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Neuroimaging for psychotherapy research: Current trends

CAROL P. WEINGARTEN[1] and **TIMOTHY J. STRAUMAN**[2]

[1]Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC, USA

[2]Department of Psychology and Neurosciences, Duke University, Durham, NC, USA

Abstract

Objective—This article reviews neuroimaging studies that inform psychotherapy research. An introduction to neuroimaging methods is provided as background for the increasingly sophisticated breadth of methods and findings appearing in psychotherapy research.

Method—We compiled and assessed a comprehensive list of neuroimaging studies of psychotherapy outcome, along with selected examples of other types of studies that also are relevant to psychotherapy research. We emphasized magnetic resonance imaging (MRI) since it is the dominant neuroimaging modality in psychological research.

Results—We summarize findings from neuroimaging studies of psychotherapy outcome, including treatment for depression, obsessive-compulsive disorder (OCD), and schizophrenia.

Conclusions—The increasing use of neuroimaging methods in the study of psychotherapy continues to refine our understanding of both outcome and process. We suggest possible directions for future neuroimaging studies in psychotherapy research.

Keywords

psychotherapy outcome; psychotherapy process; brain imaging; neuroimaging; cognitive therapy

To date there have been several reviews of neuroimaging studies for psychotherapy research. Reviews of neuroimaging studies of psychotherapy outcome were given by Beauregard (2007), Frewen, Dozois, and Lanius (2008), Karlsson (2011), Linden (2006), and Roffman, Marci, Glick, Dougherty, and Rauch (2005). Some broad and important issues for psychotherapy neuroimaging studies were also discussed by Etkin, Pittenger, Polan, and Kandel (2005) and Thase (2001). Among neuroimaging methods employed for psychological studies, magnetic resonance imaging (MRI) has become the most useful. Carrig, Kolden, and Strauman (2009) have provided an introduction for psychotherapy researchers to one of the most commonly employed MRI approaches in psychology, namely, functional MRI (fMRI). Finally, there have been reviews that show how neuroimaging studies from outside psychotherapy research per se can contribute to a neuroscience of psychotherapy (Carhart-Harris, Mayberg, Malizia, & Nutt, 2008; DeRubeis, Siegle, & Hollon, 2008; Disner, Beevers, Haigh, & Beck, 2011; Fonagy & Target, 2007; Gallese,

Correspondence concerning this article should be addressed to Carol Weingarten, Duke University, Department of Psychiatry and Behavioral Sciences, Durham, NC, USA. carol.weingarten@duke.edu.

Eagle, & Migone, 2007; Northoff, Bermpohl, Schoeneich, & Boeker, 2007; Siever & Weinstein, 2009; Weston & Gabbard, 2002a, 2002b). These reviews covered a range of complex topics including psychoanalytic and cognitive models of depression, interpersonal relationships, attachment theory, defense mechanisms, personality disorders, ego and id, schemas, and transference.

Since these earlier reviews, there has been a large increase in the number of neuroimaging studies of psychotherapy outcome and the complexity of their methods and results. Thus the goal of the current article is to provide an updated review of neuroimaging studies of the effects of psychotherapy, along with an introduction to the increasingly complex neuroimaging methods appearing in psychotherapy research. A comprehensive list of neuroimaging studies of psychotherapy outcome published as of this writing will be presented. An introduction to neuroimaging methods that have appeared in psychotherapy studies will then be provided. These methods now encompass a wide and sophisticated variety of neuroimaging modalities and, therefore, a description of basic principles of neuroimaging appearing in psychotherapy studies is timely. This description will be followed by some highlights of what the neuroimaging studies have observed about how psychotherapy affects the brain. We conclude with possible directions for future neuroimaging studies in psychotherapy research.

Neuroimaging Studies of Psychotherapy

For this review, neuroimaging studies of psychotherapy outcome were identified using earlier reviews and current Pubmed searches. Psychotherapy outcome studies published in 2006 or earlier were obtained from reviews by Beauregard (2007), Frewen et al. (2008), Karlsson (2011), Linden (2006), and Roffman et al. (2005). Two additional studies from this time period (Lindauer et al., 2005; Siegle, Carter, & Thase, 2006) were identified from citations in other articles. Studies published in 2007 or later were systematically identified from Pubmed searches using each of the terms “psychotherapy,” cognitive therapy,” or “behavioral therapy” combined with neuroimaging terms “MRI,” “photon emission,” “positron emission,” or “spectroscopy.” Titles of articles published in English were read and further assessed to identify neuroimaging studies of psychotherapy outcome or process. To decrease the size of the review, some outcome studies listed in the Pubmed searches were not included if they were based on only one or two subjects or employed treatments such as Story Memory Technique, personalized smoking cessation program, Exposure Therapy with D-cycloserine, neurofeedback or psychoneurotherapy, or virtual reality therapy.

A total of 90 neuroimaging studies of psychotherapy outcome were identified (Tables 1, 2). These included five studies that employed mindfulness based stress reduction (MBSR) or meditation/yoga (Table 2). Mindfulness, meditation, and yoga therapies were drawn originally from Asian contemplative traditions and have not usually been classified with traditional psychotherapies. However, they are types of psychological techniques that are being incorporated increasingly into psychotherapeutic programs (Hayes, Villatte, Levin, & Hildebrandte, 2011; Hofmann, Sawyer, & Fang, 2010). Also, many studies of mindfulness, meditation, and yoga interventions have employed imaging methods, such as studies of the

connectome (see below), that may become increasingly important in studies of more traditional psychotherapies. Therefore these studies were included in the present review.

Neuroimaging has been used to investigate psychotherapy outcomes for many different diagnoses and types of therapy (Tables 1, 2). The most common diagnoses have been depression, obsessive compulsive disorder (OCD), and schizophrenia. Other diagnoses included phobias, post traumatic stress disorder (PTSD), and other anxiety disorders; and a broad range of additional disorders such as multiple sclerosis, fibromyalgia, Alzheimer's disease, etc. Effects on healthy populations have also been investigated in studies of MBSR and related approaches (Table 2).

The vast majority of studies have assessed cognitive or behavioral therapies (e.g. Amsterdam, Newberg, Newman, Shults, & Wintering, 2013; Hauner, Mineak, Voss, & Paller, 2012; Hoexter et al., 2012, 2013; McGrath et al., 2013; O'Neill et al., 2012, 2013; Penades et al., 2013). However, studies of psychodynamic therapies also have been conducted, such as psychodynamic therapy of depression (Buchheim et al., 2012; Hirvonen et al., 2011; Karlsson et al., 2010) and in-patient psychodynamic therapy (Beutel, Stark, Pan, Silbersweig, & Dietrich, 2010; De Greck et al., 2011). Most treatments were within 8 to 16 weeks or sessions. Some treatments were as short as single sessions for treatment of phobias (e.g. Hauner et al., 2012; Schienle, Schäfer, Stark, & Vaitl, 2009). Long-term treatments included 15 months of psychodynamic therapy of depression (Buchheim et al., 2012), 2 years of cognitive enhancement therapy of schizophrenia (Eack et al., 2010), and 6 years of treatment of autism (Pardini et al., 2012). Studies of mindfulness or meditation approaches summarized in Table 2 have assessed effects in some participants after 2 to 4 weeks of training (Tang, Lu, Fan, Yang, & Posner, 2012) or 8 or more years (e.g. Luders, Clark, Narr, & Toga, 2011; Luders et al., 2012; Taylor et al., 2011; Wang et al., 2011)

The published studies to date have employed a wide variety of neuroimaging methods to investigate the impact of psychotherapy. Because many of the imaging methods may be relatively new to psychotherapy researchers, a brief introduction to neuroimaging methods used in these psychotherapy studies will be provided. Primary emphasis will be given to magnetic resonance imaging (MRI) since it is the dominant neuroimaging modality in psychological research.

Neuroimaging Methods

There has been interest in the brain as a mediator of effects of psychotherapy since the inception of psychotherapy, beginning with Freud (Carhart-Harris et al., 2008). Empirical investigation of how the brain may change after psychotherapy treatment has become possible largely through development of noninvasive neuroimaging methods to safely image brain structure and function in living persons. Although these neuroimaging methods comprise several types of modalities, such as MRI, positron emission tomography (PET), etc., they share two general approaches to the study of psychotherapy outcome.

One general approach employs imaging of the brain both before and after psychotherapy treatment. Pre and post-treatment brain imaging results are compared to look for changes in brain function and/or structure. Neuroimaging of persons with psychological disorders have

revealed many differences from healthy persons, such as differences in measures of regional cerebral blood flow (rCBF), change in local blood oxygenation levels, levels of brain metabolites, functional connectivity, etc. (these are described further below). Thus, the effects of treatment may involve trends towards normalization of pretreatment abnormalities, such as normalization of pretreatment hypo- or hyperactivations in brain regions (Mayberg, 2003) Alternatively, effects of treatment may show brain changes suggesting involvement of compensatory neural mechanisms, such as changes in brain regions that did not show pretreatment abnormalities or change in direction from hypo- to hyperactivation, etc. (Hauner et al., 2012). Note that different types of results may be observable in different clinical time periods. For example, some changes in regional brain activations or functional connectivity may be observable after a single treatment session, while structural changes in grey matter or white matter tracts may take weeks or months to be detectable (Hauner et al., 2012; Lutz et al., 2013; Tang et al., 2012). In this regard, neuroimaging methods measure brain changes associated with psychotherapy in the same way that psychologists and neuroscientists would measure brain changes associated with learning, with maturation, with social interaction, or simply the passage of time. Finally, although some neuroimaging measures may show changes that are correlated with changes in clinical presentation, there also may be brain changes that currently are not explainable by clinical observations, and likewise there are numerous clinical therapeutic effects without clear neuroimaging results.

The other general approach is based on imaging of the brain before psychotherapy treatment begins in order to identify brain-based predictors of response to psychotherapy treatment. These biomarker studies typically investigate correlations between pretreatment neuroimaging measures of brain function or structure and post-treatment clinical measures of response to treatment, often controlling statistically for pre-treatment clinical status (Mayberg, 2003). Thus these studies do not require post-treatment neuroimaging results. Neuroimaging measures that may be useful as predictors of treatment response may or may not indicate some abnormality in structure or function at pretreatment assessments. That is, predictors of treatment response may include brain regions that are not known to be abnormal in neuroimaging studies of the psychological disorder being treated (Premkumar et al., 2009). Such a finding could signify that having a particular neurophysiological and/or psychological function that is intact is advantageous in responding to the particular psychotherapy that was given.

Neuroimaging Modalities

The earliest psychotherapy neuroimaging studies were mostly *positron emission tomography* (PET) and *single photon emission tomography* (SPECT) studies, paralleling the importance of PET and SPECT studies in early investigations of the neural substrates of psychological phenomena (e.g. Baxter et al., 1992; Laatsch, Pavel, Jobe, Lin, & Quintana, 1999; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996) (Table 1). PET and SPECT are similar in their use of exogenous compounds that are radioactively labeled and introduced into the participant prior to scanning, usually by intravenous methods. The labeled compounds are taken up by the brain, and concentrations of the compounds in specific brain regions are then quantified to measure regional cerebral blood flow, cerebral metabolism, or receptor binding of

neurotransmitters. PET and SPECT primarily differ in the type of radioactivity emitted by the labeled compounds; PET uses labels that are positron emitters while SPECT uses gamma ray emitters.

