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Madeline M. Carrig^a; Gregory G. Kolden^b; Timothy J. Strauman^a

^a Department of Psychology and Neuroscience, Duke University, Durham, North Carolina ^b Department of Psychology and Psychiatry, University of Wisconsin-Madison, Madison, Wisconsin, USA

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PSYCHOTHERAPY RESEARCH METHODS

Using functional magnetic resonance imaging in psychotherapy research: A brief introduction to concepts, methods, and task selection

MADELINE M. CARRIG¹, GREGORY G. KOLDEN², & TIMOTHY J. STRAUMAN¹

¹*Department of Psychology and Neuroscience, Duke University, Durham, North Carolina* & ²*Departments of Psychology and Psychiatry, University of Wisconsin–Madison, Madison, Wisconsin, USA*

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Abstract

Functional magnetic resonance imaging (fMRI) has become an increasingly important methodology in the study of psychotherapy outcome and process. In this article, the authors offer a brief introduction to the use of fMRI in psychotherapy research aimed primarily at the informed clinician or investigator and with the goal of facilitating an understanding of study design and interpretation of research findings. After introducing the method and offering a rationale for its use in the study of psychotherapy, the authors outline major issues in fMRI data collection and analysis and emphasize the central role of the tasks used during the imaging session as critical to the interpretation of findings. They discuss how task selection influences the conclusions that can be drawn from fMRI studies of psychotherapeutic intervention and close with recommendations and caveats for the consumer of fMRI/psychotherapy research.

Keywords: technology in psychotherapy research & training; neuroscience; functional magnetic resonance imaging

Neuroimaging methods allow for assessment of brain function and provide a valuable means for examining the associations among neurobiology, cognition, and behavior. Moreover, these methods offer psychotherapy researchers the opportunity to examine brain-based pretreatment predictors of outcome as well as whether and how patterns of brain activation change or “normalize” as a function of treatment. In this article, we introduce one widely used neuroimaging method, functional magnetic resonance imaging (fMRI), and describe its current use in psychotherapy research. In brief, fMRI is a noninvasive technique for measuring how blood flow changes over time in areas of the brain, typically in response to a predetermined set of stimuli or tasks. As an adaptation of structural MRI, fMRI uses a combination of strong magnetic fields, radio waves, and computers to measure subtle changes in oxygen utilization from moment to moment that are presumed to correspond to variability in activation in specific brain regions. In turn, fMRI assumes that

changes in local activation in areas of the brain are correlated with changes in mental activity that can be specified under experimental conditions.

Testing Hypotheses About the Brain in Psychotherapy Research

Although efficacy studies have been a primary focus of psychotherapy researchers, it is also important to examine mediators of treatment response—intervening variables that may account statistically for the influence of the independent variable on the dependent variable—and mechanisms of treatment response—the intervening processes or events that are responsible for the observed changes associated with the treatment (Kazdin, 2007). One common potential mediator in psychotherapy research is mental activity in its various forms: for example, attention, social cognition, decision making, emotion, and attribution. The range of methods available for studying treatment-associated changes in mental

Correspondence concerning this article should be addressed to Madeline Carrig, Department of Psychology and Neuroscience, Duke University, Durham, NC 27708, USA. E-mail: madeline.carrig@duke.edu

activity is as broad as the range of measures of such activity; and, indeed, psychotherapy researchers have been creative in their use of such measures to determine whether a given treatment leads to predictable changes in some presumably important mental process (e.g., Marci & Riess, 2005; Merrill & Strauman, 2004).

With the recent emergence of noninvasive methods for assessment of brain function, researchers now have an additional methodological option: to observe neurophysiological correlates of mental processes as they occur (Huettel, Song, & McCarthy, 2004). Neuroimaging techniques do not replace behavioral measures of mental activity. Rather, when used properly, they complement such measures by allowing for assessment of functional associations among hypothesized mental processes, brain activity, and behavioral outcomes (Frewen, Dozois, & Lanius, 2008). However, neuroimaging techniques also bring additional complexity (at both conceptual and methodological levels) to psychotherapy research, and our intent in this article is to offer a brief primer for the interested reader.

