Effects on the brain of effective psychological treatments for anxiety disorders: a systematic review

Introduction: Psychological therapies can modify thoughts, feelings, and behaviors of people with mental disorders, but the underlying brain mechanisms remain to be clarified. Advances in neuroimaging techniques can help us to understand of how different psychotherapies change the human brain. This review aims to systematically investigate the brain effects of psychological therapies for adults with anxiety disorders.

Method: Several electronic databases (Medline, PsycINFO, EMBASE and EBSCO) up to April 2010 were searched. Abstracts which appeared to fulfill the initial selection criteria (structured psychological treatment in adults with anxiety disorders with at least one neuroimaging study performed before and after the treatment) were selected and their original articles were then retrieved. References from the selected English and Spanish language publications were also hand searched.

Results: Eighteen studies met the criteria for inclusion in the review. The majority of these papers reported cognitive-behavioral therapy (CBT) in specific phobia, social phobia, obsessive-compulsive disorder (OCD), posttraumatic stress disorder or panic disorder. Psychological interventions changed neural circuits involved in the pathophysiology of anxiety disorders, especially activity in frontal-striatal circuits in OCD and prefrontal areas in arachnophobia (spider phobia). However, the results are largely inconsistent among themselves and with the neurobiological models of anxiety, in particular as regards the changes on the limbic level.

Conclusions: Despite the variety of methodological concerns, initial neuroimaging studies have shown that psychological interventions can change brain function related to anxiety disorders in the patients who respond to treatment. Neuromodulation mechanisms related to specific anxiety disorders remained to be elucidated. Future studies should delineate the process of “normalization” that occurs in the brain during a psychological treatment, helping to enrich the current neurobiological models of the origins, maintenance and treatment of anxiety disorders.

Key words: Anxiety disorders, psychological treatment, neuromodulation, neural plasticity

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Efectos en el cerebro de los tratamientos psicológicos eficaces en los trastornos de ansiedad: una revisión sistemática

Introducción: Las terapias psicológicas pueden modificar los pensamientos, emociones y conductas de las personas con trastornos mentales, pero los mecanismos cerebrales subyacentes están por esclarecer. Los avances en las técnicas de neuroimagen pueden ayudar a la comprensión de cómo las diferentes psicoterapias cambian el cerebro humano. El objetivo de esta revisión sistemática es investigar los efectos cerebrales de las terapias psicológicas en adultos con trastornos de ansiedad.

Método: Se realizó una búsqueda en varias bases de datos electrónicas (Medline, PsycINFO, EMBASE y EBSCO) hasta abril 2010. Se seleccionaron los resúmenes que parecían cumplir los criterios iniciales de inclusión (un tratamiento psicológico protocolizado en adultos con trastornos de ansiedad, al menos con un estudio de neuroimagen antes y otro después del tratamiento) y se accedió a los artículos originales. Se realizó también una búsqueda manual de las referencias de las publicaciones en inglés y español seleccionadas.

Resultados: Dieciocho estudios cumplieron los criterios de inclusión en la revisión. La mayoría de estos trabajos reportaron terapia cognitivo-conductual (TCC) en fobia específica, fobia social, trastorno obsesivo-compulsivo (TOC), trastorno de estrés postraumático o trastorno de angustia. Las intervenciones psicológicas modificaron circuitos neuronales implicados en la patofisiología de los trastornos de ansiedad, en especial la actividad frontoestriatal en el TOC y
en áreas prefrontales en la aracnofobia. Sin embargo, los resultados son en gran parte inconsistentes entre sí y con los modelos neurobiológicos de la ansiedad, en particular lo que se refiere a los cambios a nivel limbico.

Conclusions: A pesar de las diversas limitaciones metodológicas, los estudios iniciales de neuroimagen muestran que las intervenciones psicológicas pueden modificar la función cerebral asociada a los trastornos de ansiedad en aquellos pacientes que responden al tratamiento. Los mecanismos neuromoduladores vinculados con cada trastorno específico están por aclarar. Futuros estudios deberán delimitar el proceso de “normalización” que ocurre en el cerebro durante un tratamiento psicológico, contribuyendo a enriquecer los modelos neurobiológicos actuales sobre la génesis, mantenimiento y tratamiento de los trastornos de ansiedad.

