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Series Title	Current Clinical Psychiatry	
Chapter Title	Neural Models of Psychodynamic Concepts and Treatments: Implications for Psychodynamic Psychotherapy	
Chapter SubTitle		
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Abstract	Psychodynamic psychotherapy can be a powerful agent of change on the levels of affect, cognition, and behavior. It has long been presumed that these changes reflect discrete therapy-related modulations of brain function. Until recently, though, there were no scientific methods available to examine directly the neural substrates of psychotherapy. The advent of modern neuroimaging techniques has provided, for the first time, a window into psychotherapy-related changes in brain physiology. Nevertheless, there remains much to learn about the effect of psychotherapy – and psychodynamic psychotherapy in particular – on brain function. This chapter will provide an introduction to the methods of functional neuroimaging in psychotherapy research, a tour through the remarkable findings that have emerged thus far, and a glimpse into the profound implications that this work could have on the future practice of psychotherapy.

Keywords (separated by '-')	Anxiety disorders - cognitive therapy - depression - functional MRI - positron emission tomography - psychodynamic therapy

Chapter 9
Neural Models of Psychodynamic Concepts and Treatments: Implications for Psychodynamic Psychotherapy

Joshua L. Roffman, Andrew J. Gerber, and Debra M. Glick

Keywords Anxiety disorders • Cognitive therapy • Depression • Functional MRI • Positron emission tomography • Psychodynamic therapy

Psychotherapy and neuroscience have arrived at a historic crossroad. Since the inception of analytic thinking in the late nineteenth century, proponents of psychotherapy have struggled with the question of how it influences brain function – and whether this relationship is relevant to the work or effectiveness of therapy. Despite decades of parallel progress in psychodynamic and neuroscientific research, until recently, there was little meaningful interaction between these fields of study. Rather, fierce ideologic and methodologic divisions persisted between investigators of "mind-based" and "brain-based" thinking.

In the last 10 years, though, a remarkable synergy between these fields has begun to emerge, with powerful (and overwhelmingly positive) implications for the future of psychotherapy. In this chapter, we describe how this transformation has taken place, focusing on the critical role of new technology in understanding brain function. We demonstrate how principles central to dynamic therapy have informed the design, implementation, and analysis of brain imaging experiments, and, conversely, we discuss the potential of brain imaging data to further refine and improve the process of psychotherapy. In summarizing the current literature on how psychotherapy affects brain function, we identify the strengths and weaknesses of this scientific undertaking, and discuss ways in which it may ultimately reshape clinical practice.

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R.A. Levy et al. (eds.), *Psychodynamic Psychotherapy Research: Evidence-Based Practice and Practice-Based Evidence*, Current Clinical Psychiatry,
DOI 10.1007/978-1-60761-792-1_9,

Psychodynamic Therapy and the Brain

A Brief History

Curiosity about the interface of psychodynamics and brain function stretches as far back as psychoanalysis itself. In 1,895, Sigmund Freud embarked upon his Project for a Scientific Psychology (or, as literally translated, "The Psychology for Neurologists"), an attempt to define the unconscious in neurological terms [1]. As mentioned in an April 26, 1,895 letter to his friend and confidante Wilhelm Fleiss:

> Scientifically, I am in a bad way; namely, caught up in "The Psychology for Neurologists," which regularly consumes me totally until, actually overworked, I must break off. I have never before experienced such a high degree of preoccupation. And will anything come of it? I hope so, but it is difficult and slow going [2].

Indeed, having reached the limits of neurologic investigation for his time, Freud abandoned the project in 1,896, only to embark on a new ("royal") route to the unconscious through dream analysis. The Project notes were sent privately to Fleiss and remained unpublished until well after Freud's death. Within the Project, though, Freud developed a prescient, theoretical framework for how neural activity underlies both normal processes (including memory, attention, and judgment) and abnormal ones (hysteria, repression, and displacement).

For the better part of a century, scientific inquiry into the mechanisms of psychotherapy was limited to observational work, often reflecting individual interactions between patients and therapists. This work evolved into a complex and largely internally valid system of psychoanalytic theory and process; however, it failed to integrate with other developments in medical science and remained entirely distant from the study of neural function [3]. (Of note, there was hardly a complete isolation of psychology and medicine: in fact, efforts in the 1940s led psychiatrists to consider psychosomatic contributions to many common medical illnesses [4, 5].)

Although a general rapprochement between psychiatry and medicine followed the introduction of psychotropic medications in the 1950s and 1960s [6], the theory and practice of psychoanalysis remained largely isolated. In the years that followed, novel neuroscientific methods shed new light on brain development, memory, psychopathology, and other elements with a close relationship to psychodynamic principles, while at the same time cognitive psychologists developed scientifically rigorous ways to understand these same phenomena. However, it was not until the 1990s – the "Decade of the Brain" – that brain and psychotherapy investigators truly began to find common ground through scientific collaboration.

In particular, one novel method to understand activity within the living brain – functional neuroimaging – has played a pivotal role in this renewed relationship. For the first time, functional imaging has provided the opportunity to correlate directly cognitive and emotional processes with brain activity profiles in both healthy individuals and those with psychiatric disorders. As a result, we are newly able to face the challenges that Freud envisioned a century ago, as recalled in a landmark paper by neuroscientist and Nobel laureate Eric Kandel: "Where, if it exists at all, is the unconscious? What are its neurobiological properties? How do unconscious strivings become transformed to enter awareness as a result of analytic therapy?" [5].

A Lingering Disparity

There is long-held consensus that talk therapies provide substantial relief for many individuals with psychiatric illness, often with similar efficacy and cost when compared to other interventions [7–9]. However, the availability of new tools to understand brain function has been slower to influence psychotherapy research than it has for cognitive psychology, neuropsychiatry, and psychopharmacology.

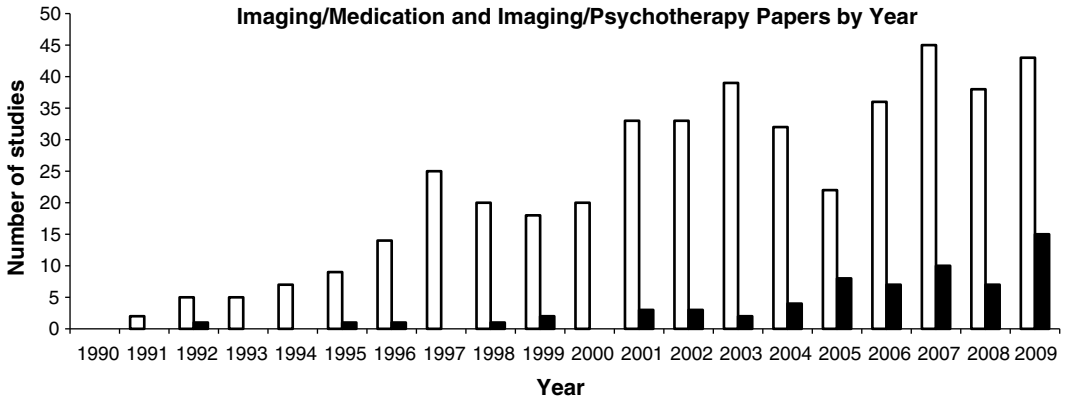

Fig. 9.1 Imaging/medication (*white bars*) and imaging/psychotherapy (*black bars*) studies by year. A Pubmed search was completed using key words related to neuroimaging (e.g., PET, fMRI, SPECT) and medication (e.g., psychotropic) to find studies including both neuroimaging and medication between 1990 and 2009. Based on the abstracts generated from this search, we selected studies based on three criteria: included studies were published in English, used human subjects, and investigated psychiatric (e.g., depression) rather than neurological (e.g., Parkinson disease) disorders. A similar search was conducted using key words related to neuroimaging and psychotherapy (e.g., psychotherapy, interpersonal therapy, cognitive behavioral therapy, and psychodynamic therapy) (Adapted with permission from Ref. [11]. Copyright © 2005 Cambridge Journals)

The extent to which psychotherapy has fallen behind psychopharmacology in this regard is dramatically evident in Fig. 9.1, which summarizes neuroimaging studies of these treatment modalities since 1990 [10, 11].

There are a number of reasons – technical, scientific, historic, even political – why this might be the case. As described throughout this book, psychotherapy research has always been, is now, and will remain, a uniquely challenging enterprise. The study of psychodynamic therapy, in particular, does not always lend itself well to the research methods that are commonplace in medicine, and often in other areas of psychiatry [12]. Neuroimaging research provides no exception to this rule. For example: at present, most functional imaging technologies cannot be used to detect meaningful brain activity patterns in individual subjects. Instead, individuals must be grouped together to acquire results that are statistically valid [13]. Therefore, because psychodynamic therapy is a highly individualized treatment that can last months or years, it would be difficult to develop standardized treatment protocols for subjects within a study cohort. In addition, even for the study of time-limited, manualized psychotherapies, there remain significant obstacles to neuroimaging investigations. Imaging studies are relatively expensive, and, with limited support from federal funding sources, cost can be a prohibitive factor. There may also be a bias toward studying the neural mechanisms of medications since they are thought of as a "biological" or "medical" intervention, while some consider psychosocial interventions relatively "soft" [10].

In spite of these complications, the use of neuroimaging has now gained substantial momentum in psychotherapy research, and this investigative approach is now extending into medical, neuroscientific, and sociocultural awareness. It is also becoming clear that these studies have important clinical implications. Understanding how psychotherapy modifies brain function could powerfully influence its perception among new patients who may be weighing it as a treatment option. Furthermore, it is not too audacious to imagine that functional imaging studies, perhaps in concert with other biological markers, could one day be used to guide treatment for individual patients. This would place psychotherapy squarely within the emerging field of individualized medicine, which many consider to be the next revolution in patient care [14].

Functional Imaging Methods and Their Application in Psychotherapy Research

Of course, these kinds of advances will be predicated on neuroimaging studies with rigorous scientific methods and robust findings. Some initial studies of neuroimaging and psychotherapy, discussed later in this chapter, illustrate some of the challenges intrinsic to this kind of research. In this section, we will introduce some basic concepts that are critical to understanding functional neuroimaging, its potential for use in psychotherapy research, and its limitations therein.

Unlike traditional brain images that produce a static picture of brain structure, functional neuroimaging provides a measure of brain activity. The most commonly used functional imaging techniques are positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) [13]. Both PET and SPECT rely on radioactive tracers that are injected into the bloodstream just prior to imaging. These tracers enter the cerebral blood supply and emit a signal, detectable with a camera placed near the patient's head. As activity increases or decreases in brain regions, blood flow to these regions rises or falls accordingly. The radiotracer signal thus also varies, making it a proxy for the level of neural activity. In other words, PET and SPECT provide a reliable but still indirect measure of neuronal firing [15]. These techniques can be used to measure either resting (baseline) activity, or changes in activity related to a task (which can range from simple finger tapping to complex cognitive or emotional paradigms). PET is more expensive than SPECT but provides much better spatial resolution. Although the amount of radiation exposure is not considered harmful, it does limit the frequency with which PET and SPECT scans can occur. For example, medical centers generally permit individuals to undergo at most two PET scans per year.

