Psychoradiological Biomarkers for Psychopharmaceutical Effects

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KEYWORDS

• Psychoradiology • Predictive imaging biomarkers • Treatment response • Antidepressants • Stimulants

KEY POINTS

- The literature on psychoradiological imaging biomarkers that target treatment response is in general highly heterogeneous, with underpowered studies and a large amount of variation in techniques and analysis approaches.
- The most replicated finding at present is the relation of antidepressant treatment response to hippocampal (subfield) size.
- Rigorous validation and replication studies are needed, with emphasis on multimodal and noninvasive imaging biomarkers, obtained in large-scale consortia.

INTRODUCTION

Despite advances in pharmacology, not all psychiatric patients respond favorably to drugs. Currently, psychiatric medication is prescribed based on a "trial-and-error" method. This means patients have to deal with nonresponse, side effects, and adverse events. For example, for major depression, only approximately 30% to 50% of patients will have full remission of symptoms after first-line treatment, with cumulative remission rates of approximately 67% after 4 trials of different antidepressants. In some instances, the evidence for pharmacologic treatment is also lacking (eg, applied in a specific disease or age range). However, progress in the understanding of disease mechanism and drug action is opening up opportunities to match therapies to patient populations and thus pave the way toward personalized medicine. The concept of personalized medicine, also called precision medicine, that is, prevention and treatment strategies that take individual variability into account, is not new: blood typing, for instance, has been used to guide blood transfusions for more than a century. This personalized approach heavily relies on biomarkers that take into account an individual's genes, environment, and lifestyle. An algorithm weighing all these factors then provides the physician with data regarding the best medical intervention for a specific patient. Recent developments of large-scale biological databases, characterization of patients (using proteomics, metabolomics, genomics, and radiomics) and computational tools for analyzing large datasets have dramatically improved the possibility of applying this concept.

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For example, personalized medicine is already revolutionizing cancer treatment, in which treatments are tailored to a tumor's genomic profile.

The application of personalized medicine to psychiatry, however, is more challenging. Yet psychiatric disorders are responsible for immense personal, social, and financial burden. Indeed, the lifetime prevalence of various psychiatric disorders among the population is approximately 30% to 40%. In contrast to cancer, there is no biological or histological test for definitive psychiatric diagnoses, because of the inaccessibility of the human brain. The diagnosis is based on a combination of symptoms alone, by standard nosology, as reflected in diagnostic manuals, such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) or the *International Classification of Diseases*. The emerging field of psychoradiology, pioneered by Gong and colleagues,[1–3] could provide biomarkers based on objective tests in support of the diagnostic classifications, as in other parts of medicine. Because of its noninvasive nature, it has great potential to revolutionize clinical psychiatry. In particular, this is plausible based on the hypothesis for psychoradiology by Gong and colleagues,[1] who proposed a "brain structure-function-behavioral conjunction" theory in which brain structural alteration leads to clinical syndrome, likely due to the conjunction impact of the impaired functional connectivity.[3–5] Progress in related work has benefitted from methodological advances for detecting the psychopathologies at individual patient level,[6,7] as Dr Hesheng Liu and his colleagues from Harvard Medical School suggest in Hesheng Liu and colleagues' article "Individual-Specific Analysis for Psychoradiology," in this issue.

Diagnostic and Predictive Biomarkers

As outlined by the Health Research Directorate of the EU, a biomarker is a biological characteristic, which can be molecular, anatomical, physiological, or biochemical in nature. These characteristics can be measured and evaluated objectively. Biomarkers are either diagnostic markers that index biological characteristics associated with health or disease, or predictive, reflecting a process associated with therapeutic response. Psychoradiology could satisfy these goals, because it can provide several molecular, anatomical, physiological, and biochemical characteristics of the living human brain. For instance, PET, single-photon emission computed tomography (SPECT) and the more recently developed technique pharmacologic MR imaging (phMR imaging) are used for molecular imaging of the brain. Anatomical characteristics can be obtained using detailed structural imaging, physiological characteristics using functional MR imaging (fMR imaging) and perfusion imaging (eg, arterial spin labeling [ASL]), and biochemical characteristics using MR spectroscopy (MRS). These psychoradiological characteristics might be part of a panel of tests that also include, for example, genetic, peripheral blood-based, or cognitive tests.