Not surprisingly, there is some skepticism about the introduction of neuroimaging techniques to the study of psychotherapy outcome and process. Does not the use of such measures at least implicitly diminish the importance of the psychological and interpersonal levels of analysis in studying psychotherapy? Are we not we simply “biologizing” what is clearly a uniquely human interaction? We prefer to take a more positive view, namely that demonstrating the impact of psychotherapy on mental processes and their neural correlates has the potential to improve both our understanding of how psychotherapy works and the effectiveness of psychotherapy as an intervention for disorders, personal problems, and relationships (Rizq, 2007). Reviews of studies conducted to date suggest that neuroimaging can elucidate the effects of psychotherapy on both mental processes implicated in a range of disorders and on brain functions associated with those processes (Frewen et al., 2008; Roffman, Marci, Glick, Dougherty, & Rauch, 2005). Integrating neuroimaging techniques into studies of psychotherapy process and outcome can help to overcome the unfortunate dualistic presumption that mental disorders are ultimately “brain disorders” and, therefore, only a “biological” intervention is appropriate. Rather, the available data indicate that psychotherapy can have a profound effect at levels of analysis from the molecular to the interpersonal (Brenner, Roder, & Tschacher, 2006; Etkin, Pittenger, Polan, & Kandel, 2005).

Rationale for the Use of fMRI in Psychotherapy Research

What justifies the added cost and complexity of fMRI in psychotherapy process or outcome research? In our view, the ultimate justification for the use of any physiological measure is its relation to the psychological constructs of interest (Cacioppo et al., 2003). For example, one might want to focus on the impact of psychotherapeutic intervention on some aspect of psychopathology potentially associated with distinct patterns of brain activity, such as anhedonia, rumination, or obsessions. Similarly, an investigator might want to use fMRI to test hypotheses about how psychotherapy leads to cognitive restructuring or insight. As long as the constructs of interest can be associated reliably with patterns of brain activation, fMRI is potentially valuable, assuming, as we argue later, that the task selected for use during scanning is appropriate for testing hypotheses that link mental activity and brain activity.

Issues in fMRI Data Collection and Analysis

Data Collection and Preprocessing

Huettel et al. (2004) provide an excellent, and accessible, overview of the physics of MRI and the biological underpinnings of the fMRI signal. In brief, fMRI takes advantage of the differing magnetic properties of oxygenated and deoxygenated hemoglobin. As the activity of neurons in the brain increases, their metabolic requirements also increase. One major source of metabolic fuel is oxygen, which is bound to hemoglobin molecules. When the body's vascular system delivers fuel to the brain cells in areas of increased activity, there is a local increase of oxygenated hemoglobin, and deoxygenated hemoglobin is flushed from the surrounding vessels. The relative increase in levels of oxygenated hemoglobin, together with a corresponding decrease in levels of deoxygenated hemoglobin, causes a local increase in the MR signal that is captured by the MRI scanner. To reflect that fMRI pinpoints locations of increased metabolic activity, fMRI data are often characterized as measuring a blood oxygen level-dependent (BOLD) contrast effect (Ogawa, Lee, Nayak, & Glynn, 1990). Hence, fMRI measures the metabolic sequelae of neuronal activity, and not such activity itself. The precise mechanisms underlying the BOLD MR signal are still not fully understood (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001); however, there is good evidence for a consistent association between the BOLD response and neuronal and synaptic activity (cf. Logothetis, 2003).

In a brain location that is responsive to the experimenter's stimulus, a characteristic curve (called the hemodynamic response) is often hypothesized to describe MR signal change over time. This curve is associated with a slight initial dip followed quickly by a noticeable increase in signal from the prestimulus baseline as blood flow, and blood oxygenation, to the stimulated area increases following the onset of neuronal activity. The BOLD response typically begins approximately 2 s after exposure to stimulus and then ramps up over the course of approximately 6 s to a new signal plateau (Buxton, 2002), with the MR signal then eventually returning to baseline. Note that the amplitude of the observed hemodynamic response might be expected to vary across participants and across areas of the brain, and that the response could be hypothesized to vary as a function of some covariate, such as experimental condition.

