

# Clinical research

## *Functional neuroimaging studies of the effects of psychotherapy*

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*It has been long established that psychological interventions can markedly alter patients' thinking patterns, beliefs, attitudes, emotional states, and behaviors. Little was known about the neural mechanisms mediating such alterations before the advent of functional neuroimaging techniques. Since the turn of the new millennium, several functional neuroimaging studies have been conducted to tackle this important issue. Some of these studies have explored the neural impact of various forms of psychotherapy in individuals with major depressive disorder. Other neuroimaging studies have investigated the effects of psychological interventions for anxiety disorders. I review these studies in the present article, and discuss the putative neural mechanisms of change in psychotherapy. The findings of these studies suggest that mental and behavioral changes occurring during psychotherapeutic interventions can lead to a normalization of functional brain activity at a global level.*

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*Dialogues Clin Neurosci.* 2013;16:75-81.

**Keywords:** anxiety disorders; brain; major depressive disorder; neuroimaging; psychotherapy

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### Introduction

It has been established for a long time that psychological interventions can markedly alter patients' thinking patterns, beliefs, attitudes, emotional states, and behaviors.<sup>1,2</sup> The neural mechanisms mediating such alterations were poorly understood before the advent of functional neuroimaging techniques (eg, single-photon emission computed tomography [SPECT], positron emission tomography [PET], and functional magnetic resonance imaging [fMRI]). Since the turn of the new millennium, a number of functional neuroimaging studies have been conducted to elucidate this important issue. Some of these studies have explored the neural impact of various forms of psychotherapy in individuals with major depressive disorder (MDD). Other neuroimaging studies have investigated the effects of psychological interventions for anxiety disorders (obsessive-compulsive disorder [OCD], panic disorder [PD], post-traumatic stress disorder [PTSD], social phobia, and spider phobia). These studies are reviewed in the present article, and the putative neural mechanisms of change in psychotherapy are discussed. Emphasis is put on brain imaging investigations of psychotherapy for major depressive disorder (MDD).

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## Selected abbreviations and acronyms

<b>ACC</b>	<i>anterior cingulate cortex</i>
<b>BATD</b>	<i>Behavioral Activation Therapy for Depression</i>
<b>CBT</b>	<i>cognitive-behavioral therapy</i>
<b>FDG-PET</b>	<i>fluorodeoxyglucose positron emission tomography</i>
<b>IPT</b>	<i>interpersonal psychotherapy</i>
<b>PD</b>	<i>panic disorder</i>
<b>rCBF</b>	<i>regional cerebral blood flow</i>
<b>VLPFC</b>	<i>ventrolateral prefrontal cortex</i>

## Neuroimaging studies of psychotherapy for MDD

To date, a few neuroimaging studies have been carried out during the resting state to measure the impact of psychotherapy in people with MDD. In one of these studies, 13 MDD patients were scanned with technetium exametizine ( $^{99m}\text{Tc}$ -HMPAO) SPECT.<sup>3</sup> After this initial scan, patients had six 1-hour weekly sessions of interpersonal psychotherapy (IPT). IPT is a brief form of psychotherapy that helps depressed individuals learn how to deal more effectively with others, to reduce conflict, and gain support from family and friends.<sup>2</sup> SPECT scans and clinical assessments were repeated at 6 weeks. Depressive symptoms decreased significantly after IPT. The decrease in depressive symptoms was associated with increased regional cerebral blood flow (rCBF) in the posterior cingulate cortex and right basal ganglia.

Brody and colleagues<sup>4</sup> have also explored the impact of IPT on regional cerebral metabolic activity in individuals with MDD. Twenty-four participants with MDD and 16 normal control volunteers (who received no treatment) underwent  $^{18}\text{F}$ FDG- (fluorodeoxyglucose-) PET scanning before and after 12 weeks. The initial  $^{18}\text{F}$ FDG-PET scan revealed that MDD participants had higher metabolism than control volunteers in the prefrontal cortex (PFC), caudate, and thalamus, and lower metabolism in the anterior inferior temporal lobe. This is consistent with neuroimaging studies of MDD showing regional metabolic abnormalities in the PFC, anterior cingulate gyrus, and temporal lobe.<sup>5</sup> Following IPT, MDD participants had metabolic changes in the direction of normalization in these brain regions. Symptomatic improvement was accompanied by significant increases in the left temporal lobe and anterior insula, and significant decreases in the right middle frontal gyrus (including both the ven-

trolateral PFC [VLPFC] and the dorsolateral PFC [DLPFC]), right dorsal caudate, and left middle anterior cingulate cortex (ACC). Moreover, improvement in cognitive function positively correlated with changes in DLPFC metabolism, whereas reductions of ventral and dorsal PFC metabolism were associated with decreases in anxiety/somatization and psychomotor retardation symptoms. Normal control volunteers had no significant changes in these brain areas.