Neurons depend on energy generated by consumption of glucose and oxygen. Thus an increase in local neural activity leads to more local use of glucose and oxygen, followed by vascular autoregulation to increase cerebral blood flow (perfusion) to deliver more glucose and oxygen to the region of activation. The dependence of neural activity on glucose, oxygen, and blood flow to meet energy needs of regional neural activation has led to several PET neuroimaging methods. Among these is a measure of cerebral metabolism that employs glucose analogs as labeled compounds, such as fluorodeoxyglucose (^{18}FDG), with PET imaging to generate brain maps of regional cerebral glucose metabolism (Brody et al., 1998, 2001b; Goldapple et al., 2004). Another PET method is based on measuring regional changes in cerebral blood flow. Cerebral blood vessels contain water, and it is possible to observe regional cerebral blood flow by using radiolabeled water ($O^{15}H_2O$) with PET imaging (Furmark et al., 2002). Because changes in regional cerebral glucose metabolism and blood flow are correlates of neural activity, they have been used to make inferences about brain function, such as studies in Table 1 characterizing resting-state brain function (Apostolova et al., 2010; Brody et al., 2001a, 2001b; Goldapple et al., 2004; Konarski et al., 2009; Lindauer et al., 2005; McGrath et al., 2013) or functional changes in association with performance of a mental or behavioral task (Furmark et al., 2002; Lindauer et al., 2008; Penades et al., 2013; Peres et al., 2007).

PET and SPECT can also be used to image the distribution of some types of neurotransmitter binding in the brain. In these studies a radioactive analog of a specific neurotransmitter(s) is used as a labeling compound and its uptake in the brain is mapped. Two neurotransmitters that have been examined in psychotherapy studies are serotonin and dopamine, both of which have been implicated in types of psychopathology such as depression. For example, changes in serotonin receptor binding have been examined after psychotherapy treatments for depression (Amsterdam et al., 2013; Hirvonen et al., 2011; Karlsson et al., 2010; Lehto et al., 2008a, 2008b).

Magnetic resonance imaging began to appear in psychotherapy outcome studies later than PET and SPECT imaging because early MRI methods had less sensitivity to changes in the brain related to mental phenomena of interest to psychological researchers. This changed with the development of functional MRI (fMRI) methods. Most MRI methods, including fMRI, rely on magnetic resonance signals that originate from protons that are endogenously present in the human body. An understanding of the proton signal source of fMRI signals, and the relationship between fMRI signals and neural function, continues to be under investigation, for example, in studies of local field potential neural signals and their relationship to fMRI signals (Kim & Ogawa, 2012; Magri, Schridde, Murayama, Panzeri, & Logothetis, 2012; Raichle, 2011). Nonetheless, currently the primary model for interpreting fMRI signals is based on the role of local hemodynamic changes that are associated with changes in neural activity (Carrig et al., 2009; Raichle, 2011).

The most prominent model for interpreting fMRI signals is the following (Huettel, Song, & McCarthy, 2009). As described above, an increase in local neural activity leads to local use of oxygen. Oxygen is delivered to brain tissue via oxygenated hemoglobin found in red blood cells. When neural activity and oxygen consumption increase, the level of oxygenated hemoglobin in blood in the localized region decreases while the level of deoxygenated hemoglobin increases. Deoxygenated hemoglobin has a magnetic property that can decrease nearby MRI signals (such as from protons of water molecules in blood vessels; Kim & Ogawa, 2012). Thus, when neural activation occurs a localized decrease in MRI signal may be observed. However, this decrease in signal is only momentary, for the consumption of oxygen is followed by a vascular response that leads to a local increase in cerebral blood flow and, therefore, an increase in the level of oxygenated hemoglobin. This local increase in blood flow then leads to an increase in the MRI signal. The vascular response is abundant such that the MRI signal increases above its baseline level, and this increased signal is the main response observed as a correlate of neural activity. The method that is based on this model is called the *blood oxygenation level dependent* (BOLD) method. The earliest MRI studies of psychotherapy outcome used this BOLD fMRI approach (Paquette et al., 2003; Wykes et al., 2002). A helpful introduction to BOLD fMRI methods for psychotherapy researchers has been provided by Carrig et al. (2009).

Findings obtained from fMRI studies often overlap with those obtained from PET and SPECT studies of cerebral blood flow or metabolism because of overlapping dependence on regional blood flow and metabolism. However, MRI has several advantages over PET and SPECT imaging including the absence of exogenous agents, absence of radioactive exposure, and better temporal and spatial resolution. For example, the temporal resolution of PET /SPECT is on the order of minutes (that is, the time required to detect a change in regional brain activation) while the temporal resolution of fMRI is on the order of seconds (Huettel et al., 2009). Thus MRI has become the dominant neuroimaging modality and Table 1 shows that most of the recent psychotherapy outcome studies have employed MRI. These include studies of psychodynamic psychotherapy (Beutel et al., 2010; Buchheim et al., 2012; De Greck et al., 2011) and numerous investigations of cognitive behavioral types of treatments (e.g. Bor et al., 2011; Doehrmann et al., 2012; Hauner et al., 2012; Kircher et al., 2013; Klumpp, Fitzgerald, & Phan, 2013; Ritchey et al., 2011; Siniatchkin et al., 2012; Yoshimura et al., 2013).

Since fMRI was first used there have been additional developments in MRI that can be applied to the investigation of psychological phenomena. Magnetic resonance spectroscopy (MRS), a method based on the influence of molecular structure on magnetic resonance signals, can be used to image specific metabolites in the brain, including N-acetyl aspartate, glutamate and glutamine, and myo-inositol. MRS is increasingly valuable for investigating neural processes associated with psychological disorders and their treatments, e.g. depression (Caverzasi et al., 2012), obsessive compulsive disorder (Brennan, Rauch, Jensen, & Pope, 2013); and schizophrenia (Port & Agarwal, 2011). Five MRS studies of the effects of cognitive or behavioral therapies for treatment of obsessive compulsive disorder have recently appeared (O'Neill et al., 2012, 2013; Whiteside, Abramowitz, & Port, 2012a, 2012b; Zurowski et al., 2012).

Advances in anatomical or structural MRI assessments of sizes and shapes of gray and white matter, cortical thickness, and surface area have meant that these methods are now sufficiently sensitive for many studies of psychological disorders and treatments, e.g. depression (Andreescu et al., 2008; Kempton et al., 2011), obsessive compulsive disorder (Pujol et al., 2011), schizophrenia (Meyer-Lindenberg, 2010; Nenadic, Gazer, & Sauer, 2012); and borderline (Schmahl & Bremner, 2006), schizotypal (Hazlett, Goldstein, & Kolaitis, 2012), and psychopathy and antisocial (Gregory et al., 2012) personality disorders. Measurements often employ automated methods, such as voxel based morphometry (VBM), for increased precision (a voxel is a three-dimensional volume element in an image, similar to a pixel element in a two-dimensional picture) (Ashburner & Friston, 2000). Structural MR imaging in psychotherapy research has included several studies of regional brain volumes as predictors of response to cognitive therapies for PTSD (Bryant et al., 2008), schizophrenia (Keshavan et al., 2011; Premkumar et al., 2009), and obsessive compulsive disorder (Hoexter et al., 2012, 2013). MRI methods have also been developed that focus on imaging an important structural component of the brain, the white matter tracts, using diffusion tensor imaging (DTI) (Johansen-Berg & Rushworth, 2009). DTI will be discussed further below in the section on structural connectivity within the brain.

Clinical MRI neuroimaging often employs the use of contrast agents, which are exogenous compounds that are introduced into the individual prior to scanning, usually by intravenous methods, to increase the visibility of some types of brain structures. Some common contrast agents use gadolinium (Gd). These contrast agents are taken up by brain regions and modulate the regional MRI signals. For example, multiple sclerosis can be characterized by gadolinium enhancing lesions in the brain. An interesting use of Gd contrast in psychotherapy research can be seen in a study of stress management therapy (SMT) of multiple sclerosis that observed changes in the number of brain lesions during and after SMT (Mohr et al., 2012).

Another relatively advanced MRI method is arterial spin labeling (ASL). ASL is used to measure cerebral blood flow or perfusion. Water molecules in blood can be magnetically “labeled” and then followed as they flow through arteries of the brain. ASL results have similarities to cerebral blood flow measured using PET and SPECT imaging, and like these methods can also be used for neuroimaging of brain function (Detre, Wang, Wang, & Rao, 2009). Although ASL has not yet appeared in traditional psychotherapy studies, it has been used in a study of meditation tasks (Wang et al., 2011).

The Connectome

One of the most important efforts in current neuroscience is the investigation of connections and pathways for information to flow within the brain (Biswal et al., 2010; Raichle, 2011). Most early neuroimaging studies investigated discrete brain regions. However, the number of discrete, observable brain regions is vastly outnumbered by connections between brain regions (Sporns, Tononi, & Kotter, 2005). Connections can be structural (that is, representing direct tissue connections between brain regions) or functional (temporal correlations between activity in discrete brain regions), and the totality of all structural and functional connections in the brain is referred to as the *connectome*. Mapping brain

connectivity shifts our attention from discrete brain regions to *networks of brain regions* that support psychological functioning and are involved in psychological dysfunction as well (Buckholtz & Meyer-Lindenberg, 2012; Fornito & Bullmore, 2012). Connectivity is a complex field, and the relation between connectivity networks and psychological functioning and behavior is in early stages of development. However, studies of connectivity are beginning to increase our understanding of how psychological phenomena are instantiated in the brain by drawing attention to the networks involved when an individual is engaged in a specific mental activity as well as during baseline or so-called "resting" states. This integrated perspective, which encompasses connectivity networks throughout the entire brain, is critical for an understanding of psychological disorders, developmental trajectories, treatments, and prevention (e.g. Perrin et al., 2012; Zeng et al., 2012a, 2012b). For example, Buckholtz and Meyer-Lindenberg have proposed that disruption of "core connectivity circuits" leads to "transdiagnostic symptoms" in psychological disorders such as decreased concentration, increased ruminating, hypervigilance, and worry (2012, p. 990). The study of the connectome is being driven especially by advancements in MRI imaging of structural and functional connectivity.

Structural connectivity: diffusion tensor imaging (DTI) of white matter— Structural connections between brain regions are hallmarked by the white matter tracts of the brain that contain myelinated axons. White matter tracts can be assessed using diffusion MRI methods such as *diffusion tensor imaging* (Johansen-Berg & Rushworth, 2009; Madden, Bennett, & Song, 2009). Proton magnetic resonance signals are affected by diffusional processes of water molecules. For example, proton MRI signals are affected by the degree to which diffusion of water molecules is unequal in different directions, i.e. anisotropic diffusion, or equal in all directions, i.e. isotropic diffusion. Water molecules in structures like axons within the brain's white matter tracts show more anisotropic diffusion along the direction of the length of the axon, while diffusion in neuronal cell bodies in gray matter is more equal in all directions (and therefore isotropic). A common measure of the degree of anisotropy of diffusion is fractional anisotropy (FA). FA can be used to image the brain's white matter tracts and this approach is referred to as tractography. Additional DTI measures that can quantify the structure of white matter connections are axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD). Although models for diffusivity continue to be refined, FA is a measure of white matter structure that depends on multiple factors related to axon characteristics, myelination, and axonal fiber orientation within each individual voxel. AD can reflect axonal features such as axon density, while decreases in RD indicate increased myelination (Tang et al., 2012).

