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Review

Neuroimaging markers of antipsychotic treatment response in schizophrenia: An overview of magnetic resonance imaging studies

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ABSTRACT

Antipsychotic drugs are the primary treatment for psychosis, yet individual response to their administration remains variable. At present, no biological predictors of response exist to guide clinicians as they select treatments for patients, and our understanding of the neurobiology underlying the heterogeneity of outcomes remains limited. Magnetic Resonance Imaging (MRI) has been applied by numerous studies to examine the response to antipsychotic treatment, though a large gap remains between their results and our clinical practice. To advance patient care with precision medicine approaches, prior work must be accounted for and built upon with future studies. This review provides an overview of studies that relate treatment outcome to various MRI-related measures, including structural, spectroscopic, diffusion tensor, and functional imaging. Knowledge derived from these studies will be discussed along with future directions for the field.

1. Introduction

Since its inception, there has been a vast acceleration in the application of magnetic resonance imaging (MRI) to characterize neural correlates of psychiatric illness. Numerous studies have applied this technology to examine the complex phenotypic manifestations and illness trajectories observed in disorders such as schizophrenia. While neuroimaging continues to hold promise as a tool for diagnostic classification, risk quantification, and prognostic assessment, the gap between existing findings and clinical practice remains significant.

Recent work, combined with evidence from decades of neuroimaging findings, has conceptualized schizophrenia as a 'dysconnectivity' syndrome consisting of abnormalities in large-scale functional networks, along with a background of neuroanatomic deficits, including ventricular enlargement and widespread reductions in grey matter (Nejad et al., 2012; van den Heuvel and Fornito, 2014). These neural mechanisms, however, are not yet able to characterize an individual patient's variation in symptom manifestation, response to antipsychotic treatment, or associated social and functional disabilities. Moving toward precision-based assessments with MRI necessitates further studies that build from our existing evidence base.

The following review first addresses the evidence supporting the existence of heterogeneous responses to antipsychotic treatment. Second, studies reporting magnetic resonance structural and spectroscopic findings associated with treatment efficacy will be discussed, followed by functional neuroimaging measures associated with outcomes to antipsychotic treatment. Finally, the potential role for neuroimaging-related measures as prognostic biomarkers of treatment response or outcomes is discussed. Within this text, various definitions of outcomes and response will be considered, in addition to stage of illness examined, given the importance of markers at both onset and in chronic illness. Measures from MRI hold promise as both noninvasive and widely accessible methods for tracking and predicting treatment outcomes in schizophrenia. This review focuses on measures associated with efficacy and outcomes to treatment, which is an important distinction from studies that examine the effect of medications on brain structure and function. Antipsychotic treatment is emphasized alongside studies examining more general outcomes to treatment approaches, which include psychosocial interventions.

1.1. Heterogeneity of treatment outcomes in schizophrenia

Chronic psychotic disorders are thought to be encoded during neurodevelopment; they typically appear insidiously during adolescence and young adulthood (Millan et al., 2016). Antipsychotic treatment primarily targets psychotic symptoms, which include hallucinations, delusions, and disorganized thought processes, but does not significantly ameliorate negative and cognitive symptoms, or the severe functional and social impairments characteristic of the illness (Kane and Correll, 2010; Millan et al., 2012; Remington et al., 2016). Moreover, response to administration of antipsychotic drugs is variable and cannot be accurately predicted by treating clinicians (Carbon and Correll,

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2014).

The heterogeneous treatment courses encountered in individuals diagnosed with schizophrenia has been described for many decades. In early longitudinal studies, conducted prior to the availability of antipsychotics and reliable classifications of psychotic disorders, evidence showed several illness courses following an initial psychotic episode (Bleuler, 1968). Subsequent to the advent of antipsychotic drugs and consistent classification systems of psychiatric illness, Huber et al. demonstrated that over a twenty-year follow-up period, patients with schizophrenia assumed up to twelve treatment trajectories, ranging from persistent and refractory to monophasic illnesses (Huber et al., 1980). More recent studies and current practice supports this vast degree of variation in response to treatment (Carbon and Correll, 2014). Psychotic illness trajectories formulate over time and, at illness onset, clinicians have no reliable biological or clinical prognostic measures that identify a patient's responsiveness to antipsychotic drugs or their future treatment outcomes.