The amount of fMRI data collected for even a single participant within the context of a single scanner session is large. A single scanner session typically consists of multiple runs; within each run, functional data are composed of a series of volumes acquired over time. The number of volumes per run is determined by the repetition time (TR), which is usually set by the experimenter to equal between 1 and 3 s. Each volume consists of a set of two-dimensional functional images, or slices; the number of slices per volume can range from one (when a specific brain region is of particular interest) to 25 or more. Each slice is itself composed of thousands of volume elements, or voxels; the number of voxels per slice is greatly impacted by the MRI scanner resolution (with higher resolutions leading to larger numbers of voxels per slice). Overall, then, each run from a single scanner session results in a four-dimensional array of fMRI data, with each data point reflecting the BOLD contrast-associated signal level corresponding to a single horizontal coordinate (X), vertical coordinate (Y , with X and Y together defining a unique voxel), slice (Z), and point in time (V). For a session using a relatively large 3-s TR and ten 6-min runs, this $X \times Y \times Z \times V$ matrix might achieve, for example, a size of $64 \times 64 \times 25$ (slices) $\times$ 1200 (volumes), reflecting a total of nearly 125 million data points per session. If a unique area (defined by X , Y , and Z) is associated with increased neuronal activity poststimulus, signal change in the area may be hypothesized to follow the characteristic hemodynamic response curve described previously when the data are plotted as a time series (i.e., across values of V).

After a scanner session is concluded and the spatial functional data have been encoded and stored electronically, a collection of steps commonly referred to as *preprocessing* is undertaken to prepare the fMRI data for analysis. The goals of preprocessing are twofold.

The first aim of preprocessing is to remove error variance from the data that results from the temporal and spatial inconsistencies inherently associated with fMRI data acquisition. Recommended procedures can include distortion correction, head motion correction, and slice timing correction. If multiple participants' data are to be compared within or across studies, preprocessing might also involve coregistration, which involves linkage of functional images and structural images such that functional activity can be correctly localized, or spatial normalization, which maps participants' functional data onto a space (brain) of a common size and shape (e.g., Talairach space; Talairach & Tournoux, 1988). A second goal of preprocessing is to prepare the fMRI data for statistical analysis. Relevant procedures include smoothing, which uses a mathematical algorithm to blur any "sharp edges" in the activity data across the brain space. The wise experimenter will collaborate with a seasoned imaging methodologist to ensure accurate completion of all necessary preprocessing steps.

Properties of fMRI as an Assessment Technique

Most of the traditional assessment tools of the behavioral sciences, such as self-report inventories and observational coding, are recognized to be vulnerable (to varying degrees) to unreliability, bias, and artifact because of the involvement of the fallible human in the measurement of the desired construct. This is no less the case for imaging data. Those interested in incorporating fMRI in designs for the study of psychotherapy will wish to consider the measure's sensitivity and reliability.

Sensitivity. In a single time point design, the experimenter must consider whether the fMRI measure is sensitive to the changes hypothesized to occur upon stimulus presentation. In the context of within-subjects psychotherapy research, another aspect of the sensitivity of fMRI data should be considered: namely, whether this assessment tool adequately captures the type and magnitude of change expected over time (e.g., before and after, or along the course of, some psychological treatment). Multiple sources contribute to the error variability ("noise") that is present in fMRI data and thereby impact on the observed sensitivity of fMRI. These include error variance attributable to the physical properties of the scanning system, head motion, and non-task-related physiological processes such as heartbeat and respiration (note that the preprocessing steps described previously can remove some, but not all, such variability; see Huettel et al., 2004). Other important sources of error variability in fMRI data include non-task-related variability in neuronal activity (e.g.,

neural response to hearing scanner sounds during data collection) and variability across participants, and/or across time, in behavior and cognition in response to an experimental stimulus. The latter form of variability can arise from (a) differences in levels of attention across participants and/or intraindividual fluctuations in arousal and attention over time (e.g., Specht, Willmes, Shah, & Jäncke, 2003); (b) inter- or intraparticipant variability in reaction time; and (c) inter- or intraparticipant variability in strategy choice in response to a particular experimental task (Huettel et al.). Such performance-related variability might be expected to increase in magnitude as the complexity of the experimental task increases (see, e.g., McGonigle et al., 2000). Thus, as a general rule, the stimulus set or behavioral task(s) used in fMRI research should be designed to elicit the maximum possible “signal” in terms of differences in brain activation associated with different responses or stimulus characteristics.