Other neuroimaging studies have examined the effects of cognitive behavioral therapy (CBT) in people with MDD. CBT seeks to train patients to identify and change negative beliefs and negative interpretations related to the past, present, and future.<sup>2</sup> In one of these investigations, Goldapple et al<sup>6</sup> used  $^{18}\text{F}$ FDG-PET to measure the brain changes induced by CBT in 17 unmedicated individuals with MDD. Participants were scanned before and after a 15- to 20-session CBT treatment. During treatment, participants learned a number of behavioral and cognitive strategies aiming to combat dysphoric mood and diminish automatic reactivity to negative thoughts and attitudes. Specifically they were taught cognitive monitoring to dismantle ostensibly complex chains of thinking and feeling into separate elements; they were also requested to increase the frequency of pleasant events in their lives, to record their thinking using thought records, and to test their interpretations and beliefs between sessions. Significant clinical improvement was noted in the 14 study completers. This improvement was accompanied by increases in the parahippocampal gyrus and dorsal ACC (Brodmann area [BA] 24), and decreases in dorsal (BA 9 and 46), ventral (BA 47 and 11), and medial (BA 9, 10 and 11) PFC. In another  $^{18}\text{F}$ FDG-PET investigation, Kennedy and coworkers<sup>7</sup> scanned 12 individuals with MDD before and after 16 weeks of treatment with CBT. Response to CBT ( $n=7$ ) was associated with increased glucose metabolism in the right inferior occipital cortex, as well as reduced glucose metabolism in the lateral orbitofrontal cortex (BA 11 and 47) and left dorsomedial PFC (BA 8).

Symptom reduction is one of the main objectives of psychotherapy. Therefore, the identification of the neural correlates of symptom reduction is a primary aim of the neuroimaging studies of psychotherapy. In this context, symptom provocation can allow researchers to compare brain responses to trigger scenarios or stimuli before and after treatment, and thus assess the impact of psychotherapy on brain activity.<sup>1</sup>

Using fMRI and a symptom provocation paradigm, Dichter et al<sup>8</sup> examined the effects of Behavioral Activation Therapy for Depression (BATD)—a form of therapy designed to enhance engagement with positive stimuli and reduce avoidance behaviors—on the neural correlates of cognitive control in emotional contexts. Fifteen people with MDD were scanned before and after therapy while they performed a task requiring cognitive control in both sad and neutral contexts. Before BATD, the participants recruited prefrontal cortical areas (right orbital frontal cortex [BA 47], right frontal pole [BA 10], and paracingulate gyrus [BA 9]) to a greater extent to cognitive control stimuli presented in sad contexts than in neutral contexts. Following BATD, decreased activation in response to cognitive control stimuli presented within a sad context was noted in these prefrontal structures. Of note, the magnitude of pre-treatment activation in the part of the paracingulate gyrus cluster responsive to treatment predicted the magnitude of depressive symptom change after BATD.

The effect of a long-term, psychodynamic intervention has been recently assessed in recurrently depressed unmedicated individuals (n=16).<sup>9</sup> Scans were conducted before and after 15 months of therapy. During scanning, descriptions containing personal core sentences previously extracted from an attachment interview alternated with presentations of attachment-related scenes with neutral descriptions. Compared with control participants, MDD participants displayed a greater activation in the subgenual cingulate cortex [BA 25], medial PFC [BA 8 and 9], and left anterior hippocampus/amygdala before treatment, and a reduction in these brain regions after long-term psychodynamic therapy. This reduction was correlated with symptom improvement.

### Putative neural mechanisms of change in psychotherapy for MDD

A limbic-cortical-striatal-pallidal-thalamic circuit has been proposed to play a pivotal role in the pathogenesis and maintenance of the MDD.<sup>5</sup> This circuit has connections to several cortical areas including the medial PFC, the dorsomedial/dorsal anterolateral PFC, the mid and posterior cingulate cortex, the anterior superior temporal gyrus, and the entorhinal and posterior parahippocampal cortices.<sup>10</sup> Several studies exploring the brain metabolic correlates of MDD have reported, during resting state, metabolic abnormalities in these structures,

including the dorsolateral prefrontal areas (known to be involved in cognitive control and working memory) and (para) limbic regions (presumably implicated in ruminative thoughts and negative emotional states).

