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FEATURE REVIEW

How psychotherapy changes the brain – the contribution of functional neuroimaging

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A thorough investigation of the neural effects of psychotherapy is needed in order to provide a neurobiological foundation for widely used treatment protocols. This paper reviews functional neuroimaging studies on psychotherapy effects and their methodological background, including the development of symptom provocation techniques. Studies of cognitive behavioural therapy (CBT) effects in obsessive-compulsive disorder (OCD) were consistent in showing decreased metabolism in the right caudate nucleus. Cognitive behavioural therapy in phobia resulted in decreased activity in limbic and paralimbic areas. Interestingly, similar effects were observed after successful intervention with selective serotonin reuptake inhibitors (SSRI) in both diseases, indicating commonalities in the biological mechanisms of psycho- and pharmacotherapy. These findings are discussed in the context of current neurobiological models of anxiety disorders. Findings in depression, where both decreases and increases in prefrontal metabolism after treatment and considerable differences between pharmacological and psychological interventions were reported, seem still too heterogeneous to allow for an integrative account, but point to important differences between the mechanisms through which these interventions attain their clinical effects. Further studies with larger patient numbers, use of standardised imaging protocols across studies, and ideally integration with molecular imaging are needed to clarify the remaining contradictions. This effort is worthwhile because functional imaging can then be potentially used to monitor treatment effects and aid in the choice of the optimal therapy. Finally, recent advances in the functional imaging of hypnosis and the application of neurofeedback are evaluated for their potential use in the development of psychotherapy protocols that use the direct modulation of brain activity as a way of improving symptoms.
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Introduction

It has long been recognised by clinicians that psychological interventions can profoundly alter patients' sets of beliefs, ways of thinking, affective states and patterns of behaviour. Yet the putative mechanisms and underlying changes in the brain have only recently attracted the attention they deserve.[1] This enterprise is important for two main reasons. First, psychotherapy needs to be based on a sound understanding of the biological processes involved. There is no reason why this general standard of contemporary medicine, which is, for example, needed in order to detect and fight potential side effects, should not apply here as well. Second, a better understanding of these biological mechanisms might aid in the improvement of therapeutic interventions or even in the utilisation of these very mechanisms, as in the case of neurofeedback.

One reason for the sluggish development of research into the neural side of psychotherapy might be that here plastic changes in the human brain have to be detected with noninvasive techniques, while conventionally plasticity research has been conducted at the cellular level. Yet the tools of noninvasive functional brain imaging can now reliably detect training- and learning-related changes in brain activation patterns in healthy volunteers,[2] and there is no reason why this should not be possible in those affected by mental disorders as well. Potentially, functional imaging can detect psychotherapy-related changes at the level of brain areas and circuits, and thus contribute to an elucidation at least of the most global neural mechanisms (Figure 1a). Such an approach would not only benefit basic research into the mechanisms of action of psychotherapy, but also aid our understanding of differences and commonalities between psycho- and pharmacotherapy, provide a further tool for the evaluation of therapy effects and, might ultimately help clinicians to select optimal

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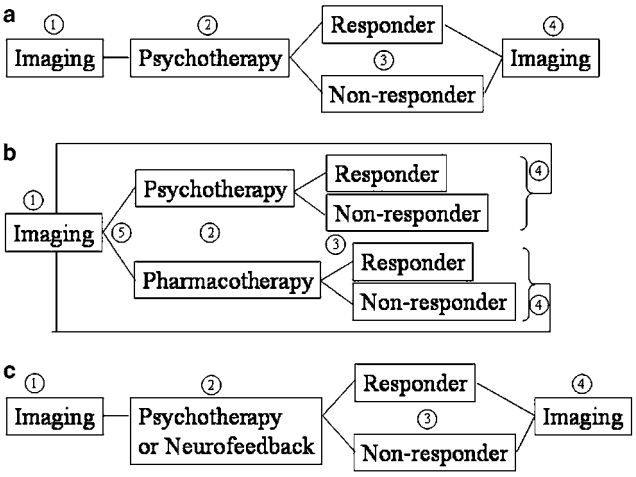

Figure 1 Three possibilities of integrating psychotherapy and functional neuroimaging with potential clinical implications. (**a**) Baseline imaging measures (with any of the technique discussed in the review) are obtained (1) before a course of psychotherapy (2), after which patients are classified as responders or nonresponders based on symptom improvement or other clinical outcome measures (3) and re-examined with the imaging protocol (4). This technique allows for the assessment of psychotherapy-related changes in brain activation and their specificity for successful outcome. With some modifications, this approach has been used in all studies cited in Tables 1–3. (**b**) Baseline imaging measures are obtained (1) before a course of either psycho- or pharmacotherapy (2), after which patients are classified as responders or nonresponders (3). This outcome information is entered into an analysis of the pretreatment imaging data (4) with the aim of deriving activation patterns that are predictive of treatment response (5). (**c**) Imaging identifies abnormal activity in a particular brain area or network in a patient (1). This abnormal brain activity is targeted by psychotherapy (based on information derived from studies of type (**a**), neurofeedback, or a combination of both (2). Patients are then classified as responders and nonresponders (3). The outcome data can then be compared with standard treatment protocols. Post-treatment imaging (4) will be informative but not mandatory.

treatment for individual patients on the basis of baseline functional activation patterns[3,4] (Figure 1b).

