Functional neuroimaging: points of intersection between biology and psychotherapy

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Review

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Functional neuroimaging: points of intersection between biology and psychotherapy

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Abstract

Objectives. In the evaluation of the biological basis of psychotherapeutic changes many researches have noticed potential effects of psychotherapeutic interventions on the neural correlates of mental illness. In a psychotherapeutic setting, modifications in individual thoughts and feelings can restore brain functioning at physiological levels. This paper gives an overview about neurobiological methods and their potential to support psychotherapy research and to examine psychotherapy effects across a number of psychiatric disorders.

Methods. Relevant informations are identified through searches of MEDLINE and Current Contents/Clinical Medicine.

Results. Studies demonstrate that it is important to consider putative neural mechanisms of psychotherapy, changes in the brain associated with psychotherapy on a global and molecular level, intervention-specific effects and prediction of outcome. Pharmacotherapy and psychotherapy converge in a common change of neuronal functions that might be detected by imaging techniques and might resemble correlates of clinical improvement.

Conclusions. Neuroimaging techniques applied to psychotherapy research are relevant for further understanding neurobiological underpinnings of psychotherapy processes and predicting treatment outcome in order to improve clinical decision-making and treatment. ***Clin Ter 2012; 163(6):e445-456***

Key words: *functional magnetic resonance imaging (fMRI), neural mechanisms, neuroimaging, photon emission computed tomography (SPECT), positron emission tomography (PET)*

Introduction

It has been a long time since some researchers have postulated that psychotherapy could deeply operate on cognitive, affective and social patterns. Since the end of the twentieth century it has been noticed an increasing interest in the combination of psychological and neurobiological approaches for the study of mental illness (1). This trend was very relevant, because it encouraged the comprehensive understanding of neurobiological processes activated during structured psychological interventions with consequent advantages in effective treatment of mental illness. Such interdisciplinary researches have been realized through the utilization of techniques investigating neural processes in the human brain in a non-invasive manner, such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI). These methods enable to measure changes in blood flow accompanying neuronal activity and are based on the paramagnetic effect of deoxygenated haemoglobin (2, 3).These non-invasive procedures are commonly used in a clinical setting to assess hemodynamic correlates of neural activity and these modalities are characterized as sensitive, effective and reliable techniques (3). It is therefore possible to study brain activity of individuals with or without psychiatric disorders and identify and compare functional neural circuitries (4).

Psychopharmacological research aims to the development of more specific and effective medications with increasingly benign side effects. Similarly there is a need of deeply investigate the mechanisms of psychotherapeutic action on biological, cognitive, and behavioural levels. In fact, yet psychotherapy research lags far behind pharmacotherapy research. This is in part due to the cost, inconvenience and difficulty of conducting and evaluating a complete course of psychotherapy treatment under controlled conditions. Up to the last decade, the biological mechanisms of psychotherapeutic actions were thought not to be amenable to neurobiological investigation. With the advent of neuroimaging techniques, the ability to probe the biological consequences of psychotherapeutic interventions has begun to come within reach, and with it the ability to document psychotherapy's effectiveness, to follow its course, and to refine its appropriate applications for selected patients and disorders (5, 6).

Over the past years, dating from Aristotle, it has always been alive a clear separation between the different purposes of psychology and medicine: psychology etymologically means "the logos of the soul" representing something of amorphous and intangible, whereas medicine is focused on the study of the body. Afterwards, it has been placed the possibility of reversing that point of view proposing the idea of

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a potential integration for mind and brain suggested by Sigmund Freud (7) and reissued by Klaus Grawe (8, 9). To treat psychology as a brain science has been made possible by the existence of neuroscience and neuroimaging techniques that created a bond between neurobiology and psychotherapy towards the emerging concept of "neuropsychotherapy" (9, 10). Walter and colleagues (10) proposed a description of the concept of "neuropsychotheraphy" ensuring as an area deputed to detect neuronal mediators and functional targets of psychotherapeutic interventions, establish new therapeutic pathways through the use of neurotechnologies, devise psychotherapeutic interventions guided by neuroscientific knowledge (10).

Putative neuronal mechanisms of psychotherapy

Many potentially unhealthy cognitive and emotional patterns targeted by psychotherapy appear to have measurable biological analogues (11). One salient example involves repression, that is the unconscious "forgetting" of threatening ideas or experiences. In a recent investigation by Anderson and colleagues (12), healthy subjects were instructed either to remember or "forget" target words. In a recall task, presentation of "forget" words was associated not only with poor recall of those words, but also with increased activation of the prefrontal cortex (PFC) and decreased hippocampal activation. These results replicated a previous study conducted by Bunge and colleagues (13), who also found that the anterior cingulate gyrus directs attention away from unwanted memories. Thus, active "forgetting" modulated by the PFC and anterior cingulate may have relevance to the psychodynamic concept of repression (14).