DTI studies are making important contributions to understanding depression (Hulvershorn, Cullen, & Anand, 2011; Murphy & Frodl, 2011; Sexton et al., 2012; Takeda, Tanaka, & Kudo, 2011), obsessive compulsive disorder (Fontenelle et al., 2009), and schizophrenia (Ellison-Wright & Bullmore, 2009; Whitford, Kubicki, & Fenton, 2011). DTI has not yet appeared in studies of typical psychotherapies. However, it has been used to study effects of cognitive remediation therapy (CRT) for schizophrenia (Penades et al., 2013), as well as a long-term, complex cognitive, behavioral, and communicative treatment of autism (Pardini et al., 2012). It has also been used to study how a nontraditional mindfulness therapy,

Integrated Body Mind Therapy (IBMT), which improved self-regulation and mood in healthy participants, led to white matter neuroplastic changes around the anterior cingulate in only 2 to 4 weeks (Tang et al., 2012).

Functional connectivity—Functional connectivity refers to temporal correlations between brain regions (Biswal et al., 2010). There are diverse measures of functional connectivity but the most productive method currently is based on temporal correlations between BOLD fMRI signals from different brain regions (Biswal et al., 2010, Raichle, 2011). In typical fMRI studies the fMRI signal is analyzed to examine increases from the baseline (or decreases in "deactivated" regions) in association with performance of some specific task in which participants are engaged (e.g., retrieving a memory, making a judgment about a stimulus, or making a choice). However, during a baseline state, such as a resting state when a participant is asked to lie quietly in the scanner without performing any specific task, fMRI signals will show spontaneous increases and decreases, i. e. spontaneous or "intrinsic" fluctuations. These intrinsic fluctuations actually constitute some 95% of an overall fMRI signal at any moment, while the task associated increases (decreases) constitute only approximately 5% of the signal (Madden et al., 2009). Intrinsic fluctuations were not usually examined in fMRI studies but were simply discarded statistically as noise. However, it turns out that these spontaneous or intrinsic fluctuations carry a great deal of information about brain function (Biswal et al., 2010; Raichle, 2011). In particular, the intrinsic fluctuations in one region of the brain are often found to be synchronized, i.e. temporally correlated, with fluctuations in other regions of the brain. In turn, such correlations are used as a measure of functional connectivity between brain regions and, therefore, are said to identify functionally connected networks of the brain. Note that the correlations can be positive or negative, i.e., activation in one region can increase or decrease in synchrony with activation in another region. Indeed, some networks show significant negative associations or "anti-correlations" between each other (Fox et al., 2005; Fox, Buckner, White, Greicius, & Pascual-Leone, 2012; Vasic, Walter, Sambataro, & Wolf, 2009). Functionally connected brain regions may or may not have direct anatomical connections (which is one important conceptual difference between neuroimaging of structural vs. functional connectivity). However, the strength of functional connectivity can be an index of the integrity of anatomical connections such as white matter tracts as well as the approximate neural 'pathways' by which two regions could be functionally associated during task performance or at rest (Horwitz et al., 2005).

The most common methods for identifying functionally connected networks can be broadly classified into seed-based versus data-driven methods such as independent component analysis (ICA) (Biswal et al., 2010; Fornito & Bullmore, 2012). Seed-based functional connectivity analyses use fMRI time course series, from voxels within a particular brain region of interest (ROI), as a "point-of-origin" to identify voxels in other parts of the brain that have time course series in synchrony with the seed region. In contrast, data-driven techniques such as independent component analysis (ICA) analyses search for synchronous brain regions that are non-overlapping. Functional connectivity can be assessed in association with specific characteristics of task performance in healthy or clinically diagnosed individuals (Josipovic, Dinstein, Weber, & Heeger, 2012; Kircher et al., 2013;

Penades et al., 2013). Currently, however, there is a particular emphasis on mapping intrinsic functional connectivity of the resting state brain. These studies are critical to a comprehensive understanding of the human connectome (Biswal et al., 2010; Raichle, 2011; Snyder & Raichle, 2012; Sporns et al., 2005). Resting-state data also have special relevance for understanding baseline features of brain function, including those that instantiate many characteristics of normal psychology and psychological disorders (e.g., psychological functions associated with the "self"). We note that psychotherapy researchers are as interested in baseline changes in psychological functioning, including those indicated by changes in resting-state activation patterns, as in changes during the performance of specific tasks. Also of note is that MRI studies of the resting-state can be easier to conduct than task-based studies for some types of clinical participants.

Numerous functionally connected networks are being identified and examined throughout the brain (e.g. Buckholtz & Meyer-Lindenberg, 2012; Lenglet et al., 2012; Raichle, 2011; Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012; Zeng et al., 2012b). A useful example of connectivity networks can be found in Raichle (2011), who highlighted seven hypothetical networks: the default mode (DMN), executive control, dorsal attention, salience, sensorimotor, visual, and auditory networks. Buckholtz & Meyer-Lindenberg (2012) highlighted four "core connectivity" networks for executive, affective, motivational, and social cognitive functions. Other studies of functionally connected networks have highlighted as few as three or four networks, typically the default mode network, cognitive control network, and affective networks (Sheline, Price, Yan, & Mintun, 2010), or 14 or more networks (Shirer et al., 2012). These networks are comprised of numerous brain regions or "nodes," many of which overlap with important regions observed in other PET and fMRI studies of regional brain activation, while other regions are drawing new attention.

Connectivity studies are leading to novel and more comprehensive insights into the neurobiological basis of many psychological disorders (Buckholz & Meyer-Lindenberg, 2012; Fornito & Bullmore, 2012; Raichle, 2011) including depression (Davey, Yucel, Allen, & Harrison, 2012; Fox et al., 2012; Perrin et al., 2012; Sheline et al., 2010; Zeng et al., 2012a, 2012b), obsessive compulsive disorder (OCD) (Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012), schizophrenia (Calhoun, Eichele, & Pearson, 2009; Lynall et al., 2010; Salomon et al., 2011), and autism (Schipul, Keller, & Just, 2012). Studies on depression are illustrative of current theorizing about functional networks and how such models can illuminate both the etiology of psychopathology and how specific treatments might lead to lasting changes in the nervous system. Although there are several network models of depression (e.g. Mayberg, 2003), we will focus on a study by Sheline et al. (2010), who examined three functionally connected networks in participants with depression: the default mode network, the affective network, and the cognitive control network.

Default mode network: The default mode network is a network of brain regions with relatively greater activation when the individual is resting or not actively engaged in a specific task (Gusnard, Akbudak, Shulman, & Raichle, 2001; Snyder & Raichle, 2012). On the other hand, regions of the DMN typically show decreased activations during intentional performance of a wide range of tasks (Raichle et al., 2001). DMN includes regions in the anterior cingulate, medial prefrontal cortex, posterior cingulate/precuneus, hippocampus,

parahippocampus and amygdala (medial temporal lobe), and thalamus. Many regions of the DMN are involved in self-referential processing (i.e. what some investigators refer to as the "neural self") as well as interpersonal function, episodic memory, future planning, and mind wandering (Buckner & Carroll, 2007; Doucet et al., 2012; Gusnard et al., 2001). Greicus, Krasnow, Reiss, & Menon (2003) hypothesized that regions in the DMN would be functionally connected in the resting state. To test this prediction they examined the intrinsic, functional connectivity of two regions of interest in the DMN, the posterior cingulate cortex/precuneus region and the ventral anterior cingulate cortex. Results showed that the regions were functionally connected to each other as well as to additional regions consistent with the DMN. Since then, use of functional connectivity methods to identify the DMN has become common. Thus the DMN can be operationalized as the set of brain regions that are synchronized with the posterior cingulate/precuneus region while the individual is at rest (i.e., not actively engaged in a specific task) (Sheline et al., 2010).

Affective network: The affective network of brain regions is involved in all aspects of emotion processing (Northoff, et al., 2006; Phan, Wager, Taylor, & Liberzon, 2002). It overlaps many regions of the DMN, including parts of the anterior cingulate (subgenual) and the amygdala. It also includes connections with the temporal poles, basal ganglia, and orbitofrontal cortex. Regions of the affective network comprise some (not all) of the regions activated using emotion tasks, such as feelings of sadness induced from autobiographical scripts (Mayberg et al., 1999), viewing negative emotion pictures (Anand et al., 2005), or rating emotional words for personal relevance (Siegle et al., 2006; Siegle et al., 2012). The affective network can be assessed using functional connectivity MRI and a seed region within the subgenual anterior cingulate (Sheline et al., 2010). Note that patterns of task-related activation within the anterior cingulate, and especially the subgenual anterior cingulate cortex, have been prominent in many studies of depression (e.g. Davey et al., 2012; Fox et al., 2012; Greicius et al., 2007; Mayberg et al., 1999; Sheline et al., 2010; Siegle et al., 2006, 2012; Vasic et al., 2009).

Cognitive control network: The cognitive control network is activated by tasks involving the intentional or automatic control of information processing, such as attention and working memory tasks. Examples of stimuli that activate this network are a visual search task (Cole & Schneider, 2007) or a multi-source interference task (Davey et al., 2012). Regions in the cognitive control network include the anterior cingulate/pre-supplementary motor area and dorsolateral prefrontal cortex (Cole & Schneider, 2007). Notably, the cognitive control network is negatively correlated ("anticorrelated") with the DMN (Fox et al., 2005), so that when one network is engaged the other tends to be disengaged or inhibited. Further, functional connectivity between the dorsolateral prefrontal cortex of the cognitive control network and the subgenual anterior cingulate cortex of the affective network also is negatively correlated (Fox et al., 2012). The cognitive control network can be assessed by using functional connectivity MRI and a seed region in the dorsolateral prefrontal cortex (Sheline et al., 2010). Patterns of task-related activation within the dorsolateral prefrontal cortex have also been prominent in studies of depression, including in studies of mechanisms of action of electroconvulsive therapy and transcranial magnetic stimulation

treatments of depression (Fox et al., 2012; Perrin et al., 2012; Sheline et al., 2010; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007).

Sheline et al. (2010) observed that these three networks showed increased connectivity to a common region in the dorsomedial prefrontal cortex in participants with depression but not in healthy individuals. Connectivity to the dorsomedial prefrontal cortex was correlated with clinician-rated depressive symptoms, suggesting that this distinctive pattern of functional connectivity was both characteristic of a depressed state and an index of symptom severity. The authors suggested that interventions that would bring about decreased connectivity between the three networks and the dorsomedial prefrontal cortex might be particularly helpful – a hypothesis that is potentially relevant both to treatment selection and to understanding mechanisms of action in psychotherapy.

Sheline and colleagues' proposal has since been supported by a recent functional connectivity MRI study of the mechanisms of electroconvulsive therapy (ECT) for depression (Perrin et al., 2012). Results showed that ECT led to a decrease in functional connectivity between the left dorsolateral prefrontal cortex and several regions of the brain, including the dorsomedial prefrontal cortex. To our knowledge this hypothesis has yet to be tested prospectively in psychotherapy research related to depression. Still, even if this pattern of correlations among brain regions is simply a biological state marker for depression, it offers an additional opportunity to measure treatment-induced change and it may provide clues regarding the neural and psychological processes involved in the maintenance and persistence of a depressed state.

Finally, a recent study of functional connectivity MRI in depression has been able to identify 100% of participants with depression and 89.7% of healthy controls using a machine learning algorithm to analyze resting state fMRI results (Zeng et al., 2012b). The functional connections that discriminated most reliably between the two groups were in the default mode and affective networks, along with a third network for visual processing involving the lingual, fusiform, inferior occipital, and calcarine gyri (Zeng et al., 2012b, pp. 1498, 1502). Abnormalities in the affective network included abnormal connectivity to the orbitofrontal cortex and basal ganglia. Connections between the cerebellum and regions of the default mode and affective networks were also found to discriminate between the groups. Overall, functional connectivity with the amygdala, anterior cingulate, parahippocampus and hippocampus were most important to discriminate between depressed and normal participants.