Most functional imaging studies into psychotherapy effects have been conducted with nuclear medicine methods like positron emission tomography (PET) or single photon emission computed tomography (SPECT), and assessed changes in brain metabolism or blood flow between a pre- and post-treatment scan. The use of functional magnetic resonance imaging (fMRI), which does not expose the patient to radiation, would potentially confer the advantage of more measurement points, including measures of brain activation during treatment or at follow-up. Yet fMRI has traditionally been used to probe the brain activation patterns during perceptual or cognitive tasks, rather than to measure baseline brain metabolism. The use of fMRI for the detection of psychotherapy-related changes thus presupposed two methodological developments, the measurement of the neural correlates of psychopathology[5] and techniques for symptom provocation in the MRI environment.[6]

In this article, I shall first review functional imaging studies that used symptom provocation techniques to mimic psychopathological states in a laboratory setting. This avenue of research has been particularly successful in obsessive-compulsive disorder (OCD) and simple phobias, and is also being pursued for social phobia, depression, and post-traumatic stress disorder (PTSD). I shall go on to review the reports of treatment trials that monitored the effects of psychotherapy with one of the functional imaging techniques, sometimes comparing it with a group receiving standard pharmacotherapy. Subheadings for the review of these studies will be according to disease (phobia, OCD, depression), rather than imaging modality. The selection of the material reviewed in this section was based on a Pubmed search for the conjunctions of the term 'psychotherapy' with 'functional imaging', 'functional magnetic resonance', 'positron emission', and 'single photon emission', on the reference sections of the retrieved original reports, and on a textbook to which the author contributed.[7] Studies on patients under the age of 18 or on single cases were not included, nor were studies employing other biological markers or looking at psychological interventions for substance abuse disorders. A search of The Cochrane Database of Systematic Reviews (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clsysrev_articles_fs.html, accessed on 14 December 2005) did not yield existing systematic reviews of this topic. In the final sections, I shall discuss potential molecular mechanisms of psychological interventions, review findings on neurobiological effects of specific psychological interventions and suggest topics for further research.

Symptom provocation and functional imaging

Symptom reduction is one of the main aims of psychotherapy in general, and can be regarded as the benchmark against which the success of behavioural and cognitive therapies is to be measured. Elucidation of the neural correlates of symptom reduction is therefore a primary goal of any investigation into the biological mechanisms of psychotherapy. The reliable induction of the symptoms in question in the imaging environment has been an important tool for this enterprise. Such a symptom provocation will permit the comparison of brain responses to trigger scenarios (e.g. for social phobia or PTSD) or stimuli (e.g. for simple phobias) before and after treatment, and thus the assessment of therapy effects on neural activation. It furthermore has the benefit of allowing the comparison of response patterns to trigger stimuli in patients and healthy controls,[8–10] elucidating

commonalities and differences in the processing of aversive material.

A paradigm for the provocation of OCD symptoms during PET scanning was developed by Rauch *et al.*[11] They demonstrated increased regional cerebral blood flow (rCBF) in the right caudate, left anterior cingulate cortex (ACC) and bilateral orbitofrontal cortex (OFC) when patients were exposed to individually tailored provocative stimuli compared to neutral stimuli. Orbitofrontal–striatal–thalamic activation was also reported by McGuire *et al.*,[12] who additionally found activity in the left hippocampus and posterior cingulate gyrus to correlate with the intensity of OCD symptoms. They suggested that the former network might reflect urges to perform compulsive movements, while the latter might be more related to the accompanying anxiety. Breiter *et al.*[8] used a similar approach with fMRI, showing increased blood oxygenation level-dependent (BOLD) signal in the right caudate, bilateral OFC, prefrontal cortex (PFC) and temporal lobes. Thus, the converging evidence from these studies points to increased neural activity in the right caudate and bilateral OFC during the experience of symptoms of OCD. Additionally, the insula seems to be activated when contamination fear is prominent.[10] OFC and insula were activated during the provocation of phobic symptoms as well,[13] as was the left amygdala.[14]

Symptom provocation studies of PTSD were based either on the presentation of trauma-related visual or acoustic stimuli or on script-driven imagery. The latter technique induces traumatic imageries and thus mimics flashbacks of the aversive events (as evidenced by both subjective ratings and psychophysiological parameters) by reading accounts of their individual traumatic experiences to patients during functional imaging.[15] Increased activation of the right amygdala was found across provocation techniques and imaging modalities,[15–17] while medial prefrontal areas were consistently reported to be less active in PTSD patients than controls when traumatic events had to be recalled.[18,19] In regions of the medial temporal cortex commonly associated with memory retrieval and visual association areas involved in mental imagery both higher and lower activation have been reported for PTSD patients, possibly reflecting the heterogeneity of patient samples across studies.