Reliability. Whether a measure possesses adequate test-retest reliability is of critical importance to the psychotherapy researcher who uses within-subjects designs, given the strong impact of reliability on statistical power in studies of change over time (e.g., Venter & Maxwell, 1999). Multiple studies have provided data relevant to assessment of the test-retest reliability of the fMRI measure (e.g., Aron, Gluck, & Poldrack, 2006; Friedman et al., 2008; Genovese, Noll, & Eddy, 1997; Kiehl & Liddle, 2003; Kong et al., 2007; Kurland et al., 2004; Loubinoux et al., 2001; Maitra, Roys, & Gullapalli, 2002; Manoach et al., 2001; McGonigle et al., 2000; Rombouts et al., 1997; Specht et al., 2003; Stark et al., 2004; Wei et al., 2004; Yoo, Wei, Dickey, Guttmann, & Panych, 2005; Zou et al., 2005). Such studies have involved a reasonable range of participant populations, experimental tasks, lengths of delay between test and retest, dependent measures (e.g., voxel-based vs. region-based activation levels), and approaches to the evaluation of reliability (e.g., numerical estimates vs. qualitative comparison of patterns of activation at test and retest). Although some have questioned the extent to which fMRI assessments are sufficiently stable over time (e.g., Chee, Lee, Soon, Westphal, & Venkatraman, 2003), studies providing the familiar intraclass correlation coefficient (ICC; Shrout & Fleiss, 1979) as a numerical estimate of fMRI's test-retest reliability have often concluded that fMRI is associated with reliabilities in the good to excellent range. Friedman et al. (2008), for example, scanned five participants in 10 MRI scanners on two consecutive days and computed a median test-retest ICC for percentage signal change of .76 (25th percentile = .67; 75th percentile = .83). Likewise,

Aron et al. (2006) scanned eight healthy adult participants on two occasions one year apart, yielding several ICCs that exceeded .80. Note, however, that studies addressing the reliability of fMRI have in general involved small sample sizes both at the participant and session levels; larger studies that provide confidence intervals for computed reliability estimates are needed.

Statistical Analysis of fMRI Data

Several different categories of approaches to the analysis of fMRI data have been developed and applied in empirical studies. Many of these approaches fall under the umbrella of the general linear model (GLM). Common voxel-based strategies include (a) the simple *t* test, which in the case of fMRI data analysis would involve evaluating whether a particular voxel is associated with poststimulus activation that exceeds some chosen threshold; (b) correlation analysis (Bandettini, Jesmanowicz, Wong, & Hyde, 1993), which evaluates the extent of linear association between the observed MR signal time course at some voxel(s) and a selected model response function (e.g., a trapezoid or other function that captures the delay, ramps, and return to baseline of the expected BOLD response; Buxton, 2002); (c) Fourier analysis (e.g., Sereno et al., 1995), which uses sine wave functions to model the periodic nature of the MR signal across experimental task and nontask blocks; and (d) the “full” GLM approach to modeling fMRI data (Friston et al., 1995), which allows for the inclusion of multiple explanatory factors (i.e., covariates) in prediction schemes. Mixed models view participants' responses as a random sample from a larger population of responses, allowing for statistical inferences of greater generality (Wells & Windschitl, 1999). Some investigators, rather than focusing on observed activation at the voxel level, choose instead to perform a region-of-interest analysis (see Poldrack, 2007), in which activation is statistically evaluated for some predetermined collection (or collections) of voxels that reflect(s) physical areas of particular experimental focus. Recently, a structural equation modeling-based approach to the analysis of fMRI data has been proposed (Kim, Zhu, Chang, Bentler, & Ernst, 2007). Finally, more exploratory, or data-driven, statistical analyses for fMRI data include independent components analysis (Bell & Sejnowski, 1995; Comon, 1994) and clustering (see, e.g., Cordes, Haughton, Carew, Arfanakis, & Maravilla, 2002).

One important matter for discussion in the arena of statistical analysis is accounting for the problem of multiple comparisons. As noted previously, the

number of voxels imaged in any given experiment may be quite large; voxel-based strategies applied to the whole brain may result in an overwhelming number of statistical tests being conducted, and—if some type of correction is not used—an uncomfortably high experimentwise risk of Type I error. In the fMRI empirical literature, among the remedies used for the problem of multiple comparisons are the Bonferroni correction, Gaussian random fields, and cluster-size thresholding.