Here, we focus on predictive psychoradiological biomarkers for pharmacotherapy as one subset of potential biomarkers in psychiatry. The main challenges of predictive psychoradiological biomarkers for psychiatric disorders are discussed and current advances outlined. The article concludes with some future directions for the translation of psychoradiological characteristics into clinically useful biomarkers.

CHALLENGES OF PSYCHORADIOLOGICAL BIOMARKERS FOR PSYCHIATRIC DISORDERS

In the field of psychiatric research, most studies use case-control designs in an attempt to uncover *diagnostic* biomarkers. However, to develop *predictive* biomarkers, studies using stratified sampling of patients are needed. In fact, Abi-Dargham and Horga[8] argue that the lack of personalized treatment in psychiatry is due to several challenges associated with discovering imaging biomarkers for psychiatric disorders, as opposed to, for example, cancer biomarkers. The first main challenge is the lack of a "gold standard" or definitive biological or histologic tests for psychiatric diagnoses. This complicates the validation of the biomarker, which requires correlative analysis of the psychoradiological characteristics against the definitive outcome. Currently, longitudinal follow-up is frequently needed to establish a final diagnosis. However, diagnostic information obtained from longitudinal follow-up is complex because it can be confounded by epiphenomenal consequences of the illness or its treatment. This precludes a direct association between the psychoradiological biomarker and brain-based phenotypes.

The second main challenge is that the pathologic features of psychiatric disease may be subtle and surface in only specific situations or under a certain cognitive load. Indeed, psychiatric disorders have been shown to be polygenic; usually the penetrance of a single gene variant is low, because the pathologic feature of that variant will only show as an added effect to the overall phenotype. Symptoms that we associate with psychiatric disorders may emerge only if the amount of (pathologic) gene variants exceeds a certain

threshold and/or these variants interact with negative environmental factors. The value of psychiatric biomarkers might therefore be dependent on studying these disorders (or individuals) under specific circumstances or conditions. To this end, challenge-paradigms have been used, and are now regarded an essential tool for the development of biomarkers. The paradigms could, for example, be task-based or pharmacologic assessments that challenge the systems or network affected in the disorder.

Some other challenges include that for PET/SPECT not all neurotransmitter systems can be currently imaged and that the development of novel tracers takes time. Furthermore, the neuroimaging field rewards novelty over replication, which explains the paucity of replicated findings, despite being essential for validation of a biomarker. Finally, a practical challenge in the development of psychoradiological biomarkers is the costs of the scans: in the United States, MR imaging scans cost approximately $600 per hour in academic centers and up to $1000 per hour for commercial centers, and PET scans range from $3000 to $5000 per scan.

CURRENT POTENTIAL PREDICTIVE PSYCHORADIOLOGICAL BIOMARKERS FOR PSYCHOPHARMACEUTICAL EFFECTS

Notwithstanding these challenges, some potential psychoradiological biomarkers have already been identified. In this article, we summarize studies aiming to establish markers of disease progression, or response to interventions (ie, predictive biomarkers). We do so for 3 prevalent psychiatric diseases and the most prescribed psychotropic medications in adults and children/adolescents, namely antidepressants for major depressive disorder (MDD), anxiolytics for anxiety disorders (ADs) and stimulants for attention-deficit/hyperactivity disorder (ADHD).[9,10] This overview is restricted to studies addressing pharmacologic treatment only. Furthermore, studies using predictive neurophysiological biomarkers (eg, electroencephalogram) are beyond the scope of this review.

