15</sup> presenting a significant change in the metabolic activity of the right caudate, which was normalized after effective behavioral therapy. This change was not observed in the patients who did not respond to treatment. When the participant data from the first study were combined with the participant data from the subsequent study, it was possible to demonstrate a statistically significant pretreatment correlation between the right orbital gyrus, caudate nucleus, and the thalamus, which decreases after effective treatment. In the previous study, similar results were found with a sample treated with behavioral therapy or fluoxetine. The finding that these effects can be demonstrated following effective treatment only with behavioral therapy (without using medication) and that the correlation between regions is not observed in healthy control subjects, suggests that the association of activity between elements of the cortical-striate-thalamic circuit may be related to expression of OCD symptoms.

Nakao *et al.*,<sup>17</sup> in order to understand the pathophys-

iology of OCD, also evaluated the regional brain changes through fMRI before and after treatment with behavioral therapy and medication, using the paradigm of symptom elicitation and cognitive tasks.

Ten patients with OCD participated in the study. Patients with comorbid axis I disorders, neurological disease, head injury, serious medical condition, history of drug or alcohol use, or IQ below 80 evaluated by the WAIS, were excluded from the study.

Ten patients were randomly assigned to receive fluvoxamine (n=4) or behavioral therapy (n=6). After treatment the clinical symptoms in both groups were significantly reduced; two patients in the medication group did not show any improvement.

Concerning the neuroimaging findings, the patients presented activation of the left orbital frontal cortex, temporal cortex, and parietal cortex during the task of symptom provocation before the treatment. After the treatment, the patients showed decrease of the activation in the orbital frontal cortex.

The study concluded that the hyperactivation of the circuits involved in the symptomatic expression of OCD, namely, orbital frontal cortex, anterior cingulate gyrus and basal ganglia, can decrease with symptom improvement. However, it is important to underscore a limitation of the study concerning the analysis of brain change. Due to the small number of participants, it was not possible to analyze separately the patterns of brain activation resulting from the intervention with behavioral therapy and with fluvoxamine.

*Studies with Panic Disorder* Two studies were performed investigating the neurobiological substrates of CBT in patients with panic disorder through PET.<sup>18,19</sup>

Prasko *et al.*<sup>18</sup> submitted resting subjects to PET scans before and after treatments with CBT and medication. All of the patients were without medication for at least 2 weeks before the first [<sup>18</sup>F]fluorodeoxyglucose (FDG)-PET procedure.

Twelve patients fulfilling the criterion for panic disorder with or without agoraphobia according to the DSM-IV participated in the study. Ten of the 12 patients suffered from agoraphobia. No other comorbidity was diagnosed. The patients were randomly distributed into the two treatment groups. The patients of both groups did not show any significant difference in symptom severity at the beginning of the study. The CBT and medication groups were composed of six individuals. The exclusion criterion included score above 15 on the

Hamilton Depression Rating Scale (HAM-D), pregnancy, having used psychotropic medication for the last 2 weeks, and suffering from serious physical disease or other psychiatric disorder other than panic and agoraphobia.

The CBT treatment consisted of psychoeducation, cognitive restructuring, training of diaphragmatic breathing and relaxation, and interoceptive and in vivo exposure. The medication group was treated with 3 months of antidepressants. All of the patients concluded the study. The participants in both groups presented significant symptom reduction following the treatment.

Prasko et al.<sup>18</sup> concluded that both treatments were effective regarding panic symptoms. The changes of brain metabolism in the cortical regions were similar for both treatments. The increased activity of the brain metabolism in the left hemisphere was mainly at the prefrontal, temporoparietal, and occipital regions and posterior cingulate. The decrease was predominantly at the left hemisphere of the frontal region, and at the right hemisphere of the frontal, temporal, and parietal region. No changes were observed in the metabolic activity of subcortical areas. The results of the study indicate that both CBT and antidepressant treatments can activate the temporal cortical processing.