All antipsychotic medications, the mainstay for treatment of psychotic symptoms in schizophrenia, target the dopamine D2 receptor (Kapur and Mamo, 2003). An individual's antipsychotic treatment is selected by a trial-and-error process, with no guidance from quantitative markers. To date, blood-based markers have not shown promise as reliable prognostic tests, including pharmacogenomics assays. While other areas of medicine have progressed toward precision medicine, psychiatric treatment lags behind. Nonresponse to antipsychotic treatment, which occurs in up to 40% of patients, accounts for immense disability and health care expenditure (Kennedy et al., 2014). Clozapine remains unique for its superior efficacy in patients who have failed other antipsychotic drugs due to unknown mechanisms. For patients who fail clozapine, electroconvulsive therapy, long known to be efficacious for psychotic symptoms, has emerged as a potential treatment (Petrides et al., 2015). Classification of patients based on responsiveness to these therapies, prior to treatment, may emerge as standard practice if reliable biomarkers are identified (Remington et al., 2015).

Across studies, definitions of response vary. An assortment of outcomes and groupings of patients are represented below and reflect the complexity of the illness and the methods for characterizing outcomes. Standardization of response criteria has been suggested by several studies (Andreasen et al., 2005; Emsley et al., 2007), including a rigorous and uniform definition of nonresponse (Howes et al., 2017). In the studies reviewed below, a variety of response criteria and definitions are mentioned.

1.2. Structural MRI studies

Overall, a greater number of studies have focused on structural neuroimaging measures than functional and spectroscopic modalities. Several studies examined ventricular size and outcome to treatment. In a prospective, longitudinal study of individuals with first-episode psychosis, Lieberman and colleagues reported that in patients with poor outcome to treatment, significant ventricular enlargement was observed from serial MRI scans over the course of several years, whereas the patients with better treatment outcomes and control subjects did not show ventricular enlargements (Lieberman et al., 2001). Supporting this finding, an independent longitudinal study reported that patients with poorer outcomes to treatment had greater ventricular enlargements over time (Ho et al., 2003). In a cross-sectional comparison of outcomes, defined by percent time hospitalized in the previous year, smaller frontal lobe volumes and larger ventricles were observed in patients with poorer outcome (Staal et al., 2001). Similarly, ventricular enlargement was shown to be specific to antipsychotic type. Lieberman et al. (2005) demonstrated that ventricular enlargement may be specific to antipsychotic treatment with first-generation drugs. A greater improvement in overall ratings of psychopathology and negative symptoms correlated with less ventricular volume increase in patients treated with olanzapine than with haloperidol. While Garver et al. (2000) argued that clustering of patients by patterns of response over time reflects biological subtypes with different rates of changes in ventricular volume, their results are inconsistent with the above findings. They showed that patients with a delayed response to antipsychotic treatment exhibit more rapid increases in ventricle volume over the course of treatment; however, non-responders to treatment showed no change in ventricular volumes in contrast to the majority of findings examining response and ventricular size. In a more recently published study, increases in ventricular volume correlated with less reductions of negative symptoms in first-episode psychosis patients during treatment with quetiapine (Ebdrup et al., 2011).