In contrast, fMRI scans do not use radiation, but rather strong magnetic fields to measure brain activity. In fact, fMRI studies are conducted using the same MRI machines that are used in clinical practice, but with different programming. Like PET and SPECT, the fMRI signal also estimates cerebral blood flow, which shows regional fluctuation based on which parts of the brain are active at a given time. In this case, the signal is generated by measuring relative concentrations of deoxygenated versus oxygenated blood. Exposure to the magnet is safe, except for individuals who have pacemakers or metallic implants in their bodies, who cannot be scanned. The fMRI environment is more restrictive than PET or SPECT, as it involves lying supine and very still within a long tubular structure. However, it is more versatile due to its better temporal resolution, which permits repeated measurements of brain activity every few seconds.

It is important to recognize that brain activity, as measured by these techniques, can reflect several overlapping neural processes related to the subject's current condition. These processes must be carefully identified and disambiguated to the greatest possible extent when conducting functional imaging analysis. First, what is the state of the subject? Is she disease-free, diagnosed with an illness but currently symptom-free, or actively symptomatic? As we are learning, baseline brain activity profiles can differ substantially based on the presence or absence of psychiatric illness. Second, if a patient is being scanned, when is the scan occurring relative to a treatment intervention? For example, most psychotherapy studies thus far conducted have imaged patients twice: once just before, and once just after completion of the treatment course. By comparing these scans, one can observe a measure of treatment effects. However, in light of the first consideration, it can be difficult to differentiate changes in brain activity that are related to the treatment itself versus those related to the (hopefully improved) state of the patient's illness. Finally, what is the subject doing in the scanner? Is he resting quietly or engaged in a task? Often, activity in brain regions is compared between these two conditions to give a measure of task-related "activation." Other designs are meant to induce symptoms while the subject is being scanned, so that they may be more readily correlated with brain activity profiles.

Other Ways to Measure Therapy-Related Changes in Physiology

While functional neuroimaging can provide detailed measures of brain function, imaging techniques can also be costly and logistically difficult to arrange. Imaging analysis requires the use of complex (and often time-consuming) statistics to convert raw signals into interpretable data. Alternatively, measures of peripheral physiology can provide useful indicators of neural activity, albeit further downstream from brain activation. Psychophysiology techniques can sensitively measure moment-to-moment fluctuations in skin conductance, heart rate, and blood pressure, and do so relatively inexpensively and non-invasively. The greatest advantage of these techniques, though, is that they can be deployed repeatedly over the course of a treatment, and even *during* treatment sessions. Some investigators have compared psychophysiology measures obtained simultaneously from the patient and therapist as an objective measure of their interaction. For example, Marci et al. reported a significant relationship between patient ratings of the therapist's perceived empathy and the concordance of skin conductance between the two during therapy sessions [16].

Even with the availability of these technologies, it is still important for scientific and philosophical reasons to ask the question of why *should* psychotherapy – and psychodynamic psychotherapy in particular – change brain function? One "bottom-up" approach to this question is to examine neural correlates of the building blocks upon which psychotherapy is based. Therefore, before considering the net effect of psychotherapy on the brain function, we will first review evidence that psychoanalytic constructs are themselves associated with meaningful changes in brain activity.

Experimental Methods and Evidence for Psychoanalytic Constructs

It is widely stated and accepted by both friends and foes of psychoanalysis that psychoanalytic constructs lack the empirical evidence, in terms of behavior and neurobiology, that is enjoyed by cognitive psychology. This deficiency is taken by some as evidence for the intrinsic "untestability" of psychoanalytic hypotheses, often ascribed to the unconscious, subjective, and interpersonal nature of the phenomena central to psychoanalytic theorizing and treatment [17–19]. Others argue that the lack of evidence demonstrates the falsehood of psychoanalytic ideas, or at least, their irrelevance to an empirically based science of the brain and mind [20]. In fact, the story is more complicated than is typically represented by either side in the discussion. Research has been accumulating, with particular growth in the past decade, which support and elaborate several basic psychodynamic hypotheses related to processes, representations, and relationships [21, 22]. This research currently focuses on phenomena in normal subjects under experimental conditions, as opposed to their action in the therapeutic setting. However, links to therapeutic action are gradually becoming more plausible, and it is likely that research will continue to bridge the gap between experimental work and psychoanalytic practice in the coming years.

Neural research on psychodynamic phenomena can broadly be divided into four domains, with significant overlap: [1] memory and learning, [2] affect, [3] social cognition and relatedness, and [4] processes such as free association and defense mechanisms that reflect the interface between consciousness and unconsciousness. As experimental methodologies have improved, each of these domains has received increasing attention by cognitive neuroscientists, yielding evidence that much important mental functioning goes on outside of awareness. Thus, research that did not start out as explicitly "psychodynamic" has pointed back towards an unconscious, representational, and relational mind, and therefore towards a recognizably psychodynamic view of mental functioning. Meanwhile, a number of psychodynamic writers have suggested ways in which the accumulating data can be used to inform thinking about psychotherapy [21–26].

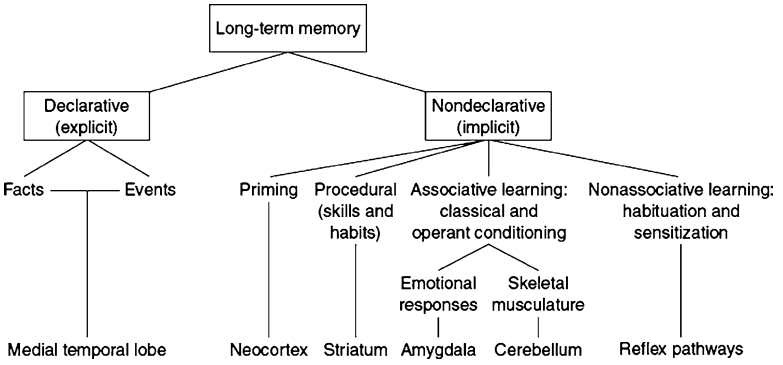

Fig. 9.2 Forms of long-term memory and associated brain regions (Reprinted with permission from Ref. [29])

Memory and Learning

Scientists, philosophers, and writers have long appreciated that much of what we know and remember is not in conscious awareness, or even accessible to awareness, at a given moment. Given our reliance on subjective reports of knowledge and memory, it has been difficult to study these phenomena systematically. Based on previous scholarship and his own clinical observations, Freud asserted that a significant portion of possible thoughts are actively excluded from awareness [27]. Due to the objectionable nature of their content, these thoughts are forced to reside in the "dynamic unconscious." However, they continue to exert a significant influence on behavior and conscious processes, including those most relevant to psychotherapy and psychoanalysis. The concept of the dynamic unconscious is often confused, both in and out of the psychodynamic literature, with the "descriptive unconscious." The latter is a more inclusive category that includes not only the dynamic unconscious, but also the preconscious (i.e., easily accessible by consciousness if one were to focus attention on this) and the non-conscious (i.e., inaccessible to consciousness because it has never been symbolized, e.g., procedural knowledge such as how to ride a bicycle) [28].

Over the past several decades, cognitive neuroscientists have developed methods for demonstrating and measuring various systems for memory and learning that have complicated relationships to consciousness (Fig. 9.2) [29–32]. Particularly relevant to psychodynamic therapy, long-term memory researchers have described an implicit (also called "non-declarative") memory system, which is not readily accessible to consciousness. The existence of implicit memories was seen by exposing subjects to stimuli so brief that they were not consciously perceived (i.e., subliminal) but yet affected their performance on later tasks. This memory is often described as "associative," though the relationship to the semantic properties that partially define declarative memories is unclear [33–36]. Investigators also found that subjects could be "primed" by consciously perceived information. Even when they did not specifically recall the information that they were previously taught, their answers to questions were influenced by having been exposed [37].

Other experimental tasks were developed to demonstrate the existence of an implicit procedural memory system, in which subjects learned motor or behavioral tasks without developing language to describe what they had learned, and sometimes without even being aware that they had learned something. For example, in the widely used Weather Task, subjects are shown one or more of a set of four symbols and asked, with no prior information, to use them to guess whether it will rain or shine [38, 39]. After responding, they are told whether they are right or wrong and the task is repeated for many trials. Subjects report the subjective experience of guessing at every answer and not learning anything during the course of the task. In fact, unbeknownst to the subject, the correct answer to each trial is calculated based on combinations of fixed probabilities assigned to each symbol.

Though subjects feel that they are guessing, their performance improves steadily during the course of the task, demonstrating that they are learning outside of awareness.

Recent functional imaging experiments have demonstrated that the brain regions subserving encoding (i.e., formation) and retrieval of explicit and implicit memory do not fully overlap. Working memory appears to rely heavily on activity in the frontal lobes, primarily in the dorsolateral prefrontal cortex. The formation of long-term declarative memories relies on structures in the medial temporal lobe, most prominently the hippocampus. There is also involvement from the amygdala and limbic system when significant affects are involved. Formation of implicit memories in priming appears to rely heavily on the frontal lobes, while formation of implicit associative memory may involve the limbic or motor systems, depending on the nature of the memory. Procedural memories formation, such as in the Weather Task, involves components of the basal ganglia, the caudate, and the putamen, if the task is predominantly cognitive, and the cerebellum and brainstem, if the task is motor. Some investigators have suggested that memories related to one's personal history, referred to as "autobiographical memory," may also use a somewhat distinct system, though the evidence remains unclear [40].

The nature of these multiple memory systems has important implications for psychodynamic theory and practice. First, there is substantial evidence that much of learning and memory takes place outside of awareness, raising the possibility for its importance in psychopathology and mental life. Given their functional and anatomical differences, it is therefore important to identify to which memory system a particular learned thought or behavior belongs. For example, a person's expectation of certain responses from a caregiver or significant other (a frequent emphasis in dynamic psychotherapy) may be encoded as an explicit memory, an implicit associative or priming memory, or a procedural memory. Several recent theorists have proposed that the procedural memory explanation is most likely [24], although all three systems may be involved to varying degrees. As each memory system has distinct modes of functioning, properties, and constraints (including capacity and method for change), identification of the role of differing memory systems in psychodynamic work is crucial. For example, it seems likely that patterns of interpersonal relatedness and emotion regulation learned in the first few years of life are encoded in a more procedural (i.e., non-symbolized) fashion. Therefore, they may be slower to change and less amenable to verbal interpretations (perhaps akin to what is described by some psychodynamic theorists as "preoedipal" content). In contrast, symptoms based in neurotic conflict that develops later in life may be represented symbolically, despite being unconscious. Such symptoms may be easier to change with accurate and timely psychodynamic interpretations (akin to so-called "oedipal" material).

Affect

Although psychodynamic thinkers have long emphasized the importance of affect, cognitive neuroscientists initially neglected this area, largely due to the difficulty of measuring or even defining it. Psychiatrists continue to debate the definitions of "mood" and "affect," and the extent to which either one can be defined objectively or subjectively. We will define affect in the broad sense as synonymous with emotion (i.e., a mental state with physiologic and psychological components).

In recent years, affect has become a major topic of research in relation to both psychopathology and normal functioning [41]. The study of fear has been made possible by observing its behavioral correlates in animals. This work led to the identification of the limbic system, particularly the amygdala, anterior cingulate, orbitofrontal, and medial prefrontal cortex, as important in affective processing [42]. Though the study and localization of other affects has been more challenging, there is growing evidence that, at least in humans, affective processing is governed by continuous properties of all affects, rather than relying on a distinct system for each feeling state.