Loughead et al. (15) conducted a study aimed to examine functional brain activation during autobiographical relationship episode narratives. fMRI studies showed an activation in brain areas known to be involved in autobiographical memory retrival, self-referential processing and emotion, subjects displayed hyperactivation in anterior cingulated, precuneus, inferior and middle frontal gyri and inferior parietal lobule. Results indicated that memory process in the brain reaches a greater level of performance in referring episodes with increased core conflictual relationship theme (15). In this perspective neuroimaging studies might have the possibility of identifying neural mechanism of different therapeutic interventions and elucidate predictive factors for successful outcomes. In 2012, Bryant and Das (16) illustrated the case of a woman affected by hysterical mutism providing the first evidence for the association of neural circuitries with the recovery of chronic conversion disorder. After treatment neuroimaging results have shown increased activation in the cerebellum and in the inferior frontal gyrus which is linked, on one hand, in a positive way to the anterior cingulated cortex whereas, on the other hand, is correlated in a negative way to the amygdala. These data seem to point out a dysfunctional modulation and interaction between speech and anxiety networks (16). Further imaging studies might improve clinical management and provide new insights on brain mechanism of self-awareness.

The course of psychotherapy may also engage dedicated neural circuitries that are particularly responsive to specific treatment. Examples of this can be found in studies related to psychodynamic and cognitive behavioural therapy (CBT). When a psychodynamically oriented therapist "takes a history", this elicits episodic memories from the patient in a focused way. However, when the same therapist observes the patient "free associate", episodic recall occurs in a less organized, more random way. Andreasen and co-workers (17) observed that while random memories engaged association cortex in frontal, parietal, and temporal regions, focused memories selectively activated verbal areas (including Broca's area and the left frontal operculum). Thus, the less "censored" process of free association may engage wider networks of association cortex, facilitating exploration of latent aspects of the patient's symptomatology or personality (14).

In CBT for depression, patients are sometimes asked to revisit bad or painful memories and explicitly re-evaluate their negativity toward the memory. Using a related paradigm in healthy subjects, Ochsner and colleagues (18) observed a relationship among reappraisal of negative stimuli, improvement in mood, and brain activity patterns. Subjects rated their mood before and after being asked to "re-interpret" highly negative scenes in a more positive light. Reappraisal was associated with both improved mood and increased activity in dorsolateral and dorsomedial PFC, but decreased activity in the amygdala and orbitofrontal cortex. These findings suggest a model of cognitive therapy: while limbic and ventral prefrontal structures generate negative affect in response to a certain stimulus, dorsal prefrontal circuitry may be engaged through reappraisal techniques to dampen this outflow from more ventral structures (19, 20).

Behavioural therapy (BT) for anxiety disorders often relies on desensitization or extinction of learned responses to anxiety-provoking stimuli. Converging evidence from animal and human studies implicates the ventral PFC and amygdala in this process (21). Targeted lesions or specific pharmacological inhibition of the amygdala interfere with fear conditioning in rodents (22), while functional neuroimaging studies in humans have consistently associated amygdalar activation with conditioned fear responses (23-26). Similar studies in rats (27) and humans (28, 29) suggest that the ventral PFC mediates the retention and recall of extinction for conditioned fear responses by keeping the amygdala in check. One might, therefore, expect extinction-based behavioural therapies in humans to work either by potentiating ventral PFC activity or attenuating the amygdala (or both) (14).

There is a great amount of studies that directly evaluate the neurobiological effects of psychotherapy in patients with mood and anxiety disorders (14). There exist many specific differences in rationale, techniques, and efficacy of the various psychotherapeutic modalities in use today (Table 1 and table 2). Symptom reduction can be considered the aim of psychotherapy and can be regarded as the benchmark against which the success of behavioural and cognitive therapies has to be measured. Elucidation of the neural correlates of symptom reduction is therefore a primary purpose when investigating biological mechanisms of psychotherapy. An important tool is the reliable induction of symptoms in the imaging environment. Such a symptom provocation will permit the comparison of brain responses

Table 1. Different approaches to psychotherapy

Type	Key factors
Psychoanalysis	It encourages the verbalization of all the patient's thoughts, including free associations, fantasies and dreams, from which the analyst formulates the nature of the unconscious conflicts which are causing the patient's symptoms and character problems.
Psychodynamic therapy	It is a form of depth psychology, the primary focus of which is to reveal the unconscious content of a client's psyche in an effort to alleviate psychic tension. Although it has its roots in psychoanalysis, psychodynamic therapy tends to be briefer and less intensive than traditional psychoanalysis.
Cognitive behavioural therapy (CBT)	It trains patients to identify and modify negative beliefs and negative interpretations of the past, present and future. Includes education, symptom and stress management strategies, desensitization to feared stimuli and cognitive challenges to change beliefs.
Interpersonal therapy (IPT)	It is a short-term therapy often used to treat depression. This treatment approach focuses on an individual's social relationships and how to improve social support. IPT therapy seeks to improve a person's relationship skills, working on communication more effectively, expressing emotions appropriately and being properly assertive in social and work situations. IPT helps patients learn how to more effectively deal with others in order to reduce conflict and to gain support from family and friends. It is usually conducted, like cognitive-behavioural therapy, on an individual basis but also can be used in a group therapy setting.
Mindfulness-based CT (MBCT)	It assumes vulnerability to relapse/recurrence of depression and arises from repeated associations between depressed mood and patterns of negative, self-devaluative, hopelessness thinking during major depressive episodes, leading to changes at both cognitive and neuronal levels. Group-based, focusing on improving awareness of negative thoughts, and disengaging from ruminative depressive processing. Teaches patients to de-centre negative cognitive sets and view these as events of the mind, rather than necessary truths.
Gestalt therapy	It stands on top of essentially four load bearing theoretical walls: phenomenological method, dialogical relationship, field-theoretical strategies and experimental freedom. Some have considered it an existential phenomenology while others have described it as a phenomenological behaviorism. Gestalt therapy is a humanistic, holistic, and experiential approach that does not rely on talking alone, but facilitates awareness in the various contexts of life by moving from talking about situations relatively remote to action and direct current experience.
Expressive therapy	It is a form of therapy that utilizes artistic expression as its core means of treating clients. Expressive therapists use the different disciplines of the creative arts as therapeutic interventions. This includes modalities such as dance therapy, drama therapy, art therapy, music therapy, writing therapy, among others. Expressive therapists believe that often the most effective way of treating a patient is through the expression of imagination in a creative work and by integrating and processing those issues that are raised in the act.
Narrative therapy	It gives attention to each person's "dominant story" by means of therapeutic conversations, which also may involve exploring unhelpful ideas and how they came to prominence. Possible social and cultural influences may be explored if the patient deems it helpful.
Integrative psychotherapy	It represents an attempt to combine ideas and strategies from more than one theoretical approach. These approaches include mixing core beliefs and combining proven techniques. Forms of integrative psychotherapy include Multimodal Therapy, the Transtheoretical Model, Cyclical Psychodynamics, Systematic Treatment Selection, Cognitive Analytic Therapy, Internal Family Systems Model, Multitheoretical Psychotherapy and Conceptual Interaction. In practice, most experienced psychotherapists develop their own integrative approach over time.

