

Functional Neuroimaging of Treatment Effects in Psychiatry: Methodological Challenges and Recommendations

Gabriel S. Dichter,^{1,2,3} Linmarie Sikich,^{1,2} Allen Song,³ James Voyvodic,³ and James W. Bodfish^{1,2}

¹Department of Psychiatry, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA

²Carolina Institute for Developmental Disabilities, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA

³Duke-UNC Brain Imaging and Analysis Center, Duke University Medical Center, Durham, NC, USA

ABSTRACT

Functional magnetic resonance imaging (fMRI) has helped to elucidate the neurobiological bases of psychiatric and neurodevelopmental disorders by localizing etiologically-relevant aberrations in brain function. Functional MRI also has shown great promise to help understand potential mechanisms of action of effective treatments for a range of psychiatric and neurodevelopmental disorders, including mood and anxiety disorders, schizophrenia, and autism. However, the use of fMRI to probe intervention effects in psychiatry is associated with unique methodological considerations, including the psychometric properties of repeated fMRI scans, how to assess potential relations between the effects of an intervention on symptoms and on specific brain activation patterns, and how to best make causal inferences about intervention effects on brain function. Additionally, the study of treatment effects in neurodevelopmental disorders presents additional unique challenges related to brain maturation, analysis methods, and the potential for motion artifacts. We review these methodological considerations and provide recommendations for best practices for each of these topics.

KEYWORDS: clinical trials, fMRI, functional magnetic resonance imaging, neurodevelopmental disorders, psychiatry

INTRODUCTION

Randomized controlled clinical trials in psychiatry are designed to evaluate the efficacy of an intervention [1, 2]. Such trials may rely on assessments of symptom severity, global functioning, and neurocognitive function as outcome measures. With the recent advent of functional brain imaging techniques, the opportunity exists to investigate the potential neurobiological mechanisms of action of interventions by comparing brain scans acquired before and after a particular treatment (or set of treatments). The use of cognitive neuroscience techniques, such as functional magnetic

resonance imaging (fMRI), to address treatment effects represents a shift to a mechanistic approach to understanding not only disease states but also treatment effects and has the potential to reveal heretofore unknown neurobiological mechanisms of treatment effects. The evaluation of treatments via functional brain imaging more closely models early drug development and basic science approaches to screening new drug therapies and thus may promote swifter transition of agents to clinical trials [3]. However, the use of fMRI in evaluating treatment effects in psychiatry also involves a number of unique methodological considerations. Our purpose here is to outline important considerations to guide design decisions in the context of particular research questions. We have incorporated general experimental and methodological principles derived from our own fMRI intervention studies [4–7] to guide investigations of treatment effects in psychiatric and neurodevelopmental disorders via fMRI.

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*Address correspondence to Gabriel S. Dichter, Ph.D., Department of Psychiatry, University of North Carolina School of Medicine, CB# 7255, 101 Manning Drive, Chapel Hill, NC 27599-7255, USA. E-mail: dichter@med.unc.edu

General Methodological Concerns

Psychometric Properties of Repeated fMRI Scans

Although a small handful of studies have examined pre-treatment fMRI scans as predictors of treatment response [8], the most common neuroimaging clinical trial design in psychiatry involves the collection of symptom and fMRI data from a patient group at least twice, once before the initiation of treatment and once after treatment course. Although far less common, additional fMRI scans may also be collected mid-way through the course of treatment as well as after treatment termination to investigate the timecourse of effects on brain activation. All of the above contexts require the collection of multiple fMRI scans from patients receiving treatment. Given the longitudinal nature of intervention studies, brain imaging methods for evaluating treatment mechanisms must meet the same psychometric properties as traditional “paper-and-pencil” outcome measures, including high test–retest reliability [9], limited practice effects, and sensitivity to change [10]. Despite methodological advances in ways to assess the test–retest reliability of functional brain imaging data [11–13], only recently have the psychometrics of repeated fMRI assessments been evaluated, with initial results suggesting high reliability in some studies [14–16] and low reliability in other studies [17–20].

Recommendations. Cognitive tasks, data acquisition parameters, and analysis methods must be selected that have adequate test–retest stability prior to use in clinical trials [21]. Researchers should also consider that stability estimates may be highly variable even in non-clinical contexts, are likely poorer in clinical contexts, and may be differentially affected by various treatment approaches. We recommend assessing test–retest stability in both basic and clinical samples prior to implementing a neuroimaging clinical trial. We also recommend tasks that have been demonstrated to robustly activate relevant neurocircuitry by multiple investigative teams across sites. Though not directly related to the psychometrics of properties of repeated fMRI scans, we further recommend stock pulse sequences available on commonly used MR scanners to facilitate multi-site studies and the use of widely accepted fMRI analysis methods [16, 22, 23] to promote validation and replication across sites.