By way of summary, neuroimaging techniques can now identify and quantify connections between brain regions in addition to findings task-related patterns of localized, regional brain activations. Study of the connectivity networks of the brain is rapidly increasing the neurobiological understanding of psychological disorders. This research is also beginning to contribute critical knowledge of neurobiological mechanisms of treatments of psychological disorders. Functional connectivity studies are beginning to appear in psychotherapy research, such as effects of cognitive treatments of schizophrenia (Kumari et al., 2009; Penades et al., 2013), panic disorder (Kircher et al., 2013), and fibromyalgia (Jensen et al., 2012). Functional connectivity studies are also increasingly common in studies of

mindfulness and meditation (e.g. Brewer et al., 2011; Jang et al., 2011; Josipovic et al., 2012; Kilpatrick et al., 2011).

Effects of psychotherapy on the brain: a selective review

Almost all neuroimaging studies of psychotherapy effects have reported significant differences in comparisons of neuroimaging findings before versus after treatment. Most findings were obtained from studies of brain function, such as task-based activations, resting-state blood flow or glucose metabolism, or serotonin or dopamine function. However, more recent studies also have detected psychotherapy-induced structural changes in the brain, such as changes in volumetric measures (Eack et al., 2010; Holzel et al., 2010; Luders et al., 2012) or measures of white matter characteristics (Luders et al., 2011, 2012; Pardini et al., 2012; Tang et al., 2012), as well as regional changes in neurochemicals (O'Neill et al., 2012, 2013; Whiteside et al., 2012a, 2012b; Zurowski et al., 2012). Overall, these studies clearly demonstrate the capacity of neuroimaging methods to detect some changes in the brain from psychotherapy treatments. And although earlier psychotherapy neuroimaging studies primarily probed for neural changes after psychotherapy treatments, more recent work includes an important focus to identify pretreatment biomarkers or predictors of treatment outcome. Indeed, 24 of the 85 studies in Table 1 reported results for predictors of treatment response, with 22 published since 2008.

Neuroimaging results from psychotherapy research encompass a wide range of complex and, at times, inconsistent findings (e.g. Amsterdam et al., 2013; Linden, 2006; McGrath et al., 2013; Ritchey et al., 2011; Roffman et al., 2005). This is not surprising considering the breadth of diagnoses and number of treatment protocols that have been investigated using many types of neuroimaging methods, participant characteristics, stimulus tasks, regions of interest, etc. In light of this complexity, the current section will focus on three disorders - depression, OCD, and schizophrenia, followed by some examples of other studies relevant to psychotherapy research to illustrate neuroimaging effects of psychotherapy. It will end with discussion of a general observation that effects of psychotherapy often implicate important connectivity networks of the brain.

Psychotherapy Outcome Studies

Depression—Neuroimaging studies of psychotherapy in depression have observed changes in many brain regions, including the cingulate gyrus (anterior, subgenual, dorsal, posterior), medial prefrontal, orbitofrontal, dorsolateral and dorsomedial prefrontal cortices, temporal lobes (hippocampus, amygdala, parahippocampus), and basal ganglia (striatum, caudate). Many of the changes have been in the direction of normalization of neural function in brain regions that showed abnormalities before treatment (e.g. Dichter et al., 2009, 2010; Fu et al., 2008; Ritchey et al., 2011). These are also important regions in brain networks known to be altered in depression. For example, Sheline's network perspective of depression, described above, highlighted abnormalities in default mode (medial prefrontal cortex, anterior and posterior cingulate, hippocampus, parahippocampus, amygdala), cognitive control (dorsolateral prefrontal cortex), and affective (subgenual cingulate, amygdala, with connections to orbitofrontal and basal ganglia regions) (Sheline et al., 2010) networks. Another model proposed that depression is a dysfunction of a limbic-cortical

network (Mayberg, 2003); limbic structures include the cingulate, amygdala, hippocampus, parahippocampus and cortical structures include dorsolateral prefrontal and medial orbit frontal cortices. Both of these network models suggest that psychotherapy treatments modulate networks that are dysfunctional in depression.

Connectivity changes within these networks via “top-down (cortico-thalamic, cortico-limbic) or bottom-up (thalamo-cortical, limbic-cortical)” mechanisms have been proposed as mediators of treatment effects (Mayberg, 2003, p. 196; Goldapple et al., 2004). Antidepressant pharmacotherapies have been postulated to work via bottom-up mechanisms that target limbic or subcortical brain regions, while psychological therapies were postulated to work via top-down mechanisms that target higher level cortical processing, such as cognitive control networks in cognitive behavioral therapies. Earlier studies of interpersonal (Brody et al., 2001b) and CBT treatments (Goldapple et al., 2004; Kennedy et al., 2007) revealed decreased FDG-PET resting glucose metabolism in frontal cortical regions after treatment. However, CBT studies also showed increased metabolism in anterior cingulate gyrus and related regions. Together these results indicated “reciprocal limbic increases… and cortical decreases” that may be the “neural correlates” of “psychological or top-down mechanisms that mediate CBT response” (Goldapple et al., 2004, pp. 37, 38).

Recent studies based on other neuroimaging approaches also indicate that psychotherapies are modulating regions within these networks. Functional MRI studies by Buchheim et al. (2012) using attachment system stimuli showed that brain activations decreased in the subgenual cingulate, hippocampus/amygdala, and medial prefrontal regions after long-term psychodynamic psychotherapy treatment. Yoshimura et al. (2013) showed that fMRI activations in response to self-referential tasks increased (positive stimuli) or decreased (negative stimuli) in the medial prefrontal and anterior cingulate regions after CBT. Amsterdam et al. (2013) used a different neuroimaging approach and investigated changes in serotonin transporter binding (SERT) after CBT. Results showed that serotonin transporter binding increased in the medial temporal lobes after CBT, consistent with “a “top-down effect of CBT on SERT binding,” i.e. a corticolimbic mechanism. Note that increased serotonin transporter binding has also been observed in studies of psychodynamic psychotherapy in depression (Lehto et al., 2008a).

One important feature of the psychotherapy studies of depression summarized in Table 1 is that more than a third report predictors or biomarkers of treatment response. Biomarker studies are important because “fewer than 40% of patients with major depressive disorder achieve remission with initial treatment” (McGrath et al., 2013, p.E1). Thus, it would be helpful to be able to predict reliably who is likely to benefit from a specific treatment. The most frequently appearing biomarker regions in neuroimaging studies of psychotherapy for depression have been within the anterior cingulate gyrus. For example, Siegle et al. (2006) showed that lower response in the subgenual anterior cingulate or higher response in the amygdala to an emotion processing task predicted better response to CBT. These investigators have conducted another study to replicate their findings and observed similar results for the subgenual cingulate although not for the amygdala (Siegle et al., 2012).

A different approach to biomarkers for CBT treatments of depression has highlighted other regions. McGrath et al. (2013) investigated neuroimaging treatment-specific biomarkers (TSB) that could differentiate patients with depression who would respond preferably to CBT versus pharmacotherapy (escitalopram). Resting state brain glucose metabolism in the insula was observed to be a useful TSB: right anterior insular hypometabolism predicted remission after CBT but not after escitalopram, while insular hypermetabloism predicted the opposite treatment response. The results suggested two different "baseline patterns" of regional brain metabolism in depressed individuals that is associated with how an individual responds to different treatment approaches. Other discriminating regions were inferior temporal, amygdala, premotor, motor, and precuneus regions. Note that the anterior cingulate, identified as a biomarker for CBT response in several other studies, was not identified here as a treatment-specific biomarker that could discriminate between CBT and escitalopram as treatments leading to remission of depression. These results indicate both the promise of pursuing psychotherapy treatment biomarkers as well as the complexity of the task ahead.

Obsessive compulsive disorder—As in studies of depression, multiple brain regions have shown changes after psychotherapy treatments for OCD and some studies indicated change in the direction of normalization of neural function of some brain regions (Freyer et al., 2011; Huyser, Veltman, Wolters, Haan, & Boer, 2010; Nabeyama et al., 2008). Regions that frequently showed changes included the right caudate, orbitofrontal, anterior cingulate, and thalamus regions. These regions all had been implicated previously in important brain networks involved in OCD (Harrison et al., 2009; Stern et al., 2012). Until recently, several studies had shown consistent results of decreased resting blood flow or glucose metabolism in the right caudate after psychotherapy (Baxter et al., 1992; Linden, 2006; Nakatani et al., 2003; Schwartz et al., 1996). However, Apostolova et al. (2010) have since described increased glucose metabolism in the right caudate after CBT. The reason for the different results is unknown, although the investigators speculated that different results may have arisen from different participant characteristics in the various studies, such as presence of comorbid major depression or early onset OCD in participant groups.

An interesting feature of psychotherapy studies of OCD is that there are now five studies that used magnetic resonance spectroscopy to examine concentrations of neurochemicals as predictors of treatment outcome or measures of change after CBT treatments. Levels of N-acetyl compounds, glutamate and glutamine, and myo-inositol in the left thalamus, N-acetyl compounds in the right pregenual anterior cingulate, or myo-inositol in the right orbitofrontal cortex predicted response to cognitive-behavioral therapy (O'Neill et al., 2012, 2013; Zurowski et al., 2012). Behavioral treatments of OCD in adults or children showed changes in levels of several neurochemicals and brain regions after treatment, including decreased glutamine and glutamate in the right caudate and increased N-acetyl compounds in the left caudate (Whiteside et al., 2012a, 2012b).

Schizophrenia—Neuroimaging studies have targeted psychotherapy treatment effects for several different domains of symptoms in schizophrenia. For example, CBT treatment of psychosis was assessed using a threatening facial expression task and showed decreased

activation of a network of brain regions (e.g. inferior frontal, insula, thalamus, putamen, occipital) involved in processing negative facial expressions after treatment (Kumari et al., 2011). Similarly, cognitive treatment for information processing impairments was associated with increased frontal activations during a working memory task (Haut, Kim, & McDonald, 2010). Cognitive therapies have also been employed to improve social cognitive functioning and at least one neuroimaging study has shown that increased cortical surface area and grey matter volume (cortical reserve) predicted faster social-cognitive improvement (Keshavan et al., 2011). Finally, an interesting study of both functional and structural connectivity networks has been conducted to examine effects of cognitive remediation therapy (CRT) in schizophrenia (Penades et al., 2013). Functional connectivity studies showed that compared with controls, participants with schizophrenia showed increased activation in regions of a central executive network (middle and inferior frontal gyri, anterior cingulate, superior and inferior parietal lobule, precuneus) during an N-back task (a type of working memory task); these overactivations decreased significantly after CRT. Participants with schizophrenia also showed increased activation in the default mode network (anterior cingulate, cingulate gyrus, precuneus/cuneus, middle temporal gyrus, supramarginal gyrus) during rest that likewise decreased after CRT. Overall, results suggested that the function of important networks was normalizing. The investigators also noted that this study was the first to show an effect of CRT treatment for schizophrenia on the default mode network, which is known for its involvement in self-referential processing, autobiographical memory, etc. DTI studies showed increased fractional anisotropy in the corpus callosum after CRT, which suggested that increased interhemispheric structural connectivity might be a factor for changes in brain function after CRT. Overall, neuroimaging effects of psychotherapy treatments of schizophrenia have shown that these treatments lead to observable changes at the neural level for many different types of distressing symptoms. We find it particularly encouraging that the studies to date suggest the possibility that psychotherapy can lead to lasting structural neuroplastic changes in regions critical to effective information processing.