Sakai et al.<sup>19</sup> also used FDG-PET to investigate the changes in the use of regional brain glucose associated with anxiety reduction after CBT treatment. The authors worked on the hypothesis that regions above the amygdala such as the medial prefrontal cortex, anterior cingulate cortex, and hippocampus could be modulated in the patients who responded to CBT. Also, the amygdala bilaterally, hippocampus, thalamus, midbrain, caudal pons, medulla, and cerebellum would present an increase in glucose uptake at the baseline condition before the treatment and would have a reduction of this activation after treatment. According to the authors, these regions would be part of the "neurocircuit of panic."

Twelve patients who fulfilled the criteria for panic disorder of the DSM-IV and who had not used fluoxetine and CBT prior to the study participated in the study. The participants had comorbidity with agoraphobia. Individuals with the following comorbidities were excluded from the study: major depression, bipolar disorder, schizophrenia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, generalized anxiety, suicide risk, substance abuse, per-

sonality disorder, and physical disease (unspecified in the study). The first PET scan was performed before the treatment with CBT and the second was performed after the treatment. The individuals remained at rest during the performance of the procedure.

CBT treatment consisted of psychoeducation, muscle relaxation training, breathing control, in vivo exposure, attention control technique, self-instruction, self-reinforcement, thought stopping, and cognitive restructuring. Eleven of the 12 patients responded to the treatment. The patient who continued to suffer panic attacks after CBT treatment was excluded from the second neuroimaging procedure.

The neuroimaging findings after CBT showed decreased metabolism in the right hippocampus, left ventral anterior cingulate cortex, left cerebellum, and pons. The increased regional brain glucose metabolism was found at the prefrontal medial region bilaterally.

The PET results following successful CBT treatment evidenced that the level of glucose uptake in the right hippocampus, medial prefrontal cortex, and left ventral cingulate cortex was modulated by the treatment. The findings are consistent with the hypothesis that regions above the amygdala can be adaptively modulated in patients who respond to CBT. Thus, Sakai et al.<sup>19</sup> concluded that improvement in panic symptoms through CBT can promote brain effects.

#### Prediction Factors of Treatment Response

Only one of the identified studies presented data concerning the second objective of this review—to identify response predictors (Table 1).

*Obsessive-Compulsive Disorder* Brody et al.<sup>20</sup> used FDG-PET to investigate if the metabolic activity of regions previously associated with OCD symptoms could predict the response to behavioral therapy. Twenty-seven patients participated in the study. All of them fulfilled criteria for OCD. All subjects were scanned at rest before the behavioral therapy or fluoxetine treatment. At the time of the procedure no subjects were taking medication. The method of allocation was based on the preference of the subjects.

The behavioral therapy group was composed of 18 participants and the medication group had nine participants. In the medication group the participants had comorbidities such as cyclothymic disorder, panic disorder, Tourette's syndrome, and social phobia. In the behavioral therapy group there was comorbidity with

cyclothymic disorder, panic disorder, and agoraphobia. In both groups the pretreatment metabolism of the left frontal orbital cortex was correlated with the percentage of decrease in the Yale-Brown Obsessions-Compulsions Scale (Y-BOCS). In the therapy group it was found that the higher metabolism at the pretreatment left frontal orbit was associated with a significant improvement in the Y-BOCS score. In the medication group, on the contrary, a lower pretreatment metabolism at the left frontal orbital cortex was associated with a significant improvement in the Y-BOCS.

The study<sup>20</sup> concluded that a higher pretreatment metabolism at the left frontal orbital cortex was associated with a better response to treatment with behavioral therapy. On the contrary, a lower metabolic activity at the left frontal orbital cortex was associated with a better response to fluoxetine treatment. The results of both groups of behavioral therapy and medication suggest that OCD patients with particular models of brain metabolism can respond preferentially to a particular type of treatment.

