FUNCTIONAL IMAGING HAS ASSUMED A CENTRAL ROLE IN NEUROSCIENCE RESEARCH IN THE PAST TEN YEARS. POSITRON EMISSION TOMOGRAPHY (PET) AND SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) ENABLE THE VISUALIZATION OF BLOOD FLOW OR GLUCOSE METABOLISM IN THE RESTING STATE. FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI) IS USED TO MEASURE BRAIN ACTIVITY IN RESPONSE TO A STIMULUS OR TASK. fMRI, IN PARTICULAR, ALLOWS INSIGHT INTO THE PHYSIOLOGY AND PATHOLOGY OF PERCEPTION AND COGNITION AND HAS BECOME AN INDISPENSABLE TOOL FOR PSYCHOLOGICAL, NEUROLOGICAL, AND PSYCHIATRIC RESEARCH. ITS CLINICAL APPLICATIONS, HOWEVER, REMAIN VERY LIMITED AT PRESENT. ITS MOST IMPORTANT CURRENT USE IS FOR PREOPERATIVE BRAIN MAPPING.

IN PSYCHIATRY, fMRI HAS LED TO AN IMPROVED UNDERSTANDING OF THE CEREBRAL CORRELATES OF PSYCHOPATHOLOGICAL PHENOMENA (e1, e2), COGNITIVE DISORDERS, AND GENETIC RISK FACTORS. STUDIES ON CHANGES IN BRAIN ACTIVITY DURING THE TREATMENT OF MENTAL ILLNESS MAY HAVE PARTICULAR CLINICAL RELEVANCE. FUNCTIONAL NEUROIMAGING HAS BEEN USED TO STUDY THE EFFECTS OF TREATMENT, NOT JUST WITH MEDICATIONS OF DIFFERENT KINDS, BUT ALSO WITH ELECTROCONVULSIVE THERAPY (e4), VAGUS NERVE STIMULATION (e5), AND, LAST BUT NOT LEAST, VARIOUS TYPES OF PSYCHOTHERAPY (Table). THIS USE OF PSYCHOLOGICAL TECHNIQUES (PSYCHOMETRY AND PSYCHOTHERAPY) IN COMBINATION WITH BIOLOGICAL TECHNIQUES (FUNCTIONAL NEUROIMAGING) TYPIFIES THE TREND IN MODERN PSYCHIATRY TOWARD THE INTEGRATION OF THESE TWO APPROACHES TO MENTAL ILLNESS, WHICH WERE ONCE WIDELY HELD TO BE INCOMPATIBLE.

POSSIBLE CLINICAL APPLICATIONS OF FUNCTIONAL NEUROIMAGING IN PSYCHIATRY INCLUDE:

- ASSESSMENT OF THE EFFECTS OF TREATMENT,
- DETERMINATION OF DIFFERENTIAL INDICATIONS FOR TREATMENT,
- IDENTIFICATION OF TARGET AREAS FOR NEUROPHYSIOLOGICAL TREATMENT METHODS, EITHER INVASIVE (DEEP BRAIN STIMULATION) OR NONINVASIVE (TRANSCRANIAL MAGNETIC STIMULATION), AND
- DEVELOPMENT OF NEUROBIOLOGICALLY INSPIRED TREATMENTS SUCH AS NEUROPSYCHOTHERAPY AND NEUROFEEDBACK.

THESE CLINICAL PROSPECTS WILL BE DISCUSSED AFTER A BRIEF REVIEW OF THE RESEARCH TECHNIQUES THEMSELVES AND OF THE STUDIES THAT HAVE BEEN PERFORMED WITH THEM TO DATE TO ASSESS THE EFFECT OF PSYCHOTHERAPY.
Research techniques of functional neuroimaging in psychiatry

The classic method of demonstrating changes in brain function after psychotherapy or pharmacotherapy involves measurement of the cerebral blood flow or glucose metabolism at rest. This technique is based on the assumption that the intervention under study achieves its beneficial clinical effect (symptom reduction) by changing baseline cerebral activity. This assumption is most plausible when the condition in question can be shown to be associated with abnormal cerebral activity before it is treated. In the absence of any reliable evidence of regional hyper- or hypoactivity at rest before treatment, there is a risk that this method will yield false negative results.