Other Studies Relevant to Psychotherapy

Psychotherapy is a complex package with many different nonspecific and specific interventions and responses within a single session, between sessions, and across sessions during time periods varying from days or weeks to years. Single time-point assessments pre- and post-treatment are essential beginnings for a cognitive neuroscience of psychotherapy but can only hint at what occurs during the process of psychotherapy and consolidation or during relapse after treatment ends. Cognitive neuroscience studies on learning, emotion processing and regulation, social cognitive and self-referential processing, neuroscience of psychopathology, and pharmacological and brain stimulation treatments can provide many useful insights for psychotherapy. However, there is also a need for investigation of more specific components of psychotherapy, including studies that use a so-called “microintervention” strategy in which single elements of a more complex psychotherapy are studied experimentally (Zaunmüller, Lutz, & Strauman, in press). Studies that are not psychotherapy outcome studies per se can still lead to insights, questions, and methodological approaches, such as novel tasks or imaging methods, that could improve neuroimaging studies of psychotherapy outcome, as well as advancing a more comprehensive understanding of the neurocognitive mechanisms involved in psychotherapy

mechanisms of change. A few examples of these kinds of studies are offered here to illustrate their potential contributions.

There is a large literature on neural mechanisms of emotion reappraisal; a meta-analysis of this work has recently appeared (Buhle et al., 2013) that highlights cognitive control regions (e.g. dorsomedial, dorsolateral, and ventrolateral prefrontal cortices; posterior parietal lobe) and the amygdala and its role in emotional responses. Eddington, Dolcos, Cabeza, Krishnan, & Strauman (2007) and Eddington et al. (2009) investigated neurocognitive systems involved in personal promotion and prevention goals, which are critical to self-regulation and function and are important constructs in some theories of depression and in self-system therapy for depression (Strauman, 2002). These studies highlighted the role of the orbitofrontal cortex in association with different types of personal goals. Buchheim et al. (2008) have investigated the attachment system, important in some psychological disorders and psychotherapy treatments, in borderline personality disorder. Kessler et al. (2011) and Loughead et al. (2010) probed neural systems involved in processing of interpersonal relationship patterns and autobiographical interpersonal memories, central to understanding self and interpersonal schema, therapeutic alliance, and conduct of many types of psychotherapy, especially psychodynamic therapies. An interesting functional connectivity study of an affective listening task, highly relevant to listening behaviors during psychotherapy sessions, showed that activation of right amygdala, insula, and auditory cortex preceded activations in homologous regions in the left hemisphere, while left auditory cortex activation preceded right amygdala decreases (Tschacher, Schildt, & Sander, 2010). Finally, neural effects of repeated exposure to fearful stimuli, a component of many therapies of phobias, has been investigated in nonclinical participants who scored high or low in fear of animals (Wendt, Schmidt, Lotze, & Hamm, 2012). Results showed that increased activation to fearful stimuli in the amygdala decreased with repeated exposure and showed fast habituation.

One particularly promising subset of psychotherapy-relevant neuroimaging studies is the investigation of mindfulness and meditation. These studies are especially interesting from a neuroimaging perspective because many have employed more advanced neuroimaging approaches, such as functional connectivity MRI, diffusion tensor imaging of white matter tracts, and arterial spin labeling (Table 2). An emphasis on mindfulness – “attentive non-judgmental focus on present experiences” (Lutz et al., 2013, p. 1) – has been common in many Asian contemplative traditions (meditation, yoga). However, it is now also being included in clinical psychotherapeutic programs, such as MBSR, dialectical behavior therapy (DBT), etc. (Hayes et al., 2011; Hofmann, et al., 2010; Tables 1, 2). Mindfulness and meditation have been the focus of many neuroimaging studies and a few representaive examples are given in Table 2. One is a study of effects of a mindfulness training (MT) in healthy persons that showed that a single session of training could influence neural activations during an emotional expectation task (Lutz et al., 2013). Another study of 6 weeks of MT in healthy participants showed that training led to increased dorsolateral prefrontal cortex activation during a Stroop task (Allen et al., 2012). Further, in that study a dose-response effect was observed, with more mindfulness practice predicting increased responses in dorsolateral prefrontal cortex, anterior insula, and medial prefrontal cortex during affective processing. Both Lutz et al. (2013) and Allen et al. (2012) described

implications of their studies for MT in clinical treatments. Other studies have involved participants with stress or anxiety disorders (e.g. Farb et al., 2010; Goldin & Gross, 2010) or discussed the important topic of interventional strategies for prevention of psychological disorders (Tang et al., 2012). Many of these studies employed methods probing functional or structural connectivity (e.g. Jang et al., 2011; Josipovic et al., 2012; Tang et al., 2012). We believe this type of research will continue to provide insights into the effects of psychological interventions on the brain that will be increasingly important for psychotherapy research.

Connectivity networks

A concluding observation about neuroimaging effects of psychotherapy from the above studies is that many brain regions that change after psychotherapy treatments are components of important brain networks. This suggests that ***a key neurobiological outcome of psychotherapy treatments is modulation and re-regulation of core connectivity networks within the brain.*** For example, as described above, several influential models have proposed that depression involves dysfunctional connectivity networks and that treatments of depression modulate these networks (Mayberg, 2003; Sheline et al., 2010). The findings summarized above are certainly consistent with this postulate.

There have been a few psychotherapy studies that specifically examined functional or structural connectivity networks. A study of CBT treatment of schizophrenia showed that task-based functional connectivity between the dorsolateral prefrontal cortex and cerebellum could predict response to CBT (Kumari et al., 2009). A study of CBT treatment of panic disorder observed that task-based functional connectivity, between the inferior frontal gyrus and amygdala, insula, and anterior cingulate regions, was increased in patients versus healthy controls although it did not change after treatment (Kircher et al., 2013). With respect to structural connectivity assessed by DTI studies of white matter tracts, Pardini et al. (2012) identified changes in white matter structure in the uncinate fasiculus, a white matter tract that connects temporal and frontal lobes, in persons with autism who had received a long-term cognitive, behavioral, and social treatment of autism. Tang et al. (2012) showed that a mindfulness IBMT training in normal persons led to improved mood and observable alterations of white matter around the anterior cingulate in only two weeks, with further white matter alterations observed after 4 weeks of training. Finally, one study has shown changes in both functional and structural connectivity networks after cognitive remediation therapy for schizophrenia (Penades et al., 2013). Taken as a whole, these findings begin to provide support for the proposal that psychotherapy effects include modulation of connectivity networks in the brain.

Note that if this proposal is correct, it may explain some clinical observations about psychotherapy treatments. One observation has been that many different kinds of psychotherapies can have quite similar outcomes, the so-called Dodo bird verdict (Luborsky et al., 2002). We speculate that although particular psychotherapy treatments may focus on interventions that target specific, relatively narrow psychological/cognitive functions and their associated patterns of regional brain activations, broader effects through the networks of the brain can be expected because the targeted psychological interventions are

instantiated at the level of the brain in a "net" of connectivity networks of brain regions. This postulate represents a neural-level analogue to the frequent observation that specific skills and insights from psychotherapy (and for learning in general) are often observed to generalize over time. If, as Buckholtz and Meyer-Lindenberg proposed, abnormalities of "core connectivity circuits" leads to "transdiagnostic symptoms" in psychological disorders (2012, p. 990), then it is reasonable to postulate that therapeutic modulation of core connectivity networks/circuits can lead to "transpsychotherapeutic" symptom improvement. Whether there are more or less efficient methods for bringing about adaptive changes in brain connectivity for particular disorders or particular types of individuals will be an especially important focus for research over the next decade.

Another interesting observation was from Boswell, Castonguay, & Wasserman's (2010) study of the use of different types of interventions on psychotherapy session outcome. The use of common factors interventions, which highlight therapist/patient relationship components of therapy, and cognitive behavioral interventions were measured. The investigators observed that: "Patients who received more common factor interventions on average rated sessions as less helpful when more CBT interventions were employed" and "using some techniques (i.e. CBT) in the context of a treatment that is highly focused on relationship factors may interfere with therapeutic impact" (Boswell et al., 2010, p. 717, 722). At a psychological level, these authors argued that psychotherapy requires a minimum degree of internal consistency in order to be effective.

Another way to understand this finding is to note that connectivity studies of the brain have identified a negative correlation between the default mode network, subserving interpersonal and self-referential processing, and the cognitive control network (Fox et al., 2005, 2012; Vasic et al., 2009). Thus one hypothesis for Boswell et al.'s finding is that extensive use of both relationship factors and CBT in a session may "interfere" with outcome, at least in the short-term, because the two kinds of interventions have relatively greater dependence on networks of the brain that are anticorrelated. For example, if a CBT intervention activates the patient's cognitive control network this could deactivate the default mode network, but a relationship intervention could require increased activation of regions within the default mode network. One need not take a reductionistic stance to consider this possibility. To some extent this hypothesis could be investigated in existing datasets by examining correlations between the use (or perceived use) of relationship-focused vs. task-focused interventions and changes in activation within the relevant brain networks. However, a study designed a priori to test this model would be ideal.

Overall, although much work is yet required, current evidence supports the value of developing a connectivity network perspective of psychotherapy to contribute to both neurobiological and clinical levels of understanding of psychotherapy. Such a broader perspective on how psychotherapy works at the level of the brain would both complement and extend the more traditional emphasis on task-specific, region-specific changes associated with psychological interventions. We believe that psychotherapy research will benefit enormously from this evolution in analytic perspective currently occurring within cognitive neuroscience as a whole.

Future Studies

Neuroimaging of psychotherapy outcome has clearly shown that psychotherapy leads to observable changes in the brain. Of course, this is hardly surprising to serious students of psychotherapy outcome and process, but the ability to observe and document not only that such changes occur but their specific characteristics and circumstances can only help to improve our understanding of psychotherapeutic processes. However, as Etkin et al. (2005) stated: “the biological study of psychotherapy has barely begun.” Neuroimaging studies of psychotherapy outcome investigating effects shortly after the end of treatment have shown increasingly complex results and effects on brain function and structure. Thus a great deal of work remains for the establishment of replicable neuroimaging findings. In addition, greater attention to psychotherapies other than cognitive behavioral types of therapies, as well as more attention to a wider spectrum of disorders, is needed. We now highlight a few additional ways in which future neuroimaging studies could be further expanded to advance psychotherapy research.

Psychotherapy process

We know almost nothing about the course of changes that occur in the brain during psychotherapy as well as during consolidation or relapse after treatment has ended. This is a pressing clinical need because many disorders, such as depression, have high rates of relapse (DeRubeis, et al., 2008). Two relevant studies, comparing emotion processing in experienced versus novice meditators (Taylor et al., 2011) and longitudinal observations of effects of mindfulness IBMT training in normal persons (Tang et al., 2010), showed that there can be significant changes in the brain during different stages of treatment at least for these interventions. Another study observed that the number of minutes of mindfulness training engaged in by healthy persons was a predictor of brain responses during affective processing (Allen et al., 2012). Brain imaging studies to observe what happens after treatments end can contribute especially to an understanding of the neurobiology of relapse. Mohr et al.’s (2012) study of a cognitive behavioral type of treatment for stress management in multiple sclerosis showed that therapy decreased the number of MRI-observable brain lesions during treatment but the effect had disappeared by 24 weeks after ending therapy.

Hauner et al.’s (2012) study of exposure therapy for treatment of spider phobia also showed differences when comparing results immediately at the end of treatment versus 6 months follow-up. For example, in response to phobogenic stimuli, there was evidence of increased activation in the dorsolateral prefrontal cortex immediately after treatment that suggested “up-regulation” of brain regions subserving emotion regulation and reappraisal. However, after 6 months follow-up this increased activity was no longer observed. On the other hand, investigators observed decreased activity in the amygdala in response to phobogenic stimuli both immediately at the end of treatment as well as at 6 months follow-up. Finally, at 6-months follow-up there were some changes observed for the first time in the visual cortex. Note that these complex results were obtained for effects of an exposure therapy that comprised only a single two hour session. Clearly there is a great deal to be learned in future studies about the time courses of effects on the brain from psychotherapy.