In their discussion, Brody *et al.*<sup>20</sup> point out that the functions ascribed to the frontal orbital cortex could explain why a higher metabolism at this region predicts a better response to behavioral therapy. Among the functions of the frontal orbital cortex they highlight which could be related to the findings of the study. First, the frontal orbital cortex is important to mediate behavioral responses in situations in which the affective value of the stimulus can change; and second, this area seems to have an important role in the mediation of extinction. In a successful treatment with behavioral therapy, the patients experience a change in the affective value that they used to ascribe to the stimulus and thus extinguish compulsions. Consequently, for Brody *et al.*,<sup>20</sup> the subjects with a higher pretreatment metabolism at the frontal orbital cortex would be more capable of changing the attribution of affective value to the stimulus and thus would be more capable of extinguishing the compulsive responses. Therefore, these abilities would allow a better response to behavioral therapy.

## CONCLUSION

This systematic review aimed to investigate CBT-related neurobiological changes in anxiety disorders, detected through neuroimaging techniques, and to iden-

tify predictors of response to treatment. Although the number of studies considered in this review is small, they demonstrate that CBT is able to modify the dysfunctional neural activity related to anxiety disorders in the patients who responded to treatment. Such result confirms previous reviews of psychotherapy and neuroimaging,<sup>1,2,4,5</sup> but the present review differs from the previous ones as it focus solely on CBT and anxiety disorders.

The studies by Straube *et al.*<sup>11</sup> and Furmark *et al.*<sup>12</sup> included in their methodology the randomization of patients for CBT and waiting-list group, thus evidencing that the neurobiological changes in the therapy group were a result of the CBT interventions rather than an effect of the passing of the time. The neuroimaging findings in studies by Paquette *et al.*,<sup>10</sup> Baxter *et al.*,<sup>15</sup> and Schwartz *et al.*<sup>16</sup> revealed that after treatment the patients presented activation similar to healthy comparison subjects.

As for the second aim of this review, the identification of treatment response predictors, Brody *et al.*<sup>20</sup> reported important results. They showed that OCD patients with particular patterns of brain metabolism can respond preferentially to a particular type of treatment. This is because the patients who responded to behavioral therapy presented a higher metabolism at the left frontal orbital cortex before the treatment. On the other hand, the lower metabolic activity at the left frontal orbital cortex was associated with better response to fluoxetine treatment. It should be highlighted that only one study was found concerning response prediction. The lack of studies about response prediction highlights the importance of future research in this area. The identification of treatment response predictors has great clinical importance, as knowledge of the pretreatment brain metabolism can eventually aid in the choice of the most indicated intervention for a given patient.

A particularly interesting aspect of the present review concerns the neuroimaging findings resulting from CBT treatment versus medication, revealing a common way of brain modification. Therefore, it suggests that psychotherapy with CBT and drug therapy may act in similar brain circuits.<sup>12,15,18</sup> Furmark *et al.*<sup>12</sup> pointed that the neural regions related to treatment with citalopram and CBT in social phobia converge to the amygdala, hippocampus, and adjacent cortical areas, and possibly mean a common way in the successful treatment of social anxiety. Baxter *et al.*<sup>15</sup> detected increased glucose metabolism in the right caudate nu-



cleus in patients with OCD. After treatment with fluoxetine and behavioral therapy, the neuroimaging studies revealed decreased activity at this region in both treatments. Finally, Prasko et al.,<sup>18</sup> studying patients with panic symptoms, concluded that treatment with CBT and with antidepressants can activate the cortical temporal processing.