Palabras clave: Trastornos de ansiedad, tratamiento psicológico, neuromodulación, plasticidad neuronal

INTRODUCTION

For some time, there has been evidence that psychological therapies can change our beliefs, thoughts, affective states and behavior patterns, however little is known about the brain mechanisms underlying these changes. The growing awareness on brain plasticity is converting the neurobiological effects of psychotherapies into a subject of great interest in the field of mental health and research on psychotherapies1. Non-invasive brain imagery methods can detect changes in the brain activation patterns associated to changes in learning or training in persons without diseases. That is why there is no reason that these should not also be done in those suffering mental disorders2. Neuroscience has developed several methods that make it possible to analyze cognitive functioning. Advances in neural imaging techniques help us to know the brain functioning and plasticity in persons with mental disorders and, by extension, to improve our understanding of the mechanisms underlying the efficacy of the treatments. This has the possibility of helping us choose, lacking other biological markers, the best treatment for each patient.

This work has aimed to make a systematic review of the precursor studies on the effects in the brain of psychological treatments for anxiety disorders. Although there are studies for other mental disorders, such as depression3-5 and schizophrenia6-8, we have preferred to restrict our review to anxiety disorders in order to maintain some homogeneity in the therapies and hypothetical structures and brain functions involved. In the same way, we have limited the search to studies referring to the adult population, whose results can reasonably not be generalized to the child population.

METHODOLOGY

Inclusion and exclusion criteria

All those studies containing original data (except for a single case studies) that fulfilled the following selection criteria were included: having conducted a structured psychological therapy on adult persons (older than 18 years) with anxiety disorders, with at least one imaging test before and another after the treatment. The patient sample should share this same principal diagnosis according to DSM/ICD criteria. Studies with concomitant pharmacological treatment were excluded. The search was reduced to articles in English and Spanish.

Search descriptor
("psychological therapy" or "cognitive behaviour therapy" or "psychotherapy" or CBT) and ("anxiety" or "panic disorder" or phobia or " obsessive compulsive disorder" or "post-traumatic stress disorder") and (PET or SPECT or fMRI or "functional imaging" or "functional magnetic resonance" or neuroimag*)

Search strategies and results

192 titles after elimination of duplicated ones

166 titles in English (164) or Spanish (2)

53 titles apparently with original data related with neuroimaging, therapy and disorders

8 pertinent articles obtained through manual search of references in reviews and key articles

15 abstracts with original data related with neuroimaging, psychological therapy and anxiety disorders in adults

18 original studies with neuroimaging, psychological therapy and anxiety disorders in adults

18 studies included. Studies with neuroimaging data before and after a protocolized psychological therapy in adults with an anxiety disorder DSM/ICD

Figure 1
Search strategy

Searches were made in MEDLINE, PsycINFO and EMBASE through Ovid simultaneously, EBSCO and finally, the search was repeated in Medline via Pubmed that collected the most recent articles still being indexed. The search began at the onset of each one of the databases up to April 2010. Manual searches were also made of references in relevant articles and reviews. The descriptors for the search were “psychological therapy” or “cognitive behaviour therapy” or “psychotherapy” or CBT and “anxiety” or “panic disorder” or phobia or “obsessive compulsive disorder” or “post-traumatic stress disorder” and PET or SPECT or fMRI or “functional imaging” or “functional magnetic resonance” or neuroimag*.

RESULTS

Specific phobia

Five studies9–13 have investigated the neurobiological effect of psychotherapy in spider phobia. Four studies approach the effects immediately following the treatment and one study gives more attention to the long term neuromodulation12. The therapy is short in all the cases, and even can be only one session (see table 1).