Study Design

Cognitive Task Selection

fMRI relies on cognitive tasks to engage relevant brain circuitry. Although it may be tempting to transfer behavioral tasks sensitive to treatment effects outside the scanner to fMRI contexts, this must be done with caution [24]. Tasks must be selected based on prior research

suggesting functional deficits in specific brain circuits in the disorder of interest and hypothesized to be impacted by the treatment under study. In most contexts there is no consensus regarding “gold standard” cognitive neuroscience tasks to address treatment effects. This lack of consensus impedes cross-site validation and replication.

Recommendations. Working groups should establish optimal tasks to assess treatment effects via fMRI in different disease and treatment contexts. One notable example of this approach is the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative, which has disseminated recommendations regarding cognitive paradigms to best measure relevant constructs in the context of schizophrenia clinical trials [25]. We recommend similar initiatives for other psychiatric and neurodevelopmental disorders to facilitate neuroimaging intervention trials.

Selection of Comparison Groups

Evaluating the effects of novel interventions using fMRI may be accomplished via different designs that largely parallel methods used in traditional clinical trials [26]. It is well known that clinical trials produce improvement in symptom measures with nonspecific origins (i.e., “trial effects”). Such effects may be due to active treatment effects, placebo effects (e.g., expectancy effects, nonspecific effects of receiving treatment), Hawthorne effects (i.e., improvements due to being in a research study), and observer effects (i.e., improvements due to being observed) [27]. Further, it is well established that even inactive placebo treatments may impact global functioning as well as fMRI outcomes [28–31].

The following design options each have unique strengths and weaknesses for establishing potential treatment mechanisms of action.

1. Comparison of pre- and posttreatment scans in a single group of patients receiving a treatment (i.e., a single-group design) [32].
2. Comparison of pre- and posttreatment scans in a patient group to a single brain scan in a control group [33].
3. Comparison of pre- and posttreatment scans in a treatment group to repeated scans in a control group [5].
4. Comparison of pre- and posttreatment scans in a patient group receiving an active treatment to repeated scans in a patient group receiving no treatment (i.e., wait-list control design) [34].
5. Double-blind comparison of pre- and posttreatment scans in a patient group receiving an active treatment to repeated scans in a patient group receiving a placebo treatment [35].

6. Comparison of pre- and posttreatment scans in patients groups receiving different active pharmacologic (i.e., an active medication comparator) or behavioral (i.e., a behavioral comparator) treatments either randomly assigned [36] or based on patient preference [37] (may be conducted either as double-blind or open-label). The goal of this approach is to determine if the effects on brain function of the different treatments are equivalent or distinct.

Recommendations. The single-group design (#1 above) confounds treatment effects with a number of other nonspecific factors and is thus recommended only for initial pilot studies. Comparison of pre- and post-treatment scans in a patient group to a single brain scan from a control group (#2 above) is not recommended because time, practice, and placebo effects are not modeled. Comparisons of pre- and posttreatment scans in a patient group to repeated scans in a control group (#3 above) allows for modeling the effects of repeated scans; however, this approach does not account for placebo effects or differential fMRI stability in patient and control groups. Thus, when adequate samples are available, the use of two patient arms (#4, #5, and #6 above) is optimal. Wait-list comparisons (#4 above) do not allow for assessment of placebo effects on brain function, which are known to be robust [38]. Thus, a double-blind placebo comparison design (#5 above) is recommended because it adequately controls for placebo response and allows for modeling fMRI stability in a patient sample. Additionally, comparisons of two active treatments (#6 above), preferably with relatively similar rates of side effects, allows for a comparison of the relative specificity of different treatments on brain function. It should be noted that when resources allow, approaches #5 and #6 may include a true control group (i.e., disorder-free) as well to establish that both patient groups replicate patterns of differences from controls at pretreatment baseline scans. Although other, more complex approaches are possible (e.g., crossover designs, nested case-control studies, discontinuation designs, etc.), they are generally not used in neuroimaging clinical trials because of their complexity and associated costs.