In such cases, functional neuroimaging with symptom provocation may be a more sensitive way of detecting treatment-related changes. The classic application of this technique is to the study of specific phobias, e.g., arachnophobia, in which clinical symptoms can be induced with appropriate pictures or film clips. The success of symptom provocation is gauged with questionnaires or psychophysiological methods. The goal is to demonstrate abnormal brain activity with functional imaging correlated with the presence of symptoms, e.g., activity in the limbic system of persons with arachnophobia while looking at pictures of spiders, but not in the limbic system of normal controls exposed to the same pictures (1). Effective treatment ought to be accompanied by a normalization of the abnormal activity in parallel with an improvement of symptoms. The major limitation of this technique is that clinically relevant conditions only rarely have such a narrowly circumscribed phenotype. In syndromes with more complex phenotypes, such as depression, a restricted focus on a single symptom in a provocation study might yield oversimplified or erroneous conclusions about disease-related changes in brain activity.

One advantage of functional neuroimaging with symptom provocation, in comparison to measurements at rest, might be a higher retest reliability, because the signal is presumably less dependent on uncontrollable factors. This question deserves systematic study, because the elimination of confounding effects, such as that of different levels of cognitive activity in the "resting states" before and after treatment, is a challenge facing all researchers that use functional neuroimaging to measure the effect of treatment.

Other poorly controllable confounding factors include the global effects of medication on brain metabolism-e.g., in studies in which patients are treated with both psychotherapy and medication-and non-specific physiological variables such as the pattern of sleep, the time since the last meal, and the consumption of caffeine and nicotine. These effects are only partly compensated for by the normalization of regional effects on global brain metabolism that is routinely performed as part of the processing of PET and SPECT images. The quantitative conclusions that can be drawn are, therefore, limited.
Treatment effects in obsessive-compulsive disorder

Current pathophysiological models of obsessive-compulsive disorder postulate uncontrolled neuronal activity in the thalamus, orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC). Pathological activation of the corpus striatum (Figure 1) might play an important causal role; this structure influences the “gating” function of the thalamus by way of a cortico-striato-thalamocortical regulatory loop. In fact, most functional neuroimaging studies at rest and with symptom provocation have revealed hyperactivity in the thalamus, OFC, and ACC, as well as in the caudate nucleus (though less consistently).

Three PET studies on the effect of psychotherapy on obsessive-compulsive disorder have been performed to date. All three showed a reduction of activity in the right caudate nucleus (2, 3, 4). Moreover, patients with obsessive-compulsive disorder were found to have an elevated correlation between striatal, thalamic, and OFC activity that was no longer present after successful treatment. This was true both for patients treated with cognitive behavioral therapy and for patients in the control group, who were treated with the selective serotonin reuptake inhibitor (SSRI) fluoxetine (2, 3). The convergence of the biological effects of psychological and pharmacological intervention is especially relevant to our understanding of the mechanisms of action of psychotherapy. A newly published fMRI study with symptom provocation (5) provides further evidence along the same lines, revealing lower activity in the thalamus, as well as in the frontal lobe and cingulate cortex, after successful treatment. The behavioral therapy (BT) and SSRI groups could not be separately analyzed in this study because of the small number of patients.

The clinically relevant question of possible differences between the cerebral mechanisms underlying obsessions and compulsions cannot yet be answered from the findings of functional neuroimaging studies. All studies involving symptom provocation were limited, for obvious practical reasons, to the provocation of obsessive thoughts (6). The intervention studies discussed above did not reveal any difference between the effects of cognitive behavioral therapy (CBT) on these two symptom complexes.

Treatment effects in phobias

Specific phobias are especially well suited for study with fMRI, because the symptoms can be provoked in a standardized manner. In contrast, symptom provocation in obsessive-compulsive disorder or post-traumatic stress disorder must be tailored to the symptoms and history of the individual patient. Symptom provocation studies monitoring the effect of treatment in phobias have yielded promising initial results.
A study on the cerebral correlates of the successful behavioral therapy of arachnophobia revealed hyperactivity in the parahippocampal gyrus and the dorsolateral prefrontal cortex before the intervention, which normalized after only four exposure sessions (7). Another arachnophobia study (8) showed that video clips of spiders provoked greater than normal activation in the insula and anterior cingulate cortex, which normalized after successful CBT.