Even apart from the issue of multiple comparisons, there are multiple data analytic challenges presented to those using the fMRI assessment tool. Defining regions of interest can be extremely difficult. Use of more sophisticated and powerful analyses, such as the full GLM, relies on the experimenter's selection of an appropriate model response function; misspecification of the model can, as usual, produce seriously misleading results. In that connection, it is unfortunate that the exact form of the hemodynamic response to particular experimental tasks, or within certain participant populations (e.g., those with pathological brain conditions), is often uncertain (McKeown et al., 1998). Furthermore, some assumptions, such as the GLM assumption of independence of residuals, are not likely to be met under certain conditions. Clearly, the further development and evaluation of methods for the analysis of functional imaging data are important areas for ongoing research.

Multiple software options are currently available for the preprocessing and statistical analysis of fMRI data, many of which are freely available to the research community. Note that some studies have indicated that the preprocessing and data analytic tools included within different software packages can have different effects on the observed error variance of functional imaging data (Shaw et al., 2003; Smith et al., 2005).

No statistical analysis, no matter how well conducted, can lend meaning to fMRI data that are insufficiently linked to the psychological constructs under investigation. Accordingly, we turn now to a brief consideration of the role of task selection in psychotherapy research using fMRI.

The Importance of Task Selection in fMRI Research

The selection of tasks for use in fMRI paradigms is akin to the selection of psychological tests in clinical assessment or the selection of process and outcome measurement tools in psychotherapy research in general. All psychological research operationalizes the mental processes of interest by identifying tasks or measures by which one may obtain observations of behavior or make inferences about underlying mental

activity (Michell, 1999). Because all psychological constructs ultimately require theory for both definition and measure, it is crucial that tasks used in fMRI by psychotherapy researchers be clearly linked to theoretical conceptions of psychopathology and change. Moreover, as the previous section illustrated, it is equally critical that tasks used in fMRI studies have been systematically examined to establish their reliability and validity in reflecting the phenomenon of interest in representative populations.

What do these basic principles mean for the design of individual studies? We offer the following generalizations as guidelines for the implementation of fMRI within investigations of psychotherapy outcome or process. First, the study should be based on a model of how the intervention works, preferably in terms of well-understood psychological constructs (e.g., learning, attitude change, skill acquisition, insight, desensitization). Such a model provides both a conceptual framework within which to generate and test hypotheses and a basis for operationalizing the variables of interest (including the stimuli or tasks used in the imaging itself). Second, the investigators should have at least tentative hypotheses about brain regions associated with such constructs. As noted, the potential for Type I error in fMRI research requires a conservative approach to hypothesis testing. Third, the study should have a well-controlled method for testing the associations among the intervention, the psychological constructs, and the brain processes of interest. In planning to meet this final goal, task selection is of paramount importance.

Task Types

Like psychological tests, tasks used in fMRI research vary widely and have included practically all forms of mental activity, from simple perceptual judgments to memory to emotion induction to making judgments about moral dilemmas. All tasks involve the presentation of some type of stimulus, to which the participant responds while concurrent brain activity is monitored. That is, a task is intended to elicit particular forms of mental activity, and associated brain activation and behavior, which are then appraised and recorded. Tasks may involve passive responses to stimuli (e.g., the observation of a picture) but may also require more active engagement or “doing something” in response to the presentation of a stimulus (e.g., cognitive reappraisal, problem solving, calculations). The ability to measure responses to stimuli that may vary widely in their cognitive demand—from the relatively passive (simple attention) to the more active (complex executive functions) engagement of the participant—is what

makes this neuroimaging method “functional” and ultimately determines the extent to which the data obtained provide useful insights into psychotherapy.

Task Selection: The Role of Theory and Previous Research

To be maximally useful in fMRI research, psychological tasks must be reliably and validly linked to the empirical literature on the neurobiology of the phenomenon of interest. For instance, a psychotherapy researcher interested in change processes involved in the treatment of major depression must select a psychological task that is linked not only to what is known about the psychological and neural processes presumably altered in depression but also to the putative change processes within the treatments being examined. Similarly, an investigator studying the effect of psychotherapy on metacognitive skills should use a task that reflects both the psychological nature of the hypothesized skill acquisition and the brain regions implicated in metacognitive information processing. Indeed, one of the challenges in the interpretation of fMRI findings is evaluating whether the task used in a particular study had a sufficient logical and empirical association with the psychological construct under investigation to provide a rigorous and meaningful test of the hypotheses under consideration.

