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REVIEW ARTICLE

Neuroimaging and the functional neuroanatomy of psychotherapy

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ABSTRACT

Background. Studies measuring the effects of psychotherapy on brain function are under-represented relative to analogous studies of medications, possibly reflecting historical biases. However, psychological constructs relevant to several modalities of psychotherapy have demonstrable neurobiological correlates, as indicated by functional neuroimaging studies in healthy subjects. This review examines initial attempts to measure directly the effects of psychotherapy on brain function in patients with depression or anxiety disorders.

Method. Fourteen published, peer-reviewed functional neuroimaging investigations of psychotherapy were identified through a MEDLINE search and critically reviewed. Studies were compared for consistency of findings both within specific diagnostic categories, and between specific modalities of psychotherapy. Results were also compared to predicted neural models of psychotherapeutic interventions.

Results. Behavioral therapy for anxiety disorders was consistently associated with attenuation of brain-imaging abnormalities in regions linked to the pathophysiology of anxiety, and with activation in regions related to positive reappraisal of anxiogenic stimuli. In studies of major depressive disorder, cognitive behavioral therapy and interpersonal therapy were associated with markedly similar changes in cortical–subcortical circuitry, but in unexpected directions. For any given psychiatric disorder, there was only partial overlap between the brain-imaging changes associated with pharmacotherapy and those associated with psychotherapy.

Conclusions. Despite methodological limitations, initial neuroimaging studies have revealed convergent and mechanistically sensible effects of psychotherapy on brain function across a range of psychiatric disorders. Further research in this area may take advantage of emerging neuroimaging techniques to explore a broader range of psychotherapies, with the ultimate goal of improving clinical decision-making and treatment.

INTRODUCTION

Functional neuroimaging studies provide a means to observe and characterize changes in brain function related to psychiatric interventions. Since the introduction of this research tool, investigators have devoted considerably more effort towards understanding the neural mechanisms of medication than of psychotherapy (Fig. 1). This disparity has persisted despite the similar costs and clinical efficacy of medication and psychotherapy for common psychiatric disorders (Antonuccio *et al.* 1995; Goldman *et al.* 1998; Satcher, 1999). Historical bias toward medications as being a clearly defined 'biological' intervention, compared with the more complex psychosocial intervention of psychotherapy (Westen *et al.* 2004), has likely

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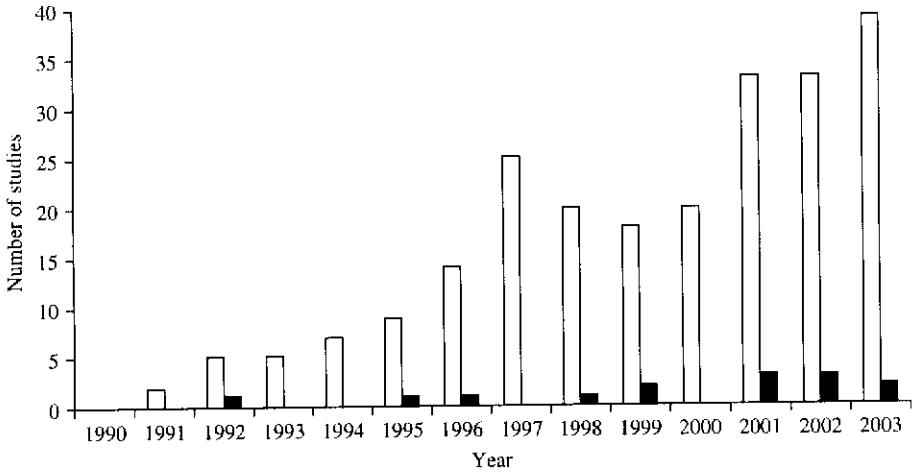

FIG. 1. Imaging/medication (□) and imaging/psychotherapy (■) studies by year. Method: An Ovid MEDLINE search was completed using key words related to neuroimaging (e.g. PET, fMRI, SPECT), and medication (e.g. psychotropic) to find studies including both neuroimaging and medication between the years 1966 and 2003. Based on the abstracts generated from this search, we selected studies based on four criteria: included studies were published in English between 1990 and 2003, used human subjects, and investigated psychiatric (e.g. depression) rather than neurological (e.g. Parkinson's Disease) disorders. A similar search was conducted using key words related to neuroimaging and psychotherapy (e.g. psychotherapy, intrapersonal therapy, cognitive behavioral therapy, and psychodynamic therapy).

contributed to this imbalance. However, as first suggested well before the era of functional neuroimaging, the changes in affect, behavior, and cognition that are mediated by psychotherapies undoubtedly have biological underpinnings (Freud, 1895). In recent years, the number of studies using neuroimaging to explicitly evaluate neural correlates of psychotherapy has steadily increased. These studies answer the call for more biologically rigorous approaches to psychotherapy research (Kandel, 1998).