The first two studies obtained very different results on the primarily involved brain areas, both for the active disorder as well as the successful treatment. Paquette et al.9 stress the participation of the dorsolateral prefrontal cortex and the parahippocampal gyrus, whose activation decreases after cognitive behavioral therapy, being similar to that of the control subjects (that is, it normalizes). Straube et al.10 indicated the hyperactivation in the insula and anterior cingulate cortex (ACC) before the therapy and the reduction of activation at its end, this being more important in the ACC, this also suggesting normalization. None detected significant activation in the amygdala in the group of patients, which is a counter-intuitive result considering the neurobiological models.

Schienle et al.11 were the first to report greater activation in the amygdala (also in the fusiform gyrus) of the patients before the therapy, compared with the control, and decreased activation in the medial orbitofrontal cortex (OFC). They did not find any direct effect of the therapy on amygdalar activation. However there was an indirect effect since the complementary analyses revealed that the clinical improvement was significantly correlated with the reduction of the activation in the insula and amygdala. The principal effect of the CBT, consisting in a single group session of 4 hours, was that of increasing (normalizing) the activity of the OFC. Furthermore, the neuromodulator effect of this single session on the OFC seems to remain stable over time, since it was maintained at 6 months in the small subsample that participated in the follow-up, that remained free of clinical symptoms12.

Along this same line, Johanson et al.13 pointed out the role of the prefrontal cortex due to its capacity to self

Table 1

| Neuromodulation in spider phobia and social phobia after psychological therapies |
|---------------------------------|-----|-----|-----|-----|-----|
| Spider phobia                   | Social phobia |
| Schienle et al (2007)           |                      |
| Schienle et al (2009)           |                      |
| "Healthy" control group (n)     | 13  | 14  | 25  | 8  |
| Waiting list group (n)          | 12  | 12  | 14  | 10 |
| Medication group (n)            | 12  | 6   | 6   | 14 |
| Therapy group                   | R   | R   | R   |
| Allotment method                | fMRI| fMRI|
| Technique                       | SP  | SP  | SP  | SP  |
| Procedure                       | CBT-G| CBT-G| CBT-G| CBT-G|
| Therapy modality                | PET | PET | PET | PET |
| Number of sessions              | 4   | 2   | 1   | 6   |
| Components of intervention      | L and R| L and R| L and R| L and R|
| Neuromodulation                 | Yes | Yes | Yes | Yes |
|                                 | R: randomized; fMRI: functional magnetic resonance; PET: Positron emission tomography; SP: symptom provocation; CT: cognitive tests; CBT-G: Cognitive-behavioral therapy- group; CgT: Cognitive therapy; L = listed; NL = not adequately listed; R: referenced.
regulate emotions. While waiting for the replication because of the small sample size and methodological limitations, they suggest that successful cognitive therapy may have inverse neuromodulator effects (increasing or decreasing activity in this brain zone, fundamentally in the right hemisphere), depending on the capacity of baseline emotional self-regulation of the patient.

In summary, the therapy was capable of reducing the psychopathological symptoms and parallely of modifying the neuronal activity in all of the studies reviewed. It seems to produce normalization after the therapy, however the brain images associated to spider phobia and their improvement only partially coincide from one study to another, which indicates that the neurofunctioning linked to this specific phobia, and to its successful treatment, are not clear and requires future research. The medial orbitofrontal cortex stands out as a target structure that could be crucial in inverse learning tasks during therapy, as a surprising piece of information, the difficulty to detect activation in the amygdala of the patients should be indicated, on the contrary to that which occurs in the control subjects and against that which would be expected from their theoretical models.

### Social phobia

Two studies\(^{14, 15}\) have investigated the effects on the brain of psychological treatment for social phobia, the first from the cognitive-behavioral orientation and the second, more recent one, using mindfulness (table 1).

