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Biology in the Service of Psychotherapy

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Neuroscience has developed a number of useful methods for analyzing cognitive function. As a result, our understanding of normal and abnormal mental function has grown substantially. These insights have improved the ability to intervene pharmacotherapeutically in the treatment of patients with mental illness. Can this new understanding also inform and improve psychotherapeutic interventions?

Psychotherapy remains one of the cornerstones of treatment for many psychopathologies, including various personality disorders. There also is evidence that the combined use of psychotherapy and medications can lead to better treatment outcome (Newton-Howes and Tyrer 2003; Zanarini and Frankenburg 2001). Despite the extensive use of psychotherapy for a number of mental disorders, we lack a biological perspective on how psychotherapy works. Investigation of the biological underpinnings of psychotherapy is important for two reasons. First, an understanding of psychotherapy is important in psychiatry's attempt to link specific mental functions with specific brain mechanisms and may aid in the analysis of how the environment affects the brain. Psychotherapy is a controlled form of learning that occurs in the context of a therapeutic relationship—and from this perspective, the biology of psychotherapy can be understood as a special case in the biology of learning (Kandel 1979). Second, insight into the biological mechanisms of psychotherapeutic action would revolutionize psychiatry by enhancing our understanding of premorbid vulnerabilities, selection of the optimal course of therapy, and evaluation of treatment outcome.

Because the neurobiological study of psychotherapy is in its infancy, any attempt to address the biology of psychotherapy at this early point will be incomplete. Nonetheless, the initial research into the biological underpinnings of psychotherapy has already provided several new insights. In this chapter, we outline where we are and how future refinements might advance the field further. Our discussion centers primarily on depression, obsessive-compulsive disorder (OCD), and anxiety, where neuroimaging work is most advanced. By con-

trast, little is known about the neurobiology of personality disorders. In considering these illnesses, we focus in particular on the use of neuroimaging for diagnosing and understanding psychopathology and for predicting the outcome of treatment and following its course.

Basal Brain Imaging: Detecting Changes Associated With Psychotherapy

Most early neuroimaging studies of psychotherapy focused on depression and OCD and examined basal brain metabolism or basal cerebral blood flow (Baxter et al. 1992; Brody et al. 1998, 2001; Martin et al. 2001; Schwartz et al. 1996). These studies have consistently demonstrated changes in brain activity in patients with these disorders when compared with healthy control subjects. Successful treatment frequently restored the brain to a state that superficially resembled the brain state of control subjects. Particularly interesting is the finding that some of the changes accompanying successful psychotherapy resembled those seen with pharmacotherapy, suggesting that, at least in some cases, both psychotherapy and drugs may act on a common set of brain targets.

Early neuroimaging studies of OCD used fluorodeoxyglucose–positron emission tomography (FDG-PET). A typical scan involves continuous acquisition for 30–40 minutes while patients are at rest and is therefore not sensitive to moment-to-moment changes in neuronal activity, as might happen during performance of a cognitive task.

In the first such study, Baxter et al. (1992) found an increase in basal glucose metabolism in the caudate nucleus of OCD patients. Treatment with either the selective serotonin reuptake inhibitor (SSRI) fluoxetine or exposure psychotherapy reversed the metabolic abnormality caused by this disorder. A subsequent study found that patients who responded to psychotherapy showed greater decreases in right caudate metabolism than patients who did not respond (Schwartz et al. 1996). Although both lacked important controls, the two studies demonstrated for the first time that psychotherapy can produce a detectable change in brain activity.

Subsequent FDG-PET studies of psychotherapy have focused primarily on depression. The most common finding in depression is a decrease in the basal activity of the dorsolateral prefrontal cortex (PFC). Less consistently reported is increased activity in the ventrolateral PFC (Drevets 1998; Kennedy et al. 1997; Mayberg 1997; Mayberg et al. 1999). Both SSRIs and electroconvulsive therapy reversed these abnormalities (Drevets 1998).

To relate these findings to psychotherapy, two studies compared interpersonal psychotherapy (IPT) with either the SSRI paroxetine or the serotonin-norepinephrine reuptake inhibitor venlafaxine in the treatment of depression (Brody et al. 2001; Martin et al. 2001). Again, psychotherapy reversed pretreatment abnormalities, including those in the PFC, similar to the effects of pharmacotherapy.

The conclusion from these two sets of studies that psychotherapy is similar to pharmacotherapy in normalizing functional abnormalities in brain circuits that give rise to symptoms is, however, potentially simplistic. With further research it should be possible to distinguish common from distinct changes among therapies. This may allow one to distinguish between brain regions that contribute to symptom improvement per se and those that contribute to the mechanisms of a particular therapy. For example, Goldapple et al. (2004) found that depressed patients treated with cognitive-behavioral therapy (CBT) show some common and some different brain changes when compared with patients treated with paroxetine. Thus, the initial idea in the literature that psychotherapy and pharmacotherapy produce similar changes is not likely to prove generally true. Indeed, firm conclusions should not yet be drawn from any of these early studies, because they are hampered by lack of or incomplete randomization for treatment types, as well as by missing controls.

Beyond Basal Brain Function: Stimulus-Responsive Imaging and Psychotherapy

Recent studies have sought to go beyond the measurement of basal metabolism by examining the effect of psychotherapy on context-specific neural responses in disease-relevant tasks (Furmark et al. 2002; Paquette et al. 2003). In one such study, Furmark et al. (2002) examined patients with social phobia treated with either citalopram or CBT, using PET measures of changes in regional blood flow secondary to neuronal activation. They had previously found that when patients with social phobia gave a prepared speech in the scanner while in the presence of others (as compared with giving the speech alone), they showed a larger increase in regional blood flow in the amygdala and hippocampus, compared with control subjects (Tillfors et al. 2001). Improvement in symptoms with treatment was accom-