Table 2. Types of Psychotherapy Formats.

Types	Characteristics
Individual Therapy	This modality involves one-on-one work between patient and therapist. It allows the patient to have the full attention of the therapist, but it does not allow the therapist to observe the patient within social or family relationships.
Family Therapy	Family therapy includes discussion and problem-solving sessions with every member of the family. Family therapy is helpful when one of the family member's physical or mental health is directly affecting family dynamics or the well-being of significant relationships. During the therapy, interpersonal relationships shared among family members are examined and communication is strengthened.
Group Therapy	Group therapy generally involves from three to fifteen patients. It offers patients the opportunity to give and receive group support in coping with their particular issues as well as to observe how they interact in group settings. It may also be a less expensive alternative to individual therapy.
Couple's Therapy	This type of therapy is geared towards married couples and those who desire to improve their functioning as a couple. This approach is most useful when it is necessary to work on dynamics within the couple.

to trigger scenarios (e.g. for social phobia or post-traumatic stress disorder) or stimuli (e.g. for simple phobias) before and after treatment, and thus the assessment of therapy effects on neural activation. It has also the advantage of allowing the comparison of response patterns to trigger stimuli in patients and healthy controls (30-32), such elucidating commonalities and differences in the processing of aversive material (Table 3).

Table 3. Studies examining the neuroanatomy of psychotherapy

Study Authors	Subjects	Treatment	Therapy type	Functional imaging technique	Post-treatment findings
Baxer et al. (1992) (33)	Patients with OCD	10 wk	BT	FDG (fluoro-deoxyglucose)-PET	A reduction in glucose metabolism in the right caudate nucleus following treatment. An uncoupling of hyperactivity in the right caudate, orbitofrontal cortex, and thalamus.
Schwartz et al. (1996) (34)	Patients with OCD	9 wk	CBT	FDG (fluoro-deoxyglucose)-PET	Reduction of metabolic activity in the caudate nucleus, especially on the right side. The initial cortico-striato-thalamic correlation described earlier again disappeared with treatment. Uncoupling was demonstrated specifically in patients who responded to psychotherapy.
Brody et al. (1998) (35)	Patients with OCD who received BT or fluoxetine	8-12 wk	BT	FDG (fluoro-deoxyglucose)-PET	For BT patients, L orbitofrontal cortex metabolism positively correlated with treatment response. Fluoxetine patients exhibited a negative correlation.
Laatsch et al. (1999) (36)	Patients with traumatic brain injury	6-35 sessions	Cognitive rehabilitation therapy	SPECT	Global increases in CBF most apparent during treatment phase.
Brody et al. (2001) (37)	Patients who received IPT or paroxetine	12 wk	IPT	FDG (fluoro-deoxyglucose)-PET	In all subjects, reductions of ventral and dorsal frontal lobe metabolism were associated with improvements in the anxiety/somatization and psychomotor retardation symptom and in the tension/anxiety and fatigue. Improvement in cognitive disturbance positively correlated with changes in dorsolateral PFC metabolism.
Brody et al. (2001) (38)	Patients who received IPT or paroxetine	12 wk	IPT	FDG (fluoro-deoxyglucose)-PET	Subjects in the paroxetine cohort were less ill at baseline, and exhibited greater improvement over time than those in the IPT group. A decrease in dorsal and ventral prefrontal cortical metabolism with IPT treatment.
Martin et al. (2001) (39)	Patients with MDD versus venlafaxine patients	6 wk	IBT	^{99m}Tc-HMPAO SPECT	An increase in blood flow in the right basal ganglia. Subjects in the IPT group also exhibited an increase in right posterior cingulate activity.
Furmark et al. (2002) (40)	Patients with social phobia versus citalopram patients	8 wk	Group CBT	PET	CBT and citalopram therapy for social phobia might dampen limbic response by different mechanisms, even if the ventral prefrontal components of these mechanisms remain unclear.
Penadés et al. (2002) (41)	Patients with schizophrenia, on olanzapine	12 wk	Group "neuropsychological rehabilitation"	SPECT	Weakly increased CBF in frontal lobe, correlated with improvement in test score. Non-specific imaging measure.
Wykes et al. (2002) (42)	Patients with schizophrenia, on antipsychotics	12 wk	Cognitive remediation therapy	fMRI	In cognitive therapy group, increased CBF in R inferior frontal cortex and bilateral occipital cortex.
Nakatani et al. (2003) (43)	Patients with treatment-refractory OCD	Varying duration	BT	Xenon-enhanced computed tomography (Xe-CT) (measures rCBF)	A significant reduction in the right caudate.
Paquette et al. (2003) (44)	Spider-phobic patients	3-4 sessions	Group CBT	fMRI	Significantly less activation in both the parahippocampal gyrus and right dorsolateral PFC, and increased activation in the right ventral PFC.