Both autobiographical scripts and visual material have been used to induce sadness in patients with depression and healthy volunteers. Beauregard *et al.*[20] found higher activation in ACC and left medial PFC in patients than controls. Mayberg *et al.*[21] found activity in the subgenual cingulate cortex to be high both when sadness was induced in healthy individuals and when dysphoric symptoms were present in patients with MDD. One consistent finding seems to be that the amygdala (particularly on the left) shows higher and/or longer responses to sadness-inducing stimuli in depressed patients than controls.[22,23] A normalisation of this induced amygdala hyperactivity has been observed after treatment with antidepressants,[22] but functional imaging studies of psychotherapy effects in depression have so far exclusively relied on resting state metabolic patterns. The same is true for most studies on OCD, while studies on phobia have utilised the symptom provocation techniques described above to assess the physiological effects of psychotherapy.

Functional imaging studies of psychotherapy effects

Obsessive-compulsive disorder

Increased activity in the right caudate was the common finding of symptom provocation studies in OCD across imaging modalities.[8,11] Correspondingly, all studies of the effects of cognitive behavioural therapy (CBT) in OCD on resting state glucose metabolism or blood flow (Table 1) so far reported a decrease in right caudate activity in treatment responders.[24–26] This decrease of caudate activity correlated with clinical improvement in one of the studies, and showed no difference between CBT and treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine.[24]

Two studies[24,25] reported a correlation between caudate, OFC and thalamus activity before treatment, which would conform to current pathophysiological models of OCD.[27,28] This correlation disappeared after treatment with either CBT[24,25] or fluoxetine,[24] again pointing to common or converging mechanisms between psycho- and pharmacotherapy. The confirmation of such converging effects would not only be clinically relevant but also help elucidate the mechanisms of psychotherapy at the cellular and neurotransmitter level.

The only fMRI study of CBT effects in OCD[29] assessed both effects on symptom provocation and on activation during a cognitive task (the Stroop task). Unfortunately, in this study, data from the CBT and the SSRI group had to be pooled because of otherwise insufficient power, which made a comparison between pharmaco- and psychotherapy impossible.

Phobias

Simple phobias are particularly suited to the investigation of treatment effects with fMRI because symptom provocation is relatively straightforward (Table 2). Whereas in most studies of OCD, PTSD and depression, the inducing triggers had to be tailored individually, the symptoms of spider phobia could be mimicked by standardised images[14] or film sequences[30] of spiders, contrasted with innocuous animals or natural objects. This use of identical stimulus material across participants removes a source of variance that is especially undesirable in studies with small sample sizes.

Paquette *et al.*[30] used this symptom provocation technique in order to assess the effect of symptom reduction by CBT directly. Before the intervention, patients showed increased activity of right dorsolateral PFC and parahippocampal gyrus to the aversive

Table 1 Psychotherapy effects in OCD

Authors	*Trial size/interventions and pre–post interval*	*Functional imaging technique*	*Post-treatment decreases*	*Post-treatment increases*
Baxter *et al.*[24]	$N=9$ CBT, $N=9$ fluoxetine, $N=4$ healthy controls[a], all 10 ± 2 weeks	FDG (fluoro-deoxyglucose)-PET, resting state, normalised data, no PVC[b]	Responders: right caudate; correlation between right OFC, caudate and thalamus	None
Schwartz *et al.*[25]	$N=9$ CBT, 10 ± 2 weeks	FDG-PET, resting state, normalised data, no PVC	Responders: caudate bilaterally; correlation between right OFC, caudate and thalamus[c]	None
Nakatani *et al.*[26]	$N=22$ CBT (some also received clomipramine), duration based on clinical improvement	Xenon-enhanced CT (measures rCBF), resting state	Right head of caudate	None
Nakao *et al.*[29]	$N=6$ CBT, $N=4$ fluvoxamine, 12 weeks	fMRI during Stroop task and symptom provocation	Bilateral OFC, DLPFC, ACC (symptom provocation)[d]	Bilateral parietal cortex, cerebellum (Stroop task)[d]

[a]Control groups are only listed where a second measurement after an interval comparable to the treatment period was obtained, not if they only served for comparison of pretreatment effects (as, e.g., in Nakatani *et al.*[26]).
[b]PVC: partial volume correction.
[c]For some parts of the PET data analysis, data were pooled with those from Baxter *et al.*[24].
[d]Because of the small *N*, data for the CBT and fluvoxamine groups were not analysed separately.