Major Depressive Disorder

Major depression is the most prevalent psychiatric disorder in adults and children in the Western world, resulting in a heavy global disease burden. First-line, evidence-based treatments for adults and children and adolescents with MDD include structured psychotherapies (eg, cognitive behavioral therapy and interpersonal psychotherapy) and antidepressant medications. Selective serotonin reuptake inhibitors (SSRIs) are most commonly prescribed, of which only fluoxetine is registered for treatment of depression and AD in children (aged 8 years and older). However, approximately 30% to 40% of patients fail to respond, and this rate is even higher in children. Because treatment efficacy only can be reliably assessed after 6 to 12 weeks of treatment, continuation of an ineffective treatment to establish treatment response'nonresponse prolongs patient suffering related to depressive symptoms and reinforces the general perception of patients that there is nothing they can do to overcome the depressive disorder (ie, facilitating demotivation).

Using structural MR imaging, a meta-analysis showed that a smaller right hippocampal volume was a significant predictor of poorer treatment response in MDD.[11] Although subsequent studies suggest that lower total hippocampal volume was largely explained by brain atrophy,[12] larger tail and subiculum volumes have been shown to be predictive of symptom reduction.[12,13] It is worth noting that longer illness duration also has been associated with smaller hippocampal volumes,[14] but this appeared to be independent of the positive relation between larger tail volumes and remission.[12] This is in line with a large body of research implicating volumetric changes to the hippocampus in the etiology of MDD.

A meta-analysis of 20 functional PET with fludeoxyglucose ([^{18}F]FDG-PET) and MR imaging studies found that higher pretreatment activity in the anterior cingulate cortex is predictive of a higher likelihood of improvement,[15] whereas higher pretreatment activation in the insula and striatum is associated with higher likelihood of a poorer clinical response. However, this meta-analysis also pointed out the substantial heterogeneity between studies, in terms of design, patient groups, and tasks used to elicit functional activation. A recent systematic review on functional connectivity studies addressing network dynamics in response to antidepressants reported that treatment response is consistently associated with increased connectivity between frontal and limbic brain regions (possibly resulting in greater inhibitory control over neural circuits that process emotions).[16] However, the most recent study found the reverse; that is, negative functional connectivity with the subcallosal cingulate cortex was associated with remission to medication, whereas positive functional connectivity scores were associated with treatment failure.[17] Interestingly, the remission and treatment failure to cognitive behavioral therapy (CBT) was predicted by exactly opposite functional connectivity scores.

Molecular imaging studies furthermore found that higher pretreatment availability and greater

occupancy of serotonin transporter (SERT) correlated with improved treatment response in the short term, using both SPECT and PET.[18,19] However, 3 studies did not find such a relation,[20–22] and another study only demonstrated this relation in a specific genotype.[23] A review focusing on MRS concluded that there is strong evidence that changes in glutamate, N-acetylaspartate, and choline demonstrate a good correlation with treatment response to pharmacotherapy.[24] However, later studies reported conflicting results. For example, greater increases in gamma-aminobutyric acid (GABA) levels were found to be significantly associated with clinical response after a week of citalopram treatment, whereas no association with glutamate was found.[25] In contrast, another study found no predictive properties of GABA but did report that decreased occipital glutamate may be a biomarker of antidepressant response.[26] Furthermore, a study at 7T investigating treatment response to the novel antidepressant ketamine found no association with pretreatment glutamate levels.[27] The investigators report that the effects of the medication were smaller than the measurement sensitivity (~8%), which might explain the variable results found at 3T, which has even lower sensitivity.

Whereas research on predictive biomarkers for adults is starting to emerge, this is limited evidence for children and adolescents. Moreover, clinical indications suggest that SSRI exposure during adolescence may lead to negative outcomes that are not seen in adult patients. For instance, the most serious side effect associated with SSRIs prescribed to children is increased suicide risk,[28] which led to a black box warning from the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2004. A small study in 13 adolescents with MDD found that the greater reduction of anxiety (but not depression) symptoms was associated with higher pretreatment fMR imaging striatal activity and lower medial prefrontal cortex (PFC) activity, in both CBT and CBT + SSRI-treated individuals.[29] In 19 medication-naïve depressed adolescents, fluoxetine-induced decreases in both limbic and frontal activation did not correspond with clinical treatment response.[30] Cullen and colleagues[31] found that treatment response to SSRIs was associated with increased amygdala functional connectivity with right frontal cortex, and decreased amygdala connectivity with right precuneus and right posterior cingulate cortex in 13 medication-naïve adolescents with MDD/AD.