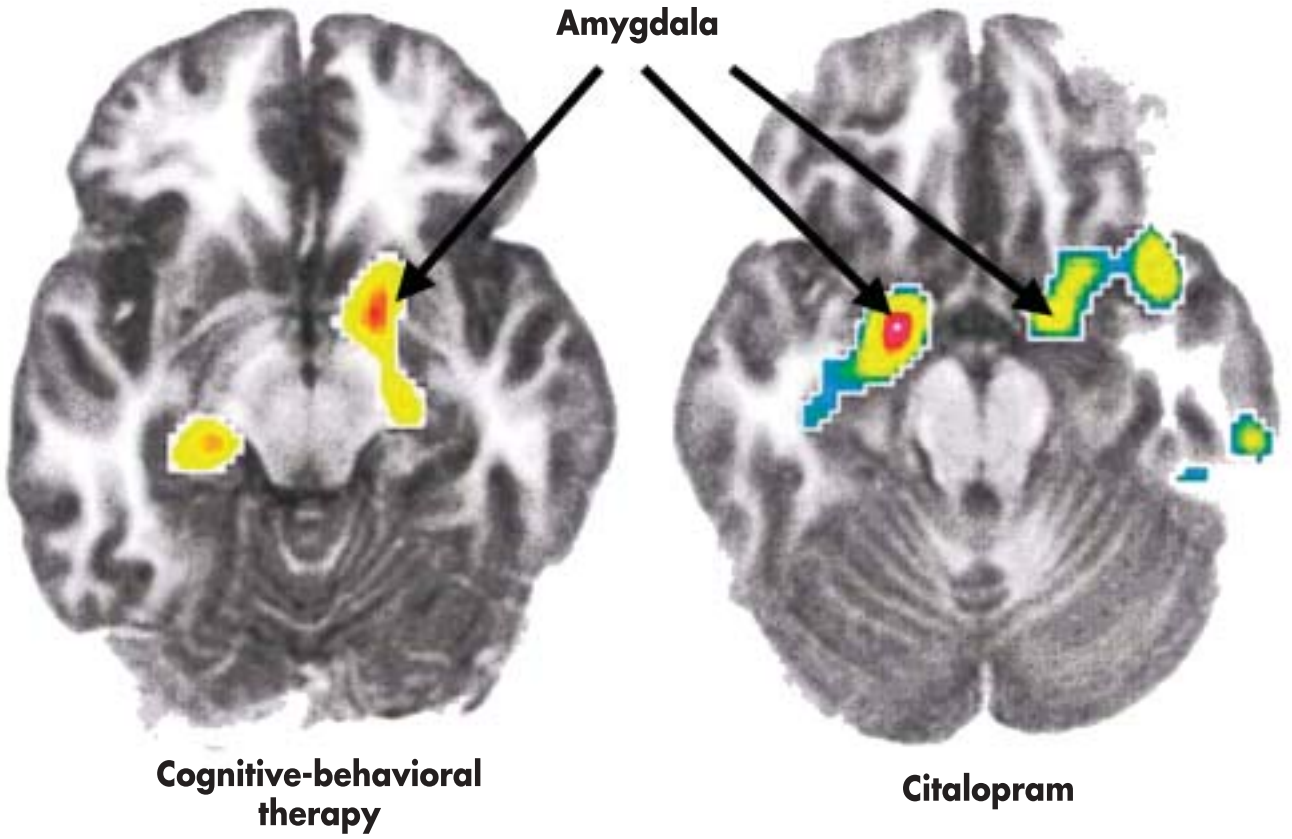

Figure 41–1. Effects of cognitive-behavioral therapy (CBT) or citalopram treatment on brain activity in patients with social phobia while carrying out a public speaking task.

CBT **(left)** and citalopram **(right)** treatment are both associated with decreased activation of the amygdala during performance of an anxiogenic public speaking task after therapy, compared with before therapy. Depicted are regions showing a significant post- versus pretreatment decrease in activity.

Source. Reprinted from Furmark T, Tillfors M, Marteinsdottir I, et al.: "Common Changes in Cerebral Blood Flow in Patients With Social Phobia Treated with Citalopram or Cognitive-Behavioral Therapy." *Archives of General Psychiatry* 59:425–433, 2002. Copyright 2002, American Medical Association. Used with permission.

panied by decreased activity in the amygdala and the medial temporal lobe in the stressful public speaking condition (Figure 41–1). No such changes were seen in waiting-list control subjects. Comparing treatment groups with a control group of waiting-list patients who received no treatment allowed the authors to rule out changes related only to subject rescanning or simply to the passage of time. Decreases in the activity of the amygdala were seen in both the CBT and the citalopram groups. The two treatment groups, however, differed with respect to neural changes outside the amygdala. Interestingly, the degree to which amygdala activity decreased as a result of therapy predicted patients' reduction in symptoms 1 year later. Unfortunately, because of small sample sizes, the study was not able to distinguish between responders and nonresponders for each modality, which might have dissociated the symptom-improving effects of the treatment from the consequences of having received the treatment per se.

Despite their limitations, both the basal metabolism and stimulus-responsive imaging investigations have demonstrated that psychotherapy produces changes in the brain, some of which may be shared with those induced by pharmacotherapy, whereas others are modality-specific. As the neurobiological substrates of psychotherapeutic change are better defined, more directed animal studies can also be focused on those brain regions and the functional networks in which they participate.

Further Clinical Applications of Neuroimaging to Psychotherapy

Neuroimaging can be a highly sensitive mode of investigation. Instead of looking at a single dependent measure (e.g., reaction times), neuroimaging simultaneously assesses the activity of every part of the brain. This flexibility can be enhanced by use of a variety of stimuli and tasks, as well as data analytic techniques that can separately probe the data for activations, connectivity, network-level interactions, and so forth.

This sensitivity has several implications. Neuroimaging may give an independent way of grouping patients based on biological variables closer to the pathogenesis of the disease. Personality disorders, for example, are even more likely than other psychiatric disorders to have distinct etiologies, yet these distinct etiologies (and mechanisms) may lead to clinically indistinguishable presentations. Subgrouping patients may reveal why some patients improve with particular therapies, and others do not, and this may better inform therapeutic decisions.

The power of novel data analysis techniques for objectively subgrouping subjects on the basis of biological criteria was illustrated by Meyer-Lindenberg et al. (2001). They found, using a multivariate analysis approach, that the expression of a brainwide pattern of activity in an individual can almost perfectly separate a group of schizophrenic patients from a control group (like a diagnostic marker). In this way they were able to separate out two independent cohorts with 94% accuracy, using only resting brain scans. Most neuroimaging studies use univariate analysis methods and examine the activity of single brain regions at a time rather than groups of areas across the whole brain. This can result in a great degree of overlap between regional activation in a disease group and in a control group—a distinction that may otherwise be easily made by multivariate analysis methods.

Alternatively, predictions of whether a particular therapy will work for a given patient may depend more on the functional characteristics of that individual's brain and less on what diagnostic group the patient is put in. In other words, understanding how that individual's brain processes particular stimuli may provide critical information for predicting treatment outcome. Neuroimaging-based quantification of regional brain function during disease-relevant and irrelevant tasks in a standardized way across patients may bring out many subtle differences. These differences may predict how a patient will process and respond to stimuli in the context of particular forms of psychotherapy, or after pharmacological treatment. Such an approach can be thought of as a "cognitive and emotional stress test" much as a cardiologist may use an exercise stress test to bring out subtle differences in cardiovascular function that will predict disease progression and possibly the medications the patient should take to achieve the optimal outcome. This approach may predict which of several treatment courses is most suitable, or may allow the progress of treatment to be monitored, and thus provide early markers of the likelihood of success long before changes in behavior can be seen. Prediction of outcome may be successful even without a full understanding of why a particular pattern of brain activation predicts better outcome.