The following example illustrates one approach to fMRI task selection in a psychotherapy research study of major depression. It has been increasingly documented that a key feature of depression is the inability to effectively regulate negative mood when it arises; in other words, depression can be viewed as a disorder of emotion regulation (e.g., Gotlib & Hamilton, 2008). Johnstone, van Reekum, Urry, Kalin, and Davidson (2007) wished to test theory-based hypotheses about the involvement of emotion regulation in depression using experimental tasks previously developed by behavioral scientists studying the basic processes of affect regulation *per se*. Brain imaging studies in healthy individuals had identified a key corticolimbic circuit involved in the top-down regulation of affective subcortical circuitry; in addition, increased left lateral prefrontal cortex (PFC) activation and accompanying decreased amygdala activation had been observed when individuals reappraised negative stimuli as less negative (Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner et al., 2004; Phan et al., 2005). Accordingly, Johnstone et al. used a picture-viewing emotion regulation task designed to elicit intentional regulation of subcortical emotional circuitry in an fMRI study comparing depressed and nondepressed adults. This task had been used with normal subjects (Urry

et al., 2006) and is similar to the task used in other studies (Jackson, Malmstadt, Larson, & Davidson, 2000; Ochsner et al., 2004; Schaefer et al., 2002). Johnstone et al. observed that depressed individuals showed a lack of engagement of lateral PFC-ventromedial PFC-amygdala circuitry previously hypothesized as necessary for down-regulation of amygdala responses to negative stimuli.

What does this example illustrate about the principles of fMRI task selection? First, it exemplifies the selection of an experimental task that is associated in a theory-based manner with the psychological construct of emotion regulation, a concept believed to be important to the elucidation of the nature of major depression and to the identification of potential mechanisms of change in its successful treatment. Second, it demonstrates the importance of selecting tasks for imaging studies that can draw upon prior research identifying relevant brain regions and neurophysiological processes. Finally, it describes the use of an experimental task that had been developed systematically in previous empirical work with both normal and clinical populations and had been shown to exhibit appropriate reliability and validity. In summary, the most useful fMRI studies of psychological treatment will attend to the development and selection of experimental tasks that maximize the interpretability of functional associations among mental activity, patterns of brain activation, and behavior.

An Empirical Example

Some promising early research has already begun to use fMRI technology in the service of the development and study of efficacious psychotherapeutic interventions. Siegle, Ghinassi, and Thase (2007), for example, took advantage of the fMRI assessment method in both their development of a new adjunctive behavioral treatment for severe major depressive disorder and in an investigation of the outcome of that treatment. Siegle et al. noted that previous neuroimaging research (as also described previously) had implicated the PFC as a possible inhibitor of activity in the amygdala and that previous treatment outcome research had supported links between increased PFC activity and recovery from depression. They theorized that an intervention targeting increasing PFC activity might diminish the emotional information processing biases observed in depression and thereby help to treat the disorder.

Siegle et al.'s (2007) “cognitive control training” (CCT) adjunctive intervention followed directly from such work and was specifically designed to increase PFC activity. The intervention was studied using a small-sample, treatment-as-usual versus CCT plus

treatment-as-usual vs. healthy control design. fMRI was one of the assessment modalities; experimental tasks had been shown in prior research to be linked to the neural processes of interest, and a mixed-effects, region-of-interest analysis was performed. Using an experimental task designed to provoke emotional processing, Siegle et al. were able to demonstrate that patients who had received the CCT adjunctive intervention exhibited less sustained amygdala activity in response to stimuli with a negative valence than before the intervention. Moreover, using an experimental task designed to invoke cognitive processing, Siegle et al. demonstrated that, compared with their levels of activation in a preintervention assessment, patients who had received CCT displayed increased PFC activity in response to the task's more difficult stimuli. By virtue of more traditional assessment measures, the investigators were additionally able to demonstrate that patients receiving the adjunctive intervention reported greater decreases in depressive symptoms and rumination over the course of treatment than the treatment-as-usual group. The authors note that their data are preliminary and that their sample is small; furthermore, fMRI assessments were reported for only the CCT group, preventing across-group comparisons of neuroimaging outcomes. Nonetheless, the Siegle et al. study clearly illuminates the promise of fMRI as a tool in the conduct of psychotherapy research. By consulting prior fMRI research, Siegle et al. were able to design a new adjunctive treatment for major depression that targeted specific brain mechanisms; by using fMRI as an assessment strategy, the investigators were able to not only demonstrate a reduction in depressive symptoms in response to the new treatment but also to provide preliminary data that speak to the hypothesized mechanisms of change.