Effects of Psychopharmacologic Agents on the BOLD Response

Quantitative fMRI

One of the major obstacles to the application of blood oxygen level dependent (BOLD) fMRI to assess effects of pharmacologic interventions is that BOLD fMRI is not a quantitative metric. In other words, BOLD fMRI as typically implemented provides measures of relative changes in brain function across conditions, but does

not provide activation metrics in meaningful absolute units. To date, BOLD imaging largely remains a qualitative assessment of brain function, and the relevant signal changes can be affected by the combined results of neuronal activity, cerebral blood flow (CBF), cerebral blood volume (CBV), and cerebral oxygen metabolism (CMRO₂). Variables such as caffeine, nicotine, pharmacologic agents, and varying severity of disease states can drastically impact resting brain perfusion and thus the hemodynamic properties and BOLD response in the brain [39, 40].

Recommendations. Researchers have investigated quantitative relations between blood oxygenation and brain metabolism over the past decade and have suggested using calibrated fMRI to achieve improved quantitative correlation with neuronal activity [41–44]. Specifically, calibrated fMRI relies on complementary measurements of CBF and CBV changes to calibrate common BOLD activation so that a specific and quantitative measurement of the regional energy metabolism in CMRO₂, which is directly proportional to neuronal activity, can be obtained. Recent reports using arterial spin labeling (ASL) techniques further suggest that dynamic measurements of CBF changes can be used to calibrate the BOLD signal [45, 46]. However, calibrated fMRI that collects dynamic BOLD and perfusion timecourses can often be time-consuming and impractical in human experiments. As such, simplified approaches that acquire only the baseline perfusion signal to normalize the BOLD signal changes may be a practical solution.

In experiments where high temporal resolution is not critical, a simultaneous acquisition of dynamic perfusion and BOLD contrasts may be adopted to achieve improved quantification of the BOLD signal. However, in contexts where high temporal resolution is required, or when the baseline perfusion level varies at a much slower temporal scale, infrequent sampling of baseline perfusion (e.g., using ASL) can be introduced among the BOLD timecourse acquisition, such that these baseline perfusion levels can be incorporated into functional analysis to remove their impact on the BOLD signal. As a result, improved correlation between the BOLD signals and underlying neuronal activity can be obtained [45].

Interpretation and Possible Confounds

Etiologic Relevance

It may be tempting to infer etiologic relevance of a particular brain region or network for a disorder based on data indicating changes in activation in that region after treatment. However, it is critical to recognize that observing changes in brain activation due to a given treatment for a psychiatric condition does not necessarily

suggest etiologic relevance of the brain region for the disorder or even for treatment effects. Put more simply, intervention effects do not necessarily indicate a causal mechanism of disease development or treatment effects. To illustrate, although aspirin relieves muscle pain, muscle pain is not caused by a lack of aspirin. Similarly, although a given intervention may change activation within a given brain network, atypical activation of that same network may not necessarily be etiologically relevant for a given disorder.

Recommendations. Inferring etiology on the basis of treatment effects must be done with caution and only on the basis of a compelling theoretical framework and auxiliary supporting data. Inferences of causality are bolstered by sequentially demonstrating abnormal brain activation in patients relative to controls as well as normalization of brain activation following treatment (i.e., a discontinuation design). In disorders where full remission is possible, it is critical to establish normalization of brain activation patterns in individuals with a history of the disorders (i.e., trait effects) as well as in individuals at risk for the disorders but currently asymptomatic (e.g., prodromal individuals or first-degree relatives of affected patients) [47]. Given these cautions, however, observing theoretically predicted changes in brain function in response to treatment may corroborate and substantiate a nomological network articulating a theory of disease etiology¹.

Intervention Effects on Symptoms Versus Brain Activation

Neuroimaging clinical trials involve collection of both symptom and fMRI data. Given the widespread heterogeneity in response to psychiatric treatments [48, 49], it is not surprising that not all patients experience significant symptom reductions even in the context of widely used and effective treatments. Additionally, given the wide interindividual differences in task-related neural activation patterns [50], it is similarly not surprising that changes in regional brain activation patterns are variable even in the context of patients with similar symptom profiles and similar profiles of symptom reductions. Thus, researchers must consider the nearly ubiquitous scenario of symptoms changes in the absence of changes in brain function or brain function changes in the absence of changes in symptoms. Additionally, psychiatric treatments may change patterns of behavior during fMRI task performance [51], resulting in yet another dissociation that must be resolved to optimally interpret neuroimaging treatment trials.

Recommendations. Investigators must specify prior to trial initiation whether symptom profiles, behavioral performance, or neuroimaging mea-

asures are of primary interest. Generally, traditional clinical trials require large samples across multiple sites and thus are not optimally suited to examine the effects of interventions on brain activation because methods for multi-site fMRI studies are still evolving [16]. In contexts where clinical efficacy is of primary concern (e.g., phase III clinical trials), neuroimaging measures may not be warranted. We thus recommend that in most contexts fMRI intervention studies examine the effects of interventions that have been previously established as effective in traditional clinical trials. This approach allows for a priori hypotheses concerning intervention effects on brain imaging metrics.