Our arguments are based on the assumption that biological variables are causal to the behavioral manifestations of psychiatric disorders and can be more sensitive indices of cognitive function. Importantly, neuroimaging measures are equally sensitive to processes at the conscious and unconscious levels, as they must both be reflected by underlying processes in the brain. Thus, neuroimaging approaches can be equally well used, no matter how the psychopathology or psychotherapy is conceptualized.

Predicting Outcome With Neuroimaging: Preliminary Evidence From Depression and Obsessive-Compulsive Disorder

The most convincing outcome predictions come from neuroimaging studies of depression. While these studies relate to the pharmacotherapy of depression, they can be at least conceptually extended to psychotherapy.

A landmark FDG-PET study of the pharmacological treatment of unipolar depression found that activity in the rostral anterior cingulate cortex (ACC) uniquely differentiated treatment responders from nonresponders (Mayberg et al. 1997). Responders were hypermetabolic prior to treatment with respect to controls, while nonresponders were hypometabolic (see Figure 41–2A). The predictive value of pretreatment activity in the rostral cingulate in depression has been confirmed by subsequent studies. Rostral cingulate activity predicted better response to paroxetine treatment (Saxena et al. 2003) as well as to partial sleep deprivation therapy (see Figure 41–2B) (Volk et al. 1997; Wu et al. 1999). More recently, Pizzagalli et al. (2001) recorded scalp EEG activity in nortriptyline-treated

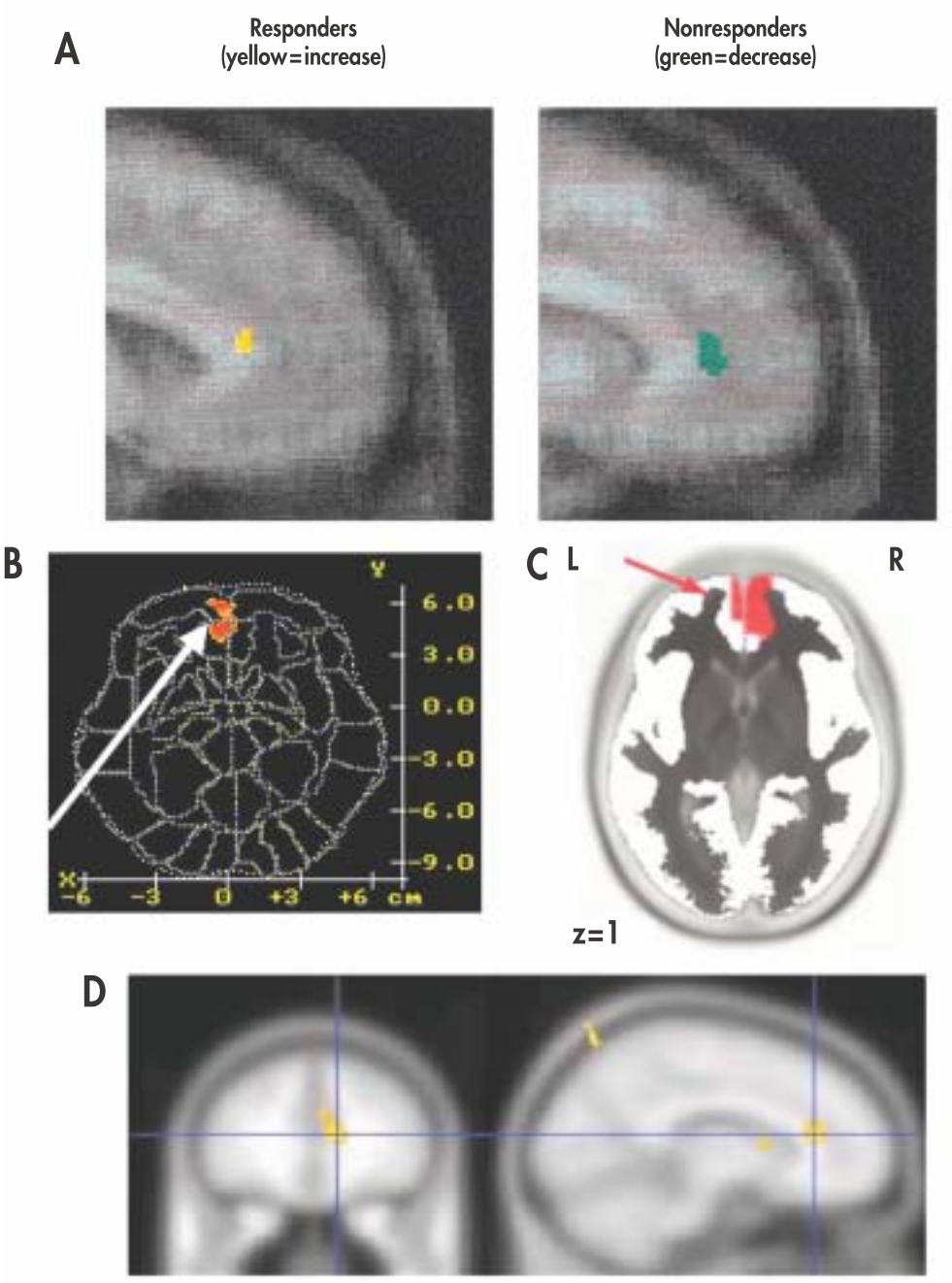

Figure 41–2. Prediction of better outcome in depression by higher pretreatment levels of rostral anterior cingulate cortex metabolism or activity.

In **(A)**, responders to antidepressants were found to be *hyper*metabolic in the rostral cingulate, whereas nonresponders were *hypo*metabolic (Mayberg et al. 1997). Basal brain metabolism (Wu et al. 1999) and theta frequency EEG signal (Pizzagalli et al. 2001) in the rostral cingulate predicted better outcome to sleep deprivation therapy **(B**) or antidepressants **(C),** respectively. **(D)** Greater functional recruitment of the rostral cingulate in an emotional activation task prior to antidepressant treatment also predicted better outcome (Davidson et al. 2003).