In summary, the current literature on psychoradiological imaging predictors that target treatment response and remission in MDD is highly heterogeneous, with generally underpowered studies and a large amount of variation in techniques and analysis approaches. At present, the most replicated finding is the relation of treatment response to hippocampal (subfield) size. In adolescents, most fMR imaging studies focused on aberrant amygdala activity, but found conflicting results, as in adult studies, possibly reflecting medication status, comorbid disorders, but also possibly reflecting technical difficulties acquiring fMR imaging signal in this area.[32] Other frontolimbic regions, including the prefrontal cortex, anterior cingulate cortex, and insula are other regions of interest in the discovery of additional predictive psychoradiological biomarkers for MDD,[33] as well as the intrinsic functional brain connectivity including greater within-network (default mode network) and between-network (default mode network and executive control network) connectivity, higher connectivity of the hippocampus with the limbic network and somatomotor network, and lower connectivity of the thalamus with the limbic network.[34]

Anxiety

ADs, including generalized anxiety disorder (GAD), panic disorder (PAD), social anxiety disorder (SAD), and simple phobias are (together with MDD) the most common psychiatric illnesses experienced, affecting an estimated 18% of people in the United States. Although both obsessive compulsive disorder and posttraumatic stress disorder have been classified as ADs in the past, they have been removed from the category in the DSM-5. The most prescribed pharmacologic treatment consists of SSRIs and serotonin and norepinephrine reuptake inhibitors, but for example, only 12% of patients with PD were in full remission after 5 years.[35] Moreover, 40% to 45% of youth with AD do not achieve remission (or a substantial reduction in symptoms) following treatment. Although most of the neuroimaging biomarker research in AD has applied psychotherapy (as this is the first-line treatment) rather than pharmacologic interventions, a few psychoradiological studies have been designed to explore brain markers of pharmacologic response in AD, as reviewed by Maron and Nutt.[36]

Predictive effects of structural measures on treatment response in AD have not been systematically evaluated as in MDD. However, small studies in patients with PD demonstrated that changes in total gray matter volume after remission were correlated with changes in clinical scores,[37] and that white matter micro-structural integrity

increased in the right uncinate fasciculus and left fronto-occipital fasciculus after remission in patients with PD on escitalopram treatment.[38]

The most recent systematic review in AD[39] indicated increased reactivity in neural networks subserving threat processing (eg, amygdala, insula (dorsal) anterior cingulate cortex (ACC) and PFC/orbitofrontal cortex) as a potential biomarker with predictive value for treatment response. For instance, in patients with GAD, higher pretreatment fMR imaging ACC and amygdala activity is associated with stronger reductions in anxiety and worry symptoms after 8 weeks of treatment with venlafaxine.[40,41] In contrast, a small sample of patients with SAD who did not respond to SSRIs demonstrated higher regional cerebral blood flow (CBF) ([^{99}mTc]HMPAO SPECT) in the left temporal cortex and the left midfrontal regions at baseline as compared with responders.[42] In another study, amygdala-frontal CBF ([^{15}O]H_2O PET) response to a public-speaking task differed between responders and nonresponders to SSRIs and placebo in a large randomized clinical trial of patients with SAD.[43] Finally, treatment response to tiagabine, an anticonvulsant drug prescribed off-label for AD, was inversely correlated with pretreatment cerebral metabolic rate of glucose uptake ([^{18}F]FDG-PET) within the ventromedial PFC in 12 patients with generalized SAD.[44]

Although the literature in AD predominantly focused on adults, an fMR imaging study in pediatric AD found that less recruitment of the dorsal ACC and dorsomedial PFC during emotional processing predicted a greater reduction in anxiety symptoms following SSRI treatment (as well as CBT),[45] similar to a prior study that found that greater activation in prefrontal regions (involved in social signals of threat) predicted better response to sertraline in anxious youth.[46]

In sum, the current literature on psychoradiological imaging predictors that target treatment response and remission in AD is limited, possibly because psychotherapy is often the first-line treatment of choice rather than pharmacologic interventions (**Table 1**).