It seems likely that distinct psychotherapies, such as IPT and CBT, exert differing effects on the brain at cellular and molecular levels.<sup>11</sup> Unfortunately, we know very little regarding this basic issue. As for the global level, reduced glucose metabolism in the orbitofrontal areas (ventromedial and ventrolateral) following CBT has been interpreted as correlates of the learned reduction of ruminations and maladaptive associative memories.<sup>6</sup> These cortical regions—which are anatomically connected to the amygdala, hypothalamus, and brain stem—are thought to be implicated in the integration of experiential stimuli with emotional salience.<sup>12,13</sup> Furthermore, the orbital frontal cortex has been shown to be involved with emotional processing biases in depressed individuals.<sup>14,15</sup> Response to CBT was also found to be associated with a reduction of glucose metabolic activity in the medial PFC.<sup>6,7</sup> This cortical area, which seems to be implicated in self-referential processing of emotional stimuli, is activated during a wide variety of emotional tasks, including attention to subjective feeling,<sup>16</sup> recollection of emotionally charged personal life events,<sup>17</sup> and processing of emotion-related meanings.<sup>18</sup>

The fMRI activation studies conducted by Dichter et al<sup>8</sup> and Buchheim et al<sup>9</sup> indicate that BATD and long-term, psychodynamic therapy can also modulate the activity of brain regions and circuits implicated in various aspects of emotion processing. The reduced activation of the anterior hippocampus/amygdala complex detected after psychodynamic therapy, in response to personally relevant material, is particularly interesting given that this cerebral structure displays enhanced reactivity in MDD.<sup>19,20,21</sup> Along the same lines, a reduction in the reactivity of the subgenual cingulate cortex was also detected in the Buchheim et al study. Now this portion of the cingulate cortex appears to be critically involved in mood dysregulation and its resolution.<sup>22</sup>

It is important to recognize that the functional neuroimaging studies of psychotherapy for MDD do not always yield similar findings. Several potentially biasing factors may lead to contrasting results and render problematic a direct comparison between these studies. For example, MDD may have many different causes that are difficult to differentiate clinically.<sup>23</sup> This may lead to a

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variability in symptoms and regional brain abnormalities across depressed individuals. The differences in rationale, technique, and efficacy of the various psychotherapeutic modalities investigated constitute another factor. Furthermore, inconsistencies in results can be produced by a more or less rigid adherence to a given framework,<sup>24</sup> varying numbers of sessions, distinct milieus (eg, individual vs group therapy), and the use of single vs multiple therapists.<sup>25</sup>

Other methodological factors that vary between neuroimaging studies of psychotherapy include the phenomena measured (eg, “metabolic activity” vs “hemodynamic activity”), the sensitivity and spatial/temporal resolutions of the neuroimaging techniques used, and the methods for examining regional brain activity (eg, voxel-based techniques, region-of-interest-based approaches).<sup>1,25</sup> The sample size, the type of control participants (eg, healthy, wait-list), and the point of the second scan within the treatment course, may also lead to divergent results.

## Neuroimaging studies of the effects of psychological interventions for anxiety disorders

A number of functional neuroimaging studies have been conducted, during resting state, to explore the effects of psychological interventions for anxiety disorders. The first of these studies was carried out by Schwartz and colleagues.<sup>26</sup> These researchers used <sup>18</sup>FDG-PET to measure regional glucose metabolism in individuals with OCD before and after 10 weeks of structured exposure and the four-step cognitive behavioral treatment method.<sup>27</sup> The goal of this treatment method is to teach people with OCD to respond to the intrusive thoughts and urges in a new and more adaptive way. The first step involves teaching patients to relabel the intrusive thoughts and urges as symptoms of the brain disorder known as OCD. In the second step, patients are encouraged to reattribute the disturbing and persistent nature of the symptoms to “false messages” arising out of a dysfunctional brain. The primary aim of the first two steps is to produce an alteration in perspective regarding OCD symptoms, which results in patients appreciating the fact that they have a critically important choice to make concerning their behavioral responses in the moments after symptoms intrude into consciousness. In the third step, patients learn to change behavioral responses while the uncomfortable intrusive thoughts

and urges are still present. In the fourth step, patients come to revalue the intrusive thoughts and urges as much less important, and the fear and anxiety associated with them vanish gradually. One aspect of this training that is especially crucial is mindfulness (or mindful awareness), ie, the ability to observe one’s own mental phenomena with the calm clarity of an “impartial spectator.”<sup>28</sup> This ability allows the patient to create a distance between his/her experience of the self and his/her experience of the OCD symptoms. It also increases his/her capacity to choose how to respond to intrusive thoughts and urges.