In this review, we will address how neuroimaging research is beginning to reveal the relationship between psychotherapy and brain function. We shall first give examples of how psychological constructs relevant to psychotherapy, such as extinction, cognitive restructuring, and repression, have been associated with discrete brain activity. While long considered the 'building blocks' of psychotherapy on a theoretical level, these constructs appear to have parallel meaning on the level of neuroanatomy. Second, we will evaluate the emerging literature on psychotherapy-related changes in brain activity profiles, drawing some preliminary comparisons among different psychotherapies, and between psychotherapeutic and psychopharmacological approaches. Finally, we will discuss how future research efforts may refine our physiological understanding of how psychotherapy works, and why this knowledge may be clinically useful.

PUTATIVE NEURONAL MECHANISMS OF PSYCHOTHERAPY

Many potentially unhealthy cognitive and emotional patterns targeted by psychotherapy appear to have measurable biological analogs (Beutel *et al.* 2003). One salient example involves repression, or the unconscious 'forgetting' of threatening ideas or experiences. In a recent investigation by Anderson and associates (2004), 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 (2001), 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.

The process of psychotherapy may also engage dedicated neural circuitries that are particularly responsive to a discrete mode of treatment. We find examples of this in studies related to psychodynamic, cognitive, and behavioral therapy; such studies have used healthy subjects to investigate analogs of specific therapy processes. 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 (1995) observed that while random memories engaged assocation 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.

In cognitive behavioral therapy (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 (2002) 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 (see also Ochsner & Feldman Barrett, 2001; Scherer *et al.* 2001).

As a final example, we turn to behavioral therapy (BT). 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 (Milad *et al.* in press). Targeted lesions or specific pharmacological inhibition of the amygdala interfere with fear conditioning in rodents (see Maren & Quirk, 2004 for a review), while functional neuroimaging studies in humans have consistently associated amygdalar activation with conditioned fear responses (Buchel *et al.* 1999; Fischer *et al.* 2000; Charney, 2003; Cheng *et al.* 2003). Analogous studies in rats (Lebron *et al.* 2004) and humans (Gottfried & Dolan, 2004; Phelps *et al.* 2004) 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 behavioral therapies in humans to work either by potentiating ventral PFC activity or attenuating the amygdala (or both).

Collectively, the growing number of studies related to the psychotherapy process point to a plausible neuronal substrate for psychotherapeutic interventions. In this setting, we have also seen emerge a critical mass of studies that directly evaluate the neurobiological effects of psychotherapy in patients with mood and anxiety disorders.

THE PROBLEM OF VARIABLE METHODOLOGY

Before examining the literature on psychotherapy and neuroimaging in detail, we must recognize that heterogeneities across these studies often limit our ability to compare them directly (Table 1). There exist many specific differences in rationale, technique, and efficacy of the various psychotherapeutic modalities in use today. Several of these modalities, including BT, CBT, and interpersonal therapy (IPT) lend themselves well to controlled experimental design by using manual-based treatment in a time-limited setting. However, even among manualized treatment programs, adherence to a given framework is often far from absolute (Ablon & Jones, 2002). In several of the reviewed studies, although the therapeutic modality is called one thing (e.g. CBT), the description of the psychotherapeutic process more closely resembles another (e.g. BT).