Source. **A:** Reprinted from Mayberg HS, Brannan SK, Mahurin RK, et al.: "Cingulate Function in Depression: A Potential Predictor of Treatment Response." *Neuroreport* 8:1057–1061, 1997. **B:** Wu J, Buchsbaum MS, Gillin JC, et al.: "Prediction of Antidepressant Effects of Sleep Deprivation by Metabolic Rates in the Ventral Anterior Cingulate and Medial Prefrontal Cortex." *American Journal of Psychiatry* 156:1149–1158, 1999. Copyright 1999, American Psychiatric Association. Used with permission. **C:** Pizzagalli D, Pascual-Marqui RD, Nitschke JB, et al.: "Anterior Cingulate Activity as a Predictor of Degree of Treatment Response in Major Depression: Evidence From Brain Electrical Tomography Analysis." *American Journal of Psychiatry* 158:405–415, 2001. Copyright 2001, American Psychiatric Association. Used with permission. **D:** Davidson RJ, Irwin W, Anderle MJ, et al.: "The Neural Substrates of Affective Processing in Depressed Patients Treated With Venlafaxine." *American Journal of Psychiatry* 160:64–75, 2003. Copyright 2003, American Psychiatric Association. Used with permission.

depressed patients, focusing on one EEG frequency band thought to be generated by the anterior cingulate. Here again patients showing electrical hyperactivity in the rostral cingulate before treatment showed better response 4–6 months after treatment, an effect that was not related to pretreatment depression severity (see Figure 41–2C). In the first study to examine functional recruitment of the rostral cingulate, rather than its baseline activity or metabolism, Davidson et al. (2003) examined functional magnetic resonance imaging (fMRI) activation in response to viewing negatively valenced visual stimuli, compared with neutral stimuli. They likewise found that higher pretreatment activation of the rostral cingulate predicted a lower depression symptom scale score 8 weeks after treatment (see Figure 41–2D).

The anterior cingulate can be divided into three divisions by anatomical and functional imaging criteria (Bush et al. 2000; Devinsky et al. 1995). Changes in both the dorsal and ventral regions of the cingulate have been seen in depression (Davidson et al. 2002; Drevets 2001; Mayberg 1997). The dorsal ("cognitive") division of the ACC is often activated by nonemotional tasks that produce conflicts between potential responses (i.e., a color-word Stroop task in which the font color of the word to be identified is incongruent with the word itself—"red" in green ink). The ventral ("affective") division of the ACC can be recruited by mood induction protocols (Bush et al. 2000; Mayberg et al. 1999).

The rostral cingulate, located between these other two subdivisions and implicated in the studies of depression summarized above, receives input from both of the other divisions of the ACC and is thought to integrate them (Devinsky et al. 1995). Thus, the rostral cingulate may be important for detecting conflict in the emotional domain and recruiting cognitive-attentional processes to resolve the conflict. In support of this view, the rostral cingulate becomes more active when subjects are asked to ignore emotional words in a word counting task than when they are instructed to ignore neutral words (Whalen et al. 1998). In this task, ignoring emotional content would be expected to increase conflict in the emotional domain.

Conflict resolution and cognitive control by the rostral cingulate may be analogous to the functions of the dorsal cingulate under conflict conditions. Kerns et al. (2004) found that the dorsal division of the ACC was activated by conflict in a color-word Stroop task. Dorsal ACC activation by this conflict predicted greater recruitment of the dorsolateral PFC on the subsequent trial. This increase in cognitive control decreased the incongruency effect, thereby leading to shorter reaction times for incongruent trials that were preceded by an incongruent trial than for incongruent trials that were preceded by a congruent trial. The dorsal ACC appeared to both resolve cognitive conflict and prime cognitive systems to better reduce conflict on the subsequent trial.

By analogy, the rostral cingulate may be recruited to resolve conflict between emotional stimuli or between conflicting mental content. In major depression, cognitive control may be important for regulating the effects of negative mood over perception, thoughts, and behavior. Patients with higher levels of activity in the rostral cingulate before therapy may thereby be in a better position for recovery.

Preliminary imaging studies of OCD implicate a different area of the PFC, the orbitofrontal cortex (OFC), in predicting treatment response. The OFC is highly activated during symptom provocation in OCD patients (McGuire et al. 1994; Rauch et al. 1994). One FDG-PET study of OCD found that lower pretreatment levels of activity predicted better response to drug therapy (Figure 41–3A) (Saxena et al. 1999). More intriguing was the finding that lower pretreatment metabolism of the OFC predicted better response to drugs than to psychotherapy, whereas higher OFC metabolism predicted the opposite (see Figure 41–3B). As in many of the other studies cited earlier, several major caveats must be considered. Subjects were not randomized, blinded, or compared with a placebo group.

Why lower OFC metabolism predicts treatment outcome is not clear. It may, for example, be related to the recruitment of this region in behavioral control and inhibition (Horn et al. 2003; Lubman et al. 2004). OFC metabolism may reflect the degree of control that patients feel they must exert on their behavior in order to satisfy their compulsions. Why OFC metabolism may predict opposite results for psychotherapy and pharmacotherapy is also unclear. Finally, because none of the outcome prediction studies in depression contrasted psychotherapy and pharmacotherapy, it is unknown whether the rostral cingulate in depression may differentially predict outcome depending on the treatment type as the OFC may in OCD.

Role of Awareness: Implications of Conscious and Unconscious for Psychopathology and Psychotherapy

Most theories of psychopathology, both psychodynamic and cognitive, emphasize the importance of unconscious processes and differentiate them from con-