Summary and Conclusions: Using fMRI in Psychotherapy Research

For the study of psychotherapy, fMRI is a potentially powerful and flexible technique. It is not without drawbacks, however. Although there is good evidence of the relationship between the BOLD response and neural activity, there still exists some uncertainty regarding the precise form and latency of the BOLD contrast signal, leading to challenges with respect to model fitting and data interpretation. The fMRI data can be associated with high levels of "noise," and research continues to address the reproducibility of patterns of activation over time. Moreover, data collection, preprocessing, and analysis can be resource intensive and methodologically challenging. For those who would consider incorporating this highly promising yet still-developing neuroimaging

method into studies of psychotherapy, we offer several recommendations.

First, the importance of experimental design cannot be overstated. To optimize the sensitivity of the fMRI method, it will be important to select tasks that elicit, as directly as possible, the psychological processes of interest and that evoke BOLD signal changes of sufficient magnitude that within- and between-subject variability can be detected reliably. Concomitantly, error variability may be reduced by, for example, providing training to participants before scanning (e.g., to minimize strategy changes over the course of one or multiple sessions). As in any psychotherapy study, control conditions should be selected carefully, counterbalancing used as appropriate, and artifactual variability and confounds minimized to the extent possible.

Second, we recommend that the experimenter consider integrating the fMRI neuroimaging method with other measures of the psychobiological processes of interest. It is rarely advisable for a psychotherapy study to use only a single questionnaire or interview instrument to assess the dependent variable (Shadish, Cook, & Campbell, 2002). The validity of functional imaging results can be bolstered considerably by a convergence of findings also drawing on behavioral assessments, self-report measures, clinician ratings, and other biologically based tools (e.g., electrical field potentials, genetics data; Huettel et al., 2004).

Third, the choice of data analytic approach should follow directly from the experimenter's research hypotheses and experimental design. The question of whether key statistical assumptions are likely to have been met should be carefully evaluated. Model response functions must be chosen judiciously, and model quality should be examined empirically (Razavi et al., 2003). In light of the complexities involved, it may be helpful to consider consultation with a statistician familiar with both functional imaging data and multivariate statistical techniques.

Fourth, and perhaps most importantly, it will be critical to focus on research that benefits from theory-driven, *a priori* hypotheses. The application of fMRI research to behavioral sciences phenomena is relatively recent; theoretical foundations are not yet solid, and there is often little previous empirical work to provide guidance regarding expectations for patterns of activation or selection of an appropriate model response function. As noted previously, the fMRI data set can have a large capacity for Type I error, and model misspecification can, as always, have serious consequences. The application of the fMRI neuroimaging method to the study of the process and outcome of treatment is an exciting, and potentially very fruitful, enterprise. However, in the

absence of theory-grounded, predetermined research hypotheses, findings from an fMRI investigation of psychotherapy should be interpreted very cautiously and conservatively, as would be findings from any study presenting exploratory or post hoc analyses.

We close with a set of questions that the reader might apply to the design or interpretation of studies using fMRI to investigate psychotherapy outcome or process. What are the psychological constructs of interest, and is “signal in the brain” relevant to understanding how psychotherapy might alter such constructs? Are there other methods (e.g., peripheral psychophysiology such as skin conductance or electroencephalogram) that could provide useful information about psychobiological processes of interest with fewer design constraints or interpretive complexities? Are the predicted associations among neurophysiology, mental activity, and behavior sufficiently articulated to allow for clear tests of those hypotheses? Above all, what does the study add to our knowledge about how psychotherapy works? We look forward to a new generation of research in which psychological and biological perspectives on psychopathology and treatment become better integrated into advancing the public health.

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