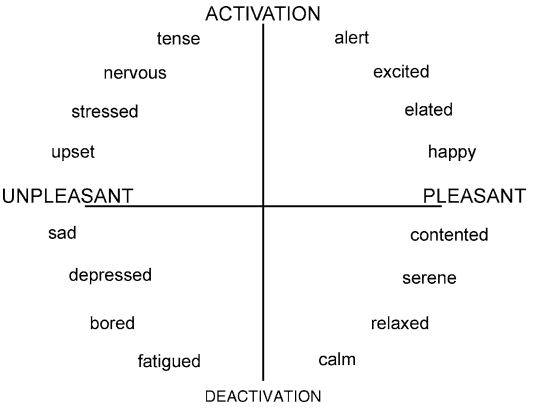

Fig. 9.3 The affective circumplex model shows how different affective states may be represented by placement on two continuous and unrelated scales: activation versus deactivation (*y*-axis) and unpleasant–pleasant (*x*-axis) (Reprinted with permission of Elsevier from Ref. [22])

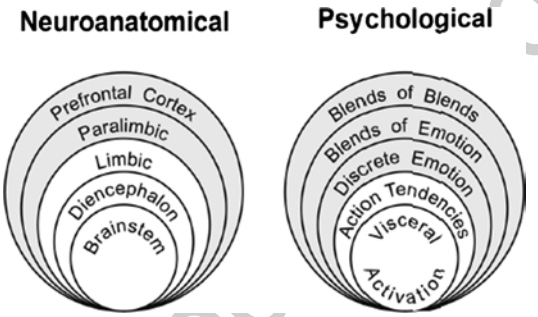

Fig. 9.4 Lane and Garfield depict hierarchical organization of emotional experience and its neural substrates. Higher levels (*larger circles*) illustrate mechanisms that add to and modulate lower levels, but do not replace them. A *white background* for lower level processes indicates an implicit process, whereas a *gray background* for a higher level process indicates an explicit process (Reprinted with permission from Ref. [25])

The circumplex model of affect [43, 44] posits that each affect is represented in the brain according to two independent properties: valence (the extent to which the affect is positive or negative) and arousal (the extent to which the affect is seen as stimulating or arousing, see Fig. 9.3). Brain systems involved in reward mechanisms, such as dopaminergic areas of the brainstem, are believed to play a role in encoding and processing valence. In contrast, systems governing attention and arousal include the reticular formation, thalamus, and dorsolateral prefrontal cortex [45]. Since both properties may be salient to the individual, they are processed in common structures such as the amygdala and anterior cingulate. With increased spatial resolution in our imaging techniques, we may learn about subdivisions of these regions relevant to different affective stimuli [46].

Psychodynamic models are concerned with how affects are generated, regulated, and expressed. Thus, neuroimaging findings suggest potential ways to measure affects that are in and out of awareness. Ochsner et al. have shown that particular brain regions are involved when subjects consciously manipulate their own affect by reappraising a visual image in a way contrary to an initial impression [47]. Lane argues that engagement of these affect regulation processes, by bringing thoughts and their associated affects into conscious awareness, forms a basic psychotherapeutic mechanism of action. He draws parallels between the hierarchical organization of psychological aspects of emotional experience and their neural substrates, suggesting that engagement of higher level systems leads to better psychological health [25] (Fig. 9.4). Etkin et al. further parceled conscious and unconscious awareness of affect by studying activation in the basolateral amygdala in response to fearful

faces [48]. They found that, when the stimuli are presented subliminally, activity in the basolateral amygdala is related to a subject's baseline trait level of anxiety, but, when stimuli are presented with the subject's conscious awareness, activity in this region is not related to anxiety. This pattern suggests that in order to understand the conscious representations of affect, we must evaluate not only automatic responses but also the compensatory responses that depend on the extent to which affect is conscious or unconscious. For example, when using imaging to distinguish between healthy controls and patients with a psychiatric diagnosis, one must always keep in mind that observed differences are just as likely to reflect the *compensation* in the individuals with the disorder as they are a core pathological feature of the disorder. Clinicians are familiar with this concept. For example, they may note an unusual degree of psychological mindedness in a patient who needed to cope with life difficulties versus a much lower level of psychological mindedness in a healthy individual who was exposed to less stress and thus never needed to develop this capacity.

Lane's typology of affect (Fig. 9.4) is useful in appreciating the range of affective phenomena that are potentially important in psychopathology and treatment. He cites behavioral and neurobiological evidence for four overlapping categories of affective processes: [1] background feeling, [2] implicit affect, [3] focal attention, and [4] reflective awareness [25]. Background feeling does not require consciousness, but is available on demand. Implicit affect is unconscious. Focal attention is a conscious spotlight on affect, related to reappraisal, as studied by Ochsner. Reflective awareness consists of an appreciation for affect in relation to self and other representations and is perhaps most central to psychodynamic theories. All are likely relevant to psychopathology and mechanisms of change. Across most psychotherapeutic modalities, it is believed that specific attention to problematic thoughts and maladaptive negative feelings helps individuals gain better control over and ameliorate the effects of these mental contents. Lane's typology is an early attempt to frame this kind of "cognitive modification" of thoughts and feelings in a general language relevant to both clinical work and neurobiology.

Social Cognition and Relatedness

Psychodynamic theorists have long argued for the important role of intrapsychic representations of relationships and interpersonal processes in the basic functioning of the mind. Early cognitive neuroscience and experimental approaches neglected social processes due to the complexity and measurement difficulties inherent to this perspective. However, along with the increasing attention on non-conscious processes and affect, cognitive scientists have also become more interested in the social brain, even coining a new subfield labeled "social cognitive neuroscience." This has been driven by success with animal models, such as Insel's work comparing monogamous and polygamous rodents [49, 50], as well as by functional neuroimaging, with its ability to study complex in vivo processes and associated cognition [51].

Many if not all aspects of the growing social cognitive neuroscience literature are relevant to psychoanalytic theory and treatment. At the most basic level, this research has led to non-analytic conceptualization and measurement of the neural basis of self versus other representations. Some evidence suggests that person (or "object" in psychoanalytic terms) representations are processed in distinct regions of the brain (i.e., the medial prefrontal cortex) [52]. There is even evidence for the possibility of dissociating brain regions involved in processing of self versus other representations [53, 54]. An alternative view is for a neuroanatomical division between processing of data about internal states (typically in the medial part of the frontal lobes) versus external behaviors and properties (typically in the lateral part of the frontal lobes) [55]. The exact location of these processes may have little impact on the theories and work of psychoanalytic treatments. Nevertheless, such work may shed light on the contrasts between self and object processing and provide tools for studying these crucial systems in association with psychopathology and treatment.

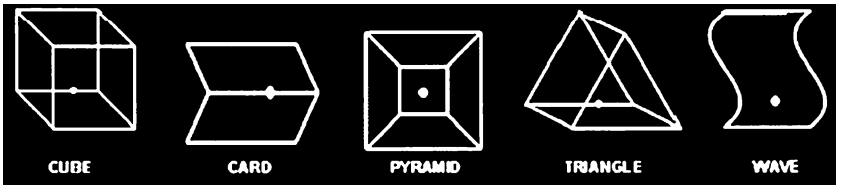

Fig. 9.5 Reversible geometric figures, as used by Peterson [22] to investigate the neural basis of bistable percepts. Each figure can be perceived either with the dot protruding out of the page or receding into the page. The neural substrate for consciously selecting either image may also subserve other conscious choices of perspective that influence our mental life, such as what goes on in psychotherapy (Reprinted with permission of Elsevier from Ref. [22])

Transference is a relational process hypothesized to be at the core of many clinical phenomena, and even the primary mechanism of change, in psychodynamic treatments [56]. Though there has been research into the effect of transference interpretations on treatment alliance and outcome [57, 58], it was thought to be difficult, if not impossible, to study the neural mechanism of the transference process (as opposed to other known cognitive phenomena). However, in the early 1990s, Susan Andersen developed a behavioral method to demonstrate and probe certain aspects of transference in a population of healthy college students. In her paradigm, subjects participate in two sessions, which they are led to believe are unrelated to one another. In the first session, the subject is asked to provide an equal number of positive and negative short descriptive sentences about one or more significant people (called significant others or "SOs") in their lives. Subjects also select a set of "irrelevant" (i.e., neither descriptive nor counter-descriptive) adjectives in relation to each SO and provide descriptors about a series of famous people. In the second session (carried out at least a month later, so as to prevent the subject from making any connection between the two), the subject is told that he will meet a stranger and is asked, in advance, to memorize a description of that stranger. The stranger or, in some experiments, multiple strangers described are, in fact, fictitious and their descriptions are constructed in one of three ways: [1] they are created from a semi-random assortment of one of the subject's own SO descriptions (padded with irrelevant descriptors), [2] they are created from a semi-random assortment of a *different* subject's SO description (padded with irrelevants), or [3] they are created from a semi-random assortment of the subject's famous person descriptors.

Andersen demonstrated that, although subjects never made the conscious connection between the strangers and their own SOs, their memory for these descriptions, affective response (in and out of awareness), and attributions to the stranger were all significantly influenced by whether the stranger resembled their own significant other or not [59–63]. Work is currently underway by Gerber and Peterson, in collaboration with Andersen, to investigate the neural bases of transference using a modified version of the paradigm suitable for the fMRI environment.

Other researchers view transference as one example of an individual having to use ambiguous stimuli to make predictions about the future [64, 65]. An incomplete set of information about a person may engage an automatic system that chooses the most likely object representation (usually outside of awareness) and fills in the missing data. Peterson and colleagues have studied the neural basis for viewing bistable percepts such as the Necker cube (where one can see one vertex of a three-dimensional cube either pointing out from the page or pointing into the page, but not both at the same time, Fig. 9.5) [66]. Frontal–striatal circuits are active when one alternates between images, suggesting a supervisory role of these circuits in other interpretations of ambiguous stimuli, such as transference.

Westen and Gabbard [67, 68] have argued that investigation into the neural basis of transference is likely to be useful for studying psychoanalytic treatments. In particular, they point to long-standing psychoanalytic debates such as whether there is one transference or many in a given clinical moment,

or whether the transference is significantly altered by real-world properties of the analyst and analytic setting (on which empirical evidence could have a useful impact). They argue that transference is predominantly a form of procedural memory. Gerber and Peterson speculate that transferential processes may have elements of multiple memory systems including procedural and associative non-declarative systems. Neuroimaging findings using the Andersen paradigm may shed light on these questions, which may then highlight properties and constraints of the transference system that are relevant to theorizing and clinical techniques. For example, we may learn that some aspects of transference are rooted in procedural memories, by noting their association with activity in the basal ganglia. These elements of transference may be learned earlier in life, change more slowly, and be more amenable to supportive interventions than to higher level interpretations. In contrast, we may learn that other aspects of transference are rooted in implicit associative memories but associating them with activity in the frontal cortex and hippocampus. These elements may stem from later conflict and change relatively quickly in response to defense interpretations. Ultimately, neuroimaging of paradigms such as Andersen's could help us clarify different aspects of transference in the laboratory in such a way that could be directly applied to clinical technique.

Attachment theory, as originated by John Bowlby and carefully operationalized by Ainsworth, Main, and others, has been influential on psychodynamic theorizing and clinical practice [69, 70]. Empirical work in both humans and animals has suggested that the attachment system is fundamental to our social processes and is likely subserved by a distinct neural mechanism [71, 72]. Recent neuroimaging work has attempted to localize these processes using attachment-related stimuli such as pictures of one's own children [73, 74]. Progress in this area will likely be relevant to our understanding of how attachment affects and is changed within the treatment environment. Such work could help clarify the extent to which insecure or disorganized attachments are rooted in neurobiologically fixed deficits whose roots do not change in treatment (though we may develop helpful compensations) versus difficulties in higher level processing that can be fundamentally altered by treatment. Attachment and psychodynamic theorists have argued about these very points. It is hopeful that neurobiological methods can advance the debate.