Table 1. *Studies examining the functional neuroanatomy of psychotherapy*

Study	Therapy type	Subjects	Comparisons	Imaging	Post-treatment findings	Comments
Baxter *et al.* (1992)	BT, 10 weeks	9 patients with OCD	9 patients with OCD, taking fluoxetine	FDG-PET, resting	1. Decreased metabolism in R caudate in both groups 2. Uncoupling of cortico-striato-thalamic circuit in combined subject pool	1. Multiple co-morbidities 2. Unclear if uncoupling occurred as effect of BT
Schwartz *et al.* (1996)	CBT, 10 weeks	9 patients with OCD, plus earlier cohort	None	FDG-PET, resting	1. Decreased metabolism in R caudate 2. Uncoupling of cortico-striato-thalamic circuit	1. Some patients also received group CBT
Nakatani *et al.* (2003)	BT, varying duration	31 patients with treatment-refractory OCD	31 healthy controls	Xe-CT, resting	1. Decreased CBF in R caudate	1. 21 patients also took clomipramine 2. Lack of standardized treatment 3. Poor sensitivity to basal ganglia
Furmark *et al.* (2002)	Group CBT, 8 weeks	6 treatment-naive patients with social phobia	6 waitlist patients and 6 citalopram patients	PET, while observed reading script	1. In CBT and citalopram groups, decreased limbic metabolism 2. In CBT group, decreased periaqueductal gray metabolism 3. In citalopram group, decreased thalamic metabolism	1. Small numbers in each group
Paquette *et al.* (2003)	Group CBT, four 3-hour sessions	12 patients with spider phobia	13 healthy controls	fMRI, while viewing spiders	1. Decreased activation in parahippocampal gyrus and dorsolateral prefrontal cortex	1. Extent of post-CBT anxiety testing unclear
Goldapple *et al.* (2004)	CBT, 15–20 sessions	17 patients with MDD	*Post-hoc* comparison to 13 patients given paroxetine	FDG-PET, resting/avoiding 'ruminating'	1. In CBT group, decreased metabolism in multiple frontal regions, increased in limbic regions 2. In paroxetine group, changes in opposite direction	1. 3 patients dropped out 2. No imaging control group
Martin *et al.* (2001)	IPT, 6 weeks	13 patients with MDD	15 patients with MDD given venlafaxine	SPECT, resting	1. In each group, increased CBF in right basal ganglia 2. In IPT group, increased CBF in R posterior cingulate	1. Semi-random design 2. Short duration of treatment
Brody *et al.* (2001*a*)	IPT, 12 weeks	14 patients with MDD	10 patients with MDD given paroxetine and 16 healthy controls	FDG-PET, resting	1. In both MDD groups, decreased metabolism in prefrontal cortex, increased in inferior temporal cortex and insula	1. Non-randomized with baseline differences between groups
Brody *et al.* (2001*b*)	IPT, 12 weeks	14 patients with MDD	25 patients with MDD given paroxetine	FDG-PET, resting	1. Correlation of symptom cluster improvement with reduced frontal lobe metabolism 2. Positive correlation for cognitive symptoms	1. Paroxetine and IPT groups apparently combined 2. No correction for multiple comparisons
Penades *et al.* (2002)	Group 'neuro-psychological rehab,' 12 weeks	8 patients with schizophrenia, on olanzapine	None	SPECT, during Tower of London task	1. Weakly increased CBF in frontal lobe, correlated with improvement in test score 2. Non-specific imaging measure	1. No control intervention

Wykes *et al.* (2002)	'Cognitive remediation therapy,' 12 weeks	6 patients with schizophrenia, on antipsychotics	6 patients with schizophrenia given occupational therapy, 6 healthy controls	fMRI, during working memory and vigilance tasks	1. In cognitive therapy group, increased CBF in R inferior frontal cortex and bilateral occipital cortex	1. Small numbers in each group
Laatsch *et al.* (1999)	'Cognitive rehab therapy,' 6–36 sessions	5 patients with traumatic brain injury	None	SPECT, presumably resting	1. Global increases in CBF most apparent during treatment phase in 3 of 5 patients	1. No specific regional hypotheses 2. No attempt to correlate imaging with neuropsych measures
Levin *et al.* (1999)	EMDR, 3 sessions	1 patient with PTSD	None	SPECT, while being read scripts	1. Increased CBF in anterior cingulate, L frontal lobe	1. Single case, no follow-up
Brody *et al.* (1998)	BT, 8–12 weeks	18 patients with OCD	9 patients with OCD given fluoxetine	FDG-PET, resting (at baseline only)	1. For BT patients, L orbitofrontal cortex metabolism positively correlated with treatment response 2. Fluoxetine patients exhibited a negative correlation	1. Group assignment based on patient preference 2. Multiple co-morbidities

BT, Behavioral therapy; CBT, cognitive behavioral therapy; IPT, interpersonal therapy; EMDR, eye movement desensitization and reprocessing; OCD, obsessive compulsive disorder; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; FDG-PET, ^{18}fluorodeoxyglucose positron emission tomography; Xe-CT, xenon-enhanced computed tomography; CBF, cerebral blood flow; fMRI, functional magnetic resonance imaging; SPECT, ^{99m}technetium hexamethylpropyleneamineoxime single photon emission computed tomography; R, right; L, left.

Methodological inconsistencies created by the use of single *versus* multiple therapists, differing numbers of sessions, and varying milieus (e.g. individual *versus* group therapy) should also be considered when comparing studies.

The neuroimaging modalities that have been employed in psychotherapy research also vary. These techniques provide indices of brain activity by measuring glucose metabolism or cerebral blood flow (CBF). Although the relationship between glucose metabolism or CBF and neuronal activity remains controversial (Giove *et al.* 2003), it is commonplace to use the term 'brain activity' essentially interchangeably with 'metabolic activity' or 'hemodynamic activity'. Among the studies reviewed below, the principal imaging techniques applied include functional magnetic resonance imaging (fMRI), ^{18}fluorodeoxyglucose positron emission tomography (FDG-PET), and ^{99m}technetium hexamethylpropyleneamineoxime single photon emission computed tomography (^{99m}Tc-HMPAO SPECT). These imaging modalities differ with respect to mechanism, image resolution, and patient-related limitations (see Dougherty *et al.* 2004 for a detailed review). Moreover, there are several methods for examining regional brain activity, including voxel-based techniques (such as SPM) and region-of-interest (ROI)-based approaches. ROI-based methods enable fewer multiple comparisons and respect anatomical boundaries. Alternatively, voxelwise methods can be more data driven (and hence less biased), and may ultimately provide a better measure of functional connectivity (Dougherty *et al.* 2004).