Furmark et al.,\(^ {14}\) studied the neurofunctional changes in patients diagnosed of social phobia without comorbidity after treatment with CBT. Although the sample was small, the study has the advantage of being able to compare the effect of both randomized treatments (CBT vs. citalopram) in addition to patients on the waiting list. Its results indicate that relatively short group therapy was as effective as citalopram to significantly reduce the severity of the symptoms. Psychological intervention had a significant effect on the cerebral blood flow (decrease of amygdalar-hippocampal activation and adjacent regions, predominantly in the right hemisphere). This therapy may also provide an action mechanism common to that of citalopram, given that the changes in activation were practically identical in both treatments. From the prognostic point of view, the activation reduction level in the amygdala and other subcortical structures correctly predicted the grade of clinical improvement at one-year of follow-up.

Goldin et al.,\(^ {15}\) used a mindfulness-based stress reduction (MBSR) and indicated that this type of intervention may have some effectiveness in social phobia. Specifically, they studied its utility to improve self-referential processing and self-view, that is distorted in these patients, according to the cognitive models of the disorder. The intervention was accompanied by neurofunctional changes (for example, decreases in the activity of the dorsomedial and medial

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**Table 2** Neuromodulation in OCD after psychological therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Healthy control (n)</th>
<th>Waiting list (n)</th>
<th>Medication (n)</th>
<th>Therapy (n)</th>
<th>Allotment method</th>
<th>Technique</th>
<th>Procedure</th>
<th>Therapy modality</th>
<th>Number of sessions</th>
<th>Components of intervention</th>
<th>Neuromodulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter et al (1992)</td>
<td>4</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>P</td>
<td>PET</td>
<td>Rest</td>
<td>CT and CBT-G</td>
<td>8-24</td>
<td>NL</td>
<td>Yes</td>
</tr>
<tr>
<td>Schwartz et al (1996)</td>
<td>13</td>
<td>4</td>
<td>9</td>
<td>9</td>
<td>P</td>
<td>PET</td>
<td>Rest</td>
<td>CT and CBT-G</td>
<td>8-24</td>
<td>NL</td>
<td>Yes</td>
</tr>
<tr>
<td>Nakao et al (2005)</td>
<td>19</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>A</td>
<td>fMRI</td>
<td>CT</td>
<td>CT</td>
<td>12</td>
<td>NL and NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Nabeyama et al (2008)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>A</td>
<td>fMRI</td>
<td>CT</td>
<td>CT</td>
<td>16 (of exposure)</td>
<td>L and R</td>
<td>Yes</td>
</tr>
<tr>
<td>Fryer et al (2010)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>A</td>
<td>fMRI</td>
<td>CT</td>
<td>CBT</td>
<td></td>
<td>L and R</td>
<td>Yes</td>
</tr>
</tbody>
</table>

OCT: Obsessive-compulsive disorder; R: randomized; P: preference of the patient; fMRI: functional magnetic resonance; PET: positron emission tomography; SP: symptom provocation; CT: cognitive tests; CBT: Cognitive-behavioral therapy; CBT-G: Cognitive-behavioral therapy-group; BT: Behavioral therapy; L = listed; NL = not adequately listed; R: referenced; NR: not referenced.
regions of the prefrontal cortex as well as in the left inferior frontal gyrus). As a whole, the authors interpreted these changes as an increase in the activity of the brain network involved in attention regulation and a reduction in that linked with the conceptual-linguistic self view. Because this was an uncontrolled pioneer study that used a cognitive test having doubtful ecological validity (the patient had to decide whether an adjective described him/her or not, but the adjectives used were selected from a database, not generated in a personalized way for each patient), its conclusions are seriously limited.

**Obsessive-compulsive disorder**

The works conducted in the USA used the PET to evaluate brain activity\(^{16,17}\), while those of the Japanese and German groups use the fMRI\(^{18-20}\) (table 2).

The first study\(^{16}\), of Baxter et al. in 1992, used the PET to investigate the changes in brain metabolism measured by resting state of patients whose principal diagnoses was OCD, before and after receiving behavior therapy (BT), comparing them with two other groups: healthy control and patients receiving treatment with fluoxetine. The BT consisted in exposure with prevention of individualized response for each case. Six patients also went to a CBT group for patients with OCT.

Seven patients from the fluoxetine group and six from the group that received BT successfully responded to their respective treatments. The “responder” patients significantly decreased the activation in the right caudate compared to the “nonresponders.”