Empathy, an inherently interpersonal process, has received considerable attention in the cognitive neuroscience literature [75–77]. Researchers have shown activation in specific brain regions, in particular the insula and the anterior cingulate cortex, that relate to both an individual's experience of his/her own distress, and his/her experience of someone else's distress. A subject's own behaviorally rated capacity for empathy is tightly correlated with the activation of these brain regions [75, 76]. In related work, Marci has shown a link between therapist empathy and physiologic correlation between patient and therapist using a measure of skin conductance [16, 78]. Marci and Riess have shown that awareness of lack of patient–therapist concordance in physiological measures can lead to significantly improved alterations in clinical interventions, helping the therapist see previously unseen anxiety in the patient [79]. Given the highly reproduced finding that patient–therapist alliance (a construct that overlaps with empathy) is closely related to therapeutic outcome, neurobiological investigation of empathy is relevant and important for our understanding of analytic treatments.

Conceptualization and empirical research into "theory of mind" (i.e., an individual's understanding about the content and functioning of other people's minds) began in the developmental psychology literature but has become an important part of work on psychopathology (in particular autism, borderline personality disorder (BPD), and schizophrenia) and therapeutic change (where it is often called "mentalization") [80–82]. Several neuroimaging researchers have found evidence for functional localization of theory of mind in the medial prefrontal cortex, interestingly close to, and undoubtedly related to, regions implicated in self-representations [83–86]. Further investigation into the nature of theory of mind, its properties, and its capacity for modification during treatment may be an important window into a psychodynamic mechanism of action. For example, it is widely hypothesized that in certain disorders such as autism, there is a relatively fixed deficit in theory of mind. However, some have argued that it is possible to significantly improve the ability of high

functioning autistic or Asperger's individuals though therapy. It would be useful to understand whether these changes affect the same areas as the underlying disorder or are more likely to affect compensatory mechanisms. Similarly, Fonagy and others have discussed impaired theory of mind in BPD. Neuroimaging could help clarify whether this is more of a stable deficit or an inhibition of an underlying capacity that can be improved through treatment [80].

The term "mirror neurons" was coined in reference to pre-motor and parietal cells in the brain of macaque monkeys that fired *both* when the animal carried out a specific action (e.g., reaching for a banana) and when the animal observed a human experimenter performing that action [87]. The translation of this concept into humans, predominantly through functional neuroimaging experiments, has received a great deal of attention within the psychodynamic literature [88–90]. Within the mirror neuron literature, dynamic theorists have seen a potential neurobiological substrate and legitimization of the psychodynamic concept of "primary identification" (i.e., a core level experience by one person of the mental state of another). However, this argument is potentially misleading in a number of ways. First, it appears to imply that the processes of empathy and identification are somehow "neurobiologically primary" rather than mediated by higher level neuro-cognitive processes, as has been well established by clinical and empirical evidence. Second, the argument is based on an extrapolation of a finding in non-human primates (where single cell recordings are possible) to humans (where at present we can only measure activation in large groups of neurons). Finally, it is unclear how the mirror neuron literature adds to the broader theory that all concepts (including self and object representations, as well as their expected actions and affects) are stored in distributed neural representations, which are, in turn, connected to representations of behaviors being carried out both by ourselves and by others. More empirical and theoretical work is required to clarify the usefulness of the mirror neuron literature to psychodynamic therapy.

Attention, Free Association, and Defense

The study of attentional processes is also important for the investigation of unconscious and clinically relevant mechanisms. Although consciousness is typically thought of as a binary phenomenon (i.e., something is either accessible or inaccessible to awareness), research into attention suggests a broad continuum in which material is more or less accessible in any given context due to a variety of factors [91, 92]. A number of studies have demonstrated preferential attention for mental contents that are less objectionable according to basic psychodynamic principles [35, 43, 93–95]. Repression, one of the most basic of all defense mechanisms, has been studied carefully from behavioral and neurobiological perspectives [64, 96]. Evidence supports the notion that motivated forgetting relies on increased activity in the dorsolateral prefrontal cortex (which may supply the motivation) and reduced activity in the hippocampus (which fails to encode the memory) [97].

Hypnosis is an extreme example of altered consciousness often associated with Freud and psychoanalysis. However, for many years, it has been on unclear empirical grounds. Recently, neuroimagers have been able to investigate hypnosis in the MRI scanner and show that it has measurable consequences in terms of brain activity that closely parallel behavioral findings [98, 99]. In particular, Raz and colleagues have shown that effects of the Stroop Task, a highly reliable and well-accepted cognitive measure, can be significantly reduced using hypnosis. In the Stroop task, subjects are presented with a series of color words (e.g., "red," "blue," "green") written in either the *same* color that the word represents (i.e., a congruent trial) or a *different* color (i.e., an incongruent trial). They are asked to indicate for each word, the color that the word is written in, ignoring what the word itself means. Because reading is automatic, subjects take longer to respond to incongruent trials than to congruent trials, no matter how hard they try or train in the task. Giving subjects the post-hypnotic suggestion that the words are "nonsense strings" effectively reduces the extent of this

effect. This reduction correlated closely with decreased activity in the anterior cingulate cortex, a structure associated with managing conflict between two stimuli seeking attention [98].

Dreams have long been of interest to psychodynamic (and especially psychoanalytic) therapists, who have theorized that dream contents may reflect relational and dynamic mental constructs that are otherwise difficult for the conscious mind to access. Recent neuroimaging findings suggest that brain regions that are highly active during REM sleep, when most dreaming takes place, may be relevant to accessing this material [100, 101]. These regions include brainstem, limbic and paralimbic circuitry. Deactivation of the dorsolateral prefrontal cortex, as also observed during REM, may facilitate retrieval of this material through disinhibition of limbic and other subcortical processes. Experience while awake is seen to influence subsequent dreaming activity [102]. Along these lines, it may be the case that certain aspects of psychodynamic therapy engage neural circuits that are also activated (or deactivated) during dreaming, facilitating the identification and resolution of deeply held intrapsychic conflicts. Further research is needed to clarify the neurobiology common to dreaming and psychodynamic therapy process, and to understand the neural mechanics of Freud's "royal route" to the unconscious.

Early evidence is even accumulating to support one of the oldest psychodynamic notions, namely that the behavior of the mind when it is not consciously being controlled – free association – consists of more than merely background noise. Researchers have begun to describe a network of cortical regions that activate in a "default mode" when the mind otherwise appears to be at rest or wandering [103, 104]. Default mode circuits could be of crucial importance in understanding the unconscious or non-conscious mechanisms that are relevant to psychodynamic processes and treatment.

Conclusions

Empirical data is clearly accumulating that is relevant to psychodynamic processes in a wide range of areas, whereas at one point, psychodynamic psychology was the only language and method for studying the unconscious, affect, interpersonal processes, dreams, defense mechanisms, and free association. In contrast, cognitive neuroscience now offers concepts and methods for this purpose as well. A useful task of psychodynamics in this context is to integrate its own large database of clinical data and theoretical constructs with the emerging empirical findings. Several writers have begun to do so, though the explosion in research makes it difficult to identify and navigate the salient neural findings [105–110]. Advances in the years to come will reveal how these two fields fit together, hopefully with direct benefit to clinical practice.

One of the principal criticisms leveled against neuroscientific investigations of psychodynamic theory and practice has been that neuroscience has very little to offer the clinician in terms of understanding his patients in a "dynamic" way or choosing his individual techniques [19, 111]. To date, it is true that findings from the neuroscience literature have had little direct influence on the thinking of analytic clinicians and their behavior in the office. However, this lack of influence will likely change in a number of ways in the not too distant future. First, dynamic clinicians have long been moving in the direction of understanding certain deficits (e.g., of cognitive functioning, affect regulation, attachment) as related to – but not the same as – dynamic conflicts. This understanding influences their conceptualization of pathology (particularly in a developmental context) and way of speaking with their patients. This movement was driven by an entire culture of change in psychiatry, psychology, and psychoanalysis, but neuroscience has played a role in making deficits more objectifiable and real.

Second, there has been a significant movement in dynamic thinking towards an object relations approach. Though this has been stimulated by many factors, one among them is the greater emphasis in neuroscience on social functioning and the growing evidence for a neurobiological attachment

system. Finally, many dynamic clinicians feel that research into the process and outcome of patients with BPD has clarified the appropriateness of a supportive–expressive model of treatment versus a more purely interpretive, classical analytic approach. Kernberg, Fonagy, Gabbard, and others have discussed the importance of matching the structure and depth of the treatment to the personality organization of the patient [80, 112, 113]. Neuroscientific studies of BPD and the mechanisms involved in its treatment (e.g., mentalization, theory of mind, affect regulation) are relatively recent, but are already starting to support and refine this approach to matching treatment and patient.

Psychotherapy in the Era of Neuroimaging

Neuroimaging techniques have begun to provide us with not only a better understanding of psychotherapy components but also the overall effects of psychotherapy on brain function. At their fullest potential, studies of how psychotherapy affects the brain can be of tremendous value to patients, therapists, and to the field as a whole. Providing patients with information on how psychotherapy changes brain function reinforces the notion that the treatment induces meaningful changes. In the dialog between patient and therapist, neuroimaging results can enhance the vocabulary of psychotherapy process and help concretize the goals of treatment. In some cases, it may even be possible to predict how well a given patient will do with a given therapeutic approach, based on that individual's pattern of brain activity at baseline. Finally, the notion that psychotherapy has a biological substrate places the intervention in the same category as other "medical" treatments that induce measurable changes in physiology, biochemistry, or morphology. This notion could be a powerful ally in combating the residual stigma associated with psychotherapy (and psychiatric treatment in general) that promotes hesitation in many potential patients, prevents the achievement of parity with other medical treatments, and nurtures an unfounded skepticism and mistrust within some elements of culture and society.

A healthy conglomeration of studies has now begun to deliver findings with clear implications for psychotherapy theory and practice [10, 114]. Even so, the story of how psychotherapy changes brain function is far from complete. Notably, as of the time of this writing, few investigators have studied explicitly the effects of *psychodynamic* psychotherapy on brain activation, although some promising work by Lehtonen and colleagues describing effects of psychodynamic therapy on serotonin transmission in depression is described in detail in Chap. 2. However, extant studies examining other psychotherapeutic modalities have clearly shed light on the same questions that will be essential to understanding how dynamic therapy changes brain function. This section will focus on how these preliminary studies have addressed three fundamental questions related to psychotherapy and brain function: [1] Does psychotherapy affect activity within brain regions known to be involved in the pathophysiology of the target disorders [2]? Does psychotherapy differ from psychopharmacology, the other mainstay of psychiatric treatment, in this regard [3]? Do different varieties of psychotherapy that are equally effective target similar brain regions, and in similar ways?

Repairing Dysregulated Neural Machinery in Anxiety Disorders

Neuroimaging studies have provided previously unimaginable insight into how and where psychiatric disorders disrupt the normal workings of the brain. While dramatic changes in the size and shape of brain structures were long ago ruled out in the study of psychiatric conditions, functional abnormalities – i.e., inappropriate activation or deactivation of identified neural regions and circuits – have been clearly demonstrated in many disorders [115]. By the same token, the first test of how

psychotherapy induces meaningful changes in brain function is whether these changes occur in implicated brain regions, and whether these changes restore normal levels of activity.