Table 2 Psychotherapy effects in phobias and panic disorder

Authors	*Trial size/interventions and pre–post interval*	*Functional imaging technique*	*Post-treatment decreases*	*Post-treatment increases*
Furmark *et al.*[34]	Patients with social phobia, $N=6$: CBT, $N=6$: citalopram, $N=6$: waiting list, all 9 weeks	PET with oxygen 15-labeled water, symptom provocation, normalised data, no PVC	Both treatment groups: bilateral amygdala, hippocampus, parahippocampal gyrus, further paralimbic areas	None
Paquette *et al.*[30]	Patients with spider phobia, $N=12$: CBT, 5 weeks	fMRI, symptom provocation	Right dorsolateral PFC, parahippocampal gyrus	Visual association areas; right inferior frontal gyrus
Straube *et al.*[31]	Patients with spider phobia, $N=14$: CBT, 2 sessions, $N=14$: waiting list	fMRI, symptom provocation	Bilateral insula, thalamus, ACC in treatment but not waiting list group	None
Prasko *et al.*[75]	Patients with panic disorder, $N=6$: CBT, $N=6$: different antidepressants, both groups 3 months	FDG-PET, resting state, normalised data	Both treatment groups: mainly right frontal and temporal regions, with partial overlap across groups	Both treatment groups: mainly left frontal and temporal regions, with partial overlap across groups

sequences. This difference disappeared after four intensive exposure sessions in a group setting. Instead, patients showed a higher activity in visual association areas for aversive than neutral sequences, similar to the pattern observed in the healthy controls. Thus, CBT seems to have led to a restitution of normal cortical processing of the spider sequences in these patients. A recent study by Straube *et al*.[31] employed a similar design, but added a waiting list patient group. Patients showed higher activation in the ACC and insula bilaterally when pretreatment fMRI was compared to healthy controls. This hyperactivation remained at the second measurement in the waiting list group, but disappeared in the group treated with CBT. Thus, again, CBT of spider phobia was accompanied by a normalisation of brain activity in specific areas. This reduction of ACC and insula activity might reflect (or underlie) the attenuation of the affective response to spiders after successful treatment.[31]

Yet these studies[30,31] probably do not present the full pattern of pathological activation in simple phobias. For example, no hyperactivity was observed before treatment in the amygdala in the study by Paquette *et al*.,[30] and neither study reported reduction of amygdala activity after treatment. This is at odds with most studies of affective stimulus processing and aversive conditioning, and indeed with current models of the pathophysiological network of simple phobias, and might be explained by habituation effects in the block design.[14]

Several studies of patients with social phobia have also shown hyperactivity of the amygdala, even with a weak form of symptom provocation, presentation of human faces.[32,33] After successful treatment, either with CBT or citalopram, activation of amygdala and hippocampus was reduced in the symptom provocation study by Furmark *et al*.,[34] who utilised a public speaking task. Again, it is interesting to observe that the pharmacological and psychological intervention seem to have modulated the same brain areas, in this case parts of the limbic system. In the studies on OCD (see preceding section), CBT and SSRI had similar effects on metabolic patterns as well, presumably leading to a reduction of the activity of fronto-striato-thalamic circuits.

Depression

While symptom provocation and resting state studies produced fairly consistent signatures of pathological metabolism for OCD (right caudate hyperactivity) and phobias (limbic and paralimbic hyperactivity), the situation is more complicated for major depressive disorder (MDD). Most studies of resting state blood flow or metabolism reported an anterior prefrontal hypoperfusion that normalised after the remission of symptoms of depression.[35,36] Conversely, the intervention study by Brody *et al*.[37] started from an initial prefrontal hypermetabolism that normalised in both the IPT- and the SSRI-treated group (Table 3).

Table 3 Psychotherapy effects in major depressive disorder (MDD)

Authors	*Trial size/interventions and pre–post interval*	*Functional imaging technique*	*Post-treatment decreases*	*Post-treatment increases*
Brody *et al*.[37]	$N=14$: IPT, $N=10$: paroxetine, $N=16$: healthy controls, all 12 weeks	FDG-PET, resting state, global normalised data, image fusion with MRI	Both treatment groups: bilateral PFC; IPT: left ventral ACC; paroxetine: left middle ACC	Both treatment groups: left temporal lobe
Martin *et al*.[39]	$N=13$: IPT, $N=15$: venlafaxine, all 6 weeks	HMPAO-SPECT, resting state, normalised data, no PVC	None	IPT: Right basal ganglia, posterior CC; Venlafaxine: right basal ganglia, posterior temporal cortex[a]
Goldapple *et al*.[38]	$N=14$: CBT, 26 ± 7 weeks (standard deviation), $N=13$: paroxetine, 6 weeks (sample from different study)	FDG-PET, resting state, normalised data, no PVC	CBT: bilateral PFC; Paroxetine: right hippocampus	CBT: bilateral hippocampus, dorsal CC; Paroxetine: left dorsolateral PFC

[a]The posterior temporal cortex activation was eliminated with one patient's exclusion.