Several additional design considerations should be taken into account when comparing these investigations. In most imaging studies of treatment effects, subjects are scanned before and after a trial of psychotherapy (or a comparison intervention), and in some cases, activation differences over time are compared with a group of healthy or waitlist control subjects. Some functional neuroimaging studies examine brain activity while the subject is resting in the scanner, others while the subject is engaged in a cognitive or affective task related to the psychiatric condition (e.g. exposure to an anxiety-provoking stimulus). Recognizing these design concerns, we now turn to the studies themselves.

BEHAVIORAL THERAPY AND OBSESSIVE COMPULSIVE DISORDER (OCD)

The first neuroimaging studies of psychotherapy, conducted by Baxter and colleagues (Baxter *et al.* 1992; Schwartz *et al.* 1996), included patients receiving BT for OCD. At the time these studies were published, a prevailing neurocircuitry model of OCD was better established than for other psychiatric conditions, thus making it an attractive focus for brain-imaging studies. OCD involves abnormally regulated cortico-striato-thalamic circuitry; provocation of OCD symptoms has been associated with increases in CBF in the orbitofrontal cortex, anterior cingulate cortex, striatum, and thalamus (McGuire *et al.* 1994; Rauch *et al.* 1994).

Baxter and associates (1992) used PET to investigate resting cerebral glucose metabolism in patients with OCD. Patients received 10 weeks of either fluoxetine ($n=9$) or BT ($n=9$), the latter focused on exposure and response prevention. Comparisons between these groups, as well as with a control group, were made at baseline and after the course of treatment. Among both groups of OCD patients, the investigators found a reduction in glucose metabolism in the right caudate nucleus following treatment; moreover, patients who responded more completely to treatment exhibited a more profound reduction than non-responders. Further, among patients who responded favorably to treatment, Baxter and associates observed an uncoupling of hyperactivity in the right caudate, orbitofrontal cortex, and thalamus. However, because medication and psychotherapy treatment groups were combined, it remained unclear whether this uncoupling occurred specifically in patients who received only BT. Psychiatric co-morbidities in many OCD subjects posed a second prominent limitation. Despite these concerns, the results were intriguing in that they not only showed a significant change in brain function following psychotherapy treatment, but also that the change occurred in the region consistent with the known pathophysiology of OCD.

In a follow-up FDG-PET study, Schwartz and colleagues (1996) examined a second cohort of nine patients with OCD. Unlike their previous study (1992), none of the subjects exhibited active psychiatric co-morbidities [although two subjects had a prior history of major depressive disorder (MDD).] Furthermore, all patients were off psychotropic medications for at least 2 weeks. Consistent with the earlier study, response to BT was associated with reduction of metabolic activity in the caudate nucleus, especially on the right side. Among patients who responded to treatment, the initial cortico-striato-thalamic correlation described earlier again disappeared with treatment. However, in this case uncoupling was demonstrated specifically in patients who responded to psychotherapy.

Analogous findings were recently reported in a larger study ($n=62$) by Nakatani and associates (2003). Using xenon-enhanced computed tomography (Xe-CT), the investigators noted a significant reduction in the right caudate following BT for OCD. However, several methodological limitations may have influenced this result, including concomitant use of clomipramine in 21 subjects, lack of standardized treatment, high drop-out rate, and relative insensitivity of Xe-CT to CBF changes in the basal ganglia.

COGNITIVE BEHAVIORAL THERAPY AND PHOBIAS

Two recent neuroimaging studies examined CBT in phobic patients, combining exposure-based treatment (akin to BT) with cognitive strategies. The cognitive components focused on changing negative misattributions related to fear-inducing stimuli. Of particular interest was the effect of treatment on activity in the amygdala and other limbic structures. Recall that while the amygdala is believed to play a central role in the fear response, 'top-down' modulation by the ventral PFC has been postulated to mediate the process of long-term extinction (Milad *et al.* in press).