This result is consistent with the idea that the caudate nucleus is involved in the expression of the symptoms in the OCD but, as the authors warn, this is not equivalent to stating that the caudate dysfunction is the “cause” of the OCD, given that all of the neural circuits involved must be taken into account. On the other hand, they also cannot find a totally satisfactory explanation why significant changes were not observed in the left caudate, contrary to that expected. After, this research group published a new work (17) that focused exclusively on psychological treatment. They used the same previous methodology with an independent sample. The combined analysis of the data of both studies collaborated the findings of the first work, extending the neuromodulation also to the left caudate.

The Nakao et al. study\(^{18}\) is innovative because it was the first to investigate the neuropsychological aspects together with the neurobiological and clinical-symptomatic ones. They used a symptom provocation paradigm, on the contrary to the previous works in which the patients were at “cognitive rest.” The obsessive-compulsive symptoms provocation stimuli during the fMRI consisted in having the patients autogenerate words related with pathological doubt, contamination, symmetry, violence, etc., that had been previously identified individually for each one. The neuropsychological function was evaluated with a classic Stroop paradigm.

Ten patients were randomly assigned to two treatments: BT \((n = 6)\) or fluvoxamine \((n = 4)\) for 12 weeks. The pre-post comparison indicated a significant clinical improvement in all except for two (both under treatment with fluvoxamine). This improvement seemed to be associated to a change in the brain activity pattern, observing a decrease in the orbitofrontal hyperactivation (under the condition of symptom provoking words) and an increase in activity in the anterior and posterior brain areas (specifically in the bilateral prefrontal cortex, bilateral and parietal anterior cingulate, and the cerebellum, during the Stroop task). Interestingly, and contrary to that expected, no activation of the caudate nucleus during the symptoms provocation task was identified. One limitation that stands out in this sense is the doubtful ecological validity of using self-generated words as an OCD symptoms provocation task (they hardly seem to generate anxiety during the fMRI as manifested by the patients) and a limited sample that does not make it possible to analyze each treatment separately. Finally, performance and brain activation of OCD patients during the execution of the Stroop task, before receiving treatment, does not seem to be different from that shown in the general population.

Using the previous work as the basis and a similar paradigm, Nabeyama et al.\(^{19}\) went back to the combined study all of clinical improvement and neuropsychological performance with the Stroop test. The sample was made up of patients and voluntary healthy subjects, matched by age and gender. All the patients significantly improved after the therapy. This improvement was accompanied by changes in brain activation. Specifically, they observed a significant reduction in the activation in different zones of both hemispheres (orbitofrontal cortex, left medial frontal gyrus, left fusiform gyrus, bilateral parahippocampal gyrus, left parietal lobe), and an increase in the activity in other regions (such as the right parietal and bilateral cerebellum). The authors suggest that the activation in the cerebellum and other zones may change with behavior therapy, which could be accompanied by neuropsychological improvement. A startling piece of information in this sense is that there were hardly any differences before the therapy between controls and patients in their performance on the Stroop test, nor was the possible effect of the practice or getting used to the task controlled.

Recently Freyer et al.\(^{20}\) compared the cognitive performance of controls and patients using the reversal learning paradigm (with a task that implies cognitive
planning and flexibility, in some aspect similar to the Wisconsin Test but with greater complexity and time pressure). The patients were hospitalized and the CBT was conducted completely during the admission (they had symptoms of severe OCD, although the diagnostic criteria used are not clearly explained). The results of this preliminary study indicate that CBT produces a neuromodulation in the frontostratial circuit, but in the opposite direction to that of the two previous studies carried out “at rest,” since the activation of the caudate increased while the patients performed the cognitive test after the therapy.