In addition to changes in ventricular size, structural MRI studies have shown morphological findings related to treatment response, largely focused on frontal and temporal brain regions. In data selected from a large population cohort, Jääskeläinen and colleagues reported that greater frontal and limbic grey matter densities are associated with improved functional and clinical outcomes to treatment (Jaaskelainen et al., 2014). Supporting this result, non-responders to treatment showed reduced grey matter volumes in middle frontal gyrus, bilaterally, and in the medial temporal cortex (Quarantelli et al., 2014). Left prefrontal grey matter volumes were associated with poorer overall functioning after one year in a small cohort of male patients with schizophrenia (Kasparek et al., 2009). Relationships were found between reductions in negative symptoms and increased thickness of middle frontal gyrus with atypical antipsychotic treatment in first-episode patients (Goghari et al., 2013; Stip et al., 2009; Yue et al., 2016), and in patients treated with clozapine relative to haloperidol (Arango et al., 2003). Prasad and colleagues demonstrated that volume of the dorsolateral prefrontal cortex positively predicted a functional outcome score that incorporated social contacts, employment, and symptomatology, after one year of treatment (Prasad et al., 2005). Treatment-resistant patients showed reduced cortical thickness in dorsolateral prefrontal cortex, indicating a pathophysiological marker for a more severe illness (Zugman et al., 2013).

Meanwhile, converging findings related to treatment outcome have been reported in medial temporal structures. Greater hippocampal volumes were associated with response to antipsychotic treatment in both cross-sectional and longitudinal studies (Panenka et al., 2007; Savas et al., 2002). Similarly, Bodnar and colleagues examined first-episode psychosis patients who were carefully classified as responders or non-responders by the Schizophrenia Working Group remission criteria, and found that responders demonstrated larger volumes of the parahippocampal cortex, bilaterally (Bodnar et al., 2011; Bodnar et al., 2012b). Further supporting the role of frontal and temporal brain volumes in response to treatment, positive relationships between change in total and temporal grey matter volumes and reductions of psychotic symptoms have been reported (McClure et al., 2006). An analysis of gyrification in individuals with first-episode psychosis revealed that non-responders to naturalistic antipsychotic treatment showed decreased gyrification in insula, frontal and temporal regions (Palaniyappan et al., 2013). In addition, hemispheric asymmetry of frontal cortex was observed in non-responders to antipsychotic treatment, along with greater thickness of temporal regions in patients with more rapid response to antipsychotic treatment (Szeszko et al., 2012).

Findings associated with treatment response have been reported beyond frontotemporal brain regions. A reduced baseline cross-sectional area of the left anterior limb of the internal capsule was noted in patients with first-episode psychosis who demonstrated clinical deterioration with one year of treatment relative to those with more stable measures of psychopathology (Wobrock et al., 2009). A greater measurement of total cortical grey matter was shown to be associated with improvement in psychotic symptoms following antipsychotic treatment, with response defined by a 15% or higher reduction in baseline symptom ratings (Zipursky et al., 1998). Similarly, a measurement of total grey matter volume change after one year of treatment showed that a greater decrease was associated with a greater need for

psychosocial support after five years (Cahn et al., 2006). A decline in social and occupational functioning was associated with a right supramarginal gyrus reduction (Guo et al., 2015). Reductions in psychotic symptoms after four weeks of antipsychotic treatment correlated with expansion of the thalamus (Strungas et al., 2003). After a much longer follow-up of seven years, reduced cerebellar volume was associated with greater symptomatology and poorer psychosocial functioning (Wassink et al., 1999). Increased striatal volume was observed in relation to reductions in psychosis after six weeks of antipsychotic treatment (Li et al., 2012). In female patients, striatal and thalamic volumes at baseline predicted remission after one year of treatment (Fung et al., 2014).

While positive findings are described above, studies have also reported consistent negative findings between morphology and response to treatment. This includes studies of early phase psychosis that utilize longitudinal study designs (Friedman et al., 1992; Lawrie et al., 1995; Molina et al., 2014; Robinson et al., 1999; Roiz-Santianez et al., 2012; Scheepers et al., 2001; van Haren et al., 2003). Consistent with these negative studies, a meta-analysis of studies focused on changes in grey matter and ventricular volume with symptoms reduction failed to show the significant results described in individual studies, including the ones outlined above (Fusar-Poli et al., 2013). Reasons for this may reflect their small sample sizes; variation in treatment approaches and definitions of response; and non-overlapping neuroimaging and analytic approaches. Due to the variance introduced by these factors, any potentially meaningful meta-analytic finding may be diminished.