Furmark and colleagues (2002) used PET to examine group CBT *versus* citalopram for treatment of social phobia. Unlike previous investigations where patients were imaged while simply resting in the scanner, here subjects were asked to read a speech about a personal experience in front of an audience of 6–8 nearby observers. Subjects were also observed at a close distance by a video camera. Prior to treatment,

subjects exhibited prominent activation in limbic structures, including the amygdala, hippocampus, and adjacent temporal cortex. Patients in the CBT arm received eight weekly group therapy sessions that specifically targeted anxiety associated with public speaking. In contrast to waitlist control subjects who did not change over time, patients in both treatment arms demonstrated a significant reduction of activity in these limbic and paralimbic regions. Of note, while no change in activity was observed in ventral PFC in the CBT group, patients receiving citalopram exhibited activity reductions in this region after treatment. Additional differences were also evident between treatment groups. Patients receiving cognitive therapy showed decreased CBF in the periaqueductal gray area, which has been associated with defense behaviors (Behbehani, 1995). Subjects taking citalopram exhibited thalamic reductions in CBF, potentially reflecting reductions in sensory input to the amygdala (Charney & Deutch, 1996). These results imply that 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. It should be noted, however, that this study included subjects with slightly varying diagnoses (e.g. specific and generalized social phobias).

Another provocation study by Paquette and colleagues (2003) related similar findings, in this case by exposing non-medicated, spider-phobic patients to pictures of spiders during fMRI scans. Compared to non-phobic control subjects, patients initially exhibited significant activation in the parahippocampal gyrus and right dorsolateral PFC†. After successful group CBT sessions using exposure therapy, patients demonstrated significantly less activation in both the parahippocampal gyrus and right dorsolateral PFC, and increased activation in the right ventral PFC. Paquette and associates linked the abatement of the parahippocampal gyrus response to a dampening of contextual memory (believed to be mediated by this structure). They further suggested that the dorsolateral PFC changes might reflect the restructuring of conscious cognitive defenses; with the completion of successful psychotherapy, less demand was placed on the dorsolateral PFC to plan a reaction to the perceived threat. This notion is consistent with Ochsner *et al.*'s recent (2004) observation that the dorsal PFC may play a role in up-regulating negative affect and limbic outflow under conditions where an aversive stimulus must assume personal salience. Following therapy, a shift of activity to the ventral PFC could prompt down-regulation of limbic activity, and consequently dampen the fear reaction. This pattern is again consistent with the findings of Ochsner *et al.* (2004), who correlated right ventral PFC activity with down-regulation of negative affect and limbic outflow when subjects were asked to de-emphasize personal connections to aversive stimuli.

Taken together, these studies are consistent with the model of BT-related desensitization to aversive stimuli described earlier in our review. Modulation of limbic activation following fear provocation may involve either reductions of CBF in limbic and adjoining paralimbic regions, or enhancement of CBF in ventral PFC, or perhaps both (as suggested by Paquette *et al.* 2003). The contributions of the *cognitive* parts of CBT to hemodynamic changes in these studies remain unclear – however, it should be noted that in both cases, the description of the therapy process clearly points more towards behavioral approaches (e.g. extinction-based processes).

COGNITIVE BEHAVIORAL THERAPY AND DEPRESSION

MDD has often been associated with alterations in prefrontal brain activity in untreated patients (Drevets, 1998), with dorsal areas (including the dorsolateral PFC) exhibiting decreased activity, and ventral frontal regions demonstrating increased activity (Dougherty & Rauch, 1997, Mayberg, 1997; Drevets, 2000; Rauch, 2003). A single functional neuroimaging study of CBT in medication-free, depressed patients has been reported by Goldapple and colleagues (2004). Neuroimaging was conducted with FDG-PET before and after the psychotherapy trial, with patients being instructed to 'avoid ruminating on any one topic' during scanning. A *post-hoc*

† It is worth noting that the lack of activation of the amygdala, while surprising, has been replicated in several other studies of spider phobia (Fredrikson *et al.* 1995; Rauch *et al.* 1995; Johanson *et al.* 1998), possibly reflecting the interaction of specific phobias and specific patterns of limbic hyperactivity.

comparison was made to a second group of patients who had been given paroxetine. Surprisingly, in the CBT group, metabolism in multiple frontal regions including the dorsolateral PFC decreased after therapy. Given the association of depression with reduced dorsolateral PFC activity at baseline, and the model of CBT elaborated earlier in this review, this finding is somewhat counterintuitive. The authors related the reduction in prefrontal metabolism to treatment-related diminution of 'active rethinking and reappraisal of emotional ideas'. This interpretation is somewhat akin to that offered by Paquette and colleagues (2003) for reduced dorsal prefrontal demand in successfully treated spider phobia. At the same time, however, it contradicts the notion that CBT *enhances* patients' abilities to reappraise affect-generating stimuli (e.g. Ochsner *et al.* 2002). Notably, among patients who received paroxetine in the Goldapple investigation, PFC metabolism *increased* with medication therapy, even though efficacy was comparable to CBT, again implying that medication and CBT may work through different mechanisms.