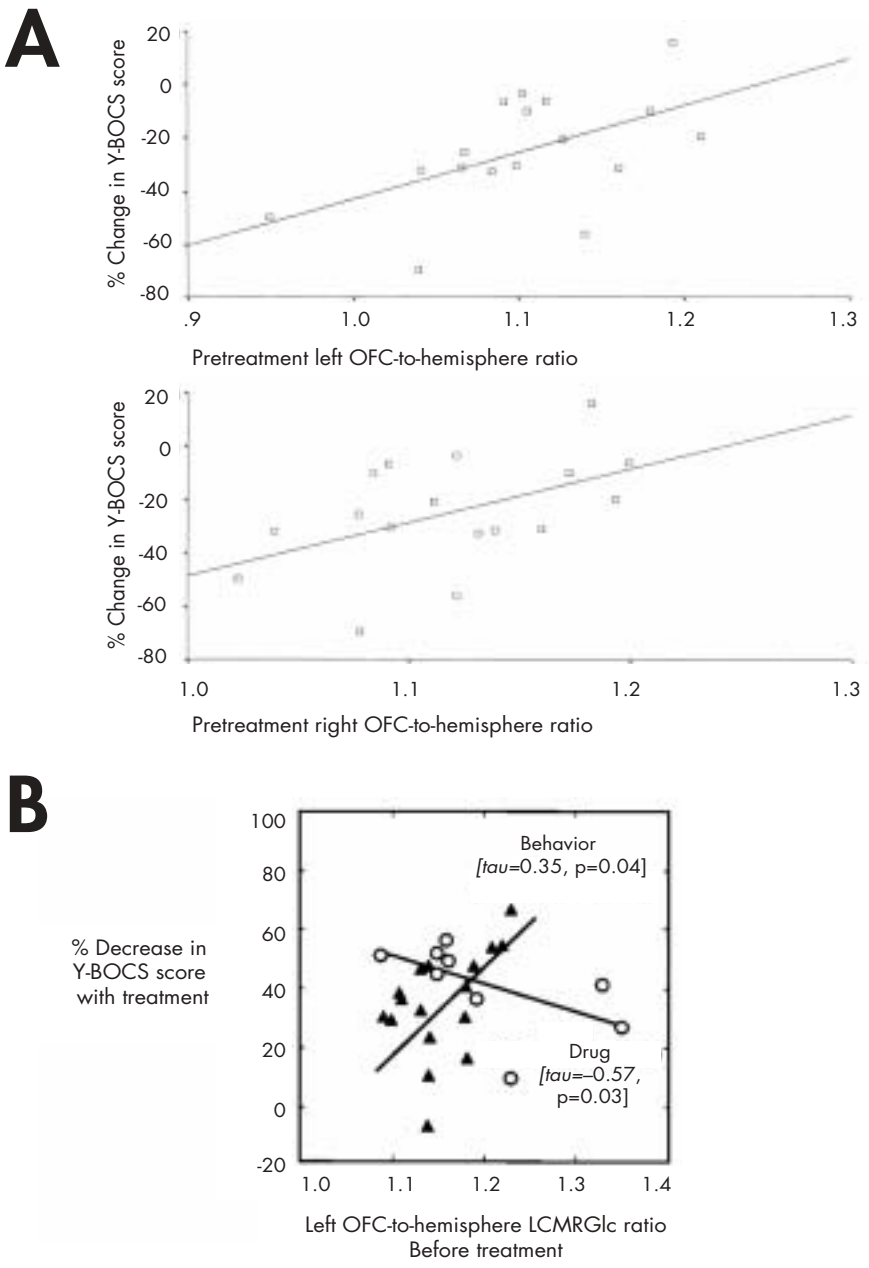

Figure 41–3. Prediction of outcome of pharmacotherapy or psychotherapy for obsessive-compulsive disorder by pretreatment orbitofrontal cortex (OFC) metabolism.

(A) Lower pretreatment metabolism in the OFC predicted better response to antidepressants (Saxena et al. 1999), reflected by a greater decrease in Y-BOCS scores, a measure of OCD symptoms. **(B)** The relationship between pretreatment OFC metabolism and outcome of behavioral psychotherapy (Brody et al. 1998) may be opposite that between pretreatment OFC metabolism and outcome of drug therapy. LCMRGlc=local cerebral metabolic rates for glucose.

Source. **A:** Reprinted from Saxena S, Brody AL, Maidment KM, et al.: "Localized Orbitofrontal and Subcortical Metabolic Changes and Predictors of Response to Paroxetine Treatment in Obsessive-Compulsive Disorder." *Neuropsychopharmacology* 21:683–693, 1999. Used with permission. **B:** Reprinted from Brody AL, Saxena S, Schwartz JM, et al.: "FDG-PET Predictors of Response to Behavioral Therapy and Pharmacotherapy in Obsessive-Compulsive Disorder." *Psychiatry Research* 84:1–6, 1998. Used with permission.

scious processes (Beck and Clark 1997; Gabbard 2005; Wong 1999). This is particularly clear in anxiety disorders. For all of their differences, these theories generally agree that an anxiety-related unconscious 1) should differ between individuals with different anxiety levels and 2) is probably the sum of a family of processes occurring outside of subjective awareness. A recent fMRI study from our laboratory (Etkin et al. 2004) has investigated these features of unconscious processing in anxiety. The results shed light on the conscious and uncon-

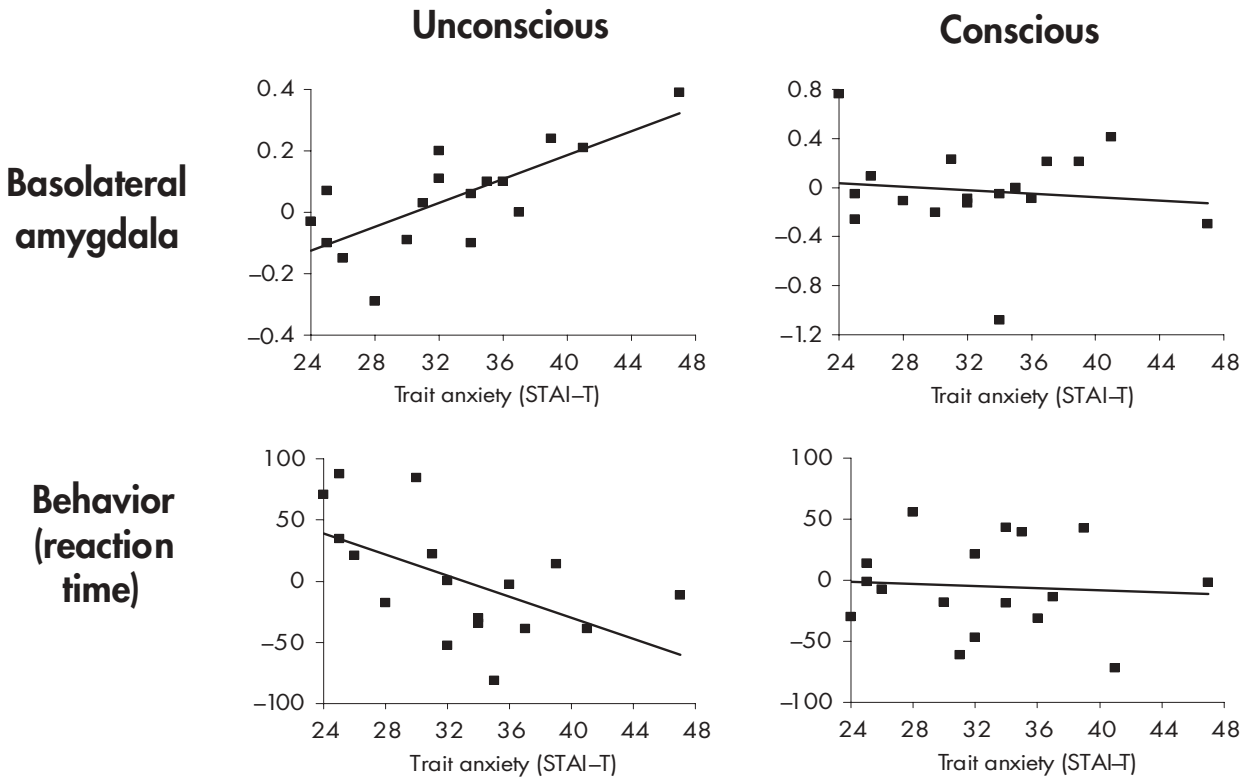

Figure 41–4. Prediction of basolateral subregion amygdalar activity by differences in baseline (trait) anxiety within a normal population during unconscious, but not conscious, processing of fearful faces.

Individual differences in baseline (trait) anxiety predicted activity in the basolateral subregion of the amygdala during unconscious, but not conscious, processing of fearful faces. Similarly, differences in trait anxiety predicted behavior (color identification reaction times) specifically during unconscious processing. STAI-T=Spielberger State-Trait Anxiety Inventory—Trait Anxiety.