The results of the PET scans revealed significant bilateral decreases in caudate glucose metabolic rates that were greater in treatment responders than those seen in poor responders. In addition, correlations of brain activity, in the right hemisphere, between the orbitofrontal gyrus and the head of the caudate nucleus, and the orbital gyrus and the thalamus, diminished significantly after effective treatment. The hyperactivity of the caudate before treatment, and the reduction of its activity after intervention, are consistent with the alleged role of this structure in the pathophysiology of OCD.<sup>26</sup>

The impact of CBT has also been investigated with <sup>18</sup>FDG-PET in individuals with PD.<sup>29</sup> The therapy was a 6-week standard group treatment program for PD, consisting of education and corrective information, cognitive restructuring, in vivo exposure, and problem solving, as well as training in diaphragmatic breathing and relaxation. The severity of panic disorder was measured with the Panic Disorder Severity Scale (PDSS). Repeat <sup>18</sup>FDG-PET scanning was carried out after 3 months. The scores of the PDSS diminished significantly after treatment. Furthermore, <sup>18</sup>FDG glucose utilization decreases were measured in the right inferior temporal gyrus, and superior and inferior frontal gyri, whereas glucose utilization increases were detected (mostly in the left hemisphere) in the inferior frontal gyrus, middle temporal gyrus, and insula. In a similar study,<sup>30</sup> decreased glucose utilization was found in the right hippocampus, left anterior cingulate, left cerebellum, and pons, whereas increased glucose utilization was detected bilaterally in the medial PFC in PD participants who showed improvement after CBT.

Other neuroimaging investigations have used a symptom provocation paradigm to measure the effects of psychological interventions for anxiety disorders. For instance, Lindauer et al<sup>31</sup> utilized <sup>99m</sup>technetium SPECT to examine the impact of brief eclectic psychotherapy

(BEP) in individuals with PTSD (these individuals were randomly assigned to the treatment or a waiting list) and traumatized control participants. BEP includes a focal psychodynamic approach and incorporates several techniques used in CBT protocols (eg, cognitive restructuring, imaginal exposure). The therapy consisted of 16 weekly individual sessions. Cerebral blood flow was measured during trauma script-driven imagery. At baseline, greater activation was measured in the right insula and right DLPFC in the PTSD group compared with the control group. After effective psychotherapy, lower activation was found in the right DLPFC relative to the PTSD patients on the waiting list. According to Lindauer and coworkers,<sup>31</sup> the decreased DLPFC activation is related to the fact that working memory is no longer occupied by traumatic memories after effective psychotherapy.

Furmark et al<sup>32</sup> have used a symptom provocation paradigm and oxygen-15-PET to measure the effects of CBT on regional cerebral blood flow (rCBF) in social phobia. Previously untreated patients with this disorder were scanned during an anxiogenic public speaking task before and after 9 weeks of treatment or waiting time. Symptoms improved significantly following CBT, but remained unchanged in the waiting list control group. In treatment responders, clinical improvement was associated with a reduced rCBF response to public speaking in the amygdala, hippocampus, and the periamygdaloid, rhinal, and parahippocampal cortices. Since the amygdaloid-hippocampal complex has been hypothesized to form an alarm system that is activated by threatening events,<sup>17</sup> Furmark et al proposed that a reduction of neural activity in this structure and neighboring cortical areas might be a mechanism by which CBT exerts its anxiolytic effect.

The results of a recent fMRI study<sup>33</sup> suggest that functional neuroimaging can predict psychotherapy success in individuals with social phobia. In this investigation, fMRI was carried out during responses to social signals of threat (fearful/angry faces) in patients with social phobia before and after 12 weeks of CBT. Whole brain voxel-wise analyses revealed that therapeutic success was predicted by increased pretreatment activation to threatening faces in higher-order visual regions (superior and middle temporal gyrus), and cognitive and emotion processing areas (dorsal ACC, dorsomedial PFC). These findings are consistent with cognitive models associating reduction in threat processing bias with clinical recovery.<sup>34</sup>

So far, a few fMRI studies have been conducted to identify changes in brain activation following CBT in spider phobics.<sup>35-37</sup> In one of these studies,<sup>35</sup> we used fMRI to measure brain responses to the viewing of film excerpts depicting spiders, 1 week before CBT and 1 week after CBT. Responders to CBT were defined as participants who were able to touch, without reporting fear reactions, an entire series of pictures depicting spiders, TV screen spiders, and real spiders. The fMRI results showed that in spider phobics before CBT, the transient state of fear triggered by the phobogenic stimuli was associated with significant activation of the right LPFC, the parahippocampal gyrus, and visual associative cortical areas. In our view, the activation of the LPFC reflected the use of metacognitive strategies aimed at self-regulating the fear triggered by the spider film excerpts, whereas the parahippocampal activation reflected an automatic reactivation of the contextual fear memory that led to the development of avoidance behavior and the maintenance of spider phobia. After successful completion of CBT, no significant activation was found in the LPFC and the parahippocampal gyrus.