In patients with social phobia, reduced activity was found in the amygdala and neighboring areas both after psychotherapy and after treatment with the SSRI citalopram (9). A possible role for the amygdala in the maintenance of phobic reactions would have implications for etiological research, as it would be most consistent with learning-theoretical models of the anxiety disorders, e.g., an anxiety conditioning model. It is hoped that further interventional studies using functional neuroimaging for treatment monitoring, beyond the small number that have been performed to date, will shed further light on this question.

Because standardized images are easiest to use in disorders with relatively homogeneous symptoms, such as isolated arachnophobia, these disorders also lend themselves particularly well to multicenter studies. Multicenter functional imaging studies along similar lines have already been carried out successfully on a nationwide level, e.g., in schizophrenia. We hope that the current initiatives in support of psychotherapeutic research will give rise to analogous projects employing standardized treatment and imaging protocols to study anxiety and obsessive-compulsive disorders.

**Functional neuroimaging and depression**

Symptom provocation under experimental conditions is more difficult in depression than in the disorders discussed above and can at best induce only some, but not all, components of the depressive syndrome. The brain areas participating in the control of mood can be detected in normal subjects by the induction of sadness with pictures or short stories; in particular, activity in the subgenual area, i.e., the portion of the cingulate gyrus that lies under the genu of the corpus callosum (10), and the amygdala is correlated with the degree of sadness. The applicability of these findings to depression is debated; one study (10) paradoxically showed that the same stimulus that induced sadness in normal persons led to a remission of symptoms in patients with depression. It seems, however, that the cerebral networks for sadness and depression do indeed overlap, at least in part.

Aside from the problem of methodologically valid symptom provocation, the use of functional neuroimaging to study the mechanisms of depression and its treatment is further complicated by the lack of an unambiguous metabolic correlate of depression in the brain.

Most studies have shown prefrontal hypoactivity normalizing after remission (12). The increase of prefrontal metabolism accompanying improvement of symptoms was independent of whether the improvement followed pharmacotherapy with fluoxetine or placebo treatment (13), e.g., inpatient hospitalization without any specific treatment of depression. Another study (14), however, yielded a contradictory result: in patients whose depressive symptoms responded well to cognitive behavioral therapy (CBT), the improvement was associated with a reduction of metabolism in the entire lateral prefrontal cortex. A reduction of prefrontal glucose metabolism was also found after successful treatment with interpersonal therapy (IPT) (15).

The authors propose the following model to explain this divergence between pharmacotherapy and psychotherapy. Activity in the prefrontal cortex declines over the course of treatment with CBT in parallel with negative thoughts. The simultaneously observed increase in the activity of the hippocampus and dorsal cingulated gyrus correlates with increased attentiveness to emotional stimuli. The effects of pharmacotherapy with SSRI-increased prefrontal activity and decreased activity in the hippocampus and other limbic areas, such as the ventral cingulate gyrus—are in the opposite direction to those of CBT because they reflect a direct influence on synaptic transmission, rather than cognitive control (14).

This model is of interest because it is not limited to a change in the activity of a single region of the brain. In a disorder as complex as the depressive syndrome, clinical improvement probably results from a modification of the interactions of multiple brain regions. In any case, the differences between treatment types should be investigated in further prospective studies employing standardized imaging techniques.

Functional imaging in the more restricted sense, i.e., the measurement of blood flow, blood oxygenation, or glucose metabolism with PET, SPECT, or fMRI, hardly permits
any inferences to be drawn about molecular mechanisms. This might be achievable with a combination of these techniques with molecular imaging methods, such as radioligand PET or SPECT and magnetic resonance spectroscopy. With its high spatial resolution, functional neuroimaging permits more precise identification of the target areas for molecular imaging.