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Goldapple et al. (2004) (45)	Patients with MMD versus patients given paroxetine	15-20 sessions	CBT	FDG (fluoro-deoxyglucose)-PET	Metabolism in multiple frontal regions including the dorsolateral PFC decreased after therapy. Subjects in the CBT group exhibited significant increases in activity in the hippocampus, parahippocampal gyrus, and dorsal cingulate gyrus. In the paroxetine group, subjects exhibited less activity in hippocampal and parahippocampal regions, as well as decreased activity in the posterior cingulate and ventral subgenual cingulate.
Prasko et al. (2004) (46)	Patients with panic disorder who received CBT or different antidepressants	12 wk	CBT	FDG (fluoro-deoxyglucose)-PET	In both treatment groups a decrease of right frontal and temporal regions with partial overlap across groups.
Nakao et al. (2005) (47)	Patients with OCD	12 wk	CBT	fMRI	An increase of bilateral parietal cortex cerebellum. Decrease bilateral orbitofrontal cortex (OFC).
Straube et al. (2006) (48)	Patients with spider phobia versus waiting list	2 sessions	CBT	fMRI	Decrease of bilateral insula, thalamus, anterior cingulate cortex (ACC) in treatment but not waiting list group.

Basal Brain Imaging: detecting changes associated with psychotherapy and pharmacotherapy

Most neuroimaging studies of psychotherapy have focused on depression and obsessive-compulsive disorder (OCD) and have examined basal brain metabolism or basal cerebral blood flow (CBF) in these disorders (33-35, 37, 39). Several published studies are consistent in demonstrating changes following psychotherapy in brain activity in patients with these disorders when compared with healthy subjects. Successful treatment frequently restored the brain to a state that superficially resembled that of comparison subjects. Particularly interesting is the finding that some of the changes accompanying successful psychotherapy resembled those seen with pharmacotherapy, with the suggestion that, at least in some cases, psychotherapy and medications may act on a common set of brain targets (5).

Early neuroimaging studies of OCD used fluorodeoxyglucose-positron emission tomography (FDG-PET). Baxter et al. (33) found an increase in basal glucose metabolism in the caudate nucleus of OCD patients. Treatment with either the selective serotonin reuptake inhibitor (SSRI) fluoxetine or exposure psychotherapy reversed the metabolic abnormality associated with the disorder. A more recent study found that patients who responded to psychotherapy showed greater decreases in right caudate metabolism than patients who did not respond (34).

Subsequent FDG-PET studies of psychotherapy have focused primarily on depression. The most common finding is a decrease in the basal activity of the dorsolateral prefrontal cortex, with a less consistent increased activity in the ventrolateral prefrontal cortex (49-52). Both SSRIs and electroconvulsive therapy reversed these abnormalities (51). Two studies compared interpersonal psychotherapy with either the SSRI paroxetine or the serotonin-norepinephrine reuptake inhibitor venlafaxine in the treatment of depression (37, 39). Again, psychotherapy reversed pretreatment abnormalities, including those in the prefrontal cortex, with final effects very similar to pharmacotherapy (5).

The conclusion is that psychotherapy is similar to pharmacotherapy in normalizing functional abnormalities in brain circuits that give rise to symptoms. It is likely, however, that this view is incomplete. Further research could distinguish common from distinct changes among these very different forms of therapy (45).

Stimulus-responsive imaging of the effects of psychotherapeutic interventions

Recent studies have sought to go beyond the measurement of basal metabolism by examining the effect of psychotherapy on context-specific neural responses in disease-relevant tasks (40, 44). Tillfors et al. (53) found that when patients with social phobia gave a prepared speech in the scanner in the presence of others, they had a larger increase in regional blood flow in the amygdala and hippocampus, compared with control subjects (53). Improvement in symptoms with treatment was accompanied by decreased activity in the amygdala and the medial temporal lobe in the stressful public speaking condition. Using PET measures of changes in regional blood flow secondary to neuronal activation Furmark et al. (40) examined patients with social phobia treated with either citalopram or cognitive-behavioral group therapy.

Decreases in the activity of the amygdala were seen in both the cognitive-behavioural therapy and the citalopram-treated groups. The two treatment groups, however, differed with respect to changes outside the amygdala. Interestingly, the degree to which amygdala activity decreased as a result of therapy predicted the reduction in patients' symptoms one year later.