We also know very little about the neurocognitive processes and mechanisms that are activated in response to the multiple events that take place during a psychotherapy session. Here we comment on one aspect of most psychotherapies, namely, that these take place within the structure of interpersonal interactions between patient and therapist. For some psychotherapies this relationship is central to the therapeutic process, for example, by way of interpersonal schema or the transference. And it is likely a universal characteristic of psychotherapy to create and build upon a sense of remoralization and hope as the working relationship begins (Howard, Lueger, Maling, & Martinovic, 1993).

Neuroimaging studies of interpersonal or social cognition comprise one of the most important current fields of inquiry in the neurosciences, and there is a wealth of information from social cognitive neuroimaging that may be useful for psychotherapy researchers (Carhart-Harris et al., 2008; Fonagy & Target, 2007; Gallese et al., 2007; Hruby et al., 2011; Northoff et al., 2007; Siever & Weinstein, 2009; Weston & Gabbard, 2002a, 2002b). Nonetheless, more empirical studies of patient-therapist interactions would be useful. There are a number of models or paradigms that could be applied to the question of how in-session interactions facilitate change. For instance, from a cognitive perspective the therapist (and the interaction itself) can be viewed as a ‘priming’ mechanism that triggers habitual information processing such that the therapist and patient can observe its immediate consequences and analyze them (Merrill & Strauman, 2004). Another perspective, which intersects with developmental models of the ontogeny of the self and interpersonal cognition, is focused on the role of mentalizing, mirroring, and the attachment system in psychotherapy mediated by way of the relationship between therapist and patient (Fonagy & Bateman, 2006; Gallese et al., 2007; Korner, Gerull, Meares, & Stevenson, 2006).

Hyperscanning—With respect to in-session interactions, there is a recent advance in neuroimaging that has not yet been applied to psychotherapy research but may be of special value, namely, hyperscanning. Hyperscanning is the simultaneous neuroimaging of more than one person that affords new opportunities for the study of social interactions (Montague et al., 2002). Chou, Weingarten, Madden, Song, & Chen (2012) highlighted several aspects of hyperscanning that are useful to consider for psychotherapy research. First, as noted by Montague et al. (2002), Dumas (2011), and others, almost all previous brain imaging studies relevant to interpersonal interactions have been based on experiments in which one person is studied alone. This isolation arises from technical requirements of most brain imaging methods, such as restricted head movements during PET and MRI imaging, the small dimensions of MRI scanner bores, etc. Many kinds of social cognitive processing can be studied in an isolated individual, such as memories or schema about interpersonal relationships, emotional responses of the private individual, thinking about what is in an other’s mind, observation of photographs or reading, and imagining or planning how interpersonal relationships might be different. However, even these activities derive from a history of interpersonal interactions in dyads and groups. Ultimately, to gain a solid neurocognitive understanding of interpersonal interactions it will be necessary to conduct brain imaging research on both (or more) persons simultaneously in the midst of real-time interactions (Dumas, 2011; Schilback et al., 2006).

Second, the capability to conduct neuroimaging of two or more persons simultaneously is now being advanced, especially with advances in internet and computing technologies that allow for simultaneous control of and data processing from multiple scanners. The ability to conduct brain imaging on two or more persons simultaneously currently includes fMRI (Montague et al., 2002; Krill & Platek, 2012) as well as EEG and near infrared spectroscopy (NIRS) methods (Cui, Bryant, & Reiss, 2012; Dumas, Nadel, Soussignan, Martinerie, & Garnero, 2010) (Chou et al., 2012). The ability to perform fMRI hyperscanning of two persons has revealed that regions of the reward system, specifically the left caudate and putamen, were activated during cooperation between two persons (Krill & Platek, 2012). This observation would not have been possible without the ability to conduct neuroimaging during an actual verbal interaction. Hyperscanning has also revealed the existence of a phenomenon labeled *interbrain synchronization*. Synchrony in interpersonal interactions had been observed by use of behavioral and physiological measures (Feldman, 2007; Feldman, Magori-Choehn, Galili, Singer, & Louzoun, 2011). For example, studies of synchrony between a child and mother and father have observed synchronization of behaviors and physiological measures. Now, however, synchrony can also be observed for measures of brain activity. Hyperscanning has revealed interbrain synchrony, such as synchronization of alpha-mu band EEG signals from parietal regions during a task of observing another's hand movements (Dumas et al., 2010) and increased coherence of NIRS signals from the frontal regions of participants cooperating in a game (Cui et al., 2012). Interbrain synchrony is an aspect of interpersonal psychological functioning that can only emerge within the real-time experience of two persons interacting.

Finally, EEG and NIRS hyperscanning have technical characteristics that allow for the possibility of conducting studies with both participants physically present to each other (Chou et al., 2012). Social cognitive studies are often conducted using two-dimensional representations of others in photographs, videos, mirrors, etc. rather than direct observation of the other person. It is an open question whether there will be differences in how the brain responds to representations of others versus the real person. For example, brain responses to two-dimensional representations can differ from responses to actual three-dimensional objects and this may be true for persons as well (Snow et al., 2011). MRI, PET, and SPECT methods have technical features that limit whether participants can directly observe other people during scanning. However, EEG and NIRS have better technical possibilities for direct observation of others during scanning (usual or hyperscanning).

One example of how hyperscanning could be applied to the study of psychotherapy process could be for investigations of Resonating Minds Theory (RMT) and the Therapeutic Cycles Model (TCM), which describe models for within-session (or across sessions) process and therapeutic changes that are focused on patient-therapist interactions (McCarthy, Mergenthaler, Schneider, & Grenyer, 2011; Mergenthaler, 2008). Investigation of these models has included simultaneous measures of patient and therapist behaviors (e.g. emotional tone) over the time course of a therapy session. These studies could logically be extended to neuroimaging measures. We also note that RMT and TCM are already informed by neurobiological considerations (Mergenthaler, 2008). Although solutions to the technical complexity and limitations of hyperscanning methods are still being developed it is hopeful

that hyperscanning will become a valuable part of the neuroimaging repertoire. When it does, it may open many possibilities for research into the interpersonal components of psychotherapy.

To summarize, a neuroscience of psychotherapy process is in early stages of development. Here we have highlighted consideration of neuroimaging studies of longitudinal changes as well as probing more deeply into the nature of interpersonal interactions. Advances in neuroimaging technology are increasing possibilities for new approaches to these and other psychotherapy process questions.

Biomarkers and predictors of treatment response

One important trend in recent psychotherapy neuroimaging studies is identification of neuroimaging biomarkers or predictors of treatment response. Identification of predictors of treatment response could ultimately be clinically useful for selection of personalized, individualized treatments. At this time, predictor studies in psychotherapy research are still in early stages of development. Most predictor studies have been based on group results, whereas it is predictions about individuals that will be most clinically useful and about which more studies are required. Further, most predictor studies have not yet been replicated (McGrath et al., 2013). An example of limited replication is Siegle et al.'s (2006) study of predictors of response to CBT treatments of depression that identified biomarkers in the subgenual cingulate and amygdala: Siegle et al. (2012) replicated the finding in the subgenual cingulate but not the amygdala (McGrath et al., 2013). Nonetheless, the current studies are a basis for hope that psychotherapy treatment specific biomarkers will be identified.

If and when neuroimaging biomarkers are identified, although MRI and other kinds of neuroimaging scans are costly it is possible that they may be used to help individuals select treatments of psychological disorders (McGrath et al., 2013; Siegle et al., 2012). In anticipation of this development, a study of patient and provider attitudes towards the use of neuroimaging scans to select an individualized treatment for depression has been conducted (Illes, Lomberg, Rosenberg, & Arnow, 2009). Perhaps surprisingly, patients indicated that neuroimaging would make them *more* likely to consider psychotherapy treatment and *more* likely to address interpersonal contributions to depression. On the other hand, providers thought that brain imaging would lead to more interest in pharmacotherapy. The authors suggested that the support for psychotherapy evidenced by patients might be explained by increased acceptance and decreased stigma around a diagnosis of depression. In any case, the study indicates that there could be a high degree of interest from patients with depression to receive an MRI scan to help select treatment and this could lead to increased patient interest in obtaining psychotherapy treatments.

If and when neuroimaging for persons with depression or other psychological disorders translates from research to the clinical sphere for selection of individualized treatments, there will be need for neuroimaging studies of treatments that could be selected. So far a good body of work has been developing for cognitive behavioral therapies (and pharmacotherapies and brain stimulation methods). More neuroimaging studies of

psychodynamic therapy, as well as interpersonal, self, etc. psychotherapies, will be needed to provide equally strong neuroimaging evidence for selection.

Connectome

Finally, studies of the connectome are redefining our understanding of the neural foundations of normal psychology and psychological disorders. There is growing information on how mental and behavioral tasks influence numerous connectivity networks of the brain, and how psychological disorders show disturbances in these networks. Studies of pharmacotherapies, brain stimulation treatments, and a few psychotherapies have begun to show that treatment effects at the neurobiological level can be mediated by changes in connectivity networks. A study of resting-state functional connectivity as a measure of effects of cognitive behavioral therapy is beginning (Dunlop et al., 2012). Changes in connectivity networks, functional and/or structural, may be key neurobiological outcomes of psychotherapy treatments and it is now timely to directly investigate how psychotherapy affects the connectivity networks of the brain.

Conclusion

The study of psychotherapy outcome and process via neuroimaging is now well established. There is clear evidence that psychotherapy is associated with reliable changes in brain function and structure. Although the overall set of findings is growing and complex, from a functional network perspective there is beginning to be a set of patterns that characterize successful psychotherapy outcome both within and across disorders. Cooperation between psychotherapy researchers and neuroscientists will enhance the progress of this growing field. By understanding how psychotherapy impacts the brain, we can provide better outcomes to our patients and ultimately use the resulting knowledge to develop new ways to maximize the effectiveness of psychological interventions. Our hope is that the present review represents a contribution to that effort. We also are optimistic that, with the rate of growth in psychotherapy neuroimaging research, this review will soon need to be updated.