Table 1
Predictive biomarkers of nonresponse in MDD and AD (as indicated by level I evidence [systematic reviews and meta-analysis])

Structural imaging	↓ Volume of hippocampus (MDD adults)
CBF	↓ Baseline CBF in ACC (MDD adults)
task-fMR imaging	↓ Reactivity in amygdala, insula, (dorsal) ACC and PFC/OFC (MDD and AD children and adults)
rs-fMR imaging	↓ Functional connectivity between frontal and limbic brain regions (MDD adults)

Abbreviations: ↓, indicates a reduction; ACC, anterior cingulate cortex; AD, anxiety disorder; CBF, cerebral blood flow; fMR imaging; functional magnetic resonance imaging; MDD, major depressive disorder; PFC/OFC, prefrontal cortex/orbitofrontal cortex; rs-fMRI, restingstate-fMRI.

Attention-Deficit/Hyperactivity Disorder

Psychostimulants, including methylphenidate (MPH) and dexamphetamine, are generally considered first-line management for the core symptoms of ADHD. Although stimulants are successful in reducing ADHD symptoms, it has been estimated that 10% to 30% of patients with ADHD do not respond adequately to MPH.[47] In contrast to MDD and AD, substantially more imaging research has been performed in children with ADHD compared with adults. Therefore, studies in this section are grouped only by neuroimaging measure used and not by age.

Structural MR imaging findings in children with ADHD include a thinner pretreatment left medial PFC[48] and smaller corpus callosum,[49] reversed caudate asymmetry and smaller retro-callosal parietal-occipital white matter volumes,[50] as well as smaller posterior cerebellar lobes[51] in nonresponders. Moreno and colleagues[52] found a correlation between caudate nucleus and nucleus accumbens volumes and clinical and neuropsychological improvement after MPH treatment in 27 medication-naïve children with ADHD. This is in line with a meta-analysis reporting that reduced basal ganglia volume is the most prominent and replicable structural abnormality in ADHD.[53]

Most studies, however, have used invasive imaging with PET and SPECT, assessing dopamine (DA) transporter and D_1 and D_2 receptor availability, along with brain perfusion studies. Pediatric nonresponders to MPH seem to have different patterns of CBF ([^{99}mTc]HMPAO SPECT) in the frontal-striatal circuitry and the posterior attentional system.[54] In addition, children with ADHD who displayed higher off-medication CBF ([^{15}O]H_2O PET) in the midbrain, posterior cerebellum, and middle frontal gyrus were less likely to respond to MPH on current ADHD rating scales.[55] Similarly in adults, a large retrospective study in 157 patients demonstrated that prefrontal CBF change to a sustained attention task was a highly sensitive and specific predictor of response to stimulants, with prefrontal pole activation predicting adverse responses and deactivation predicting

good responses.[56] As for the dopamine system, high DAT binding was associated with poor response to stimulant treatment (and presence of homozygosity of the 10-repeat allele on the DAT-1 gene) in a small sample of children.[57] It was further observed in children that the lower the baseline striatal D_2 levels ([^{123}I]IBZM SPECT), the lower the response rate.[58] In adults, 2 studies found, contrary to results in children, that medication-naïve patients with high striatal DAT availability ([^{99}mTc]TRODAT SPECT) responded better to therapy with MPH than those with low DAT availability.[59,60]

A surprisingly small number of studies have investigated the relation between brain function and treatment response, despite the wealth of fMR imaging studies on the effect of stimulants on, for example, inhibition tasks. However, one study focusing on functional connectivity in children found that a good response to MPH is associated with reduced ventral striatal connectivity with the inferior frontal cortices when compared with poor responders.[61]

In sum, very few studies using nonionizing techniques have investigated treatment response in ADHD, and all have been in children. This might be due to the generally high treatment response of approximately 70%. However, this does not mean that we cannot improve treatment outcomes using personalized medicine, because many patients experience side effects, and therefore adherence can be low, especially in adults (**Table 2**). ADHD patients can be divided into several subgroups based on the different manifestations of EEG, which could predict their different treatment outcomes.[62] For the biomarker of brain volume detected by MRI, the degree of hippocampal subfields volume reduction in schizophrenia was associated with the dosage of antipsychotics.[63] The possible use of biomarkers for dose optimization would be beneficial in clinical practice.