Decreases in lateral prefrontal metabolism were also observed after successful treatment with CBT.[38]

In this study by Goldapple *et al.*,[38] the group that underwent pharmacological treatment differed from the CBT group in that it showed an *increased* metabolism in left dorsolateral PFC after the trial. Although this finding does not directly contradict that of Brody *et al.*,[37] because in that study the decrease of PFC metabolism in the SSRI group was more ventral and lateral, it indicates that mechanisms of pharmaco- and psychotherapy might be more divergent in MDD than in the disorders discussed above. Yet one region of convergence of the two approaches seems to be in the right basal ganglia, where another recent study[39] found increased activity after successful treatment with either IPT or venlafaxine, a combined serotonin and norephinephrine reuptake inhibitor.

The functional imaging studies of therapy effects in MDD thus yielded partly heterogeneous results across studies and also across treatment approaches. The heterogeneity across studies might be an effect of the many different symptoms that can contribute to a diagnosis of MDD according to the DSM IV,[40] the use of resting state (rather than symptom provocation) paradigms and the absence of well-characterised and replicable abnormalities prior to treatment.[41] It is also important to consider that all of the PET or SPECT studies on treatment effects in depression reported normalised, rather than absolute or quantitative regional blood flow or glucose metabolism (Table 3) (the same applies to studies on phobia and OCD, Tables 1 and 2). The normalisation approach yields ratios of activity for each region of interest (ROI) compared to the global mean of the whole brain or the ipsilateral hemisphere. Thus, changes in global brain metabolism or blood flow between pre- and post-treatment scan can influence the outcome in a ROI. An absolute increase in rCBF or regional glucose metabolism might still result in a lower ratio to global activity, if the latter increases more, and would thus be reported as post-treatment decrease of normalised activity. Fully quantitative studies[42] would be a way to resolve this issue, but are considerably more difficult and invasive.

Another important feature of the methodology employed in the reviewed studies is the absence of corrections for differences in tissue volume. Decreased regional blood flow or glucose metabolism, as measured by PET or SPECT, does not necessarily reflect reduced neural activity, but might be an effect of locally reduced grey matter volume. This 'partial volume effect' is due to the low spatial resolution of these techniques. It has been shown to explain, at least partly, reduced blood flow and metabolism in subgenual cingulate cortex in patients with depression.[43] In this data set, full correction for cortical volume differences even resulted in a reversal of the effect, with patients showing higher metabolic activity than controls.[44] Thus, any local hypometabolism in a patient group can be an effect of cortical volume loss in that area, although volume loss in areas outside the limbic–cortico–striato–pallido–thalamic loop has rarely been reported in MDD.[45]

Whether loss of brain tissue might have thus explained some of the metabolic decreases after treatment cannot be determined based on the present state of the literature. While some studies on children suffering from OCD found grey matter decreases after treatment with the SSRI paroxetine,[46,47] volumetric measures were stable in a group of adult patients with unipolar depression over a 3-month period of treatment with antidepressants.[43] It would certainly be helpful if future functional imaging studies also included high-resolution MRI before and after treatment to determine potential structural changes and enable partial volume correction.

At present, the available evidence suggests that any model that relies on global frontal hypometabolism to explain symptoms of depression and its reversal to account for treatment effects would be oversimplifying the complex nature of cortico-cortical and subcortical interactions in affective disorders. The difference between the neural correlates of clinical improvement after pharmacological and psychological interventions[37,38] is a case in point. These differences were particularly pronounced in the study by Goldapple *et al.*,[38] where opposite changes were observed in PFC (decrease after CBT, increase after paroxetine) and limbic areas (increase after CBT, decrease after paroxetine). The authors interpreted the specific CBT-related changes in brain activation as correlates of the learned reduction of ruminations and maladaptive associative memories (frontal decreases) and increased attention to emotional stimuli (limbic increases). The differences between CBT and pharmacotherapy were explained in the framework of top-down versus bottom-up effects, with CBT operating more through the former and pharmacotherapy more through the latter (e.g. limbic and subcortical areas).