**Functional neuroimaging and neurophysiological treatment**

The reproducibility of the above-described changes in resting brain metabolism in depression is not merely of theoretical interest. Mayberg and colleagues recently published a pilot study of deep brain stimulation (DBS) in the cingulate region in patients with intractable depression (16). They made explicit use of the findings of functional neuroimaging to provide a rationale for this type of treatment and to choose the target site of stimulation.

In this study, DBS electrodes were implanted into the white matter underlying the subgenual cingulate cortex in six patients. The authors of the study, using PET, had previously found this area to be hyperactive in patients with depression. Four patients were clinically improved six months after implantation. The small number of cases and the lack of a control group make it difficult to generalize from these findings. Larger, controlled studies of cingulate DBS must certainly be awaited before the clinical utility of this method can be assessed.

**Perspectives for functional neuroimaging in clinical psychotherapy**

Functional neuroimaging may perhaps point the way toward less invasive treatment strategies, including what has been called “apparatus-based psychotherapy” (17). New technical improvements enabling real-time analysis of fMRI data have led to the development of neurofeedback techniques based on fMRI, which are analogous to earlier ones based on electroencephalography (EEG). Just as in classic biofeedback, persons undergoing neurofeedback train themselves to regulate their own brain activity. Subjects in a pilot study were able to manipulate the fMRI activity of their anterior cingulate cortex voluntarily (Figure 2) (19).

This type of training can only be performed over the course of several sessions in an MRI scanner and therefore requires a certain amount of discipline on the part of the patient. Moreover, any clinical effects it might have, such as an improvement of depressive symptoms after voluntary suppression of cingulate activity, remain to be demonstrated. Initial clinical findings have been published for this form of training when used to treat pain (20).

Another approach to neurobiologically based psychotherapy is neuropsychotherapy. In this approach, the scientific understanding of dysfunctional regulatory circuits in various mental illnesses is exploited to develop psychotherapeutic techniques that can specifically influence these circuits (21).
Functional neuroimaging finds further application in psychiatry as a means of monitoring treatment effects and of studying the neurophysiological correlates of response and non-response to treatment. The difficulty (and often impossibility) of predicting a patient’s responsiveness to a certain type of pharmacotherapy or psychotherapy on clinical grounds alone is one of the greatest problems currently facing clinical psychiatry. In the future, functional neuroimaging may help us predict the likelihood that a particular form of treatment will be successful before it is initiated (22). This information can be used in clinical decision-making, e.g., in the decision whether to apply pharmacotherapy or psychotherapy.

Some initial results of this type are already available. In a study of patients with obsessive-compulsive disorder, a relationship was found between glucose metabolism in the left orbital frontal cortex and the success of either behavioral therapy or treatment with fluoxetine (23). A high metabolic rate was correlated with good responses to behavioral therapy, but poor responses to pharmacotherapy. It is clearly not possible to make any treatment recommendations on the basis of this small, non-randomized study. Nonetheless, the concept underlying it seems promising, i.e., that differences between specific pathophysiological mechanisms can be used to identify subgroups within a clinical diagnostic category that are more likely to respond to certain forms of treatment.

With the exception of a few case studies (22), functional neuroimaging studies involving psychotherapy have been limited, so far, to manualized short-term therapies such as cognitive behavioral therapy and interpersonal therapy. A further extension of functional neuroimaging to the study of psychodynamic techniques would certainly be of great interest, particularly because concrete hypotheses on their neurobiological effects have already been proposed on the basis of experimental studies of plasticity in animals (24).

In conclusion, the newer methods of functional neuroimaging, particularly functional magnetic resonance imaging, have already made major contributions to basic research in psychiatry. They now seem to have arrived at the threshold of clinical applicability. The application of functional neuroimaging to psychotherapy would not imply that older, psychological techniques have been discarded and replaced by newer, biological ones. Rather, it would enable further refinement of the indications for, and use of, therapeutic methods in the light of an improved neurobiological understanding of mental illness.

Conflict of Interest Statement

The authors declare that no conflict of interest exists according to the Guidelines of the International Committee of Medical Journal Editors.

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For e-references please refer to the additional references listed below.