Source. Reprinted from Etkin A, Klemenhagen KC, Dudman JT, et al.: "Individual Differences in Trait Anxiety Predict the Response of the Basolateral Amygdala to Unconsciously Processed Fearful Faces." *Neuron* 44:1043–1055, 2004. Used with permission.

scious components of anxiety and delineate new ways of evaluating the mechanisms whereby anxious subjects respond to treatment.

Etkin et al. (2004) examined a group of normal volunteers and exposed them to fearful faces. While none of these participants had anxiety disorders, they represented the range of baseline (trait) anxiety present in the normal population. Fearful facial expressions are culturally conserved signals of threat that have been shown to stimulate activity in the amygdala (Aggleton 2000; Ekman et al. 1969). These faces were presented for conscious or unconscious processing; the latter was achieved through backward masking, which entails presenting a fearful face very rapidly and immediately followed by a neutral face. This procedure renders stimuli consciously nonreportable. While viewing these faces, subjects were engaged in a color identification task not related to the emotion expressed on the face. Reaction times in this task could show the effects of emotion if processing the emotional content affected the attentional resources available for the color identification task.

Etkin et al. (2004) found that individual differences in trait anxiety predicted activity in the amygdala, as well as reaction times and activity in cortical regions important in attention (see Figures 41–4 and 41–5). However, the relationships of brain activity or behavior to trait anxiety were seen only when stimuli were processed unconsciously. Etkin et al. therefore identified a network of brain regions important in the unconscious emotional vigilance commonly described behaviorally for nonclinically anxious individuals and patients with anxiety disorder (see Figure 41–5) (Mogg and Bradley 1998). This network involved the amygdala in emo-

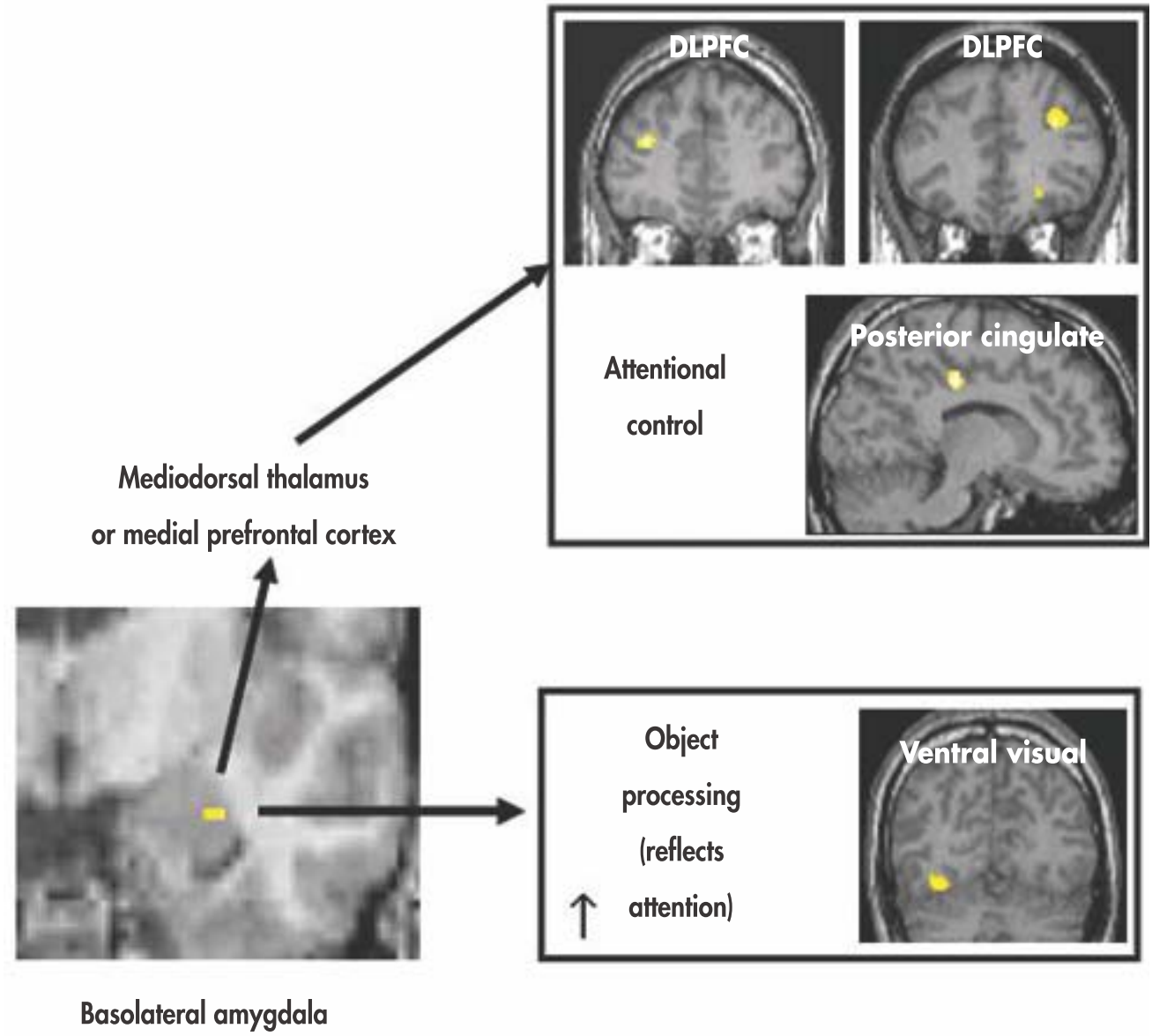

Figure 41–5. Identification of an unconscious emotional vigilance network in anxiety (Etkin et al. 2004).
Unconscious trait anxiety–correlated activations are seen in the basolateral amygdala, dorsolateral prefrontal cortex (DLPFC), posterior cingulate, and a number of ventral visual areas. These regions may thus form an unconscious emotional vigilance network that directs attention for enhanced processing of unconscious threat (DLPFC and posterior cingulate), which was reflected in enhanced activation of object processing areas in the ventral visual stream.
Source. Reprinted from Etkin A, Klemenhagen KC, Dudman JT, et al.: "Individual Differences in Trait Anxiety Predict the Response of the Basolateral Amygdala to Unconsciously Processed Fearful Faces." *Neuron* 44:1043–1055, 2004. Used with permission.

tional evaluation and the dorsolateral PFC and the posterior cingulate cortex in directing attention for better processing of the unconscious threat. The network also contained a number of ventral visual regions important in the processing of objects, particularly faces. Enhanced activity in these visual regions is thought to reflect the effects of enhanced attention. Emotional arousal led to faster color identification reaction times, but, again, only when emotion was processed unconsciously.