The theoretical framework proposed by Goldapple *et al.*[38] to account for the observed differences in the neural effects of psycho- and pharmacotherapy is attractive because it recognises that any therapeutic improvement of a complex disorder like depression is likely to be mediated through altered interactions between several brain areas rather than unidirectional changes in a single region. It also allows for predictions about changes in specific networks based on the content and behavioural targets of a particular psychological intervention. However, it will ultimately have to be tested in prospective trials comparing pharmaco- and psychotherapy effects in depression, ideally with the inclusion of molecular markers of their respective effects at the synaptic level.

Molecular mechanisms of psychotherapy

What, then, can we infer from the functional imaging literature on the molecular mechanisms that underlie or modulate responses to psychotherapy? In the

absence of molecular imaging studies (e.g. PET with neurotransmitter receptor ligands) of psychotherapy effects, these inferences will have to be indirect. We can evaluate the extant functional imaging studies of psychotherapeutic interventions as to their compatibility with and impact on current neurobiological and neurochemical models of psychological disorders, and we can adduce parallels from pharmacological or alternative interventions, where molecular imaging studies have indeed been performed.

With the development of specific radiotracers of the serotonin transporter (SERT) for SPECT and PET,[48,49] *in vivo* molecular imaging studies of the effects of SSRIs have become feasible. The main consistent finding across these studies has been that radiotracer binding to SERT decreases with SSRI treatment, reflecting the expected blockade of binding sites by the SSRI. Blockade of SERT by SSRI has been documented for midbrain, striatum, amygdala and further subcortical areas. It has been shown to occur in healthy individuals[50] and in patients with depression,[50–52] social phobia[53] and OCD.[50,54] SERT occupancy was around 80% at therapeutic doses of the SSRIs fluoxetine, citalopram, sertraline and paroxetine and the serotonin and norephinephrine reuptake inhibitor velafaxine.[50]

How can these findings be related to the changes observed in the functional imaging studies discussed in this paper? The molecular imaging studies indicated SSRI binding to SERT in areas, where the functional imaging studies showed reduced blood flow[34] or glucose metabolism[24] in SSRI responders, for example, the amygdala for social phobia[53] and the striatum for OCD.[50] SERT-mediated reuptake of serotonin into the presynaptic cell, which is partly blocked by administering an SSRI, is an ATP-dependent and thus metabolically very demanding process. The reduced metabolic activity in these areas after treatment with an SSRI might thus reflect the decreased activity of SERT. Reduced striatal glucose metabolism in OCD and reduced limbic blood flow in social phobia were also observed after CBT.[24,34]

The similarity of the functional imaging findings indicates a convergence of the neural pathways that mediate pharmacotherapy and psychotherapy effects, at least for phobia and OCD. This convergence and the commonalities in the clinical effects might suggest that psychotherapy effects in anxiety disorders can also be mediated through the serotonin system.[55] However, this claim is at present not supported by biochemical or molecular imaging evidence for changes in the serotonin system after psychological interventions. Future studies of psychotherapy in anxiety disorders should therefore assess potential changes in neurotransmitter metabolites to determine which system is likely to be involved. Concurrently, molecular imaging will be needed to determine the level at which these changes take place. This would have to involve radiotracers that probe the presynaptic (e.g. transporter proteins), postsynaptic (e.g. receptors) and postreceptor (e.g. proteins involved in signal transduction) levels of synaptic transmission.[49] Functional imaging studies as discussed in this paper cannot resolve the molecular pathways mediating the therapy effects, but may play an important role in defining the target areas to be probed with the molecular techniques.

The molecular underpinnings of psychotherapy effects in depression likewise still wait to be explored. Molecular imaging studies of nonpharmacological interventions have only been performed for total sleep deprivation.[56] The therapeutic success of sleep deprivation was associated with lower binding of a dopamine D2 receptor ligand and thus higher dopamine release, and with reduction in cingulate perfusion. Reduced ACC glucose metabolism was also observed in patients with MDD who responded to IPT.[37] This might implicate the dopamine system in the therapeutic effects of IPT, but the other monoamine neurotransmitters have been shown to influence the activity of the cingulate as well.[37,57] The reduced activity in lateral PFC, as evidenced by reduced glucose metabolism, after both IPT[37] and CBT[38] has been suggested to be an effect of increased synaptic serotonin, either through GABAergic inhibitory interneurons or direct suppression of glutamatergic activity.[37] Yet, multiple neuromodulator systems could be responsible. Direct molecular imaging of psychotherapy effects in depression will therefore be paramount. Again, functional imaging has identified key nodes in the pathophysiological network of depression, such as the cingulate, basal ganglia, lateral PFC and hippocampus, that will be worthwhile targets for these molecular studies.