Alternatively, in certain contexts brain imaging may be used in an experimental manner to test the effects of novel treatments. In this framework, fMRI tasks may be used to evaluate changes in neural activation or connectivity associated with changes in symptom severity. fMRI tasks capable of indexing symptom change can then be used to help develop treatments that are designed to target neural circuitry changes associated with symptom change. One example of this is research on the effects of instructional treatment for dyslexia that has yielded information about novel targets for interventions [52–55].

Heterogeneity of Treatment Response

In nearly all contexts, the effects of psychiatric interventions are highly heterogenous. [48, 49] Thus, a primary motivating factor in neuroimaging clinical trials is to link changes in brain function with variability in treatment response.

There are two primary analytic approaches to address heterogenous treatment response:

1. *Comparison of responders versus nonresponders:* Symptom-based cutoff scores determining treatment responder status may be established a priori and then treatment-related changes in brain activation may be compared between responders and nonresponders. However, this strategy may have relatively low-statistical power to detect effects because of the sample sizes of responder and/or nonresponders subgroups. Additionally, patients with nearly equivalent treatment response may be categorized to different responder groups (i.e., one as a responder and one as a nonresponder).
2. *Covariation of treatment response:* An alternative analytic approach is to covary treatment response as a continuous variable in the analysis of neuroimaging data. This approach addresses parametric linkages between changes in regional brain function and the magnitude of symptom changes. In many contexts, the covariation approach will yield greater statistical

¹We thank an anonymous reviewer for raising this point.

power because the dimensional nature of the clinical outcome measure is maintained.

Treatment Effects on fMRI Task Performance

Interventions designed to ameliorate core symptoms of a disorder may produce improved neurocognitive function that in turn improves fMRI task performance (e.g., accuracy, reaction time, or eye gaze patterns).

Recommendations. In contexts where fMRI task performance is not related to the putative effects of an intervention, task performance should be equated (if possible) [51] or modeled during fMRI data analyses [56]. However, caution is warranted because improved task performance may be related to intervention effects in unforeseen ways, and thus group matching or covariation may attenuate power to detect treatment effects on brain activation.

Psychopharmacologic Side Effects and Dosing

Recommendations. Side effects are common in psychopharmacologic trials, even amongst patients receiving blinded placebo treatments [27]. Side effects that impact attention (e.g., dizziness, drowsiness) may affect task-related brain activation as well. Additionally, there may be differential effects on brain activation of differing medication dosages, even in the context of similar clinical benefits.

Recommendations. If sample sizes allow, secondary analyses should be conducted that subgroup patients on the basis of particular side effects profiles or by final medication dosage or that analyze only the subgroup of patients without significant side effects or with the same final medication dosage.

Considerations for fMRI Intervention Studies in Neurodevelopmental Disorders

Excessive Motion Artifacts. As with all neuroimaging studies, data quality in neuroimaging clinical trials is paramount. Data quality may be compromised by noise intensity spikes, ghosting, flow artifact, susceptibility artifacts, physiological noise (breathing, heart-beat), and participant motion. Participant motion is a critical consideration in the context of neurodevelopmental disorders (e.g., autism, Fragile X syndrome) that are, by definition, present in childhood and, in many contexts, are characterized by either movement disorders and/or repetitive behaviors [57]. Additionally, when scanning young children, the presence of anxiety increases the likelihood of participant motion. Finally, certain treatments, including neuroleptic agents, may produce extrapyramidal side effects that increase head motion [58]. Thus, issues of data quality related to participant motion are particularly critical in fMRI clinical trials involving pediatric samples with neurodevelopmental disorders.

Recommendations. Minimizing participant motion is vital because task-related changes in BOLD signals are relatively small compared to motion-related changes in BOLD signal [59], and mathematical corrections for head motion are imperfect [60]. Further, signal changes due to motion may correlate with functional BOLD signal changes resulting in activation patterns that spuriously appear to be a function of the fMRI task [61]. Measures of heart rate and respiration should be collected and modeled during data analysis [62, 63] (see Figure 1). Controlling for head motion is critical, via bite bars, semiflexible face masks, head-conforming foam, or pillows. As in all pediatric and clinical studies, scanner acclimation involving a mock scanner is essential (these methods have been detailed elsewhere [64, 65]), and there are established behavioral paradigms to promote decreased motion during scanning [66, 67]. These considerations are particularly salient in the context of neurodevelopmental disorders where anxiety is prevalent and may systematically attenuate with repeated scan sessions. Additionally, self-report measures of anxiety collected at pre- and posttreatment scans may be used to assess for differences in anxiety levels that may be statistically modeled during data analysis [68], though this approach may be problematic in treatments designed to reduce anxiety or in disorders where self-reports are of questionable validity.