More recent work has used structural MRI and graph theoretical measures to examine response to antipsychotic treatment. In a cohort of 80 patients examined during 12 weeks of treatment, measures of gyrification across the brain were entered into a connectomic analysis to examine large-scale patterns of structural covariance (Palaniyappan et al., 2016). This approach, which examines cortical folding patterns between responders and non-responders, may reflect developmentally mediated dysconnectivity. Non-responders to treatment showed an overall unstable pattern of increased segregation, and impaired integration of structural relationships, possibly reflecting poor information flow throughout the brain.

1.3. Treatment outcomes and diffusion tensor imaging (DTI)

In addition to studies of grey matter, several investigations, reviewed below, examined efficacy of antipsychotic treatment along with measures of white matter integrity. Studies using DTI frequently measure fractional anisotropy (FA), which represents the movement of water diffusion and provides a putative measure of myelination and organization of white matter tracts. Most published studies were designed to examine changes in DTI measures in relation to antipsychotic exposure (Bartzokis et al., 2011; Samartzis et al., 2014; Szeszko et al., 2014). However, a few report state-dependent changes in white matter related to the amelioration of psychotic symptoms. Reductions in FA were reported in the uncinate and superior longitudinal fasciculi in first-episode psychosis patients with poor outcome to treatment, measured at 6 months (Luck et al., 2011). Consistent with this report, Zeng and colleagues found that over the course of 8 weeks of antipsychotic therapy, increases in FA of the superior longitudinal fasciculi was coupled with more efficacious treatment (Zeng et al., 2016). Reis Marques et al. (2014) reported findings from a longitudinal study of 63 first-episode psychosis patients with response criteria determined by the Schizophrenia Working Group (Andreasen et al., 2005). No change was found in FA following twelve weeks of antipsychotic treatment, but a negative correlation was observed between baseline psychopathology and FA. Other studies in first-episode psychosis patients reported widespread increases in fractional anisotropy in patients with greater reductions in ratings of psychopathology (Mitelman et al., 2006; Serpa et al., 2017). One report found an increase in mean diffusivity in a small cohort of patients with significant reductions in psychotic symptoms after one month of antipsychotic treatment (Garver et al., 2008). More recent work has broadened the scope applicability for DTI to inform treatment response by using network-based methods. Crossley et al. (2017) used DTI tractography, graph analysis and network-based statistics to examine antipsychotic treatment in a cohort of first-episode patients. They found that ultimate responders to 12 weeks of treatment display greater efficiency in their baseline DTI-derived structural connectomes, which may reflect a capacity for more organized information flow throughout the brain.

1.4. Spectroscopic neuroimaging studies

Several studies focused on treatment-related MR spectroscopy (MRS) analyses. While two studies failed to demonstrate a correlation between changes in dorsolateral prefrontal cortical MRS assessments of N-acetylaspartate and changes in symptomatology (Bertolino et al., 2001; Ertugrul et al., 2009), the majority of studies demonstrate an elevated concentrations of glutamate in nonresponsive illness. In a longitudinal study, de la Fuente-Sandoval and colleagues demonstrated that glutamate concentrations within the striatum remain elevated in non-responders to four weeks of antipsychotic treatment (de la Fuente-Sandoval et al., 2013). A study of clozapine responsiveness also demonstrated increased glutamate in the striatum in refractory patients (Goldstein et al., 2015). Furthermore, a group of published studies consistently reveal increased glutamate concentrations in the anterior cingulate cortex in patients who do not respond to antipsychotic treatment (Demjaha et al., 2014; Egerton et al., 2012; Mouchlianitis et al., 2016). However, in contrast to these results, one study showed that an improvement in negative symptoms correlates with increased prefrontal glutamate concentration in chronic patients with schizophrenia between a washout and follow-up, post-treatment scan, inconsistent with the above results (Szulc et al., 2011). The correspondence between the overall finding of increased glutamate in treatment non-responders is promising and merits further study into whether non-responders to treatment represent a non-dopaminergic subtype of patients with a distinct abnormality of the glutamatergic system (Howes and Kapur, 2014).