In definitive, our review of the studies on OCD and neurofunctioning shows the utility of psychological therapy to improve the clinical symptoms and to produce changes in the brain. The activation changes indicated seem at least partially consistent with the dysfunctionality (vs. hyperactivity) theory in the fronto-subcortical circuits (that connect the orbitofrontal cortex, caudate and thalamus, among others) as mediator of the OCD symptoms. However, the scarce coincidence regarding the specific brain areas primarily involved in the disorder and their disorders stands out. This not only indicates the complexity of the clinical picture but also the need to homogenize the procedures for their study. On the other hand, the neuropsychological performance of the patients and its comparison with that of the controls requires further investigation, as well as the differences between dysfunctional brain activation “at rest” vs. during the execution of tasks. Finally, almost all the studies have reported that they used BT, but it is not always clear what an “exclusively” behavioral psychological therapy is because of the inexact limits used to define cognitive behavioral therapy.

### Post-traumatic stress disorder

Four studies on the neuromodulator effect of psychological therapy in post-traumatic stress disorder (hereinafter, PTSD) comply with the criteria of our review (table 3).

The Dutch team headed by Lindauer performed the first work on neuromodulation in PTSD using “brief” eclectic psychotherapy (16 individual sessions held weekly). The therapy includes exposure techniques but fundamentally focuses on the integration of the memories of the trauma into the patient’s memory system. Specifically, they were interested in the changes produced in the hippocampal volume (using MRI), although they also evaluated the amygdala and parahippocampal gyrus. The patients were compared with a control group that had experienced traumatic events without developing PTSD. The results partially confirmed the hypothesis: the hippocampal volume was less than that of the control, but it was not significantly modified after four months of

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Neuromodulation in PTSD and in the anxiety disorder after psychological therapy</th>
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<tbody>
<tr>
<td></td>
<td>Post-traumatic stress disorder</td>
</tr>
<tr>
<td></td>
<td>Anxiety Disorder</td>
</tr>
<tr>
<td>&quot;Healthy&quot; control group (n)</td>
<td>14</td>
</tr>
<tr>
<td>Waiting list group (n)</td>
<td>9</td>
</tr>
<tr>
<td>Medication group (n)</td>
<td></td>
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<tr>
<td>Therapy group</td>
<td>A</td>
</tr>
<tr>
<td>Allotment method</td>
<td>fMRI</td>
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<tr>
<td>Procedure</td>
<td>CT</td>
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<tr>
<td>Therapy modality</td>
<td>TCC</td>
</tr>
<tr>
<td>Number of sessions</td>
<td>4-10</td>
</tr>
<tr>
<td>Components of intervention</td>
<td>Pardon, rest NL and NR</td>
</tr>
<tr>
<td>Neuromodulation</td>
<td>Yes</td>
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</tbody>
</table>

PTSD: Posttraumatic stress disorder; R: randomized; fMRI: functional magnetic resonance; MRI: structural magnetic resonance; PET: positron emission tomography; SPECT: Single Photon Emission Computed Tomography; SP: symptom provocation; CT: cognitive tests; CBT: Cognitive-behavior therapy; CBT-G: Cognitive-behavioral therapy-group; PEB: Brief eclectic psychotherapy; EMDR: Eye Movement Desensitization and Reprocessing; L = listed; NL = not adequately listed; R: referenced; NR: not referenced.
therapy (that was successful on the clinical level). A later study of this group\textsuperscript{23} used the same therapy but evaluated the neuromodulation differently, with a symptoms provocation paradigm and SPECT. Among the changes detected, the decrease of the activation of the frontal medial gyrus (dorsolateral prefrontal cortex) after the therapy stood out.

Farrow \textit{et al.}\textsuperscript{23} studied the change of brain activation by fMRI after a mean of 7 sessions of CBT (modified to include a social component on "pardon"). On the contrary to previous studies, that dealt with neuromodulation link to symptom improvement, Farrow \textit{et al.} investigated the changes associated to what we could call "intermediate variable:" social cognition. The hypothesis is that the PTSD symptoms could be affecting this type of cognition, giving rise to less activation in the brain regions involved, and the CBT could produce normalization in them.