Effects of Development on Intervention Effects.

As discussed in a preceding section, dissociations may exist between the effects of an intervention on symptom profiles, regional brain activation, and task-related behavior. These potential confound are compounded in the context of pediatric neuroimaging treatment trials, where relations between symptoms, behavior, and brain activation may be variable across development. Additionally, such interactive effects may be heterogenous in pediatric disorders [69].

Recommendations. Similar to prior recommendations in the context of adult neuroimaging treatment trials, investigators must specify a priori whether symptom profiles, behavioral performance, or neuroimaging measures are of primary interest. In the context of pediatric treatment trials, it is critical to consider developmental effects on the specified target of the intervention. Initial neuroimaging investigations of treatment trials should begin with studies using adult sample and then systematically downward extend to younger samples in order to methodically understand the complex interactions between development and treatment effects on brain, behavior, and symptoms.

Differences in Brain Morphometry. As in cross-sectional clinical fMRI studies, treatment fMRI studies are sensitive to potential differences in the size of various brain regions in clinical contexts [70]. Volume

Effects of regression filtering to remove respiratory noise

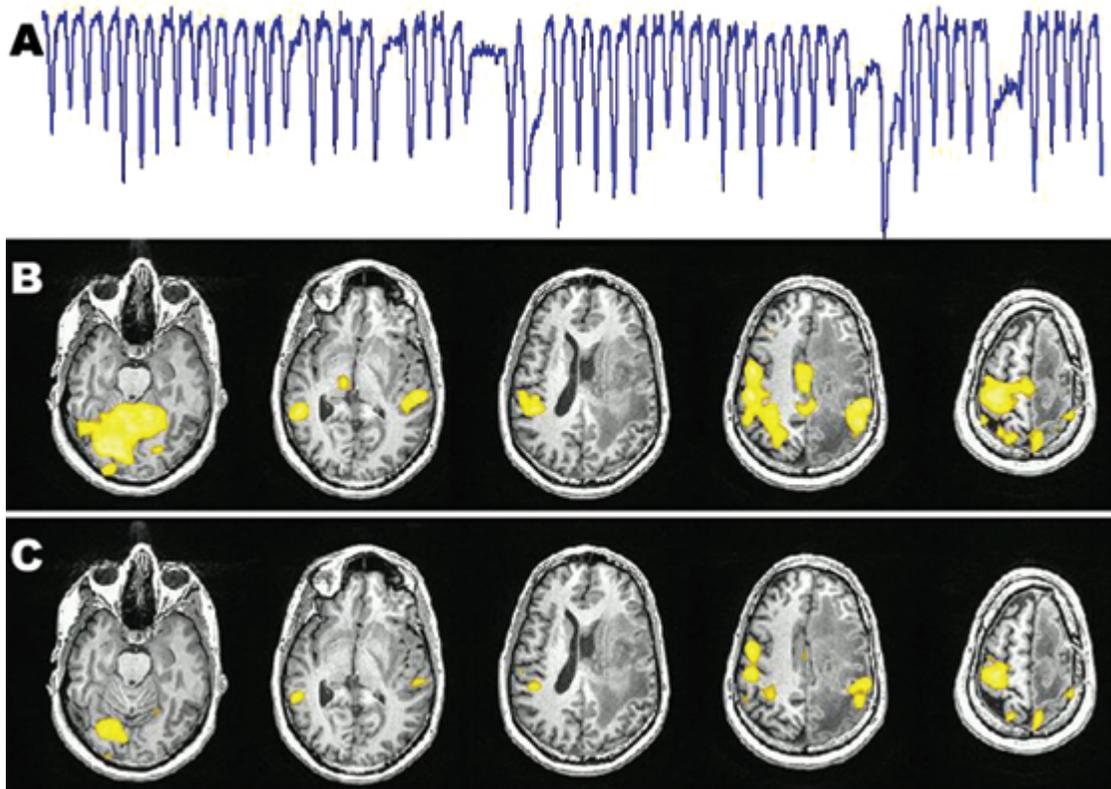


FIGURE 1. Functional MRI (fMRI) activation maps depicting the effects of regression filtering to remove respiratory noise. The fMRI task is a simple hand sensorimotor task. This patient had a large left frontal glioblastoma and irregularity in his respiration pattern during the scan (A) that caused significant artifacts in the motor activation map (B). These artifacts were filtered out to produce a more specific motor function map (C). The noise removal was done using regression filtering implemented in fScan [63] based on the RETROICOR method of Glover and colleagues [90].

differences have been identified in key neuroanatomic regions in numerous neurodevelopmental disorders, including autism [71], Fragile X syndrome [72], and Williams Syndrome [73].