1.5. Evidence from task-based functional MRI (fMRI) studies

Functional activation of brain regions by cognitive paradigms has been examined in the context of treatment outcomes in patients with schizophrenia. While some studies reported no changes in activation during treatment (Blasi et al., 2009; Snitz et al., 2005), others reported treatment-related findings, primarily in frontal and striatal regions. Passive viewing of emotionally negative stimuli in the context of successful antipsychotic treatment over twenty-two weeks was associated with significant increases in activation of the dorsolateral prefrontal cortex, anterior cingulate cortex and striatum (Fahim et al., 2005). In clozapine-treated patients, responders showed increased activation of dorsomedial prefrontal regions (Potvin et al., 2015). Though not addressing antipsychotic treatment, increased dorsolateral prefrontal activity was also noted to predict successful response to cognitive behavioral therapy for psychotic symptoms (Kumari et al., 2009). Moreover, Bodnar and colleagues observed increased activation in posterior cingulate in non-remitters relative to patients who responded to treatment during memory encoding, indicating more engagement of portions of the default mode network during the task (Bodnar et al., 2012a). A study by van Veelen et al. (2011) found that in treatment naive first-episode psychosis patients, nonresponse to a ten-week trial of antipsychotic treatment was associated with greater dysfunction of dorsolateral prefrontal activation during a working memory task. Two studies highlighted changes in activation of the striatum with antipsychotic treatment. In contrast to the findings above, engagement of the ventral striatum during reward processing was normalized with efficacious treatment with atypical antipsychotic treatment in first-

Table 1
Summary of neuroimaging findings.

Structural studies	Psychotic patients who did not respond to antipsychotic treatment showed increased ventricular volume and reduced frontal and medial temporal lobe grey matter over time (Bodnar et al., 2012b; Ho et al., 2003; Jaaskelainen et al., 2014; Lieberman et al., 2001). Some evidence implicates changes in other brain regions (Li et al., 2012; Palaniyappan et al., 2013).
Diffusion tensor Imaging studies	Reduced FA has been found in in non-responders, though studies are limited (Luck et al., 2011; Zeng et al., 2016).
Spectroscopic studies	Persistent prefrontal and striatal glutamate levels are observed in non-responders to antipsychotic treatment (de la Fuente-Sandoval et al., 2013; Demjaha et al., 2014; Egerton et al., 2012; Mouchlianitis et al., 2016).
Task-based functional studies	Normalization and increased dorsolateral prefrontal and striatal activation is reported in responders, across studies (Bodnar et al., 2012a; Nielsen et al., 2012).
Functional connectivity studies	Increases in functional connectivity between striatum, prefrontal cortical regions, and hippocampus are observed with treatment in responders (Kraguljac et al., 2016b; Sarpal et al., 2015). Normalization of large-scale functional networks is also implicated (Lottman et al., 2017; Lui et al., 2010).

episode patients (Nielsen et al., 2012), and antipsychotic-induced weight gain was associated with increased reward-dependent activation within the striatum in the context of treatment response, suggesting a relationship between cognitive engagement and metabolic outcomes (Nielsen et al., 2016). More recent work has further differentiated antipsychotic treatment response by a reward-related mechanism (Vanes et al., 2018). Further supporting the view that non-responders to treatment may exhibit a non-dopaminergic pathophysiology, in this study, responders to treatment displayed significant attenuated reward-related striatal activation compared to both treatment-resistant patients and healthy volunteers.

1.6. Functional connectivity and treatment outcomes

In recent years, there has been an acceleration of published findings reporting changes in resting-state functional connectivity during antipsychotic treatment. Resting-state scans are a convenient method for examining the functional architecture of the brain without the need for cognitive paradigms. Analytic approaches to resting state connectivity data range from correlations between targeted regions of interest to assessments of global connectivity interested in small-world properties of information flow throughout the brain.