The principal finding of the work seems to support normalization: CBT significantly reduces PTSD symptoms and the improvement is accompanied by greater activation in the brain areas involved in social cognition (using data from their previous study with healthy persons as a reference, specifically in the left medial temporal gyrus and in the posterior cingulate gyrus). However, the changes in the brain were not reflected in significant pre-post differences in the social cognition evaluated with clinical scales. This is a preliminary study with no control group that does not make it possible to definitively distinguish if the intervention is the cause of the changes observed.

Pagani \textit{et al.}\textsuperscript{24} used the SPECT to investigate brain changes associated to reprocessing therapy and Eye Movement Desensitization and Reprocessing (EMDR). Fifteen patients were compared with a control group exposed to the same type of traumatic events but not diagnosed of PTSD. The authors indicated that the therapy was effective in 11 cases according to the DSM-IV criteria (without stating what this really means or providing additional clinical measures) and, in principle, it also seems to be associated to normalization, mainly in perlimbic areas. Disappearance after the treatment of the differences between controls and responding patients supports this conclusion as well as the appearance of significant differences when compared with the nonresponders. However, the pre-post measures do not show significant intragroup changes in brain activation. The brevity of the therapy and limited time to when the second scan was performed are potentially explanatory factors of this negative result, the authors suggesting that it could be preventing the detection of individual changes in brain activations.

In summary, the review on PTSD shows that there is great methodological heterogeneity (the division of the PTSD into different subtypes depending on the reciprocating traumatic event standing out), that prevents a definitive conclusion on where the principal neuromodulating effects of the different therapies investigated are produced.

### Anxiety disorder

Two works\textsuperscript{25, 26} investigate the neural correlates of psychological therapy in anxiety disorder (table 3). In the Prasko \textit{et al.} study\textsuperscript{25}, the patients were randomly assigned to two treatments for three months: CBT (n = 6) or antidepressants (n = 6; citalopram, sertraline and venlafaxine). PET (at rest paradigm) was used to study brain activation.

The pre-post comparison showed significant improvement in both groups, however the psychological treatment seemed to produce greater decrease of the symptoms. Both treatments produced changes in brain activation in different frontal and temporal gyri (in general in frontal and prefrontal, temporal, parietal and occipital areas, although not always coinciding). Both types of treatment seem to also be associated to a combined effect of predominantly lateralized profile (that is, increase of activation in the left hemisphere accompanied by decrease in the right, although not exclusively). The CBT seems to be the only one that achieved an increase in left insula activity. Surprising, no changes were detected in activation in the limbic area (hippocampus, parahippocampal gyrus and amygdala), which is supposed to be activated during the anxiety attack.

Sakai \textit{et al.}\textsuperscript{26} used the PET and CBT in individual format. Eleven out of the 12 patients showed significant improvement after the intervention (at least 50% reduction in symptoms). Similarly to the previous study, a combined effect of greater activation in some regions (prefrontal medial region bilaterally) and a decrease in others (right hippocampus, left ventral anterior cingulate cortex, uvula and left cerebellum uvula and pyramis and pons) was observed after successful therapy. Some significant correlations between clinical changes and brain activation changes after the therapy were also found.

Thus, it seems that CBT achieves normalization of the brain (hyper)activation associated to anxiety disorder, although some inconsistencies are also present with the neuroanatomic theory of the disorder (for example, decrease in the activation of the amygdala is not observed). The decrease in activity in the hippocampus also is not correlated with symptomatic improvement. On the other hand, the mechanism by which the therapy increases activation (in the prefrontal medial cortex) or decreases it (in the anterior cingulate cortex) is not clear, although the authors offer some tentative suggestive interpretations while waiting for studies with larger samples, control group and using a symptom provocation paradigm (vs. at rest).
LIMITATIONS

Some methodological limitations stand out from the studies reviewed, among them the following:

I) A first limitation common to all of them consists in the use of a relatively small sample size. This restricts the statistical power, increasing the risk of false negatives and the inconsistency of the results and limits the generalization of the findings.

II) Not all of the studies reviewed included a control group without mental disorder in order to make pre–treatment comparisons. This lack makes it difficult to interpret the findings, as it prevents reaching an unequivocal determination of the psychological importance of the distinctive patterns of the brain function observed in the patients in baseline.