Recommendations. Normalization to standard stereotaxic space in fMRI treatment studies of neurodevelopmental disorders should be done with caution. When differences in brain morphology have been documented, regional mean signal change analyses performed in native subject space may be optimal [60, 74]. An additional consideration is that, although most fMRI studies test for regional differences in MR signal intensity, differences in brain morphometry may manifest in terms of the spatial extent, rather than magnitude, of brain activity [75]. Thus, effects of signal extent, as well as intensity, should be evaluated.

Analysis of Pediatric Neuroimaging Data. Although fMRI studies of neurodevelopmental disorders typically include pediatric samples [76, 77], and non-clinical fMRI studies have been carried out even with infants [78], best practices for the analysis of pedi-

atric brain imaging data are still evolving [51]. Similar to cross-sectional pediatric functional brain imaging studies, researchers conducting pediatric treatment neuroimaging trials must decide whether to analyze pediatric brain imaging data using normalization to adult template brains, normalization to pediatric template brains, or in native space using either automated or expert manual segmentation.

Recommendations. Despite initial evidence that brain imaging data from children as young as 7 years old may be adequately normalized with adult brain templates [79, 80] the use of adult brain templates and atlases for normalization and segmentation pediatric brain imaging data may impose biases and limitations for estimates of both brain structure and brain function [81, 82]. Multiple pediatric brain templates and pediatric brain scan data repositories are available [81, 83–86]. These templates allow for automated analytic procedures with accurate spatial normalization for adults and children. Additionally, there is initial evidence that study-specific “internal” or “local”

pediatric templates (i.e., derived by averaging brains of study subjects themselves) may provide reasonable estimates of brain structure relative to “external” pediatric templates [82]. In summary, although there is not yet clear consensus regarding whether to use adult template, pediatric template, or native space approaches, there is initial evidence that in the context of template approaches, pediatric templates, rather than adult reference data, should be used.

There are no studies addressing direct comparisons between results using expert manual segmentation of pediatric brain imaging data versus normalization to appropriate pediatric templates, and this more research is needed to provide firm guidance in this regard. It is clear that there is a great deal of individual variability in brain morphometry, even in healthy adults, prompting some to suggest that normalization to standard stereotaxic space should be done with caution [74, 87], particularly in the context of pediatric samples [65]. It should be noted that currently available pediatric templates are derived from nonclinical samples, and thus the suitability of such templates for longitudinal studies involving samples with neurodevelopmental disorders is not yet known. Future research comparing expert hand tracing

to age-appropriate pediatric samples derived from cohorts with different forms of psychiatric and neurodevelopmental disorders are needed before best practices can be determined. Future research is also needed to examine linkages between the differences in brain morphometry across development and differences in the extent and magnitude of neural activations.

REPRESENTATIVE RESULTS

Preliminary Case Study Findings

Figure 2 illustrates preliminary case study findings from two case studies randomized to the active study arm in a larger double-blind randomized controlled trial comparing citalopram treatment to placebo treatment in adults with diagnoses of Autistic Disorder or Asperger’s Disorder and moderate-to-high levels of repetitive behaviors [7]. Participants completed an fMRI oddball target detection task both before and after approximately 12 weeks of treatment with citalopram, a selective serotonin reuptake inhibitor. This task is sensitive to functional frontostriatal abnormalities in individuals with autism spectrum disorders that are correlated with the severity of repetitive behaviors [88, 89]. One participant (Case