## Conclusion and future directions

The neuroimaging studies reviewed in this article suggest that alterations in thought patterns, beliefs, feelings, and behaviors occurring during psychotherapeutic interventions can lead to a normalization of functional brain activity at a global level. These interventions seem to exert potent modulating effects on the brain regions and circuits mediating the symptoms of MDD and anxiety disorders.<sup>2</sup> However, the meaning of the brain changes associated with such interventions remains unclear. For example, the reduction in the medial PFC activity<sup>9</sup> following psychodynamic therapy might suggest that a function of this brain region—the extinction of learned associations—may no longer be required when the patient is no longer ruminating, rather than the increased activity at baseline representing a source of the pathology. Similarly, increased metabolism in a given brain region may reflect a downstream effect of decreased inhibition in a separate cerebral structure that is more proximate to the functional abnormality.

There is now evidence that psychotherapeutic interventions can modulate different types of neural processes. With respect to this issue, Lehto and colleagues<sup>38</sup> have used SPECT and the (123I)β-CIT radi-

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oligand to compare, in depressive outpatients, serotonin transporter (SERT) levels before and after 12 months of psychodynamic psychotherapy. Midbrain SERT levels significantly increased during psychotherapy. Such an increase might have contributed to an enhancement of serotonergic activity in the previously depressed participants.<sup>38</sup>

Psychotherapeutic interventions might also cause structural brain changes. In regard to this question, a diffusion tensor imaging (DTI) study<sup>39</sup> was recently conducted to investigate this possibility. Outpatients diagnosed with MDD underwent DTI before and after a 4-week course of guided imagery psychotherapy. Fractional anisotropy (FA)—which is thought to reflect microstructural properties of white matter such as myelination, axon caliber, and fiber density<sup>40</sup>—was measured in depressed patients and healthy controls, before and after treatment, using whole brain voxel-wise analysis. Following treatment, depressed participants showed a significant reduction in their symptoms. Clinical improvement was associated with higher FA in the right thalamus. At an early stage of the intervention, higher FA was found in a part of the frontal lobe associated with emotion regulation.

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## Los estudios de neuroimágenes funcionales de los efectos de la psicoterapia

Desde hace tiempo se ha establecido que las intervenciones psicológicas pueden alterar marcadamente los patrones del pensamiento, las creencias, las actitudes, los estados emocionales y las conductas de los pacientes. Previo a la incorporación de las técnicas de neuroimágenes funcionales se conocía poco sobre los mecanismos neurales que mediaban estas alteraciones. Desde el comienzo del nuevo milenio se han realizado algunos estudios de neuroimágenes funcionales para abordar este importante tema. Algunos de ellos han explorado el impacto neural de diferentes formas de psicoterapia en sujetos con trastorno depresivo mayor. Otros estudios han investigado los efectos de las intervenciones psicológicas en los trastornos ansiosos. En este artículo se revisan estos estudios y se discuten los mecanismos neurales de cambio reconocidos en la psicoterapia. Los hallazgos de estos estudios sugieren que los cambios mentales y conductuales que se producen durante las intervenciones psicoterapéuticas pueden llevar a una normalización de la actividad cerebral funcional a nivel global.

## Études de neuro-imagerie fonctionnelle sur les effets de la psychothérapie

Les interventions psychologiques sont connues depuis longtemps pour leur capacité à nettement modifier les schémas de pensée, les croyances, les attitudes, les états émotionnels et les comportements des patients. Avant l'ère des techniques de neuro-imagerie fonctionnelle, les mécanismes neuronaux liés à ces troubles étaient peu connus. Depuis ce nouveau millénaire, plusieurs études de neuro-imagerie fonctionnelle ont été conduites pour aborder cette importante question. Certaines d'entre elles ont examiné l'impact neuronal de différentes formes de psychothérapie chez des patients ayant un épisode dépressif caractérisé. D'autres ont analysé les effets des actions psychologiques sur les troubles anxieux. Dans cet article, j'examine ces études et j'analyse les mécanismes neuronaux présumés du changement en psychothérapie. Leurs résultats suggèrent que les modifications mentales et comportementales intervenant pendant les psychothérapies peuvent conduire à une normalisation de l'activité cérébrale fonctionnelle à un niveau global.

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