Molecular mechanisms of psychotherapy: empirical reflection – mood disorders

Some researchers have assessed whether there are concomitant brain changes as a result of a psychological intervention. Laatsch et al. (36) have studied subjects with traumatic brain injury in treatment with cognitive rehabilitation therapy. They have found significant increases in CBF demonstrating a relationship between cognitive therapy and changes in brain circuitries. In particular, authors have provided data on an increase in regional cerebral blood flow in bilateral occipital-temporal areas, left insula, right middle occipital gyrus and left inferior occipital gyrus (36).

Penadés et al. (41, 54) repeatedly investigated schizophrenic patients' rehabilitation through cognitive therapy. They found improvements in verbal and non-verbal memory, executive functions and social functioning. These results probably suggested a link between enhancements in neuropsychological performance and decreased functional hypoactivity in the prefrontal areas. Wykes et al. (42) concentrated their study on patients recruited from community psychiatric services. They noticed improvements in memory function, such highlighting the specificity of brain activation changes in the frontocortical areas, in the right inferior frontal gyrus and left and right occipital cortex.

The first functional brain imaging studies on depressed subjects was performed by Brody et al. (38). They enrolled 24 subjects with unipolar major depressive disorder (MDD) treated with either paroxetine or IPT and 16 normal control subjects without treatment. The authors found that patients with MDD had regional brain metabolic abnormalities at baseline that tended to normalize with treatment. In particular both treatment groups showed decreases in normalized prefrontal cortex (paroxetine-treated bilaterally and IPT-treated on the right) and left anterior cingulate gyrus metabolism, and increases in normalized left temporal lobe metabolism. Martin et al. (39) observed brain blood flow alteration in 28 subjects treated with venlafaxine hydrochloride and IPT by SPECT scans. They found that limbic blood flow increased in the right basal ganglia with both IPT and venlafaxine, while subjects IPT-treated showed increased blood flow in the right posterior cingulate. Goldapple et al. (45) investigated neural changes in depressed patients treated with CBT by considering response-specific regional changes following various modes of antidepressant treatment. They assessed that CBT determined significant metabolic changes, in particular increases in metabolic activity within the hippocampus/parahippocampal gyrus and dorsal cingulate cortex, decreases in dorsalateral and ventrolateral prefrontal regions, orbital frontal regions, the posterior cingulate, the inferior parietal regions, and in inferior temporal regions.

As assessed by Cabeza and Nyberg (55) and Duncan and Owen (56) the dorsolateral prefrontal cortex, particularly within the left hemisphere, is widely known as a seat for many higher-order executive cognitive functions such as working memory and cognitive flexibility; altered function within the dorsolateral prefrontal cortex may reflect improved problem-solving or reductions in negative affect and associated cognition. Conversely, Ochsner and Gross (57) and Northoff et al. (58) studied a functional architecture for the cognitive control of emotion and they concluded that altered activity within ventrolateral prefrontal regions, particularly within the right hemisphere, as well as within anterior and posterior cingulate and medial prefrontal regions may reflect improved affect regulation and self-perception. Paquette et al. continued their scientific research on sustainable development and explored the fundamental question of psychoneuroterapies in patients affected by major depressive disorder. They found a normalization in beta brainwaves in paralimbic areas related to a reduction in patients levels of depression (59).

In a recent paper Dichter et al. (60) sough to investigate the impact of brief behavioral activation therapy on prefrontal brain function. This study provides evidence of the effects of brief behavioral activation therapy in depressed patients, reflected by a decreased activation in the paracingulate gyrus, the right orbital frontal cortex and the right frontal pole. These results suggest that behavioral activation therapy might act in brain networks by modulating cognitive control in affective contexts (60). Thanks to brain imagining great advantages have been made concerning the comprehension of neural substrates. Vocks and coworkers investigated brain activation patterns during processing of body images. After behavioral interventions, patients with eating disorders consistently showed greater activity in the left middle temporal gyrus than comparison subjects (61). Taken together, these outcomes suggest that CBT and IPT might involve neural circuitries acting on problem-solving capacity, self-perception and emotion (62). A better understanding of neuropsychobiological bases of these psychiatric disorders might derive by future studies comparing different symptoms and functional connectivity analyses.

Molecular mechanisms of psychotherapy: empirical reflection – anxiety disorders

Some relevant study examined correlation between changes in glucose metabolic rates and OCD. Baxter et al. (33) and Schwartz et al. (34) investigated local cerebral metabolic rates for glucose using PET and Nakatani et al. (43) measured the regional CBF using the xenon-enhanced computed tomography. They noted similar patterns characterized by decreases of glucose metabolic rates in the right caudate nucleus. Nakao et al. (47) applied functional neuroimaging studies to OCD subjects and found that patients showed decreased activation of brain regions such as dorsolateral–prefrontal and anterior cingulate cortices. They hypothesized that a brain circuit involving these brain regions may mediate OCD symptoms. Subsequently, neuroanatomical findings in the pathophysiology of OCD

have demonstrated that executive dysfunction implicates the dorsolateral-prefrontal cortex, caudate nucleus, thalamus and striatum (63). Apostolova and coworkers evaluated cerebral metabolic changes with treatment of OCD. Improvements of obsessive-compulsive symptoms was correlated with increased glucose metabolism in the right caudate nucleus (64). In the context of pediatric OCD, Huyser et al. developed a study to observe functional abnormalities in brain systems. During planning, decreased right posterior prefrontal activity was found in obsessive-compulsive pediatric patients in comparison with control subjects (65). In a more recent study, Huyser et al. identified that the OCD group exhibited a higher activation of the anterior cingulate cortex and bilateral insular cortex than normal comparison subjects free of any major psychiatric diseases (66).