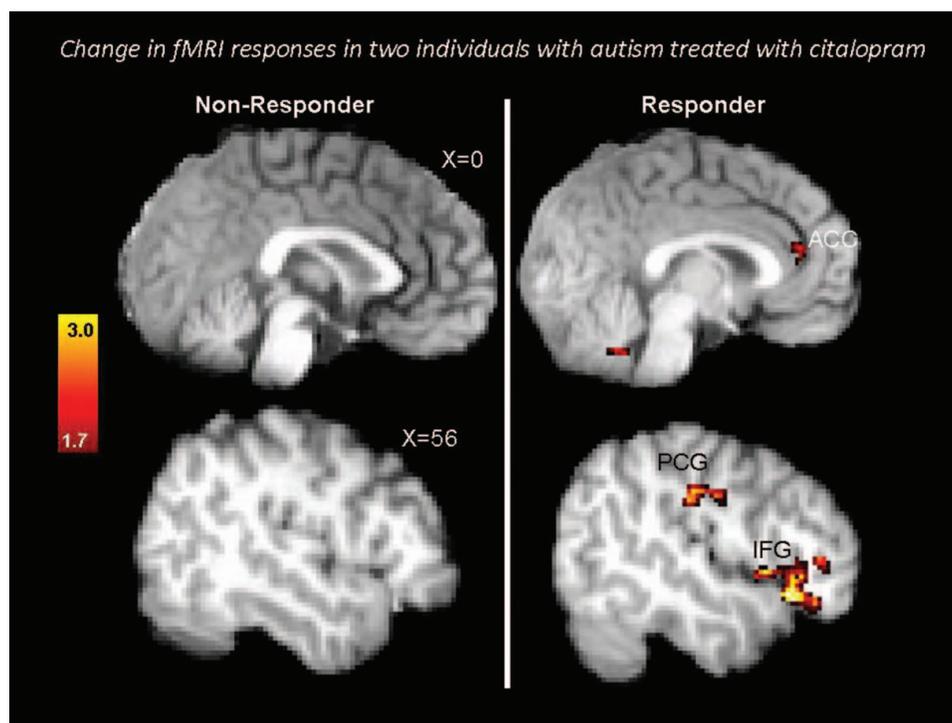


FIGURE 2. Single-subject fMRI activation change maps in native subject space depicting areas of statistically increased activation after citalopram treatment for repetitive behaviors in two individuals with autism spectrum disorders. The fMRI task was an oddball target detection paradigm designed to recruit brain areas subserving cognitive control. Case 1 (left) was a treatment nonresponder and Case 2 (right) was a treatment-responder. The figure illustrates increased activation in relevant brain areas in the treatment responder but not in the treatment nonresponder. Contrasts are thresholded at corrected $Z > 1.7$. Reprinted from Dichter et al (2010) [7].

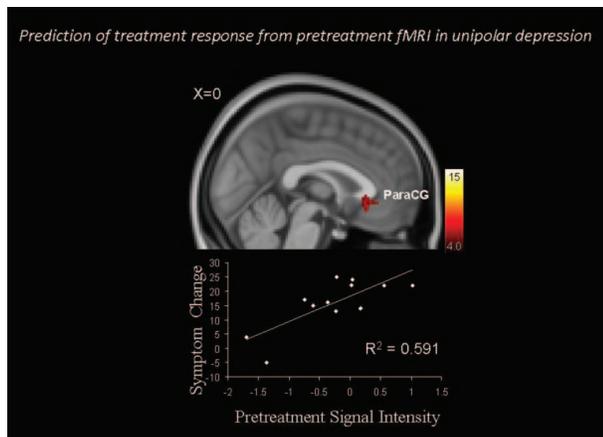


FIGURE 3. Relations between pre-treatment fMRI and response to psychotherapy treatment in unipolar depression. The top panel illustrates a cluster within the ventral paracingulate gyrus (ParaCG) that predicted change in Hamilton Rating Scale for Depression (HAM-D) [91] scores after psychotherapy in individuals with unipolar major depressive disorder. The fMRI task focused on decision making and reward processing. Contrasts are thresholded at corrected $Z > 4.0$. Adapted from Dichter *et al.* (2009) [5].

1) showed no reductions in repetitive behaviors whereas the other (Case 2) showed marked reductions. Brain activation in relevant prefrontal regions, including the dorsal anterior cingulate cortex, increased in only the participant whose repetitive behavior symptoms improved. Although these are case study findings and thus must be interpreted with caution, these proof-of-principle findings suggest that functional brain imaging

may be valuable for initial studies designed to elucidate potential mechanisms of action of targeted interventions. We highlight, however, the further research with adequate samples would be essential to derive any substantive findings from these case study reports.

Prediction of Treatment Response

Figure 3 illustrates results from an antidepressant treatment fMRI trial [5, 6]. Outpatients with unipolar major depressive disorder participated in a pretreatment fMRI scans that utilized a Wheel of Fortune decision-making and reward processing task [Ernst, 2004]. After the pretreatment scans, patients received a 9-week course of behavioral activation treatment, a form of individual psychotherapy. The figure demonstrates an activation cluster during the reward selection phase of the task that predicted subsequent response to treatment. Future research will evaluate the prospective utility of this finding to predict treatment response in a new group of patients. More generally, this approach illustrates the potential utility of using pretreatment fMRI data to predict individualized treatment response.