Table 2
Predictive biomarkers of nonresponse to MPH in ADHD

Structural imaging	↓ Volume of caudate, cerebellum, corpus callosum, prefrontal cortex (children)
CBF	↑ CBF in midbrain, posterior cerebellum, and middle frontal gyrus, ACC, the left claustrum, and the right (children and adults)
DAT	↓ Striatal DAT in adults, ↑ DAT in children

Abbreviations: ↓, indicates a reduction; ↑, indicates a increase; ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; CBF, cerebral blood flow; DAT, dopamine transporter; MPH, methylphenidate.

FUTURE DIRECTIONS FOR PREDICTIVE PSYCHORADIOLOGICAL BIOMARKERS FOR PHARMACEUTICAL TREATMENT EFFECTS

None of the potential psychoradiological biomarkers reviewed are yet of sufficiently established clinical utility to inform the selection of a specific pharmacologic compound for an individual patient. Most studies described have been conducted in small samples or had clear shortcomings in their clinical design and treatment outcome assessment (which is beyond the scope of this article to review). Nevertheless, there is strong consensus that advanced multimodal approaches, combining neuroimaging, genetic, and proteomic techniques, should contribute to discovery of novel treatment predictors in psychiatric disorders. Progress so far has been sufficient to warrant enthusiasm, in which application of neuroimaging-based biomarkers would represent a paradigm shift and modernization of psychiatric practice. Therefore, the development of clinically useful biomarkers should be a top priority of mental health research, as recognized by the National Institute of Mental Health (NIMH), FDA, and EMA. The recently developed NIMH Research Domain Criteria (RDoC) Framework may aid in development of psychoradiological biomarkers by classifying mental disorders based on dimensions of observable behavior and neurobiological mechanisms, rather than symptoms alone. Furthermore, RDoC also suggests that several circuit-based behavioral dimensions may be shared across psychiatric disorders. However, it is important to note that the transition to RDoC will take time, and the question arises if and when treatment planning should be adjusted to this new framework. Moreover, it remains to be established whether RDoC parameters will be the ideal way forward to categorize or even dimensionally evaluate psychiatric patients.

Validation and Replication

Because the ultimate goal of psychoradiological biomarkers is to aid clinical practice and thus provide useful information over and above symptomatic and sociodemographic data, the next step is to validate potential biomarkers rigorously. Validation would entail demonstration that a biomarker can perform effectively and reproducibly and can facilitate improvement of treatment outcome or

prediction of prognosis in individual patients. Especially the latter is difficult. What is needed now is external validation of potential psychoradiological biomarkers in independent clinical samples of sufficient size and description in terms of their predictive value, sensitivity and specificity for a desired outcome. Although a biomarker would typically have sensitivity and specificity values higher than 90%, a modest predictive value might be clinically impactful, if the standard care is based on an arbitrary decision between 2 comparable alternatives. Then, longitudinal randomized designs are needed to quantify the clinical utility of the biomarkers, by demonstrating that in a biomarker-guided treatment arm versus a nonguided arm, their use is associated with a reduction in morbidity and improvement in quality of life. An example of a study evaluating the use of changes in face recognition in the first 2 weeks of antidepressant use in MDD as a predictive biomarker is the PReDiCT-trial, in which a validated algorithm is currently being tested in a pan-European multicenter randomized controlled trial.[64]