Perhaps the clearest example of regional brain dysfunction in psychiatric conditions is obsessive compulsive disorder (OCD). One of the most consistently replicated findings in psychiatry neuroimaging research involves abnormal activity in cortico-striato-thalamic circuitry in OCD. Baseline activity in the orbitofrontal cortex (OFC), anterior cingulate cortex, striatum, and thalamus is increased in OCD, and this pattern is exacerbated by symptom provocation [116, 117]. Further, the degree of hyperactivity intercorrelates among these regions [118]. Within the striatum, the caudate nucleus in particular is thought to contribute to OCD symptoms by inappropriately managing cognitive and emotional impulses, leading to their dysregulated expression [119].

In the first published investigations of the neural effects of psychotherapy, Baxter, et al.[118] studied the effects of behavioral therapy (BT) on OCD. In two cohorts, the investigators found that successful BT was associated with significant reduction in caudate nucleus activity, as well as a decoupling of hyperactivation in the caudate, OFC, and thalamus. Although BT does not explicitly rely on psychodynamic formulation or technique, nonetheless Baxter and associates were aware of at least one dynamic implication of their work:

> Another basal ganglia function, "gating," by which certain motor, sensory, and perhaps cognitive impulses are either allowed to proceed through to perception and behavior or are held back ("filtered") and dissipated, seems to speak to the psychodynamic concept of disordered "repression" in OCD [118].

They also note that the emotional dysregulation seen in some individuals with Huntington's disease correlates with decreased caudate activity in these patients [120], again speaking to the role that the caudate may play in gating emotional impulses.

The neural circuitry underlying phobias has also been clearly established, involving increased activity in limbic, paralimbic, and ventral prefrontal regions. This pattern is entirely in keeping with studies associating the amygdala and adjacent structures with conditioned fear responses, and the ventral prefrontal cortex with both retention and recall of conditioned fear and in planning responses to frightening stimuli [121]. One might imagine, for example, that among individuals with specific phobias, exposure to the fear-inducing stimulus would cause increased activity in the amygdala, related to recognition and generation of the fear response, and in the prefrontal cortex, related to planning a strategy for confrontation (or retreat).

Several recent neuroimaging investigations suggest that psychotherapy for specific phobias targets these same regions. In a study of individuals with social phobia, Furmark et al. [122] examined the effect of cognitive behavioral therapy (CBT) on brain activation following symptom provocation. Prior to treatment, subjects exhibited increased activity in the amygdala and other limbic structures when asked to read a speech about a personal experience in front of multiple observers. Following eight sessions of group CBT, the same individuals demonstrated significantly lower activation of these regions when performing the same task as before. Another provocation design by Paquette et al. [123] examined changes in brain activation related to group CBT for spider phobia. With successful treatment, patients exhibited a decline in parahippocampal gyrus and prefrontal cortex activation when exposed to pictures of spiders. Analogous posttreatment reductions in amygdala hyperactivity were observed in another investigation of spider phobia, this one using only a single session of intensive exposure therapy [124]. Again, none of these studies was geared towards measuring effects of *psychodynamic* interactions on brain function. Nevertheless, given the generative roles of prior (usually developmental) traumatic experiences on phobic responses and the undoing of phobias through a therapeutic relationship, it is likely that dynamic factors play an implicit role even in CBT for phobias [125]. It remains to be seen to what extent changes in prefrontal and limbic regions as a result of CBT actually reflect dynamic processes.

Contrasting Effects of Psychotherapy and Psychopharmacology on Brain Function

For many psychiatric conditions, psychotherapy and psychopharmacology offer equivalent efficacy (or, in some cases, synergistic beneficial effects). However, do their similar clinical effects reflect parallel changes on brain activity? Evidence from other areas of medicine seems to challenge this notion. For example, while beta blockers, ACE inhibitors, and diuretics are all effective treatments for hypertension, each works through a unique mechanism (i.e., by affecting sympathetic or vascular tone, or circulating volume). With the complex neural pathophysiology of depression, it would not be surprising to see that different treatment modalities target different components of the disorder. Functional neuroimaging provides the ability to compare directly the neural mechanisms of action of psychotherapy and psychopharmacology. More importantly, as we shall later discuss, this information may one day be useful in predicting which type of therapy best matches up against a given individual's pattern of brain susceptibility – just as optimal selection of blood pressure medications can be guided by individual risk patterns (e.g., co-morbid diabetes, heart disease, or kidney disease) [126].

The question of how psychotherapy compares to pharmacotherapy in influencing brain function has been of interest to neuroimaging investigators since Baxter et al.s' first study of OCD. Indeed, in that investigation, BT was contrasted with fluoxetine on treatment-related changes in brain activity [118]. Both treatments, as it turned out, reduced activity in the caudate nucleus and disrupted the pattern of tandem hyperactivity in cortico-striato-thalamic circuitry. However, in a subsequent study conducted by Brody et al. [127], a strikingly different pattern emerged with respect to activity in another region implicated in OCD, the OFC. Taking a slightly different approach, Brody et al. examined whether baseline brain activity alone might predict response to BT versus fluoxetine. Among responders to BT, the degree of baseline activity in the left OFC cortex positively correlated with responsiveness to treatment. However, among responders to fluoxetine, the opposite pattern emerged: those with *less* baseline activity in the left OFC were more likely to respond to treatment. This same divergent pattern has been replicated in separate studies of paroxetine [128] and BT [129]. Offering an explanation for this pattern, Brody et al. proposed that "subjects with higher pre-treatment metabolism in the OFC may have a greater ability to change the assignment of affective value to stimuli," a process that more explicitly relies on psychotherapy than psychopharmacology.

Comparisons of brain activity response to psychotherapy versus medication have also intrigued investigators studying depression. In an FDG-PET study of CBT versus paroxetine, Goldapple, Mayberg and colleagues [130] focused on how these respective treatments changed brain function. Their report focused on prefrontal, limbic, and paralimbic structures that had previously been implicated in the pathophysiology of depression. Once again, a provocative contrast emerged between the two treatments (despite similar efficacy). In the paroxetine group, treatment resulted in increased prefrontal activity, and diminished activity in the hippocampus and subgenual cingulate cortex. However, in those patients receiving CBT, treatment response was associated with decreased prefrontal activity, and increased hippocampal and dorsal cingulate cortex activity – almost completely opposite to the paroxetine group. This finding is also somewhat counterintuitive, given the well-established role of the prefrontal cortex in stimulus appraisal, strategy planning, and direction of attentional resources – all elements that are actively re-trained during CBT. Rather, as the authors speculated:

> Hippocampal and mid and anterior cingulate increases coupled with decreases in medial frontal, dorsolateral, and ventrolateral prefrontal activity with CBT treatment might be nonetheless interpreted as correlates of CBT-conditioned increases in attention to personally relevant emotional and environmental stimuli associated with a learned ability to reduce online cortical processes at the level of encoding and retrieval of maladaptive associative memories, as well as a reduction in both ruminations and overprocessing of irrelevant information [130].

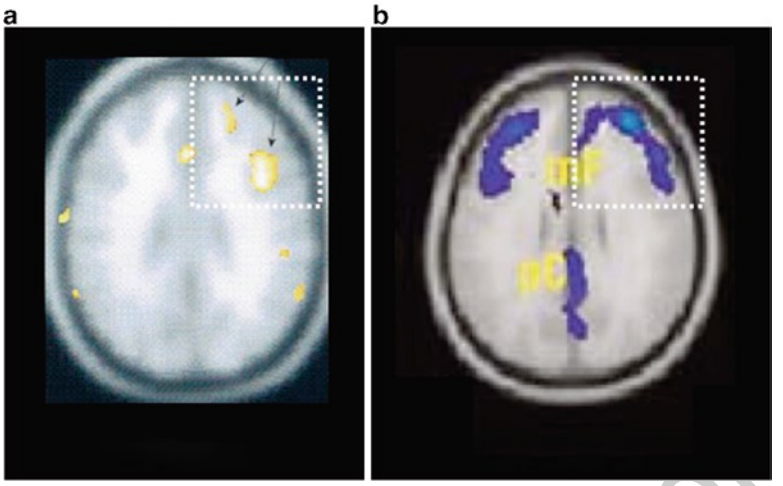

Fig. 9.6 Decreases in prefrontal activity (*dashed box*) seen after trials IPT (**a**) and CBT (**b**) ((**a**) Reprinted with permission from Ref. [132]; (**b**) reprinted with permission from Ref. [130]. Copyright © American Medical Association)

While this explanation is certainly plausible, it remains theoretical and, as we shall later consider, fails to account for other critical factors that might account for this apparent discrepancy. Impressively, though, Kennedy, Mayberg and colleagues have replicated their findings of decreased prefrontal deactivation in CBT responders, although in a more medial prefrontal region than previously reported. Kennedy et al. also replicated the previous finding of opposing changes in the anterior cingulate cortex in response to CBT (increased activity) versus a pharmacologic intervention, venlafaxine (decreased activity) [131].

In a second study comparing psychotherapy to paroxetine for depression, Brody et al. this time focused on interpersonal therapy (IPT) [132]. However, unlike the Goldapple investigation of paroxetine versus CBT [130], in this case the two treatments similarly affected the prefrontal cortex (decreasing activity) as well as limbic and paralimbic regions (increased activity in the insula and left inferior temporal lobe). This pattern is noteworthy on two fronts: on the one hand, the same pharmacologic intervention (paroxetine) appeared to work in opposing directions relative to psychotherapy in the Goldapple and Brody studies, and on the other, differing psychotherapeutic approaches appeared to induce similar changes in both studies (Fig. 9.6).

While this pattern makes it difficult to draw conclusions about whether psychotherapy and psychopharmacology induce similar changes in brain activity, it has even more hair-raising implications for psychotherapists, who sometimes ardently prefer one therapeutic approach over another. Can it be possible that, despite their dissimilarities in theory and practice, that various types of psychotherapy ultimately change the brain in similar ways?

Contrasting Effects of Varying Psychotherapeutic Approaches on Brain Function

With only few published studies available to weigh this important question – and no head-to-head investigations of the effects of different psychotherapies on brain function – it is impossible to formulate a definitive answer at present. It is likely that the answer will require a more complex experimental design than contrasting pre- and posttreatment scans of patients in different psychotherapy

groups, as well as independent replication of the results. However, let us first take a step back, and carefully consider the argument for why differing effects on brain activity might be expected.

The studies mentioned thus far used either CBT or IPT to treat depression. Consistent with a wealth of clinical experience and validation, both interventions were successful in improving depression symptoms, performing comparably to antidepressant intervention. However, while IPT and CBT are similar in that they are both time-limited, manual-guided treatments, in theory, the work of therapy differs substantially in these treatments. Unlike CBT, IPT focuses primarily on improving interpersonal relationships, often drawing material directly from the patient–therapist relationship. With a greater focus on transference, certain psychodynamic elements are touched upon more explicitly in IPT. Moreover, cognitive and dynamically oriented therapies may draw on different memory systems (described in earlier), as cognitive therapy may more strongly rely on declarative memories, and dynamic therapy on implicit memories.