Mechanisms of Treatment Effects

Figure 4 illustrates the effects of psychotherapy on brain responses during reward anticipation in the same group of outpatients with unipolar depression [5]. Depressed outpatients repeated the same reward-processing task after completing the course of psychotherapy. To model the effects of repeated scans, a group of matched nondepressed control participants were scanned on two occasions separated by the same length of time. The clusters

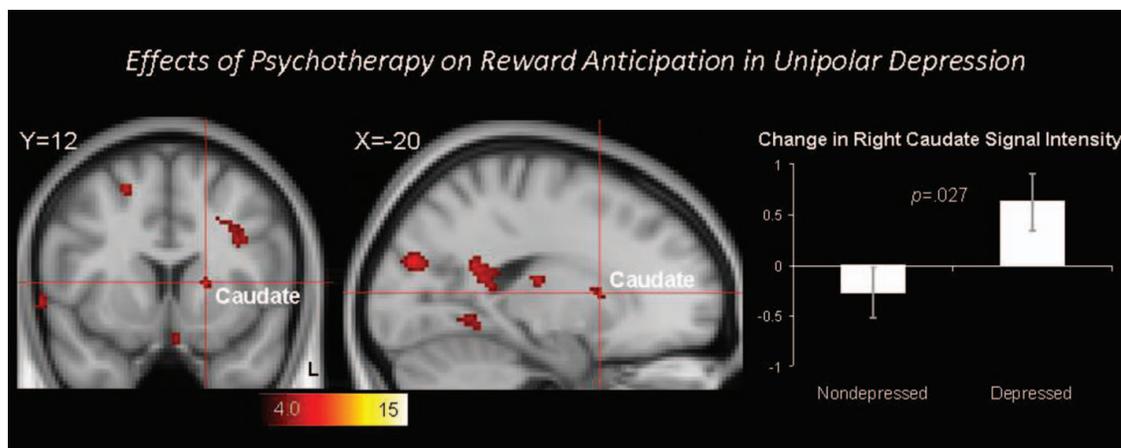


FIGURE 4. The effects of psychotherapy on reward anticipation in unipolar depression were examined by comparing the change in brain activation in depression patients scanned before and after treatment with the change in brain activation observed in controls scanned twice. The red clusters reflect significant Group (depressed, nondepressed) X Time (Time 1, Time 2) interaction effects, and include the right caudate cluster highlighted by the cross hair. The bar graph illustrates that the depressed group showed significantly increased activation in this right caudate cluster after psychotherapy. Contrasts are thresholded at corrected $Z > 4.0$. Error bars represent standard errors of the mean. Adapted from Dichter *et al.* (2009) [5].

in the figure, including the right caudate nucleus, indicate brain regions with significantly different change in activation in the depressed group relative to the non-depressed group. This approach illustrates not only the potential to use functional brain imaging to probe the effects of an intervention of brain function, but one approach to controlling for repeated scan sessions when examining treatment effects.

SUMMARY

The emergence of fMRI as a powerful cognitive neuroscience tool to study brain processes has facilitated clinical research into the neural underpinnings of psychiatric disorders. A relatively novel application of fMRI is to study the effects of behavioral and psychopharmacologic treatments for psychiatric disorders. The ultimate promise of this approach is to understand the potential mechanisms of action of effective interventions, to stimulate the development of novel compounds by understanding the neurobiological effects of treatment agents, to better understand treatment response heterogeneity, and to prospectively predict treatment response via pretreatment fMRI scans. Advances in pediatric fMRI allow for inclusion of young children in fMRI protocols [64], enabling the use of fMRI to investigate treatment effects in pediatric samples with neurodevelopmental disorders.

Despite the knowledge to be gained by using fMRI in clinical trial contexts, this approach holds a number of methodological challenges. Although optimal designs are in many cases context-specific, general recommendations include evaluation of fMRI test-retest stability, standardization of fMRI task selection, selection of optimal comparison groups and study designs, a priori identification of primary outcome measures, matching or controlling for differences in fMRI task performance, side effects and dosing, the use of quantitative fMRI metrics, covariation of physiologic signals, adequate control of subject motion, fMRI acclimation, and the use of pediatric templates when templates are used. The adoption of best practices will increase the pace of fMRI intervention studies, thereby facilitating the understanding of treatment effects and the development of novel interventions.

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