Several studies have shown state-dependent changes in functional interactions between subcortical and prefrontal regions during treatment. An increase in functional connectivity of the striatum with critical limbic and prefrontal regions, including the hippocampus, dorsolateral prefrontal and anterior cingulate cortices, was associated with greater efficacy of a twelve-week trial of antipsychotic treatment in twenty-four first-episode patients with schizophrenia (Sarpal et al., 2015). Baseline striatal connectivity at treatment initiation also demonstrated success as a prognostic marker of response to antipsychotic treatment in two independent cohorts (Sarpal et al., 2016), and as a mediator of the negative relationship between duration of untreated psychosis and response to antipsychotic treatment (Sarpal et al., 2017). A role for connectivity changes involving the striatum, hippocampus, and the anterior cingulate cortex in the mechanism of response is further supported by other longitudinal, treatment-based studies (Anticevic et al., 2015; Kraguljac et al., 2016b). In addition to the striatum, ventral tegmental area and midbrain connectivity strength to the anterior cingulate cortex positively correlated with good response to a six-week course of risperidone (Hadley et al., 2014). Taken together, these studies provide important evidence that successful antipsychotic treatment is associated with increases in functional synchrony within a network of structures implicated in the pathophysiology of schizophrenia.

While the studies above focused on connectivity of specific subcortical structures, additional studies have examined assessments of large-scale functional connectivity networks in the context of therapeutic efficacy. Successful treatment with olanzapine was associated with increases in connectivity within the default mode network (Sambataro et al., 2010). Abnormal connectivity within the dorsal attention network in patients, relative to healthy volunteers at baseline, was attenuated with antipsychotic treatment (Kraguljac et al., 2016a). Six weeks of antipsychotic treatment was noted to be associated with normalization of functional connectivity between canonical functional networks and subcortical structures in the context of symptom reduction (Lui et al., 2010). In more recent studies, novel analytic methods of functional connectivity have shown normalization of networks, or null findings with antipsychotic treatment (Bai et al., 2016; Guo et al., 2017a; Guo et al., 2017b; Lottman et al., 2017; Wang et al., 2017). One recent study with a small number of patients demonstrated significant connectivity deficits in patient who failed treatment clozapine (Mcnabb et al., 2018). Though a general theme of normalization within these whole-brain networks is noted, it is also apparent that analytic approaches vary significantly and do not facilitate the convergence of these findings. Further studies are needed that consolidate these datasets and analytic approaches and reconcile with subcortical region of interest analyses.

2. Discussion

What could we take away from the studies described above? Collectively, there is evidence that neuroimaging markers may shed light on the mechanism associated with successful treatment to antipsychotic drugs, information that might provide prognostic information and dissect the heterogeneity encountered during treatment of psychotic symptoms with antipsychotic medications (Table 1). Findings from structural MRI studies indicate that non-responders to treatment exhibit greater ventricular volumes, along with decreased grey matter volumes in frontal and medial temporal regions and other limbic and cortical structures. Some consistency is observed between structural and functional MRI studies, though the variance in this literature is considerable. While there is some evidence that non-responders to antipsychotic treatment display decreased white matter integrity in various tracts, findings from DTI studies are limited in numbers. Explicit conclusions cannot be confidently made linking treatment response to MRS measures, though recent spectroscopic studies consistently differentiate responders from non-responders with glutamatergic measurements in the striatum and ventromedial prefrontal cortex. Evidence from fMRI studies indicate that responders show increased activation and connectivity in functional circuits centered around the prefrontal cortex, striatum, and other subcortical structures. It is unknown what the relationship is between findings from each individual imaging modality, especially between the structural and functional findings highlighted above. The conclusions in this review are like those drawn from previous discussions of neuroimaging and antipsychotic treatment response (Dazzan et al., 2015; Kani et al., 2017), and important questions remain: are non-responders to treatment a unique subset of patients? And can response to a treatment parse the clinical heterogeneity encountered during treatment of schizophrenia?