Intervention-specific effects

The functional imaging studies of psychological interventions in mental disorders, which were reviewed in the previous sections, elucidated some of the neural correlates of symptom reduction and general clinical improvement. In most studies that compared pharmacological and psychological interventions (with the exception of Goldapple *et al.*,[38]) the effects on cerebral metabolism were rather similar. Thus, they are informative on the dysfunctional circuits generating the symptoms of a specific disease and potentially useful for treatment evaluation, but reveal little about any specific neural mechanisms through which psychotherapy might operate. In order to clarify the neural mechanisms of a psychological intervention, it will probably not suffice to compare it to standard pharmacotherapy in a classic controlled trial setting. Rather, investigators will have to change the parameters of the treatment protocol, varying the desired mental states that they aim to induce, and apply it across different patient groups. While this will be very challenging even with the most standardised CBT protocols, the results obtained with hypnosis, targeting specific mental states, and with neurofeedback, explicity targeting specific brain areas, are encouraging.

Functional imaging of hypnosis

Positron emission tomography images were acquired during hypnosis while participants were exposed to nociceptive stimuli. Hypnotic suggestions selectively targeted the intensity and the affective component of the pain.[58] In the latter case, the painful experience was reported as being less aversive, and ACC (but not somatosensory cortex) activity was reduced.[59] Conversely, when the intensity of pain was modulated by hypnosis, activity in the somatosensory cortex contralateral to the stimulated hand was attenuated.[60] Similar results were obtained during hypnosis-induced depersonalisation.[61]

These studies revealed the neural correlates of different aspects of hypnotic analgesia. They showed ACC or somatosensory cortex to be suppressed, depending on the content of the hypnotic suggestions. Yet by what mechanism are these areas suppressed? Studies of hypnotic induction and suggestion indicate that activation of medial PFC and left dorsolateral PFC[62] might be nonspecific features of hypnosis through which the effects on specific symptoms are mediated.

Neurofeedback with functional magnetic resonance imaging

While hypnosis, in this respect similar to some CBT protocols, aims to induce certain mental states (and the accompanying physiological reaction), the new technique of neurofeedback directly targets the activity of a specific brain area. This technique, originally developed with EEG slow cortical potentials at low spatial resolution for binary communication with paralysed patients,[63] has recently been expanded for fMRI, using techniques for real-time image analysis. Weiskopf *et al*.[64] used such a brain–computer interface to train a volunteer to modulate the BOLD signal in his own ACC. The point about this approach is that participants are not supposed to modulate activity of a certain brain region by engaging in a specific task (e.g. increase activity in the fusiform face area by mental imagery of faces), but learn to evoke a mental state that reliably corresponds to a certain activation level in that region. For this reason, 'noneloquent' regions of the brain are ideally targeted to demonstrate the feasibility of the fMRI-based neurofeedback technique.

The initial approach of deCharms *et al*.[65] combined the induction of a specific mental state (imagining a hand movement) with neurofeedback training, which allowed their volunteers to enhance activity in primary motor cortex without actually performing a movement. Such a self-regulation of cortical activity by neurofeedback might play a therapeutic role in its own right, and first reports on pain reduction by modulation of ACC activity[66] are encouraging. The studies reviewed here might help define target areas for the transfer of this technique to symptom reduction in psychiatric disorders. However, any lasting therapeutic effect in psychiatric patients would probably require a modulation of functional connectivity patterns[67] rather than solitary brain regions and thus presuppose further methodological developments.

Similar considerations apply to the assessment of therapy effect with the symptom provocation-based functional imaging. While this technique provides an important instrument for the detection of neural changes during psychotherapy, any stable changes in neural networks or 'rewiring' should become manifest in changes in functional connectivity patterns that can be detected in asymptomatic states as well.

In sum, studies of hypnosis have revealed the ability to selectively suppress ACC or somatosensory cortex during nociceptive processing, depending on the aspect of pain that was to be influenced. The regulation of the activity of a particular brain area might also be achieved directly by neurofeedback. Combined with the evidence from symptom provocation techniques, this technique may eventually result in the development of neuroimaging-based psychotherapies (Figure 1c). Beyond the interesting clinical possibilities, these prospects also present new ethical challenges and will surely have an impact on the mind-brain debate in the years to come.