Such differences may not affect the *outcome* of CBT and IPT, but they certainly should affect the *process*. In this sense, it is unfortunate that most of the currently published neuroimaging studies that focus on psychotherapy failed to include process measures and measures of treatment adherence. Without such measures, it remains possible that despite the differing "brand names," elements of IPT contributed to CBT sessions, and vice versa. Along the same lines, it is possible that symptom improvement was significantly influenced by alternate therapeutic approaches.

This risk is more than theoretical: other investigators examining psychotherapy process with rigorous criteria strongly suggest that psychotherapeutic approach is often more eclectic than intended. For one manualized trial of IPT versus CBT [133], in *both* treatment groups, process and outcome were more closely related to cognitive behavioral techniques. Conversely, in another investigation of CBT for depression [134], psychodynamic elements both influenced the course of treatment and the outcome [135]. Many would argue that dynamic factors influence treatment process and outcomes even in psychopharmacology [136, 137] or general medical settings [138], even without the caregiver explicitly employing psychodynamic techniques. As such, even though psychodynamic psychotherapy has not "explicitly" been studied with neuroimaging, in all likelihood, dynamic elements influenced both outcome and brain activity even for patients receiving behavioral or cognitive behavioral therapy in the studies described earlier. Regardless, it is impossible to reliably disentangle the effects of varying psychotherapy techniques on brain function without measures of adherence or process.

By the same token, the oft employed "pre–post" model of comparing brain activity before and after a course of psychotherapy relates much more directly to outcome than to process. In the studies described earlier, while CBT and IPT appeared to exert very similar effects on brain function *as a result of* therapy, parallel changes may or may not occur *during* therapy. The ability to measure brain activation patterns serially over the course of psychotherapy – or, better, to measure them during psychotherapy sessions themselves – will be instrumental in addressing this question, especially when viewed alongside measures of psychotherapy process.

Thus, while the question "Does psychotherapy change brain function?" appears to be convincingly answered, the questions of "How does psychotherapy change brain function?" and, more specifically, "How do different psychotherapies change brain function?" remain largely unexplored. In the next section, we will consider how these questions might best be addressed in future studies, as well as the unique implications that these studies may have on the practice of psychodynamic psychotherapy.

Synthesis and Future Directions

Given the broad range of findings reviewed in this chapter, it is a significant challenge to synthesize it into a reliable set of conclusions. However, analogous to the method of psychodynamic therapy itself, perhaps it is more useful to comment on the process of this review than on its detailed contents

(though we will attempt to do some of both). We begin by suggesting several things that we feel that the literature *does* support.

First, we believe that given the sheer volume of scientifically sophisticated empirical investigations on psychotherapy, affect, social processes, and non-conscious mechanisms (including but not limited to dreams, hypnosis, free association, and defense mechanisms), it is increasingly clear that neurobiological research is relevant to psychodynamic concepts and treatment. That said, we have no doubt that controversy will continue to rage about the applicability of this work to the day-to-day thinking of psychodynamic theorists and clinicians. It is helpful and responsible to question the application of individual findings when the methods of investigation are so different. However, we believe it is irresponsible and counterproductive to the field when some generalize that criticism to a condemnation of the usefulness of all neurobiological research, particularly without a first-hand knowledge of that literature [17, 19].

To date, a number of important brain systems and associated regions have been implicated as important to psychodynamically relevant hypotheses. These include limbic and paralimbic structures (e.g., amygdala, insula, OFC), memory systems (e.g., dorsolateral prefrontal cortex and hippocampus), conflict management and affect regulatory systems (e.g., anterior cingulate cortex and medial prefrontal cortex), attentional systems (prefrontal, cingulate, and parietal cortices), and planning and procedural memory systems (basal ganglia).

It is perhaps equally, if not more important, to be open and frank about what the neurobiological literature does not do, and in some cases will never do, in reference to psychodynamic thinking. First, we believe that it is a fundamental error to look toward neurobiology to "prove" that psychodynamic thinking and therapy are fundamentally "true." The body of theory and clinical work is too vast and heterogeneous for this to be possible. Furthermore, it does not seem reasonable to think that any body of concepts, particularly one that has historically isolated itself from empirical methods, is not in need of modification. This attempt is merely the flip side of the equally false argument that empirical research has "proven" psychoanalysis to have no scientific foundation [20]. Phrasing the argument in either of these ways is counterproductive as it encourages zealotry and selective interpretation of the data, as opposed to the careful scientific elaboration of complicated theories and integration of information from multiple perspectives.

Second, it seems increasingly clear that the neurobiological literature does not provide a consensus on the existence of the "unconscious mind" according to psychodynamic principles. On the one hand, it is now widely accepted by cognitive neuroscientists that important mental functioning takes place outside of awareness [139]. However, the properties and constraints of non-conscious systems – whether called unconscious, implicit, procedural, or by some other name – are complex and remain to be successfully elaborated. It appears likely that there are multiple brain systems involved in non-conscious processes, including implicit associative and implicit procedural memories, and that these systems may have links to alternate ways of thinking about non-conscious processes in psychodynamic theory (e.g., oedipal versus pre-oedipal functioning).

Third, it is important for empirical investigators and psychodynamic theorists or clinicians to be open about the ways in which new experimental paradigms and methodologies capture some, but never *all* aspects of a clinical phenomenon. It is a central fact of all scientific investigation that one needs to reduce a complex real-world phenomenon into a set of component parts in order to study it usefully. This should not be taken to be equivalent to the statement that experimental models have nothing relevant to teach us about the clinical situation [22].

Finally, we must be aware of the temptation, particularly in the era of neuroimaging, to point to particular brain regions and look for localization of individual psychodynamic processes. Given the distributed nature of brain processes and the complex interdigitation of the machinery that drives cognitive, emotional, and social processes, it is difficult to imagine wholly discrete, unambiguous localization for any particular concept, whether it be the unconscious mind, repression, transference, or structural change. Suggesting otherwise may limit the success of the dialog on these topics.

Despite these caveats, there are a number of exciting directions to which the research reviewed in this chapter seems to point. We believe that as experimental paradigms improve, accumulating data will help us identify properties and constraints of neurobiologically based systems relevant to psychodynamic theory and practice. Once these measures are well understood, it will lead to iterative testing and refinement of psychodynamic concepts and theories about normal and pathological functioning. Ultimately, these measures will also be incorporated into clinical research and lead to the iterative testing and refinement of clinical theories and techniques. Progress in clinically relevant neurobiological research will likely also depend on the further development of cutting-edge technologies that allow for measurement of brain function in the therapist's office. Psychophysiological (e.g., skin conductance, heart rate variability) and near-infrared imaging (which measures cortical activation without requiring the heavy machinery of MRI or PET) may be important in this regard, though new technologies may emerge as well [16, 140].

Though less an area of current empirical investigation, it is likely that other empirical methods now gaining currency in experimental psychiatry will become useful for psychodynamic work as well. In particular, genetics and temperament are two important (and likely related) areas of research that are undoubtedly relevant to the variability of patient outcome in psychodynamic treatment, and ultimately to our understanding of the mechanisms of psychopathology and therapeutic change. Interestingly, Freud and other psychodynamic theorists were not opposed to the importance of hereditary and temperamental factors in understanding patients, though they have had a mixed reception in the broader psychoanalytic literature [141, 142]. On the other hand, the neurobiology and genetics of temperament is a rapidly expanding area, with an abundance of recent studies establishing how certain genetic variants predispose towards affective, harm avoidance, and novelty-seeking traits through their actions on discrete neural systems [143, 144].

Though still somewhat distant, it is not difficult to imagine some of the useful consequences of a successful program of neurobiological research into psychodynamic theories and treatments. Theorists and clinicians have long wished for a better ability to predict response in patients, so as to assist in their ability to recommend which treatments for which patients. As is currently being sought with regard to other treatments in psychiatry, sophisticated research may find patterns of neurobiological activity in response to specific tasks that is predictive of psychotherapy outcome.

Two investigations of psychotherapeutic interventions have offered extremely promising preliminary results in this regard. In a study comparing BT to fluoxetine for OCD, Brody et al. [127] found that a baseline scan differentially stratified responders from non-responders for the two treatments. Patients who were to receive fluoxetine ultimately demonstrated the best response if they had low baseline activity in the left OFC, while those who would receive BT exhibited better responses if they had high activity in the same brain region. After conducting baseline scans of patients with depression, Siegle et al. [145] found that increased activity in the amygdala, and decreased in the subgenual cingulate cortex predicted significantly better responsiveness to CBT. These results have clearly important clinical implications: they suggest that a baseline brain scan can provide objective biomarkers that, if shown to be reliable, may be used to determine the likelihood of a good treatment response for a given individual. Ongoing work by Roffman and colleagues, described in detail in Chap. 16, is examining whether baseline scans likewise can predict responsiveness to psychodynamic therapy.

Equally tantalizing is the possibility that we may investigate the effectiveness of individual interventions (e.g., supportive versus transference interpretations) using in-session neurobiological techniques. Perhaps, we will someday have more sophisticated ways to gage when the alliance is strong enough to make deeper interpretations helpful [16, 57]. As all of medicine moves towards individualized treatments, psychodynamic psychotherapy will keep pace [14].

Even before these advances, clinicians can anticipate using what we learn from neurobiological research to influence their conceptualization of patients' problems and their vocabulary for discussing such concepts with their patients. Contemporary clinicians have been greatly affected in how they talk to their patients by concepts such as attachment, mentalization, and empathy, so it is not hard to imagine that new research will yield useful changes in language too.

On another practical level, psychodynamic-neurobiological research has immediate implications for the education of psychiatrists, psychologists, therapists, and other mental health professionals. Psychodynamic teaching in psychiatry residencies and psychology graduate programs has recently been under threat specifically because critics have complained that it is not tied to a scientific literature [146]. However, even in the setting of rapidly expanding neuroscience curricula, program directors for the most part remain highly committed to psychotherapy training [147]. New research will address that challenge and also improve the teaching of concepts and techniques that have often relied more on the charisma and persuasive powers of the teacher than on the merit of the ideas. Furthermore, the ideas contained in a careful discussion of psychodynamic-empirical research are likely to be useful to trainees of many kinds. Cappas et al. suggest seven "principles of brain-based psychotherapy" about which there is considerable (with the possible exception of Principle 5) consensus [148]:

1. Genetics and environment interact in the brain to shape the individual.
2. Experience transforms the brain.
3. Memory systems in the brain are interactive (i.e., memory storage and retrieval depends on context and should not be treated as a perfect account of what happened).
4. Cognitive and emotional processes work in partnership.
5. Bonding and attachment provide the foundation for change.
6. Imagery activates and stimulates the same brain systems as does real consensus.
7. The brain can process nonverbal and unconscious information.

As research progresses, we will undoubtedly further refine and add to the principles that can usefully be taught to trainees along with their empirical foundations.

Without surrendering the core skepticism toward certainty that characterizes both good science and good psychodynamic thinking, we believe that the future of close collaboration between empirical researchers and psychodynamic theorists and clinicians is bright. As long as a mutually respectful dialog is allowed to develop, the progress in this area will drive improvements in our theory and in our clinical work with patients.