The fact that brain activations and reaction times were not correlated with anxiety during consciously processed fear illustrates another important point: conscious processes may secondarily regulate unconscious biases. Distinguishing between conscious and unconscious processes may be essential for understanding both psychopathology and psychotherapy. For example, certain therapies (or drugs) may alter the capacity for secondary regulation of unconscious biases, but not

the biases per se. Alternatively, the effectiveness of a therapy may relate to its ability to normalize unconscious biases. One can imagine two simple ways in which biases may be corrected. Excessive unconscious amygdala activation brought about by anxiety may be normalized through changes occurring primarily in the amygdala or by recruitment of additional areas, perhaps top-down inhibitory areas in the frontal cortex. Thus, neuroimaging can help distinguish conscious from unconscious brain changes and identify which particular brain changes are responsible for the behavioral improvement.

Functional Correlates of Personality Disorders

Relatively few studies have examined the neural basis of personality disorders. Of these, most have focused on borderline personality disorder (BPD) or antisocial personality disorder, and in particular on patients' impulsivity. Despite limited data, results from these studies generally point to abnormalities in the ventromedial PFC and OFC. These areas have been implicated in the inhibition of inappropriate behavior (Horn et al. 2003; Lubman et al. 2004) and appropriate decision making within the emotional or personal domains (Bechara et al. 1997; A.R. Damasio et al. 1990; H. Damasio et al. 1994). Deficits in impulse control are important elements of several personality disorders (American Psychiatric Association 2000).

Several studies have found, using FDG-PET, broad decreases in prefrontal metabolism in BPD patients (De La Fuente et al. 1997; Soloff et al. 2000, 2003). De la Fuente et al. (1997) found decreased activity in the medial and lateral PFC, including in the ACC in BPD patients. Soloff et al. (2000, 2003) found decreased metabolism in the medial OFC of BPD patients (see Figure 41–6A and B), with the degree of orbitofrontal hypometabolism related to self-report and interviewer-assessed measures of impulsivity (Soloff et al. 2003). Schmahl et al. (2003) compared neural activation during script-guided imagination of abandonment situations with activation during imagination of neutral situations in BPD patients and control subjects. The BPD patients showed decreased activation, relative to controls, in the ACC and amygdala/hippocampus, and increased activation in the dorsolateral PFC.

Other studies point to serotonergic dysfunction in the ventromedial PFC in BPD. Fenfluramine is a compound with serotonergic activity. Challenge with fenfluramine leads to increased metabolism in the PFC. This increase was blunted in the medial and orbitofrontal regions of the PFC of patients with BPD, as well as in several regions outside of the frontal lobe (see Figure 41–6A) (Schmahl et al. 2002; Soloff et al. 2000). To more directly probe the serotonergic system, one can inject subjects with a radioactively labeled compound that binds proteins important for serotonin function, and image the degree of binding throughout the brain with the PET camera. Leyton et al. (2001) found decreased binding of a serotonin precursor in the medial PFC and ACC in BPD patients (see Figure 41–6C). This deficit was more severe in patients with higher impulsivity scores. Finally, two studies of impulsive aggressive patients with a variety of personality disorders found baseline and fenfluramine-induced deficits in the ventromedial PFC, similar to those described above for BPD patients (Goyer et al. 1994; Siever et al. 1999).

Functions of Reduced Activity in the Ventral Frontal Cortex

What are the consequences of reduced activity in ventromedial and orbitofrontal circuitry in individuals with BPD or antisocial personality disorder? Some insight into this question comes from studies of damage to these areas. Antonio Damasio and colleagues characterized subjects with lesions in the ventromedial PFC and found that they displayed problems in decision making, particularly in the interpersonal and emotional domains (Bechara et al. 1997; A.R. Damasio et al. 1990; H. Damasio et al. 1994). When asked to carry out tasks that require the development of a strategy for long-term benefit, subjects with ventromedial PFC lesions developed neither a discriminative skin conductance response indicating the correct choice nor a successful long-term strategy (Bechara et al. 1997). Lesions of the medial OFC in experimental animals result in reduced behavioral inhibition, and the "orbitofrontal syndrome" in humans consists of disinhibited, socially inappropriate behaviors; impulsivity and aggression; and emotional lability (Blair 2001; A.R. Damasio et al. 1990; H. Damasio et al. 1994; Goldman-Rakic 1987; Malloy et al. 1993). These personality changes can even result in sociopathic behavior.

Taken together, these findings suggest that the abnormalities in the ventromedial and orbitofrontal cortex found in BPD and antisocial personality disorder may reflect the deficits in behavioral inhibition that are common across several personality disorders. Other than impulse control, however, our understanding of the neurobiology of personality disorders is rudimentary.