The study by Farrow et al.<sup>13</sup> stands out because of its distinct methodology. It proposed to identify the brain areas involved with social cognition in PTSD patients—specifically, the ability to forgive and experience empathy—and found attenuated activation of the related areas with the referred cognitive processes. It may be speculated that numbing symptoms related to the group could impair such abilities as empathy and forgiveness, as the individuals have difficulty feeling such emotions as intimacy and tenderness and feel disconnected from themselves. The study by Farrow et al.<sup>13</sup> showed that CBT can help in the remission of PTSD symptoms as well as promote the activation of brain areas related to social cognition of empathy and forgiveness. In their meta-analysis study, Etkin and Wager<sup>21</sup> underscore that PTSD is a more complex disorder than the other anxiety disorders, specifically social and specific phobia. This is because the patients with PTSD displayed a pattern of activation and hypoactivation that differed from those of other pathologies. The results revealed more frequent hyperactivity in the insula and amygdala in patients with social and specific phobia than in PTSD patients. Also, only patients with PTSD displayed hypoactivation of the dorsal and rostral anterior cingulate cortex and medial prefrontal cortex. For the authors, PTSD may be related to a dysfunction in the system of emotional regulation in which fear by itself is only an element of this system, while social and specific phobia would be related to a stage of intense fear and therefore would present greater activity of the insula and amygdala.

It should be mentioned that the heterogeneity of the studies presented here limits the possibility of direct comparison (Table 2). In many of them, such as Baxter et al.,<sup>15</sup> Schwartz et al.,<sup>16</sup> and Brody et al.,<sup>20</sup> although the therapeutic modality was referred to as behavioral therapy, in the description of strategies there was reference to cognitive techniques, suggesting that it was CBT. The different number of sessions also made it difficult to compare them. The neuroimaging methods in the studies were also different, as four studies used fMRI and six used PET. Other considerations must be

made as for the methods of the studies. Some studies used control groups while others did not. For evaluation of neurobiological alterations, three types of experimental paradigms were used—symptom provocation, cognitive tasks performance, and testing at rest. Most importantly, all the reviewed studies are small in sample size. This limitation restricts statistical power, enhances false negative results, and therefore has limited generalizability. To elucidate differences in brain changes resulting from cognitive behavior therapy, a larger number of patients must be examined before and after treatment. Further studies in this area need to be undertaken. Nakao et al.,<sup>17</sup> for instance, carried out a study with OCD patients, where the patterns of brain activation resulting from the comparison between behavioral therapy and fluvoxamine could not be statistically analyzed separately, due to the small number of participants. However, Schwartz et al.<sup>16</sup> combined results from a previous study<sup>15</sup> and were able to replicate the original findings. Despite these acknowledged limitations, it can be concluded that CBT may indeed promote neurobiological changes.

The investigation of changes in brain activity resulting from therapy is a new area of research which has major implications for better understanding the mechanisms of formation and maintenance of symptoms. Moreover, they can help reveal the biological mechanisms associated with the improvement of symptoms due to successful CBT treatment. After an analysis of studies we could propose plans for the performance of new clinical trials which can answer questions on neurobiological changes and psychotherapy. The methodology of studies should include randomized comparison groups for waiting list and a placebo group. We would thus have more evidence that the brain changes that occurred would be due to interventions with psychotherapy.

While Etkin and Wager<sup>21</sup> in their meta-analysis of structures related to disorders of specific and social phobia and PTSD found a common route for anxiety that would be the hyperactivation of the amygdala and insula, in the present systematic review we did not find such a model of activation. Possibly, this different result is related to the small number of studies that met the criteria for our review. Consequently, the inconsistency of results indicates the need for future research. However, the studies included in our systematic review pointed out in their neuroimaging findings structures that participated both in the brain circuits involved with extinction and in those involved with cognitive regulation of emotion. The results