[AU1]

References

[AU2]

1. Freud S. Project for a scientific psychology; 1895.
2. Masson JM, editor. The complete letters of Sigmund Freud to Wilhelm Fleiss 1887–1904. 3rd ed. Cambridge: Harvard University Press; 1995.
3. Kandel ER. Biology and the future of psychoanalysis: a new intellectual framework for psychiatry revisited. Am J Psychiatry. 1999;156:505–24.
4. Alexander F. Psychosomatic medicine: its principles and applications. New York: WW Norton; 1950.
5. Kandel ER. A new intellectual framework for psychiatry. Am J Psychiatry. 1998;155:457–69.
6. Price BH, Adams RD, Coyle JT. Neurology and psychiatry: closing the great divide. Neurology. 2000;54:8–14.
7. Antonuccio DO, Danton WG, DeNelsky GY. Psychotherapy versus medication for depression: challenging the conventional wisdom with data. Prof Psychol Res Pract. 1995;26:574–85.
8. Goldman W, McCulloch J, Cuffel B, Zarin DA, Suarez A, Burns BJ. Outpatient utilization patterns of integrated and split psychotherapy and pharmacotherapy for depression. Psychiatr Serv. 1998;49:477–82.
9. Satcher D. Mental health: a report of the surgeon general. In: USPH editor, Service; 1999.
10. Roffman JL, Marci CD, Glick DM, Dougherty DD, Rauch SL. Neuroimaging and the functional neuroanatomy of psychotherapy. Psychol Med. 2005;35:1–14.
11. Roffman JL, Marci CD, Glick DM, Dougherty DD, Rauch SL. Neuroimaging and the functional neuroanatomy of psychotherapy. Psychol Med. 2005;35:1385–98.
12. Westen D, Novotny CM, Thompson-Brenner H. The empirical status of empirically supported psychotherapies: assumptions, findings, and reporting in controlled clinical trials. Psychol Bull. 2004;130:631–63.
13. Dougherty DD, Rauch SL, Rosenbaum JF. Essentials of neuroimaging for clinical practice. Washington, DC: American Psychiatric Association; 2004.

14. Jones DS, Perlis RH. Pharmacogenetics, race, and psychiatry: prospects and challenges. Harv Rev Psychiatry. 2006;14:92–108.
15. Giove F, Mangia S, Bianciardi M, et al. The physiology and metabolism of neuronal activation: in vivo studies by NMR and other methods. Magn Reson Imaging. 2003;21:1283–93.
16. Marci CD, Ham J, Moran E, Orr SP. Physiologic correlates of perceived therapist empathy and social-emotional process during psychotherapy. J Nerv Ment Dis. 2007;195:103–11.
17. Green A. What kind of research for psychoanalysis? In: Sandler J, Sandler A-M, Davies R, editors. Clinical and observational psychoanlaytic research: roots of a controversy. Madison: International Universities Press; 2000. p. 21–6.
18. Perron R. Reflections on psychoanalytic research problems – the French speaking view. In: IPA, editor. An open door review of outcome studies in psychoanalysis. London: Research Committee of the International Psychoanalytic Association; 1999. p. 8–19.
19. Hoffman IZ. "Doublethinking" our way to scientific legitimacy: the desiccation of human experience. In: Winter meeting of the American Psychoanalytic Association. New York; 2007.
20. Torrey EF. Does psychoanalysis have a future? No. Can J Psychiatry. 2005;50:743–4.
21. Westen D. The scientific status of unconscious processes: is Freud really dead? J Am Psychoanal Assoc. 1999;47:1061–106.
22. Peterson BS. Clinical neuroscience and imaging studies of core psychoanalytic constructs. Clin Neurosci Res. 2005;4:349–65.
23. Westen D. Implications of developments in cognitive neuroscience for psychoanalytic psychotherapy. Harv Rev Psychiatry. 2002;10:369–73.
24. Westen D, Gabbard GO. Developments in cognitive neuroscience: I. Conflict, compromise, and connectionism. J Am Psychoanal Assoc. 2002;50:53–98.
25. Lane RD, Garfield DAS. Becoming aware of feelings: integration of cognitive-developmental, neuroscientific, and psychoanalytic perspectives. Neuropsychoanalysis. 2005;7:5–30.
26. Beutel ME, Stern E, Silbersweig DA. The emerging dialogue between psychoanalysis and neuroscience: neuroimaging perspectives. J Am Psychoanal Assoc. 2003;51:773–801.
27. Ellenberger HF. The discovery of the unconscious; the history and evolution of dynamic psychiatry. New York: Basic Books; 1970.
28. Sandler J, Holder A, Dare C, Dreher AU. Freud's models of the mind: an introduction. Madison: International Universities; 1997.
29. Kandel ER, Kupferman O, Iverson S. Learning and memory. In: Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science. New York: McGraw-Hill; 2000. p. 1227–46.
30. Baddeley A. Working memory: looking back and looking forward. Nat Rev Neurosci. 2003;4:829–39.
31. Schacter DL, Slotnick SD. The cognitive neuroscience of memory distortion. Neuron. 2004;44:149–60.
32. Smith EE, Kosslyn SM. Encoding and retrieval from long-term memory. In: Cognitive psychology: mind and brain. Upper Saddle River: Prentice Hall; 2007. p. 195–246.
33. Kihlstrom JF. The cognitive unconscious. Science. 1987;237:1445–52.
34. Kihlstrom JF. Availability, accessibility, and subliminal perception. Conscious Cogn. 2004;13:92–100.
35. Wong PS, Bernat E, Snodgrass M, Shevrin H. Event-related brain correlates of associative learning without awareness. Int J Psychophysiol. 2004;53:217–31.
36. Wong PS. Anxiety, signal anxiety, and unconscious anticipation: neuroscientific evidence for an unconscious signal function in humans. J Am Psychoanal Assoc. 1999;47:817–41.
37. Ochsner KN, Chiu CY, Schacter DL. Varieties of priming. Curr Opin Neurobiol. 1994;4:189–94.
38. Knowlton BJ, Squire LR, Gluck MA. Probabilistic classification learning in amnesia. Learn Mem. 1994;1:106–20.
39. Knowlton BJ, Mangels JA, Squire LR. A neostriatal habit learning system in humans. Science. 1996;273:1399–402.
40. Svoboda E, McKinnon MC, Levine B. The functional neuroanatomy of autobiographical memory: a meta-analysis. Neuropsychologia. 2006;44:2189–208.
41. Barrett LF, Mesquita B, Ochsner KN, Gross JJ. The experience of emotion. Annu Rev Psychol. 2007;58:373–403.
42. LeDoux J. The emotional brain, fear, and the amygdala. Cell Mol Neurobiol. 2003;23:727–38.
43. Russell JA. Core affect and the psychological construction of emotion. Psychol Rev. 2003;110:145–72.
44. Posner J, Russell J, Peterson BS. The circumplex model of affect: an integrative approach to affective neuroscience, cognitive development, and psychopathology. Dev Psychopathol. 2005;17:715–34.
45. Gerber AJ, Gorman DA, Posner JE, Colibazzi T, Peterson BS. Functional MRI investigation of the affective circumplex, in preparation.
46. Paton JJ, Belova MA, Morrison SE, Salzman CD. The primate amygdala represents the positive and negative value of visual stimuli during learning. Nature. 2006;439:865–70.

47. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JD. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci. 2002;14:1215–29.
48. 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. 2004;44:1043–55.
49. Insel TR. A neurobiological basis of social attachment. Am J Psychiatry. 1997;154:726–35.
50. Insel TR, Young LJ. The neurobiology of attachment. Nat Rev Neurosci. 2001;2:129–36.
51. Ochsner KN, Lieberman MD. The emergence of social cognitive neuroscience. Am Psychol. 2001;56:717–34.
52. Mitchell JP, Heatherton TF, Macrae CN. Distinct neural systems subserve person and object knowledge. Proc Natl Acad Sci USA. 2002;99:15238–43.
53. Kelley WM, Macrae CN, Wyland CL, Caglar S, Inati S, Heatherton TF. Finding the self? An event-related fMRI study. J Cogn Neurosci. 2002;14:785–94.
54. Northoff G, Heinzel A, de Greck M, Bermpohl F, Dobrowolny H, Panksepp J. Self-referential processing in our brain – a meta-analysis of imaging studies on the self. Neuroimage. 2006;31:440–57.
55. Lieberman MD. Social cognitive neuroscience: a review of core processes. Annu Rev Psychol. 2007;58: 259–89.
56. Cooper A. Changes in psychoanalytic ideas: transference interpretation. J Am Psychoanal Assoc. 1987;35: 77–98.
57. Hoglend P, Amlo S, Marble A, et al. Analysis of the patient–therapist relationship in dynamic psychotherapy: an experimental study of transference interpretations. Am J Psychiatry. 2006;163:1739–46.
58. Luborsky L, Crits-Christoph P. Understanding transference: the core conflictual relationship theme method. 2nd ed. Washington, DC: American Psychological Association; 1998.
59. Andersen SM, Baum A. Transference in interpersonal relations: inferences and affect based on significant-other representations. J Pers. 1994;62:459–97.
60. Andersen SM, Glassman NS, Chen S, Cole SW. Transference in social perception: the role of chronic accessibility in significant-other representations. J Pers Soc Psychol. 1995;69:41–57.
61. Andersen SM, Reznik I, Manzella LM. Eliciting facial affect, motivation, and expectancies in transference: significant-other representations in social relations. J Pers Soc Psychol. 1996;71:1108–29.
62. Berk MS, Andersen SM. The impact of past relationships on interpersonal behavior: behavioral confirmation in the social-cognitive process of transference. J Pers Soc Psychol. 2000;79:546–62.
63. Glassman NS, Andersen SM. Activating transference without consciousness: using significant-other representations to go beyond what is subliminally given. J Pers Soc Psychol. 1999;77:1146–62.
64. Erdelyi MH. The unified theory of repression. Behav Brain Sci. 2006;29:499–511.
65. Peterson BS. Indeterminacy & compromise formation: implications for a psychoanalytic theory of mind. Int J Psychoanal. 2002;83:1017–35.
66. Raz A, Lamar M, Zhu H, et al. The role of frontostriatal circuits in perceiving bistable percepts furing fMRI, submitted for publication.
67. Westen D, Gabbard GO. Developments in cognitive neuroscience: II. Implications for theories of transference. J Am Psychoanal Assoc. 2002;50:99–134.
68. Gabbard GO. What can neuroscience teach us about transference? Can J Psychoanal. 2000;9:1–18.
69. Cassidy J, Shaver PR, editors. Handbook of attachment: theory, research, and clinical applications. New York: Guilford Press; 1999.
70. Fonagy P, Leigh T, Steele M, et al. The relation of attachment status, psychiatric classification, and response to psychotherapy. J Consult Clin Psychol. 1996;64:22–31.
71. Leckman JF, Herman AE. Maternal behavior and developmental psychopathology. Biol Psychiatry. 2002;51: 27–43.
72. Insel TR. Is social attachment an addictive disorder? Physiol Behav. 2003;79:351–7.
73. Bartels A, Zeki S. The neural correlates of maternal and romantic love. Neuroimage. 2004;21:1155–66.
74. Buchheim A, George C, Kachele H, Erk S, Walter H. Measuring adult attachment representation in an fMRI environment: concepts and assessment. Psychopathology. 2006;39:136–43.
75. Lamm C, Batson CD, Decety J. The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. J Cogn Neurosci. 2007;19:42–58.
76. Singer T. The neuronal basis and ontogeny of empathy and mind reading: review of literature and implications for future research. Neurosci Biobehav Rev. 2006;30:855–63.
77. Shamay-Tsoory SG, Lester H, Chisin R, et al. The neural correlates of understanding the other's distress: a positron emission tomography investigation of accurate empathy. Neuroimage. 2005;27:468–72.
78. Marci CD, Orr SP. The effect of emotional distance on psychophysiologic concordance and perceived empathy between patient and interviewer. Appl Psychophysiol Biofeedback. 2006;31:115–28.
79. Marci C, Reiss H. The clinical relevance of psychophysiology: support for the psychobiology of empathy and psychodynamic process. Am J Psychother. 2005;59:213–26.
80. Fonagy P, Target M, Gergely G, Jurist EL. Affect regulation, mentalization, and the development of self. London: Other Press; 2002.