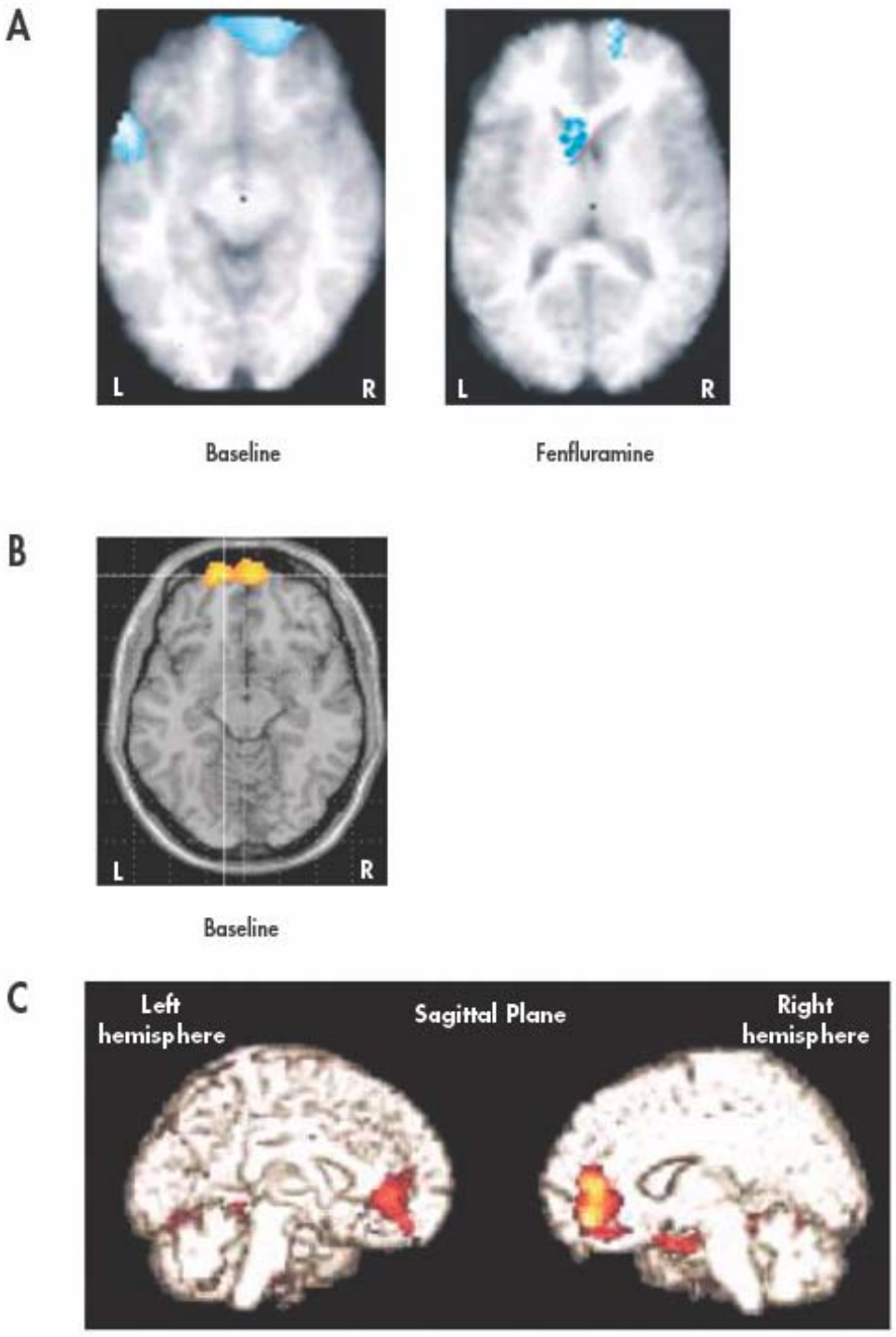

Figure 41–6. Deficits in basal brain metabolism and serotonergic function in patients with borderline personality disorder (BPD).

(A and B) The medial orbitofrontal cortex (OFC) showed less basal brain metabolism in BPD patients (indicated by the blue clusters in **(A)** and the orange cluster in **(B)** (Soloff et al. 2000, 2003). Challenge with fenfluramine, a compound with serotonergic properties, also revealed less recruitment of orbital regions in BPD patients than in control subjects (Soloff et al. 2000). **(C)** The binding of a serotonin precursor was decreased in the anterior cingulate and ventromedial prefrontal cortices of BPD patients (Leyton et al. 2001).

Source. **A and B**: Reprinted from Soloff PH, Meltzer CC, Greer PJ, et al.: "Fenfluramine-Activated FDG-PET Study of Borderline Personality Disorder." *Biological Psychiatry* 47:540–547, 2000. Used with permission; Soloff PH, Meltzer CC, Becker C, et al.: "Impulsivity and Prefrontal Hypometabolism in Borderline Personality Disorder." *Psychiatry Research* 123:153–163, 2003. **C:** Leyton M, Okazawa H, Diksic M, et al.: "Brain Regional Alpha-[^{11}C]Methyl-L-Tryptophan Trapping in Impulsive Subjects With Borderline Personality Disorder. *American Journal of Psychiatry* 158:775–782, 2001. Copyright 2001, American Psychiatric Association. Used with permission.

Outcome Prediction in Patients With Personality Disorders

How might the findings summarized above—on the role of the rostral cingulate and OFC in prediction of treatment response in patients with depression and OCD—apply to patients with personality disorders? The mutually exclusive relationship between rostral cingulate and depression versus OFC and OCD suggests that there may be disease-specificity to brain areas with prognostic value, even in diseases that can be treated with the same treatment modality or drug. Personality disorders are a highly varied category of mental illnesses and are often comorbid with mood and anxiety disorders. As such, prediction of treatment outcome may be less readily accomplished than with depression and OCD. Outcome prediction for each dimension of a personality disorder may need to be examined separately, which would necessitate use of more stimulus-responsive imaging modalities.

The conflict detection and resolution function of the rostral cingulate and the behavioral inhibition function of the OFC may both turn out to be very relevant for the capacity of patients with personality disorders to recover. Psychotherapies call on patients to understand the beliefs underlying their actions and exert control over those beliefs and over their own behavior. One can imagine that conflicts would be frequently created between patients' hardened (likely unconscious) beliefs and their attempts to understand their behavior and correct these maladaptive beliefs. The ability to respond to and resolve these conflicts may involve recruitment of rostral cingulate–based neural circuitry. Those patients who can better recruit the rostral cingulate may be those who better resolve these conflicts and better respond to therapy. Similarly, patterns of thought or action in personality disorders may be so characteristic as to become compulsive, and a role for the OFC in regulating these patterns, as in OCD, may also relate to the capacity of patients to correct their thoughts and actions.

Conclusion

The biological study of psychotherapy is in its infancy, but several lines of evidence point to an important future role for neuroimaging in evaluating the mechanisms and outcome of psychotherapy. Imaging can contribute to an analysis of the mechanisms of pathogenesis of a mental disorder and it may provide meaningful predictions of treatment outcome. Although only a handful of neuroimaging studies have probed the biological deficits in personality disorders, they have been useful in identifying an important role for the ventral prefrontal cortices in impulse control among patients with BPD or antisocial personality disorder. A clearer direction for how neuroimaging will contribute to the psychotherapeutic treatment of patients with personality disorders will come when the biology of psychotherapy and personality disorders is more fully examined. We propose several points that may guide this process.

First, it is now clear that psychotherapy can induce robust changes in brain function that are detectable with neuroimaging. These findings must now be systematically explored. For example, the anxiety results described above suggest important mechanistic differences between processes operating at conscious and unconscious levels.

Second, prior to psychopharmacological treatment, the function of certain brain regions can predict the degree of patient improvement at follow-up, and there may be some degree of disease-specificity with respect to which region is most predictive of outcome. The anterior cingulate and orbitofrontal cortices, regions identified for the drug treatment of depression and OCD, may also be prognostic regions for psychotherapy outcome, as they are involved in conflict detection and resolution and in behavioral inhibition—functions that may be central targets of psychotherapy. Further investigation will show whether regions with prognostic value are specific to the type of disease or the form of treatment, and whether differential response to drug or psychotherapy can be predicted before treatment. In addition, understanding the brain regions and cognitive functions that best predict treatment response may allow the development of pharmacological agents that specifically enhance these cognitive processes and activity within prognostic regions. Combining novel pharmacological agents with psychotherapy may therefore lead to improved outcome (Ressler et al. 2004).

Third, deficits in impulse control in certain personality disorders have been associated with abnormalities in the ventromedial prefrontal and orbitofrontal cortices. Identification of deficits in these regions may point to the type of tasks and stimuli that will best probe the role of ventral prefrontal regions in behavioral inhibition, which may be very relevant for the ability of a patient to recover through psychotherapeutic treatment.

There is no longer doubt that psychotherapy can result in detectable changes in the brain. We now need to focus on the best neuroimaging approaches that will assist clinically relevant decisions relating to psychopathology and psychotherapy.

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