Prasko et al. (46) conducted a study on 12 subjects suffering from panic disorder and observed changes in brain metabolism with right-left difference: decreases were detected in the right hemisphere and increases in the left hemisphere. It has been demonstrated that in right hemisphere regions decreases of glucose metabolic rates influence problem-solving capacity and emotional processing, while in left hemisphere increases of glucose metabolic rates act on resting-state brain activity and reflective function (62). Beutel et al. investigated functional neuronal correlates and disease specificity of panic disorder. Treatment response was associated with a changes in fronto-limbic patterns (67). Freyer et al. (68) conducted a study aiming to evaluate the effect of CBT on frontostriatal activation in patients suffering from OCD. CBT effects resulted in a more stable activation in the caudate nucleus and the pallidum. CBT improves obsessive-compulsive symptoms and attenuate brain imaging abnormalities in regions linked to the pathophysiology of anxiety (68).

Furmark et al. (40) observed in patients with social phobia treated with either citalopram or CBT a decreased CBF bilaterally in the amygdala, hippocampus, and in the periamygdaloid, rhinal, and parahippocampal cortices. This condition was associated with alleviation of social anxiety and consequently lower public speaking fear, that is correlated to a diminished amygdala activity. It has been demonstrated that a reduced activity in the hippocampus and medial temporal lobe may be associated with emotion, memory and emotion's influence on perception of fear states (62, 69).

Farrow et al. (70) conducted a study on a sample of individuals with PTSD. They demonstrated a significant activation within the middle temporal gyrus and the posterior cingulated gyrus and concluded that the pattern of findings are consistent with improved fear extinction.

Neurofunctional changes underlying effective anti-anxiety treatments have been analyzed in subjects suffering from spider phobia. Paquette et al. (44) conducted the first neuroimaging investigation of CBT effects using an emotional activation paradigm and the study group was exposed to the projection of film painting spiders. Before CBT-treatment authors pointed out an activation in the dorsolateral prefrontal cortex and in the parahippocampal gyrus. After successful CBT there was no remarkable activation in the above-mentioned brain regions. It has been argued that those regions are clearly involved in the pathophysiology of spider phobia, since the activation of the dorsolateral prefrontal cortex aimed at self-regulating the fear and the parahippocampal activation is associated with to an automatic reactivation of the contextual fear memory. Straube et al. (48) measured brain activation to spider videos in a sample composed of 42 subjects. They found that phobic individuals showed greater activation than healthy control subjects in the insula and anterior cingulate cortex (ACC). More recently, Schienle et al. (71, 72) assessed temporal changes in brain activation and their investigation revealed a temporal stability of CBT-treatment effects in spider-phobic individuals. They showed decreased activation in the OFC, a brain region considered as the core area of cognitive strategies to regulate emotion and the stimulus-outcome associations. Taken together, these outcomes suggested that sites of action for CBT-treatment of spider phobia involved different brain regions and clinical improvement was accompanied by an attenuation of these brain responses.

Some researchers have used magnetic resonance spectroscopy to study patients with schizophrenia in order to assess the regional specificity of changes of metabolite signal intensities in schizophrenia. Premkumar et al. performed a study evaluating N-acetyl-aspartate concentrations that measures neuronal/axonal integrity. N-acetyl-aspartate levels in the anterior cingulate cortex seem to be progressively increased after psychological interventions (73). On the other hand, Haut et al. conducted a study to estimate prefrontal activity in chronic schizophrenia. It was the first scientific study to measure, after cognitive program, an increased prefrontal cortex activity areas, structures liked to attention and working memory (74).

Following consensus on neuroimaging techniques applied to psychotherapy to investigate the neuronal basis of mental illness, therapeutic interventions such as mindfulness training programs and meditation practice are also attracting interest in neuroimaging research. Mindfulness training programs contribute to give progress in understanding neurobiological of psychiatric diseases also considering their influence on recent advantages in treatment. Wang et al. sought to identify neural correlates in the brain regions that belong to changes in regional cerebral blood flow after two different meditation practices. Functional imaging research showed an increased functional activity in the insula and the precentral gyrus (75). An experimental psychopathology research was conducted by Hölzel et al. applying mindfulness-based stress reduction. This study provided evidence that changes in gray matter density occurred in several brain areas such as posterior cingulated cortex, temporo-parietal junction and cerebellum (76). Taken together, these findings saggest that several coordinated cognitive processes are present during meditation practice and also raise important methodological issues.

In summary, different studies have identified brain structures in patients with psychiatric disorders showing changes such us brain blood flow and glucose metabolic rates during or after psychological interventions. Some results even suggest that changes in brain function may be associated with psychological rather than pharmacological treatment. Neural changes occur in brain regions with very specific functions, therefore these findings could explain the fact that psychological interventions might lead to changes in brain

activity by acting on problem-solving capacity, relational processing and affective regulation (62).

Advances in the neuroimaging of psychotherapy

Neuroimaging can be a highly sensitive mode of investigation (5). This sensitivity has several implications. First, neuroimaging may provide an independent way of grouping patients based on specific biological variables, that are closer to aspects of the pathogenesis of the disease. Major depression, for instance, is likely to have multiple distinct etiologies, and these distinct etiologies may be clinically indistinguishable. Patient subgrouping may reveal why some patients improve with particular therapies and others do not.