81. Corcoran R, Frith CD. Autobiographical memory and theory of mind: evidence of a relationship in schizophrenia. Psychol Med. 2003;33:897–905.
82. Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a 'theory of mind'? Cognition. 1985;21: 37–46.
83. Saxe R, Moran JM, Scholz J, Gabrieli J. Overlapping and non-overlapping brain regions for theory of mind and self reflection in individual subjects. Soc Cogn Affect Neurosci. 2006;1:229–34.
84. Mitchell JP, Banaji MR, Macrae CN. General and specific contributions of the medial prefrontal cortex to knowledge about mental states. Neuroimage. 2005;28:757–62.
85. Happe F. Theory of mind and the self. Ann N Y Acad Sci. 2003;1001:134–44.
86. Gallagher HL, Frith CD. Functional imaging of 'theory of mind'. Trends Cogn Sci. 2003;7:77–83.
87. Iacoboni M, Dapretto M. The mirror neuron system and the consequences of its dysfunction. Nat Rev Neurosci. 2006;7:942–51.
88. Olds DD. Identification: psychoanalytic and biological perspectives. J Am Psychoanal Assoc. 2006;54:17–46.
89. Gallese V. Mirror neurons and intentional attunement: commentary on olds. J Am Psychoanal Assoc. 2006;54:47–57.
90. Rizzolatti G, Fadiga L, Fogassi L, Gallese V. Resonance behaviors and mirror neurons. Arch Ital Biol. 1999;137:85–100.
91. Posner MI, Rothbart MK. Research on attention networks as a model for the integration of psychological science. Annu Rev Psychol. 2007;58:1–23.
92. Raz A, Buhle J. Typologies of attentional networks. Nat Rev Neurosci. 2006;7:367–79.
93. McGinnies E, Bowles W. Personal values as determinates of perceptual fixation. J Pers. 1949;18:224–35.
94. Blum GS. An experimental reunion of psychoanalytic theory with perceptual vigilance and defense. J Abnorm Psychol. 1954;49:94–8.
95. Silverman LH, Weinberger J. Mommy and I are one: implications for psychotherapy. Am Psychol. 1985;40: 1296–308.
96. Shevrin H, Ghannam JH, Libet B. A neural correlate of consciousness related to repression. Conscious Cogn. 2002;11:334–41 [discussion 42–46].
97. Anderson MC, Ochsner KN, Kuhl B, et al. Neural systems underlying the suppression of unwanted memories. Science. 2004;303:232–5.
98. Raz A, Fan J, Posner MI. Hypnotic suggestion reduces conflict in the human brain. Proc Natl Acad Sci USA. 2005;102:9978–83.
99. Raz A, Shapiro T. Hypnosis and neuroscience: a cross talk between clinical and cognitive research. Arch Gen Psychiatry. 2002;59:85–90.
100. Maquet P. Functional neuroimaging of normal human sleep by positron emission tomography. J Sleep Res. 2000;9:207–31.
101. Maquet P, Peters J, Aerts J, et al. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature. 1996;383:163–6.
102. Maquet P, Laureys S, Peigneux P, et al. Experience-dependent changes in cerebral activation during human REM sleep. Nat Neurosci. 2000;3:831–6.
103. Andreasen NC, O'Leary DS, Cizadlo T, et al. Remembering the past: two facets of episodic memory explored with positron emission tomography. Am J Psychiatry. 1995;152:1576–85.
104. Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN. Wandering minds: the default network and stimulus-independent thought. Science. 2007;315:393–5.
105. Gabbard GO, Westen D. Rethinking therapeutic action. Int J Psychoanal. 2003;84:823–41.
106. Liggan DY, Kay J. Some neurobiological aspects of psychotherapy. J Psychother Pract Res. 1999;8:103–14.
107. Gabbard GO. A neurobiologically informed perspective on psychotherapy. Br J Psychiatry. 2000;177:117–22.
108. Peled A, Geva AB. Brain organization and psychodynamics. J Psychother Pract Res. 1999;8:24–39.
109. Olds DD. Connectionism and psychoanalysis. J Am Psychoanal Assoc. 1994;42:581–611.
110. Westen D. The scientific legacy of Sigmund Freud: toward a psychodynamically informed psychological science. Psychol Bull. 1998;124:333–71.
111. Blass RB, Carmeli Z. The case against neuropsychoanalysis: on fallacies underlying psychoanalysis' latest scientific trend and its negative impact on psychoanalytic discourse. Int J Psychoanal. 2007;88:19–40.
112. Gabbard GO, Gunderson JG, Fonagy P. The place of psychoanalytic treatments within psychiatry. Arch Gen Psychiatry. 2002;59:505–10.
113. Kernberg O. Psychoanalysis, psychoanalytic psychotherapy and supportive psychotherapy: contemporary controversies. Int J Psychoanal. 1999;80:1075–91.
114. Linden DEJ. How psychotherapy changes the brain – the contribution of functional neuroimaging. Mol Psychiatry. 2006;11:528–38.
115. Mitterschiffthaler MT, Ettinger U, Mehta MA, Mataix-Cols D, Williams SC. Applications of functional magnetic resonance imaging in psychiatry. J Magn Reson Imaging. 2006;23:851–61.

116. McGuire PK, Bench CJ, Frith CD, Marks IM, Frackowiak RS, Dolan RJ. Functional anatomy of obsessive–compulsive phenomena. Br J Psychiatry. 1994;164:459–68.
117. Rauch SL, Jenike MA, Alpert NM, et al. Regional cerebral blood flow measured during symptom provocation in obsessive–compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. Arch Gen Psychiatry. 1994;51:62–70.
118. Baxter LR, Schwartz JM, Bergman KS, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive–compulsive disorder. Arch Gen Psychiatry. 1992;49:681–9.
119. Baxter LR, Schwartz JM, Guze BH, Bergman K, Szuba MP. Neuroimaging in obsessive–compulsive disorder: seeking the mediating neuroanatomy. In: Jenike MA, Baer L, Minichiello WE, editors. Obsessive–compulsive disorders: theory and management. 2nd ed. St. Louis: Mosby-Year Book; 1990. p. 167–88.
120. Baxter Jr LR, Mazziotta JC, Pahl JJ, et al. Psychiatric, genetic, and positron emission tomographic evaluation of persons at risk for Huntington's disease. Arch Gen Psychiatry. 1992;49:148–54.
121. Milad MR, Rauch SL, Pitman RK, Quirk GJ. Fear extinction in rats: implications for human brain imaging and anxiety disorders. Biol Psychol. 2006;73:61–71.
122. 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. Arch Gen Psychiatry. 2002;59:425–33.
123. Paquette V, Levesque J, Mensour B, et al. "Change the mind and you change the brain": effects of cognitive–behavioral therapy on the neural correlates of spider phobia. Neuroimage. 2003;18:401–9.
124. Goossens L, Sunaert S, Peeters R, Griez EJ, Schruers KR. Amygdala hyperfunction in phobic fear normalizes after exposure. Biol Psychiatry. 2007;62:1119–25.
125. Menninger WW. Integrated treatment of panic disorder and social phobia. Bull Menninger Clin. 1992;56: A61–70.
126. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA. 2003;289:2560–72.
127. Brody AL, Saxena S, Schwartz JM, et al. FDG-PET predictors of response to behavioral therapy and pharmacotherapy in obsessive compulsive disorder. Psychiatry Res. 1998;84:1–6.
128. 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. 1999;21:683–93.
129. Yamanishi T, Nakaaki S, Omori IM, et al. Changes after behavior therapy among responsive and nonresponsive patients with obsessive–compulsive disorder. Psychiatry Res. 2009;172:242–50.
130. Goldapple K, Segal Z, Garson C, et al. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Arch Gen Psychiatry. 2004;61:34–41.
131. Kennedy SH, Konarski JZ, Segal ZV, et al. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. Am J Psychiatry. 2007;164:778–88.
132. Brody AL, Saxena S, Stoessel P, et al. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: preliminary findings. Arch Gen Psychiatry. 2001;58: 631–40.
133. Ablon JS, Jones EE. Validity of controlled clinical trials of psychotherapy: findings from the NIMH treatment of depression collaborative research program. Am J Psychiatry. 2002;159:775–83.
134. Hollon SD, DeRubeis RJ, Evans MD, et al. Cognitive therapy and pharmacotherapy for depression: singly and in combination. Arch Gen Psychiatry. 1992;49:774–81.
135. Jones EE, Pulos SM. Comparing the process in psychodynamic and cognitive–behavioral therapies. J Consult Clin Psychol. 1993;61:306–16.
136. Knobel M. Psychodynamics of psychopharmacology. J Nerv Ment Dis. 1961;133:309–15.
137. Mintz D. Psychodynamic trojan horses: using psychopharmacology to teach psychodynamics. J Am Acad Psychoanal Dyn Psychiatry. 2006;34:151–61.
138. Weyrauch KF. The personal knowledge of family physicians for their patients. Fam Med. 1994;26:452–5.
139. Hassin RR, Uleman JS, Bargh JA. The new unconscious. New York, NY: Oxford University Press; 2005.
140. Izzetoglu K, Bunce S, Izzetoglu M, Onaral B, Pourrezaei K. Functional near-infrared neuroimaging. Conf Proc IEEE Eng Med Biol Soc. 2004;7:5333–6.
141. Gay P. Freud: a life for our time. New York: Norton; 1998.
142. Hartmann H. Ego psychology and the problem of adaptation. New York: International Universities Press; 1958.
143. Hariri AR, Drabant EM, Weinberger DR. Imaging genetics: perspectives from studies of genetically driven variation in serotonin function and corticolimbic affective processing. Biol Psychiatry. 2006;59:888–97.
144. Ebstein RP. The molecular genetic architecture of human personality: beyond self-report questionnaires. Mol Psychiatry. 2006;11:427–45.
145. Siegle GJ, Carter CS, Thase ME. Use of FMRI to predict recovery from unipolar depression with cognitive behavior therapy. Am J Psychiatry. 2006;163:735–8.

146. Weissman MM, Verdeli H, Gameroff MJ, et al. National survey of psychotherapy training in psychiatry, psychology, and social work. Arch Gen Psychiatry. 2006;63:925–34.
147. Roffman JL, Simon AB, Prasad KM, Truman CJ, Morrison J, Ernst CL. Neuroscience in psychiatry training: how much do residents need to know? Am J Psychiatry. 2006;163:919–26.
148. Cappas NM, Andres-Hyman R, Davidson L. What psychotherapists can begin to learn from neuroscience: seven principles of a brain-based psychotherapy. Psychother Theory Res Pract Train. 2005;42:374–83.

Author Queries

Chapter No.: 9 0001331389

Queries	Details Required	Author's Response
AU1	Please update Refs. [45,66].	
AU2	Please provide complete details for Refs. [1,9].	