In addition to changes in the PFC, Goldapple and associates also described changes in limbic and paralimbic activity after treatment. However, once again a differential pattern emerged for subjects receiving CBT and paroxetine. 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. Based on these results, and on known functional and anatomic relationships between implicated brain regions (Friston, 1994; Horwitz *et al.* 1999), Goldapple and colleagues proposed a modality-specific model of treatment response in depression. Antidepressant medications appear to have exerted 'bottom-up' effects by disengaging ventral frontal and limbic regions. In contrast, CBT effected 'top-down' changes by reducing cortical processing in favor of ventral and limbic regions mediating attention to personally relevant emotional and environmental stimuli. Again, this result (and interpretation) oppose the emotion regulation model of Ochsner and colleagues (2002), who posit that ventral frontal and limbic hyperactivity exacerbate negative affect. To reconcile these differences, we invoke the notion that brain activation represents an interaction between treatment protocol and underlying brain state (Seminowicz *et al.* 2004). In this case, while both investigations involved cognitive restructuring, Goldapple *et al.* examined patients with depression, and Ochsner *et al.* looked at healthy controls. Bearing this same interaction in mind, we may consider whether psychotherapies other than CBT induce similar changes in brain activity among patients with depression.

IPT AND DEPRESSION

IPT, like CBT, is a manualized, time-limited therapy that lends itself well to controlled trials. However, in contrast to CBT, IPT emphasizes improving interpersonal relationships, often drawing directly on the relationship between patients and their therapists. Several recent studies have examined changes in CBF associated with the treatment of depression with IPT. In each case, neuroimaging comparisons were made to a second group of depressed patients receiving pharmacotherapy.

In a 6-week study of 28 patients with MDD, Martin and associates (2001) compared the effects of IPT and venlafaxine (37·5 mg daily) on regional CBF using ^{99m}Tc-HMPAO SPECT. Subjects had been drug-naive or drug-free for the 6 months preceding the study. After baseline scans, subjects in the IPT group received 6 weeks of psychotherapy by the same therapist, while those in the venlafaxine group were seen for 15 minutes every 2 weeks. Both groups improved clinically, and in both groups Martin and co-workers observed an increase in blood flow in the right basal ganglia. However, subjects in the IPT group also exhibited an increase in right posterior cingulate activity. Consistent with Goldapple and colleagues (2004), Martin *et al.* underscored the importance of limbic and paralimbic recruitment in psychotherapy-mediated changes; however, it should be noted that Martin and colleagues described changes only in one specific paralimbic region.

Bearing this single finding in mind, it is important to note several methodological limitations of this study. Martin and colleagues

employed a semi-randomized design, in which subjects with a strong preference for IPT or venlafaxine could choose that treatment; four subjects pre-selected venlafaxine, while one chose IPT. Of note, striatal perfusion appeared greater at baseline among subjects in the IPT group, potentially reflecting this design limitation. Additional problems included a lack of comparison to healthy control subjects, failure to exclude co-morbid anxiety disorders, and the relatively poor resolution of subcortical structures by SPECT. Finally, it is important to note that patients in the venlafaxine group demonstrated a more robust response to treatment. It may be argued, though that both treatments were sub-optimal, given the relatively low dose of venlafaxine and the brief duration of IPT.

A longer, 12-week study of similar design was conducted by Brody and co-workers (2001*a*), who used PET to examine 24 patients who received IPT or paroxetine. While this study included a control group of healthy subjects, all patients were allowed to self-select into the drug or therapy groups. Of note, subjects in the paroxetine cohort were less ill at baseline, and exhibited greater improvement over time than those in the IPT group. However, these design limitations aside, Brody *et al.* found a decrease in dorsal and ventral prefrontal cortical metabolism with IPT treatment directly analogous to that described by Goldapple *et al.* (2004). In addition, the authors described an increase in metabolism in limbic and paralimbic regions (in this case, the right insula and left inferior temporal lobe) in both treatment groups compared to controls. Unlike Goldapple, though, Brody and associates reported a decrease in PFC activation with paroxetine.

In a follow-up study using a larger cohort of 39 patients receiving either paroxetine or IPT for MDD, Brody and colleagues (2001*b*) attempted to correlate treatment-related changes in brain activity with improvement in specific mood symptom clusters. In all subjects, reductions of ventral and dorsal frontal lobe metabolism were associated with improvements in the anxiety/somatization and psychomotor retardation symptom clusters of the Hamilton Depression Rating Scale, and in the tension/anxiety and fatigue clusters of the Profile of Mood States. Interestingly, improvement in cognitive disturbance positively correlated with changes in dorsolateral PFC metabolism. This finding is especially germane in light of the negative correlation between activity in the dorsolateral PFC and improvement on global depression scores after CBT. This distinction suggests that while CBT may specifically dampen 'over-thinking' and rumination aspects of dorsolateral PFC function in depression, IPT potentially improves *general* cognitive abilities mediated by this region. Again these findings must be interpreted cautiously pending replication, and in consideration of design limitations: no effort was made to separate patients receiving IPT or paroxetine for correlations with hemodynamic changes, and no correction for multiple comparisons was implemented despite a total of six symptom clusters being assessed in each of 12 ROIs.