The power of novel data analysis techniques for objectively subgrouping subjects on the basis of biological criteria was illustrated by Meyer-Lindenberg et al. (77). They used multivariate analysis and found that the expression of a brain-wide pattern of activity in an individual almost perfectly separated a group of schizophrenic patients from a comparison group, like a diagnostic marker. In this way they were able to use resting brain scans to separate out two independent cohorts with 94% accuracy (5).

Predictions of whether a particular therapy will work for a given patient may, instead, depend more on the functional characteristics of that individual's brain than on the specific diagnosis. Neuroimaging-based quantification of regional brain function during disease-relevant and irrelevant tasks may predict how a patient will process and respond to stimuli in the context of particular forms of psychotherapy, or after pharmacological treatment. This is based on the assumption that biological variables cause the behavioural manifestations of psychiatric disorders and therefore are likely to be more sensitive indices of underlying pathology than symptoms. Moreover, neuroimaging measures are also sensitive to processes both at the conscious and unconscious levels (5).

Predicting outcome with neuroimaging

The most convincing outcome predictions come from neuroimaging studies of depression. While these studies relate to the pharmacotherapy of depression, they can be at least conceptually extended to psychotherapy. A Landmark FDG-PET study of the pharmacological treatment of unipolar depression found that activity in the rostral ACC uniquely differentiated treatment responders from non-responders (78). Responders were hypermetabolic prior to treatment with respect to comparison subjects, while non-responders were hypometabolic. The predictive value of pre-treatment activity in the rostral ACC in depression has been confirmed by subsequent studies. Rostral ACC activity predicted better response to paroxetine treatment (79) as well as to partial sleep deprivation therapy (80, 81). More recently, Pizzagalli et al. (82) recorded scalp electroencephalography (EEG) activity in nortriptyline-treated depressed patients, focusing on one EEG frequency band thought to be generated by the anterior cingulate. Again, patients showing electrical hyperactivity in the rostral cingulate before treatment showed better response 4-6 months after treatment, an effect that was not related to pre-treatment depression severity. In the first study examining functional recruitment of the rostral cingulate, rather than its baseline activity or metabolism, Davidson et al. (83) registered fMRI activation in response to viewing negatively valenced visual stimuli, compared with neutral stimuli. They likewise found that higher pretreatment activation of the rostral cingulate predicted a lower depression symptom scale score 8 weeks after treatment (5). In major depression, cognitive control may be important for regulating the effects of negative mood over perception, thoughts, and behaviour. Patients with higher levels of activity in the rostral cingulate before therapy may thereby be in a better position for recovery (5).

Preliminary imaging studies of OCD implicate a different area of the prefrontal cortex, the orbitofrontal cortex (OFC), in predicting treatment response. The OFC is highly activated during symptom provocation in OCD patients (84, 85). One FDG-PET study of OCD found that lower pre-treatment levels of activity predicted better response to drug therapy (86), lower pre-treatment metabolism of the OFC predicted better response to medications than to psychotherapy, whereas higher OFC metabolism predicted the opposite result (35).

Kumari et al. (87) investigated neurological basis of responsiveness to CBT in schizophrenic patients. They found a relationship between post-CBT improvements and a more evident activity within the dorsolateral prefrontal cortex.

In conclusion, specific brain areas may predict a beneficial response to CBT-treatment in patients with mental illness. Prediction of treatment response in general is difficult and a matter of actual discussion, and to date clinical evaluation remains much better established. These findings need to be replicated in relatively larger samples and supplemented with pre-CBT assessment of relevant functions using sophisticated neuropsychological tests to confirm the neuropsychological significance of neuroimaging techniques predictors in a direct manner.

Functional brain imaging: implications for psychotherapeutic interventions

Nuclear imaging techniques enable an evaluation of dynamic changes in neural activity. These variations can be charted with accuracy and occur in regions known to support cognition and behaviour. Advanced neuroimaging methods allow to identify a relationship between impairments in cerebral regions and pathological outcomes. It represents a tool for predicting psychiatric diseases with regard to devise an appropriate psychotherapeutic intervention and anticipate a possible chronic evolution. Neuroimaging studies might yield benefits in clinical diagnosis developing an earlier identification of the illness and its possible course; as a result of that a psychiatric intervention could be provided in an effective and efficient way.

In clinical practice, knowledge derived from anatomic images complements information collected from medical examination. The clinician has to recognize the biological contribution of the disorder and, by that means, may help alleviate the severity of impairment and shorten the duration of mental illness.

Thereby, neuroimaging techniques could emerge as a key method in clinical diagnosis of psychiatric disorders. The information performed by a neurobiological assessment of the subject affected by psychiatric illness would strengthen the diagnostic objectivity of many psychiatric disorders. Neuroimaging techniques earn a special emphasis as the important theme of a refined research and programmed psychotherapeutic interventions.

The availability of a wide range of diagnostic possibilities offered by modern neuroimaging may bring to light risks and limitations, so an appropriate and economical use of these tools is recommended in order to control and minimize false discovery rates. In fact, the image recognized at first glance may not be responsible for the clinical findings. The correlation of image pathology and clinical findings requires functional and topical anatomic knowledge.