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Table 1

Neuroimaging studies of psychotherapy

Study	Therapy	Imaging	Results
Depression			
		MRI	
Buchheim 2012 (MDD)	PSY, 15mo	fMRI, pre, post	Attachment picture with personal sentence task showed decreased activation in the left anterior hippocampus/amygdala, subgenual cingulate, and medial prefrontal cortex post-tx
Costafreda 2009 (MDD)	CBT, 16wk	sMRI, pre	Predictor: no predictor of response to CBT tx
Dichter 2009 (MDD)	BAT, 8–14wk	fMRI, pre, post	Reward processing task showed changes in paracingulate gyrus, orbitofrontal gyrus, and caudate post-tx
Dichter 2010 (MDD)	BAT, 8–14wk	fMRI, pre, post	Cognitive control emotion processing task showed decreased activation in paracingulate gyrus, orbitofrontal cortex, and frontal pole post-tx; predictor: activation in paracingulate gyrus pre-tx predicted response to tx
Forbes 2010 (MDD)	CBT, 8wk	fMRI, pre	Predictors: during reward processing task, increased striatal activity during reward anticipation predicted lower level of anxiety symptoms post-tx; increased striatal activity during reward outcome predicted better clinical severity post-tx
Fu 2008 (MDD)	CBT, 16s	fMRI, pre, post	Sad facial processing task showed decreased amygdala and increased dorsal anterior cingulate activity post-tx. Predictor: increased dorsal anterior cingulate activity at baseline predicted greater improvement post-tx
Lehto 2008a (AtD, NAtD)	PSY, 12mo	SPECT, pre, post	Midbrain serotonin transporter density increased post-tx in AtD; striatum dopamine transporter density did not change post-tx
Lehto 2008b (MDD, DD)	PSY, 1yr	SPECT, pre, post	Midbrain serotonin and striatum dopamine transporter binding did not change post-tx
Mackin 2013 (LLD)	PST, 12wk	sMRI, during tx	Nonresponders showed decreased cortical thickness in multiple regions in comparison with tx responders
Ritchey 2011 (MDD)	CBT, 30wk	fMRI, pre, post	Predictors: emotion processing tasks at baseline showed that increased activation in ventromedial prefrontal cortex (overall contrast), and in left anterior temporal lobe/ventrolateral prefrontal and right dorsolateral prefrontal cortices (negative versus positive emotion contrast), predicted greater improvement post-tx
Siegle 2006 (MDD)	CBT, 12wk	fMRI, pre	Predictor: during negative word emotion task, lower subgenual cingulate and higher right amygdala activity predicted better response to tx
Siegle 2012 (MDD)	CBT, 16–20s	fMRI, pre, post	Predictor: during negative word emotion task at baseline, lower subgenual anterior cingulate activation predicted better response to tx
Yoshimura 2013 (MDD)	CBT, 12wk	fMRI, pre, post	Self-referential processing task showed increased activation for positive stimuli or decreased activation for negative stimuli in the medial prefrontal and ventral anterior cingulate cortices
		PET	
Brody 2001a (MDD) (B, F, K, L, R)	IPT, 12wk	PET-FDG, pre, post	Resting metabolism in right prefrontal cortex and left anterior cingulate gyrus decreased post-tx; in left temporal lobe resting metabolism increased post-tx
Brody 2001b (MDD) (R)	IPT, 12wk	PET-FDG, pre, post	Resting metabolism in ventral frontal lobe, ventral anterior cingulate gyrus, and anterior insula decreased with improved mood; in dorsolateral prefrontal cortex resting metabolism increased with improved cognition
Goldapple 2004 (MDD) (B,F,K,L,R)	CBT,15–20s	PET-FDG, pre, post	Resting metabolism increased in hippocampus and dorsal cingulate and decreased in dorsal, medial, and ventral frontal cortex post-tx

Study	Therapy	Imaging	Results
Hirvonen 2011 (MDD)	PSY, 16wk	PET, pre, post	Dopamine receptor binding did not change in striatum or thalamus post-tx
Karlsson 2010 (MDD)	PSY, 16wk	PET, pre, post	Serotonin receptor binding increased post-tx
Kennedy 2007 (MDD)	CBT, 16wk	PET-FDG, pre, post	Resting metabolism decreased in bilateral lateral orbitofrontal, left dorsomedial prefrontal, posterior cingulate, and right thalamus; increased in subgenual cingulate, right inferior occipital and occipital-temporal, and left inferior temporal regions post-tx
Konarski 2009 (MDD)	CBT, 16wk	PET-FDG, pre	Predictor: increased resting metabolism in the pregenual/subgenual anterior cingulate region predicted nonresponse to tx
McGrath 2013 (MDD)	CBT, 12wk	PET-FDG, pre	Predictors: in the right anterior insula, decreased resting metabolism predicted remission after CBT treatment while increased metabolism predicted remission after escitalopram pharmacotherapy
		SPECT	
Amsterdam 2013 (MDD)	CBT, 12wk	SPECT, pre, post	Serotonin transporter binding increased in bilateral medial temporal lobes post-tx
Martin 2001(MDD) (B, F, K, L, R)	IPT, 16wk	SPECT, pre, 6wk	Resting blood flow in right basal ganglia and posterior cingulate increased at 6 weeks of tx
Obsessive Compulsive Disorder			
Nakatani 2003 (F, K, L, R)	BT, variable	CT-Xe, pre, post	Resting blood flow in right caudate decreased post-tx
		MRI	
Freyer 2011	CBT, 8–12wk	fMRI, pre, post	Strategy switching task showed increased activation in right putamen and caudate post-tx; smaller changes in right pallidum post-tx correlated with greater clinical improvement
Hoexter 2012	CBT, 12wk	sMRI, pre, post	Orbitofrontal, anterior cingulate, temporolimbic, striatum or thalamus regional volumes did not show changes post-tx
Hoexter 2013	CBT, 12wk	sMRI, pre	Predictor: larger volume in right medial prefrontal predicted response to tx
Huyser 2010 (child)	CBT, 16s	fMRI, pre, post	Tower of London task showed increased activation in left dorsolateral prefrontal and parietal cortices post-tx
Nabeyama 2008	BT, 12wk	fMRI, pre, post	Stroop task showed increased activation in cerebellum and parietal cortex and decreased activation in orbitofrontal cortex, middle frontal gyrus, and temporal regions post-tx
Nakao 2005 (K, L)	BT, 12wk	fMRI, pre, post	Provocation task showed decreased activation in orbitofrontal, dorsolateral prefrontal, and anterior cingulate cortices post-tx; Stroop task showed increased activation in cerebellum and parietal cortex post-tx
O'Neill 2012 (child)	CBT, 12wk	^{1}H-MRS, pre, post	Predictors: baseline N-acetyl compounds, glutamine and glutamate, and myo- inositol levels in left thalamus predicted response to tx
O'Neill 2013	CBT, 4wk	^{1}H-MRS, pre, post	Predictors: baseline N-acetyl compounds in right pregenual anterior cingulate cortex predicted response to tx
Whiteside 2012a	BT, 8wk	^{1}H-MRS, pre, post	Increased N-acetyl aspartate in left caudate post-tx; changes in levels of many neurochemicals correlated with changes in symptom measures
Whiteside 2012b (child)	BT, 10–18s	^{1}H-MRS, pre, post	Decreased glutamine and glutamate levels in right caudate post-tx
Zurowski 2012	inCBT, 3 mo	^{1}H-MRS, pre, post	Predictor: myo-inositol in right orbitofrontal cortex predicted response to tx
		PET	
Apostolova 2010	CBT, 40s	PET-FDG, pre, post	Resting metabolism in right caudate increased post-tx
Baxter 1992 (F, K, L, R)	BT, 10wk	PET-FDG, pre, post	Resting metabolism in right caudate decreased post-tx

Study	Therapy	Imaging	Results
Brody 1998 (R)	BT, 8–12wk	PET-FDG, pre	Predictor: higher resting metabolism in left orbitofrontal cortex predicted greater response to tx
Saxena 2009	CBT, 4wk	PET-FDG, pre, post	Resting metabolism decreased bilaterally in thalami and increased in right dorsal anterior cingulate post-tx
Schwartz 1996 (B, F, K, L, R)	CBT, 10wk	PET-FDG, pre, post	Resting metabolism in bilateral caudate decreased post-tx
		SPECT	
Yamanishi 2009	BT, 12wk	SPECT, pre, post	Predictor: increased blood flow in bilateral orbitofrontal cortex at baseline predicted greater response to tx
Schizophrenia			
		MRI	
Bor 2011	CRT, 7wk	fMRI, pre, post	Spatial n-back task showed increased activation in left inferior and middle frontal gyri, cingulate, inferior parietal lobule/precuneus post-tx
Eack 2010	CET, 2yr	sMRI, pre, post	Increased volumes in left hippocampus, parahippocampal gyrus, fusiform gyrus, and amygdala post-tx
Haut 2010	REM, 4–6wk	fMRI, pre, post	Working memory tasks showed increased activation in bilateral frontopolar, anterior cingulate, and left dorsolateral prefrontal cortex regions post-tx
Keshavan 2011	CET, 2yr	sMRI, pre	Predictor: larger cortical surface area and gray matter volume predicted faster social cognitive response to tx
Kumari 2009	CBT, 6–8mo	fMRI, fcMRI, pre	Predictors: during working memory task, increased activation in dorsolateral prefrontal cortex and increased dorsolateral prefrontal cortex-cerebellum connectivity predicted better response to CBT
Kumari 2010	CBT, 6–8mo	fMRI, pre	Predictors: during monitoring of voices task, increased activation in left inferior frontal gyrus, thalamus, and precuneus predicted better response to tx; decreased deactivation in inferior parietal and medial prefrontal regions predicted better response to tx
Kumari 2011	CBT, 6–8mo	fMRI, pre, post	Facial anger and fear emotions task showed decreased activation in inferior frontal, insula, thalamus, putamen, and occipital regions post-tx
Penades 2013	CRT, 4m	fcMRI, DTI, pre, post	N-back test showed normalization of activation patterns in the central executive and default mode networks post-tx; increased fractional anisotropy in genu of the corpus callosum post-tx
Premkumar 2009	CBT, 6–8m	sMRI, pre	Predictors: increased gray matter volumes of right cerebellum (lobule VII), inferior parietal lobule, superior temporal gyrus, left precentral gyrus, cuneus, and cerebellum (Crus I) predicted response to tx
Wykes 2002 (R)	CRT, 12wk	fMRI, pre, post	Verbal working memory task showed increased activation in frontal and occipital regions post-tx
		SPECT	
Penades 2002 (R)	NPR, 12wk	SPECT, pre, post	Tower of London task showed increased blood flow in prefrontal regions post-tx
Other conditions			
		MRI	
Beutel 2010 (Panic)	inPSY, 4wk	fMRI, pre, post	Negative emotion tasks showed increased activation in amygdala and hippocampus and decreased activation in prefrontal regions pre-tx that normalized post-tx
Bryant 2008a (PTSD)	CBT, 8s	fMRI, pre	Predictor: during facial expression of fear task, increased activation in amygdala and ventral anterior cingulate regions predicted poor response to tx
Bryant 2008b (PTSD)	CBT,8wk	sMRI, pre	Predictor: larger rostral anterior cingulate cortex predicted response to tx
DeGreck 2011 (Somato)	inPSY, 60d	fMRI, pre, post	Rewarding versus nonrewarding task activations normalized in left postcentral gyrus and right ventroposterior thalamus post-tx