WHERE DO WE STAND? THEMES AND LIMITATIONS

Several themes emerge when considering these studies in aggregate. First, psychotherapy-related changes in brain activation appear strikingly similar within patients who share the same psychiatric diagnosis. For example, despite their methodological limitations and heterogeneities (e.g. patients receiving concomitant pharmacotherapy or multiple types of psychotherapeutic interventions), each of the reports examining psychotherapeutic interventions for OCD yielded comparable results. In each case, BT resulted in decreased metabolism in the caudate nucleus, a finding consistent with the well-established pathophysiology of the disorder (Saxena *et al.* 1998). Moreover, both fluoxetine and psychotherapy for OCD appear to uncouple dysfunctional cortico-striato-thalamic circuitry. In two studies examining patients with phobias, a reduction in limbic or paralimbic activity was observed following treatment, again consistent with the hypothesized pathophysiology. Among studies of depression, following successful psychotherapy with CBT or IPT, patients surprisingly – but consistently – exhibited decreased activity in dorsal frontal regions and increased activity in ventral frontal and subcortical regions (notably including limbic and paralimbic structures).

It is particularly intriguing that in MDD, both CBT and IPT have been associated with a

similar pattern of CBF alterations. Given the different theoretical approaches of these two treatments, how might we account for this common pattern? As suggested above, when considering the interacting effects of psychiatric condition and therapeutic approach on brain activity, perhaps underlying pathophysiology is the predominant factor. Another possibility, as suggested by Caspar (2003), is that while neuroimaging technologies allow us to visualize a 'final common pathway' of sorts, the more relevant changes in brain physiology attributable to psychotherapy may involve more microscopic phenomena. It is conceivable, although presently difficult to confirm, that CBT and IPT exert differing effects on cellular or even molecular levels. A third possible explanation is suggested by the work of Ablon & Jones (2002). Studying patients with MDD, these authors used a standardized measure (the Psychotherapy Q-sort) to compare psychotherapy process variables in transcripts of CBT *versus* IPT sessions. These process variables were related to the contributions of the patient, therapist, and the patient–therapist interaction. Ablon & Jones observed that successful IPT and CBT sessions both conformed strongly to the same set of process variables, implying that despite therapists' differing theoretical orientations, the work of therapy remained quite similar. It is tempting to speculate that the similarity of CBF changes seen after IPT and CBT reflects a neural correlate of this phenomenon.

Regardless of what mechanism might best explain the observed similarities of CBT and IPT for depression, these findings point to the need for adherence measures when attempting to ascribe treatment effects to any particular psychotherapeutic approach. This notion becomes critical when attempting to match specific psychotherapeutic interventions with specific changes in brain activation profiles. For example, in both studies of CBT for phobic disorders (Furmark *et al.* 2002; Paquette *et al.* 2003), it appeared that behavioral interventions predominated over cognitive ones – thus, it is not surprising that the CBF correlates of symptom improvement so closely matched those predicted by animal and healthy human analog models of behavioral therapy.

A second recurring theme of this review, especially among studies of MDD, is that while psychotherapy and pharmacotherapy achieved similar efficacy, they were associated with overlapping but not identical – changes in brain-imaging profiles. Moreover, patients who received pharmacotherapy exhibited less reliable patterns of brain activation than those who were treated with psychotherapy, even when the same medication (paroxetine) was used in different studies (Brody *et al.* 2001*a*; Goldapple *et al.* 2004). This discrepancy has also been observed among studies examining exclusively psychopharmacological interventions (e.g. Brody *et al.* 1999; Kennedy *et al.* 2001). Seminowicz and colleagues (2004) have attempted to explain these differential effects through a path-modeling meta-analysis of studies involving medication and CBT to treat depression. Their analysis, which includes subjects from the Goldapple *et al.* (2004) study, assumes that treatment response is dependent not just on specific interventions but rather on the interaction of pre-treatment brain state, brain responsiveness, and treatment choice. They suggest that among responders to CBT, fronto-frontal processing abnormalities appear to predominate, while those who ultimately respond to medications exhibit altered fronto-limbic dysregulation. However, the predictive validity of this model has yet to be tested prospectively. The use of such general descriptors 'limbic' and 'frontal' should also be viewed with caution, given the considerable structural and functional heterogeneity of these regions.