**TABLE 2. Methodology of Studies**

|                               | Disorders                     |                              |                             |                             |                               |                            |   |                             |                            |
|-------------------------------|-------------------------------|------------------------------|-----------------------------|-----------------------------|-------------------------------|----------------------------|---|-----------------------------|----------------------------|
|                               | Spider Phobia                 | Social Phobia                | PTSD                        | OCD                         | Panic                         |                            |   |                             |                            |
| <b>Studies</b>                | <b>Paquette et al. (2003)</b> | <b>Furmark et al. (2002)</b> | <b>Farrow et al. (2005)</b> | <b>Baxter et al. (1992)</b> | <b>Schwartz et al. (1996)</b> | <b>Brody et al. (1998)</b> | <b>Nakao et al. (2005)</b>              | <b>Prasko et al. (2004)</b> | <b>Sakai et al. (2006)</b> |
| Healthy comparison group      | 13 subjects                   | 14 subjects                  |                             | 4 subjects                  | 4 subjects                    |                            |   |                             |                            |
| Comparison waiting-list group |                               | 12 subjects                  |                             |                             |                               |                            |   |                             |                            |
| Medication group              |                               | 6 subjects                   |                             |                             |                               |                            |   |                             |                            |
| Therapy group                 | 12 subjects                   | 6 subjects                   |                             | 9 subjects                  |                               | 9 subjects                 | 4 subjects                              | 6 subjects                  |                            |
| Allocation method             | 13 subjects                   | 6 subjects                   | 13 subjects                 | 9 subjects                  | 9 subjects                    | 18 subjects                | 6 subjects                              | 6 subjects                  | 12 patients                |
| Experiment                    | Random                        | Random                       | fMRI                        | Subject preference          | PET                           | Subject preference         | Random                                  | Random                      |                            |
|                               | fMRI                          | fMRI                         | Social cognition activation | PET                         | PET                           | PET                        | fMRI                                    | PET                         | PET                        |
|                               | Symptom provocation           | Symptom provocation          |                             | Rest                        | Rest                          | Rest                       | Symptom provocation and cognitive tasks | Rest                        | Rest                       |
| Therapeutic modality          | CBT                           | CBT                          | CBT                         | BT                          | BT                            | BT                         | BT                                      | CBT                         | CBT                        |
| Number of sessions            | 4 sessions                    | 8 sessions                   | 4-10 sessions               | 8-24 sessions               | 8-24 sessions                 | 8-24 sessions              | 12 sessions                             | 20 sessions                 | 10 sessions                |

fMRI = functional magnetic resonance imaging; PET = positron emission tomography; BT = behavioral therapy; CBT = cognitive behavior therapy; PTSD = posttraumatic stress disorder; OCD = obsessive-compulsive disorder

showed that CBT especially regulated the dysfunctional neural circuits involved with the regulation of negative emotions and fear extinction.

The literature shows that many mental disorders are involved with the inability to control fear<sup>22,23</sup> and difficulty in regulating negative emotions.<sup>24,25</sup> These data suggest that the conditioning of fear and the difficulty in regulating emotions play a major role in the formation and maintenance of anxiety disorders. Mocaiber et al.<sup>24</sup> highlight the research on neural circuits of extinction which has an important clinical implication. This is because anxiety disorders are in part characterized by resistance to the extinction of emotional reactions to anxiogenic stimuli and by avoidance behaviors.

It is important to highlight that CBT treatment contains specific techniques (exposure, distraction, and cognitive restructuring) which allow both the extinction of conditioned fear and the cognitive regulation of emotions.

Cognitive behavior therapy has proved to be effective in the treatment of various mental disorders, although

the neurobiological effects of its action are little known. CBT favors the restructuring of thought, modification of feelings and behaviors, and promotes new learning. Consequently it involves synaptic changes.<sup>26</sup> This review had the aim of identifying the studies that have proposed to understand the brain alterations resulting from CBT. The investigation of changes in brain activity resulting from successful CBT treatment allows us to clarify the neural substrates underlying psychotherapy.

Neuroimaging studies provide a means to observe and characterize changes in brain functioning related to psychological and pharmacological interventions. Consequently, to understand how individuals process a stimulus can be an important piece of information for therapeutic response.<sup>4</sup>

The neuroscientific findings associated with the neuroimaging studies can enhance our knowledge of the neurobiological foundations of psychotherapies, as well as improve interventions in order to increase treatment efficacy.

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