Study	Therapy	Imaging	Results
DeLange 2008 (CFS)	CBT, 6–9mo	sMRI, pre, post	Grey matter volume in lateral prefrontal cortex increased post-tx
DeVito 2012 (SUD)	CBT, 8wk	fMRI, pre, post	Stroop task showed decreased activation in anterior cingulate, inferior frontal gyrus, and midbrain post-tx
Doehrmann 2013 (SAD)	CBT, 12 wk	fMRI, pre	Predictors: during facial and emotion processing task, increased activity in dorsal and ventral occipitotemporal cortices predicted response to tx
Felmingham 2007 (PTSD) (F, K)	CBT, 8wk	fMRI, pre, post	Fear processing task showed increased activation in rostral anterior cingulate activity and decreased activation in right amygdala post-tx
Han 2012 (OLG addiction)	family tx, 3 wk	fMRI, pre, post	Parental love visual stimulation task showed increased activation in right caudate nucleus post-tx
Hauner 2012 (Ph-spider)	exposure tx, 1s	fMRI, pre, post, 6mo	Spider image viewing task showed increased activation in right dorsolateral prefrontal cortex and decreased activation in amygdala, insula, cingulate, and ventromedial prefrontal cortex post-tx; decreased activation in right dorsolateral prefrontal cortex and bilateral fusiform/lingual gyrus regions 6 months post-tx. Predictors: right lingual gyrus activation during the spider image viewing task immediately post-tx predicted response to tx after 6 months
Jensen 2012 (Fibromy)	ACT, 12wk	fMRI, fcMRI, pre, post	Pain task showed increased activation in left inferior frontal gyrus post-tx; increased ventrolateral prefrontal–thalamic connectivity post-tx
Kircher 2013 (Panic)	CBT, 12s	fMRI, fcMRI, pre, post	Fear conditioning task showed decreased activation in left inferior frontal gyrus post-tx; task based functional connectivity did not show changes post-tx
Klumpp 2013 (SAD)	CBT, 12wk	fMRI, pre, post	Predictors: during a fearful face emotion task pre-tx, activations in superior and middle temporal and inferior frontal gyri, dorsal anterior cingulate, dorsomedial prefrontal and orbitofrontal regions predicted response to tx
Lindauer 2005 (PTSD)	BEP, 4mo	sMRI, pre, post	Hippocampal volumes showed no change after tx
Maslowsky 2010 (GAD)	CBT, 8wk	fMRI, pre, post	Facial emotions task showed increased right ventrolateral prefrontal cortex activity post-tx
Mohr 2012 (MS)	SMT, 24wk	GdMRI, pre, 24wk post	Gd enhancing brain lesions decreased during tx, but not sustained post-tx
Paquette 2003 (Ph-spider) (B, F, K, L, R)	CBT, 4wk	fMRI, pre, post	Spider film viewing task showed decreased activation in right dorsolateral prefrontal cortex and parahippocampal gyrus post-tx
Pardini 2012 (Autism)	CT, BT, AAC, 6yr	DTI-MRI	Increased uncinate fasiculus fractional anisotropy correlated with more tx
Schienle 2007 (Ph-spider)	CBT, 1s	fMRI, pre, post	Spider image viewing task showed increased activation in medial orbitofrontal cortex post-tx; symptom reduction correlated with decreased activations in right amygdala and left insula.
Schienle 2009 (Ph-spider)	CBT, 1s	fMRI, pre, 6 mo post	Spider image viewing task showed increased activation in medial orbitofrontal cortex at 6 months post-tx
Schnell 2007 (BPD) (K)	inDBT, 12wk	fMRI, pre, post	Emotion arousal task showed decreased activation in left amygdala and bilateral hippocampi post-tx
Siniatchkin 2012 (ADHD)	RCT, 10d	fMRI, pre, post	Go/No-go task showed increased activation in anterior cingulate and dorsolateral prefrontal cortex regions post-tx
Straube 2006 (Ph-spider) (B, F, K, L)	CBT, 2s	fMRI, pre, post	Spider film viewing task showed decreased activation in insula and anterior cingulate cortex post-tx
Van Paasschen 2013(AD)	CR, 8wk	fMRI, pre, post	Face-name recognition task showed increased activation in bilateral insula, left middle frontal and right angular gyri post-tx
Vocks 2011 (eating)	CBT, 10wk	fMRI, pre, post	Body image viewing task showed increased activation in left middle temporal and bilateral middle frontal gyri post-tx
		PET	

Study	Therapy	Imaging	Results
Cervenka 2012 (SAD)	CBT, 15wk	PET, pre, post	Greater change in dopamine receptor binding potential in medial prefrontal cortex and hippocampus correlated with decreased anxiety post-tx
Förster 2011 (MCI, AD)	CI, 6mo	PET-FDG, pre, post	Resting metabolism showed less decline post-tx in comparison with controls
Furmark 2002 (Ph-social) (F, K, L, R)	CBT, 9wk	PET-H20, pre, post	Public speaking task showed decreased blood flow in bilateral amygdala hippocampus, and surrounding regions post-tx
Praško 2004 (Panic) (B, F, K, L)	CBT, 3 mo	PET-FDG, pre, post	Resting metabolism increased in left brain but decreased in right brain regions
Sakai 2006 (Panic) (K)	CBT, 6mo	PET-FDG, pre, post	Resting metabolism decreased in right hippocampus and left anterior cingulate, cerebellum, pons post-tx; increased in bilateral medial prefrontal cortex post-tx
		SPECT	
Laatsch 1999 (TBI) (R)	CRhT, 6–36s	SPECT, pre, end, 3–12mo post	Resting blood flow in multiple regions increased post tx
Lindauer 2008 (PTSD)	BEP, 16wk	SPECT, pre, post	Personal trauma script listening task showed decreased activation in the right middle frontal gyrus post-tx
Peres 2007 (PTSD)	exposure tx, 8wk	SPECT, pre, post	Memory retrieval task showed increased activation in bilateral parietal and left prefrontal, thalamus, and hippocampus regions, and decreased activation in left amygdala post-tx

Notes. Neuroimaging studies of psychotherapy treatments. **Study.** First author of each study is given. Note is made if the study was included in reviews by (B) Beauregard (2007), (F) Frewen et al. (2008), (K) Karlsson (2011), (L) Linden (2006), (R) Roffman et al. (2005). (Child) = pediatric study. (Conditions): AD = Alzheimer's disease, ADHD=attention deficit hyperactivity disorder, AtD = atypical depression, BPD = borderline personality disorder, CFS = chronic fatigue syndrome, DD = double depression, fibromy = fibromyalgia, GAD = generalized anxiety disorder, LLD= late life depression, MCI = mild cognitive impairment, MDD = unipolar depression, major depression, major depressive disorder, MS = multiple sclerosis, NAtD = Non atypical depression, OLG addiction = on-line game addiction, Ph = phobia, PTSD = posttraumatic stress disorder, SAD = social anxiety disorder, somato = somatoform disorder, SUD = substance use disorder, TBI = traumatic brain injury. **Therapy.** In = in-patient therapy; d = days, mo = months, s = sessions, wk = weeks, yr = years. AAC = augmentative and alternative communication therapy, ACT = acceptance and commitment therapy, BAT = behavioral activation therapy, BEP = brief eclectic psychotherapy, BT = behavioral therapy, CBT = cognitive or cognitive behavioral therapy, CET = cognitive enhancement therapy, CI = cognitive intervention, CR = cognitive rehabilitation, CRhT = cognitive rehabilitation therapy, CRT= cognitive remediation therapy, DBT = dialectic behaior therapy, IPT = interpersonal therapy, NPR = neuropsychological rehabilitation, PST = problem solving therapy, PSY = psychodynamic psychotherapy, RCT = response cost and token approach, REM = cognitive remediation training, SMT = stress management therapy. **Imaging.** CT-Xe = xenon enhanced computed tomography, DTI-MRI = diffusion tensor imaging magnetic resonance imaging, fMRI = functional MRI, fcMRI = functional connectivity MRI, GdMRI = gadolinium enhanced MRI, ^{1}H-MRS = proton magnetic resonance spectroscopy, PET = positron emission tomography, PET-FDG = PET fluorodeoxyglucose, sMRI = structural MRI, SPECT = single photon emission computed tomography. Pre = scans conducted before therapy; post = scans conducted at or immediately after the end of therapy; specified length of time indicates longer-term follow-up scans. **Results.** A few examples of results from each study are presented.

Table 2

Other psychological therapies: mindfulness, meditation, yoga

Study	Therapy	Imaging	Results
		MRI	
Allen 2012 (healthy)	MT, 6wk	fMRI, pre, post	Affective Stroop task showed increased activation in dorsolateral prefrontal cortex during executive processing post-tx; predictor: during negative emotion processing, increased minutes of MT practice predicted increased activation in dorsolateral prefrontal, anterior insula, and medial prefrontal regions
Brewer 2011 (healthy)	C, CA, LK, >10yr	fMRI, fcMRI, post	Meditation task showed decreased activation in medial prefrontal and posterior cingulate cortices; resting or meditation showed increased functional connectivity between posterior cingulate, dorsal anterior cingulate, and dorsolateral prefrontal cortex
Farb*2010 (stress)	MBSR, 8wk	fMRI, post	Sad movie viewing task showed decrease responses in cortical midline regions and Wernicke's and Broca's language regions post-tx
Goldin*2010 (SAD)	MBSR,2mo	fMRI, pre, post	Breath attention task showed increased activation in parahippocampus, middle occipital gyrus, inferior and superior parietal lobule, cuneus/precuneus post-tx
Holzel*2010 (stress)	MBSR, 8wk	sMRI, pre, post	Decreased gray matter density in right basolateral amygdala post-tx
Jang 2011 (healthy)	BWVM, 40mo	fcMRI, post	Resting state showed increased functional connectivity to medial prefrontal cortex area within default mode network
Josipovic 2012 (healthy)	FA, NDA, >8yr	fcMRI, post	Focused attention meditation task showed increased anti-correlation of functional connectivity between extrinsic (task positive) and intrinsic (task negative, default mode) networks; nondual awareness task showed decreased anti-correlation between extrinsic and intrinsic networks
Kilpatrick*2011 (healthy)	MBSR, 8wk	fcMRI, post	Listening task showed increased functional connectivity in auditory and visual networks; increased anti-correlations between auditory and visual cortex, and between auditory cortex and anterior default mode network post-tx
Luders 2011 (healthy)	M, 5–46yr	DTI-MRI, post	Increased fractional anisotropy in superior longitudinal fasiculus, corticospinal tract, uncinate fasiculus
Luders 2012 (healthy)	M, 5–46yr	sMRI, DTI-MRI, post	Increased corpus callosum thickness and fractional anisotropy
Lutz 2013 (healthy)	M, 1s	fMRI, post	Emotional expectation task showed increased prefrontal activation post-tx; dorsomedial prefrontal and insula activations decreased with increasing trait mindfulness
Tang 2012 (healthy)	IBMT, 2wk, 4wk	DTI-MRI, pre, post	Regions around the anterior cingulate gyrus showed decreased axial diffusivity after 2weeks tx; decreased radial diffusivity and increased fractional anisotropy after 4 weeks tx
Taylor 2011 (healthy)	Zen, >1000hr; MM, 7d	fMRI, post	Mindful emotion processing tasks showed that activations decreased in medial prefrontal and posterior cingulate cortices in experienced meditators; decreased in left amygdala in beginners
Wang 2011(healthy)	Kun, >30yr	ASL-MRI	Meditation task showed changes in blood flow in frontal, anterior cingulate, limbic, and parietal lobes
		SPECT	
Moss*2012 (MCI)	KK, 8wk	SPECT, pre, post	Resting blood flow increased in multiple regions post-tx and correlated with changes in measures of tension, depression, fatigue, and anger

Notes. Neuroimaging studies of other psychological interventions (mindfulness, meditation, yoga) selected from studies published 2010 to present.

*study identified from Pubmed searches. tx= therapy or intervention.

Study. First author of each study is given. (Condition): MCI = mild cognitive impairment, SAD = social anxiety disorder, stress = normal participants seeking stress reduction programs. **Therapy.** D = days, hr = hours, mo =months, s=sessions, wk = weeks, yr = years. BWVM = brain wave vibration mind-body, C = concentration meditation, CA = choiceless awareness meditation, FA = focused attention,

IBMT = integrative body-mind training, KK = Kirtan kriya, Kun = kundalini yoga, LK = loving kindness meditation, M = meditation unspecified, MBSR = mindfulness-based stress reduction, MT = mindfulness training, NDA = nondual awareness. **Imaging**. ASL – MRI = Arterial spin labeling magnetic resonance imaging, DTI-MRI = diffusion tensor imaging MRI, fMRI = functional MRI, fcMRI=functional connectivity MRI, sMRI = structural MRI, SPECT=single photon emission computed tomography. **Results.** A few examples of results from each study are presented.