General discussion and conclusions

Functional neuroimaging is a promising tool for the investigation of the brain changes induced by psychotherapy. So far, only few studies have used it to assess the effects of CBT in OCD and phobia, and of CBT and IPT in depression. In OCD, psychological intervention led to decreased metabolism in the caudate and a decreased correlation of right OFC with ipsilateral caudate and thalamus. The hyperactivity of the caudate in OCD and its activity decrease after intervention conform to its putative role in the pathophysiology of this disorder. Dysfunctional striato-thalamic pathways have been implicated in inefficient thalamic gating, leading to hyperactivity in orbitofrontal and other cortical areas.[68] Such a scenario would be compatible with the functional neuroimaging findings, especially if increased caudate activity led to disinhibition of the thalamus by means of the direct pathway, which would indeed increase the correlation between caudate, thalamus and OFC activity. Finer resolution of functional imaging studies (e.g. in order to look for evidence of suppression of activity at the level of the globus pallidus internus) would be required to further disentangle the differential contribution of the basal ganglia to the pathophysiology of OCD. The prominent reduction of caudate activity after treatment might be explained in the context of the high level of striatal plasticity that has been shown in numerous studies of implicit and associative learning in human and animal models.[69,70]

In phobia, the most consistent effect of successful CBT on brain activation was a decrease in limbic and paralimbic areas. It is plausible that decreasing

amygdala activation, in particular, should accompany the reduction of phobic symptoms because both mechanical lesions and chemical suppression of the amygdala have consistently resulted in a reduction of both subjective and psychophysiological measures of fear.[71] However, based on these functional imaging findings alone, we cannot determine whether the decrease in amygdala activity after treatment was the cause or rather the effect of symptom reduction. Altered neural processes in other brain areas (which might have been interindividually more variable and therefore not detected in group analysis) could have resulted in the originally offensive stimuli being perceived as less aversive with the consequence of reduced firing of amygdala neurons. More detailed investigations of network changes during the treatment of anxiety disorders, involving measures of functional[67] or effective[72] connectivity, will be required in order for such questions to be addressed.

Interestingly, in both OCD and phobia, similar effects were obtained in the CBT and SSRI-treated groups. These findings, albeit preliminary, point to a common final pathway for the neural changes underlying the clinical effects of a biochemical and a psychological intervention. It is remarkable that the difference in the effects between drugs with similar pharmacological effects (fluoxetine and citalopram) across different disease groups (OCD: decrease of caudate activity and OFC-caudate-thalamus correlation;[24] phobia: decrease of limbic and paralimbic activity[34]) was much more pronounced that than between drug and psychotherapy within the same disease group. Thus, the brain changes induced by and underlying the effects of therapy seem to be more dependent on the original dysfunctional area or neural network than on the nature of the intervention. This view is supported by evidence from an FDG-PET study by Saxena *et al.*,[73] which reported major differences between OCD and depression in the pretreatment metabolic patterns that predicted a clinical response to paroxetine.

Studies of depression yielded a less consistent pattern than those of OCD and phobia, with reports of both decreases and increases in prefrontal metabolism after successful treatment, and considerable differences between pharmacological and psychological interventions in some studies. Some of these inconsistencies might be attributable to a lack of replicable baseline abnormalities of regional cerebral metabolism in depression. In general, the small number of functional imaging studies on psychotherapy effects (2–4 per disease group) and enrolled patients (not more than 30 in any of the studies, considerably less in some) warrant replication with larger patient samples before the clinical utility can finally be assessed.

Of the reviewed studies, five assessed changes in glucose metabolism, three measured blood flow and three measured changes in task-induced blood oxygenation (the BOLD signal of fMRI). While all these physiological parameters are considered indirectly to reflect neuronal activity, they are governed by different regulatory system and are thus prone to influences from different confounding variables, for example, changes in neurovascular coupling in elderly patients in the case of fMRI.[74] Thus, it would be desirable for future functional imaging studies of therapy effects to follow standardised protocols, or at least include a standardised component to which individual research groups could add their own paradigms.

For PET or SPECT studies, future protocols should include the comparison of baseline activity with a control group, the acquisition of MR images for partial volume correction, and, ideally, quantification of glucose metabolism or blood flow. For BOLD fMRI, which is by its very nature a relative measure, control tasks of basic sensory stimulation (that are not expected to lead to different activation patterns in relation to treatment) might be useful in order to corroborate the specificity of the effects of interest. Wherever possible, research should also aim at integrating functional imaging with molecular techniques such as radioligand imaging or biochemical analysis of metabolites in order to elucidate the molecular mechanisms of psychotherapy and its commonalities and differences with pharmacotherapy.

The experience with functional imaging studies of psychotherapy so far has been that in some disorders (e.g. OCD) findings were rather consistent while for others (e.g. depression) they differed across studies and treatment modalities. Findings in OCD are compatible with a model of initial hyperactivity in a striato–thalamic–orbitofrontal network, which is normalised in a similar way after treatment with either psycho- or pharmacotherapy. Conversely, in depression, psycho- and pharmacotherapy seem to operate through different pathways, one more 'top-down', the other more 'bottom-up'. We will have to hope that as more evidence from functional and metabolic imaging becomes available, more detailed models of the neural pathways of psychotherapy effects can be constructed.

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