To generate a larger pool of potential biomarkers, it is essential that obligatory replication using identical paradigms in well-powered studies needs to be accepted as the norm. For instance, whereas amygdala activity in response to emotional stimuli was reported as a potential fMR imaging biomarker predicting symptom reduction in MDD and AD, it was found to have low within-subject reproducibility.[65] In addition, it is necessary to familiarize ourselves with the limits of our imaging techniques. As mentioned previously,[27] the expected change in the physiologic parameter of interest should be large enough as to overcome the intrinsic variability of our measurement. Biomarker development requires a priori designed, large-scale multisite treatment efficacy, notably randomized controlled trials with coordinated, pre-planned analysis plans that include independent validation, rather than post hoc sharing of data sets acquired from multiple studies with differing goals. To this purpose, reproducibility across sites should be tested using quality assurance tests on scanners as well as specific (automated) analysis software for data processing.

Multimodality

Given the multimodal nature of findings, it appears most promising to increase single-subject prediction accuracies by integrating biomarkers from neuroimaging data, genetic, and clinical information. Combining these modalities does not only hold the promise of more accurate predictions, but also enables the identification of the most efficient, nonredundant set of predictors. There is a definite lack of studies integrating clinical, genetic, and imaging information using machine learning approaches.[66] For instance, Whitfield-Gabrieli and colleagues[67] integrated clinical parameters and neuroimaging markers in patients with SAD (rs-fMR imaging and DTI), and predicted response to CBT substantially better than a current clinician-administrated measure of disease severity. Support vector machine classification was 84.6% accurate for predicting MPH response in ADHD using pretreatment demographic, clinical questionnaire, environmental, neuropsychological, neuroimaging, and genetic data,[68] although the neuroimaging measures were not the most differentiating subset of features. Another approach with potential would be normative modeling; an approach, which unlike machine learning approaches that use clustering to categorize cohorts, aims to map variation within the sample. In that way, it allows for parsing heterogeneity, while still allowing predictions at a patient-specific level.[69]

Noninvasive Biomarkers

Predictive biomarkers should not only be reliable and reproducible, but they should ideally also be as noninvasive as possible. Therefore, psychoradiological biomarkers ideally also should not make use of radiation or external contrast agents. For example, well-validated task-fMR imaging paradigms could be used to target specific cognitive functions or behavioral patterns that are aberrant in specific disorders or across RDoCs to discover biomarkers.[70] A more recent noninvasive technique is phMR imaging, which is based on the principle that neurotransmitter-specific drug challenges evoke regional changes in neurovascular coupling and resultant changes in brain hemodynamics. We have shown that phMR imaging may be a suitable alternative to assess the 5-HT and DA system,[71–73] although the field still has to establish itself in terms of sensitivity and specificity compared with conventional methods, such as PET and SPECT.[74] Nevertheless, by using phMR imaging in clinical trials, we were able to demonstrate important age-dependent changes induced by the SSRI fluoxetine and MPH on the developing brain.[75,76] Thus, in the near future phMR imaging could become the technique of choice to investigate differences in predictive biomarkers regarding treatment outcome across the life span, as there are notable differences in the neurobiological correlates of patients in different age cohorts (despite similarities in the clinical picture and

longitudinal course of psychiatric disorders in children and adults). In addition to phMR imaging, MRS could also be an interesting noninvasive imaging modality to aid in psychiatric biomarker research. Application of MRS at high field strengths and advances in acquisition protocols have improved MRS data significantly over the past decade.[77] Furthermore, MRS can directly measure concentrations of 2 of the most important neurotransmitters in the brain, that is, glutamate and GABA. These measurements are not based on hemodynamic measurements and are therefore less influenced by cardiovascular changes that can be induced by comorbid illness, medication, or age. In sum, the literature on psychoradiological imaging biomarkers that target treatment response is in general highly heterogeneous, with underpowered studies and a large amount of variation in techniques and analysis approaches. The most replicated finding at present is the relation of antidepressant treatment response to hippocampal (subfield) size. But with rigorous validation and replication studies, with emphasis on multimodal and noninvasive imaging biomarkers, obtained in large-scale consortia, psychoradiological biomarkers for psychopharmaceutical effects have the potential to revolutionize clinical psychiatry.

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