III) In two of them, the participants had not been randomized to the treatment conditions, and thus were included in a specific treatment group based on their preferences, following a potentially biased procedure.

IV) Only 5 studies included a control group on the waiting list, so that information on whether the treatment and an equivalent time without treatment differ in regards to the neural imaging profiles is lacking.

V) Most include self–report indexes, but do not analyze the value of these indexes as predictors of brain activity. The compiling of these data make it possible to analyze the potential individual differences that could arise not only between clinical groups and non–clinical ones but also within each group in terms of response for a certain experimental paradigm.

VI) Almost no study included a condition in rest state and another in activation state during the functional neural imaging, with the exception of the Johanson et al. work.

VII) The studies have mainly focused on the description of the neural correlates of the CBT and the BT in comparison with the pharmacological treatment or with a condition without treatment. It would be interesting to make a comparison between the different psychological therapies or of these with other nonstructured or supportive psychological interventions.

VIII) The follow-up is sometimes limited to a few weeks, so that little can be known about the stability of the changes over time and if a more extensive treatment would result in another type of brain activation pattern.

IX) Anxiety disorders have high psychic comorbidity that complicates the selection of the samples and interpretation of the data.

In addition to these methodological limitations, the same heterogeneity of the studies complicates their comparison. There are specific differences in the basics, technique, and efficacy of the different psychotherapeutic modalities in use at present. Several of these modalities, including BT and CBT, allow us to conduct a controlled clinical trial based on a manual and within a limited time. However, even between manualized treatment programs, adherence to a given work outline is far from being absolute. In several of the studies reviewed, although the therapeutic modality is defined in a certain way, the description of the treatment can often be confused with another one. Equally, the methodological inconsistency attributable to the use of a single therapist or multiple therapists, of the differences in the number of sessions, or formats in which the therapies are offered (for example, individual versus group therapy) should be considered.

CONCLUSIONS

The studies reviewed clearly demonstrate that psychological therapies, predominantly CBT, modify neuronal activity associated to the different anxiety disorders. In some cases, the modification produces changes that are similar to the initial response of persons without these disorders, which although can either be interpreted as a normalization of the brain activity, however, in other cases the interpretation is not as clear. In the same way, some speculation is necessary to explain the deviations observed in regards to the biological models of the disorders, for example, the nonexistence of changes in the amygdala after the therapy and anxiety disorder or the neurobiological effects observed after the drug therapy.

Roffman et al. stress that in spite of the fact that psychotherapy and pharmacotherapy reached similar efficacy, the brain changes they provoke in some measure coincide, but are not identical. This is also important in the studies with psychopharmaceuticals: even with the same medication (for example, paroxetine for major depression), discrepancies are observed in the brain activation patterns. This evidence suggests interaction of more factors than normally considered (and control) and experimental studies.

On the other hand, the fact that the changes in brain activation over time correlate with improvement of the symptoms does not imply an action mechanism of the treatment. It could be confusing changes that occur during the treatment with changes that are consequence of the treatment. Modern brain imaging technology is still too rudimentary to elucidate the neurobiological mechanisms involved in brain changes. New technological developments, such as near–infrared spectroscopy (NIRS), or two–photon excitation microscopy, may make it possible to use less invasive and more continuous measurements of the therapeutic process.
From the clinical point of view, functional neural imaging may help us in the choice of an adequate treatment by means of greater knowledge of the response predictors. It not only may offer us data regarding the baseline activity on the expected effects of the treatment, but the level of reduction of activation in certain structures may help us predict long-term grade of clinical improvement. A promising example of this is found in the study of Furmark et al.14.

In summary, while waiting for near future studies with greater rigor and methodological sophistication to provide more clarifying data on the action mechanisms on the neuroanatomical, cellular or molecular level of psychotherapies, the current evidence consistently supports the existence of changes in the brain activation patterns after the implementation of effective psychological therapies.

REFERENCES