A third theme is that each study used two rounds of neuroimaging – one before treatment, and the other afterward – and the majority involved patients resting passively during scans. A potential confound of this approach is that while changes in brain activation over time may reflect correlates of symptom improvement, they do not necessarily imply a *mechanism* of treatment action, on either neuroanatomical or cellular/molecular levels. This is problematic even among those studies where subjects were actively participating in cognitive or behavioral tasks related to their underlying disorder. For example, in the Furmark *et al.* (2002) study, the lack of ventral PFC activation following the completed course of treatment was surprising given its proposed role in modulating limbic outflow; however, it is possible that such increased activity occurred *during* the treatment,

and was missed because the second scan occurred after the completion of therapy. (Of note, neuroimaging studies involving drug interventions suffer from a similar limitation, since it is difficult to differentiate brain activity changes that occur *while* an individual is actively taking a medication from those that occur as a *consequence* of taking the medication.) Thus, while this review strongly suggests that significant, and in many cases, unique changes in the brain are associated with psychotherapy, little can be concluded about the precise neurobiology and mechanisms involved in these changes.

FUTURE STUDIES OF PSYCHOTHERAPY AND BRAIN FUNCTION

A logical next step in addressing the problem of mechanism would involve, at the 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 this manner. However, novel neuroimaging technologies hold some promise for these applications. One such tool, 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 (for a review see Strangman *et al.* 2002) and in research involving basic auditory and cognitive processing (Sato *et al.* 1999). A second optical technique currently in development, two-photon microscopy, can potentially image deeper brain activity *in vivo* even on the cellular level (Miller, 2003); it has been suggested that in the future this technique may find its way into psychotherapy research as well (Zabarenko, 2004). Just as psychophysiological recording methods have been used to permit simultaneous measurements from both patient and therapist (e.g. Marci *et al.* 2004), 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.

On the more immediate horizon, investigators have already begun to use functional neuroimaging to predict treatment outcome. This work is akin to recent studies that have used electroencephalography (EEG) within 48 h of starting treatment to predict whether patients will ultimately respond to antidepressants (e.g. Cook *et al.* 2002). Brody and associates (1998) reported differential responses to behavioral therapy and fluoxetine for OCD based on pretreatment PET scans. Among patients who received BT, Brody observed a positive correlation between treatment response and baseline metabolism in the left orbitofrontal cortex; however, the inverse pattern was seen among patients in the fluoxetine group. This finding involves a region implicated not only in the pathophysiology of OCD (McGuire *et al.* 1994; Rauch *et al.* 1994), but also in desensitization of anxiety-provoking stimuli as described earlier (Gottfried & Dolan, 2004; Phelps *et al.* 2004). Brody and colleagues thus propose that patients with increased orbitofrontal cortex activity at baseline may be predisposed to benefit from extinction-based therapy for OCD. However, as patients in the Brody *et al.* study were allowed to select their own treatment group, this interpretation must be viewed with caution. While additional prospective studies in this area are needed, the ability to construct individualized treatment plans using biological markers (such as neuroimaging) could ultimately allow patients and clinicians to move away from the current 'trial-and-error' approach, minimizing frustration as well as lost time and expense.

Thus far neuroimaging studies of psychotherapy have focused on manual-driven, time-limited treatments. However, much is to be gained by subjecting other commonly used therapeutic techniques to investigation with functional neuroimaging methods. For example, a single case report illustrates the normalization of serotonin receptor binding, as determined by SPECT, in a patient with borderline personality disorder following 1 year of psychodynamic psychotherapy (Viinamaki *et al.* 1998). Still, at present there are no published reports of brain activation changes associated with either psychodynamic psychotherapy or dialectical behavioral therapy, two empirically supported treatments widely in use. Another case report describes increased CBF in the anterior cingulate gyrus and frontal lobe following eye movement desensitization and reprocessing

(EMDR), a novel (although not yet empirically validated) treatment for post-traumatic stress disorder (Levin *et al.* 1999). Several studies have demonstrated increased frontal lobe metabolism following cognitive rehabilitation therapies for schizophrenia (Penades *et al.* 2002; Wykes *et al.* 2002) and traumatic brain injury (Laatsch *et al.* 1999; Strangman *et al.* in press). Finally, with a renewed focus on psychotherapy as an alternative treatment to medications in child and adolescent patients, extension of neuroimaging studies to include this population is warranted. This work could also elucidate the unique effects of age-appropriate treatments on the developing brain. Child imaging will presumably rely on imaging methods that avoid ionizing radiation; the safety of repeated measures in children is another important consideration.

CONCLUSION

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 well underway, initial forays into the neuroimaging of psychotherapy have suggested plausible and apparently convergent mechanisms by which therapy changes the brain. The specific implications of this research on clinical practice remain uncertain, but it is likely that additional work in this area will further demystify and validate psychotherapy in the eyes of patients and clinicians alike (Gabbard, 2000; Beutel *et al.* 2003). Functional neuroimaging also 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 time-honored mainstay in psychiatric treatment.

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DECLARATION OF INTEREST

None.

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