Neuroimaging studies have revealed sensible effects of different modalities of psychotherapy on brain function with demonstrable neurobiological correlates across a range of mental illnesses. Functional neuroimaging investigations of psychotherapy give evidence that specific brain areas can be neurophysiologically and neurochemically modulated, and these changes concern key regions involved in perception, pain sensation, movement, cognitive and emotional processing (88). Cerebral activity modulation and regional specialization might suggest complex interaction of several neurotransmitters driving different neural circuitries. In a systematic review Frewen and his coworkers have identified some brain areas that exhibit changes in glucose metabolism and brain blood flow, in particular dorsolateral, ventrolateral and medial prefrontal cortices, anterior cingulated, posterior cingulated and insular cortices (89). In this perspective functional imaging can be potentially used to monitor treatment effects and aid in the choice of the optimal therapy. In the context of psychotherapeutic effect on brain activity, cognitive therapy and interpersonal therapy represent the most commonly used interventions and there is good evidence that these psychotherapies are able to modulate brain responses, improve symptoms and reduce relapse (88). On the other hand, neuroimaging studies demonstrated that dynamic psychotherapy stimulated brain cells and produced changes in cerebral metabolic rates (90). In a recent original investigation de Greck and colleagues (91) have compared twenty acute somatoform disorder patients with twenty healthy controls treated with multimodal psychodynamic psychotherapy. After a psychodynamic treatment program patients experienced major improvement in mood and relieved somatic symptoms of depression. The fMRI comparison reported that patients compared to controls showed underactivation in the left postcentral gyrus and the right ventroposterior thalamus. Furthermore it has been observed an activation of the left postcentral gyrus that appears to be related to remission of somatic symptomatology (91). The effort of further studies in this area may take advantage of neuroimaging techniques to investigate a wider range of psychotherapeutic interventions with the purpose of improving clinical decision making, treatment and outcomes.

A logical next step in addressing this problem would involve, at least, additional functional scans interpolated during the course of therapy, and at best, real-time imaging during psychotherapy sessions themselves. Technical and logistical limitations of fMRI, PET, and SPECT preclude the naturalistic use of these imaging tools in such a manner. However, novel neuroimaging technologies hold some promise for these applications. For instance, near-infrared spectroscopy (NIRS) permits measurement of cortical CBF less invasively than fMRI, and is both more portable and less expensive. Safe and practical for repeated measures, NIRS has been employed to measure CBF in patients with a variety of neuropsychiatric conditions (92) and in research involving basic auditory and cognitive processing (93). A second optical technique currently in development, two-photon microscopy, can potentially image deeper brain activity in vivo even on the cellular level (94); it has been suggested that in the future this technique may find its way into psychotherapy research as well (95). Just as psychophysiological recording methods have been used to permit simultaneous measurements from both patient and therapist (96), the use of next-generation, non-invasive optical techniques could also permit simultaneous measurements in clinical settings, providing a powerful assay of patient–therapist interactions (14). For future investigations, protocols should compare the effects of different methodologically psychotherapeutic approach and wherever possible, research should include molecular techniques such as radioligand imaging or biochemical analysis of metabolites to integrate functional neuroimaging techniques.

Conclusions and recommendations

Medical and technical advantages in neuroradiology have led to new diagnostic and therapeutic approaches in medicine due to the highly invasive nature of the classic neuroradiologic procedures. Neuroimaging techniques are present in the current practice and their clinical value has been established also as important research tools. These techniques have been developed in the second half of the twentieth century and within a few decades they have replaced the traditional procedures.

While functional neuroimaging techniques have revolutionized biological psychiatry research over the past decade, the potential of neuroscientific tools to explore and refine psychosocial interventions remains largely untapped. With efforts to understand basic psychological constructs in neurological terms, initial forays into the field of neuroimaging of psychotherapy have suggested plausible and apparently convergent mechanisms by which therapy changes the brain. The specific implications of this kind of research on clinical practice remain uncertain, but it is likely that additional work in this area will further demystify and validate psychotherapy for patients and clinicians alike (11, 97). Pharmacotherapy and psychotherapy converge in a common change of neuronal functions that might be detected by imaging techniques and resemble the correlate of clinical improvement. Functional neuroimaging offers the promise to improve clinical outcomes in two ways: first, by helping to inform treatment selection, and second, by providing an enhanced vocabulary for discussing psychological and therapeutic concepts central to psychotherapy. The added perspective of functional brain imaging, when used to its full potential, may thus strengthen the credibility and utility of a timehonoured mainstay in psychiatric treatment (14).

Abbreviations

^{99m}Tc-HMPAO SPECT = (99m)technetium-hexa-methyl-propylene-amine-oxime SPECT
ACC = Anterior cingulate cortex
BDNF = Brain-derived neurotrophic factor
BT = Behavioural therapy
CBASP = Cognitive behavioural-analysis system of psychotherapy
CBF = cerebral blood flow
CBT = Cognitive behavioural therapy
EEG = Electroencephalography
FDG-PET = Fluorodeoxyglucose-positron emission tomography
fMRI = Functional magnetic resonance imaging
IPT = Interpersonal therapy
MBCT = Mindfulness-based CT
MDD = Major depressive disorder
NIRS = near-infrared spectroscopy
OCD = Obsessive-compulsive disorder
OFC = Orbitofrontal cortex
PET = Positron emission tomography
PFC = Prefrontal cortex
PTSD = Post-traumatic stress disorder
SPECT = Photon emission computed tomography
SSRI = Selective serotonin reuptake inhibitor
Xe-CT = Xenon-enhanced computed tomography

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