More work is required for a clear understanding of the neural pathophysiology underlying therapeutic effects of antipsychotic medications. This will require replication of study designs, strict and consistent outcome measures based on standardized rating scales, consolidation of

multimodal datasets from multicenter studies. In addition, improved integration between clinical trials and MRI scanning will help bridge the gap between our clinical observations and circuit-level neural measures. Future work may also determine whether MRI markers are strengthened with combinations of demographic, neurocognitive, and pharmacogenomic markers of treatment outcome. While this review focuses on antipsychotic drugs, other treatment modalities that have shown efficacy for psychosis should be examined, including neuromodulatory techniques such as electroconvulsive therapy, transcranial magnetic stimulation, and various psychosocial interventions. Contextualizing psychotic symptoms dimensionally across disorders, in line with the Research Domain Criteria, may also enhance our strategies for precision medicine and enrich our neuroimaging-based measures by identifying structures and neural circuits that serve as treatment targets (Ford et al., 2014; Insel, 2014). Future directions for the field also include the merging of neuroimaging measures with machine learning and other complex analytic approaches to transition from descriptions of differences between groups of patients, to inferences that can be made for an individual (Bzdok and Meyer-Lindenberg, 2018; Mourao-Miranda et al., 2012). The fruits of this line of work should lead the field toward precision medicine approaches to treatment of schizophrenia (Abi-Dargham and Horga, 2016).

In conclusion, existing studies point to the possibility that the heterogeneity in clinical outcomes to antipsychotic treatment in patient with schizophrenia may reflect neurobiologically distinct patient subtypes. These results have not integrated with clinical algorithms, which necessitates further work. To develop novel therapeutic approaches, focusing clinical trials on specific clusters of patients with distinct biological profiles may maximize efficacy of pharmacological and nonpharmacological interventions. Progress in this endeavor will accurately cluster clinical populations prior to treatment for more efficacious and personalized results. Neuroimaging may continue to play a crucial role in this effort.

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References

Abi-Dargham, A., Horga, G., 2016. The search for imaging biomarkers in psychiatric disorders. Nat. Med. 22, 1248–1255.
Andreasen, N.C., et al., 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. Am. J. Psychiatry 162, 441–449.
Anticevic, A., et al., 2015. Early-course unmedicated schizophrenia patients exhibit elevated prefrontal connectivity associated with longitudinal change. J. Neurosci. 35, 267–286.
Arango, C., et al., 2003. The relationship of clozapine and haloperidol treatment response to prefrontal, hippocampal, and caudate brain volumes. Am. J. Psychiatry 160, 1421–1427.
Bai, Y., et al., 2016. Altered resting-state regional homogeneity after 13 weeks of paliperidone injection treatment in schizophrenia patients. Psychiatry Res. 258, 37–43.
Bartzokis, G., et al., 2011. Long acting injection versus oral risperidone in first-episode schizophrenia: differential impact on white matter myelination trajectory. Schizophr. Res. 132, 35–41.
Bertolino, A., et al., 2001. The effect of treatment with antipsychotic drugs on brain N-acetylaspartate measures in patients with schizophrenia. Biol. Psychiatry 49, 39–46.
Blasi, G., et al., 2009. Changes in prefrontal and amygdala activity during olanzapine treatment in schizophrenia. Psychiatry Res. 173, 31–38.
Bleuler, M., 1968. A 23-year longitudinal study of 208 schizophrenics and impressions in regard to the nature of schizophrenia. J. Psychiatr. Res. 6, 3–12.
Bodnar, M., et al., 2011. The parahippocampal gyrus as a neural marker of early remission in first-episode psychosis: a voxel-based morphometry study. Clin. Schizophr. Relat. Psychoses. 4, 217–228.
Bodnar, M., et al., 2012a. Functional magnetic resonance imaging correlates of memory encoding in relation to achieving remission in first-episode schizophrenia. Br. J. Psychiatry 200, 300–307.
Bodnar, M., et al., 2012b. Neural markers of early remission in first-episode schizophrenia: a volumetric neuroimaging study of the parahippocampus. Psychiatry Res. 201, 40–47.
Bzdok, D., Meyer-Lindenberg, A., 2018. Machine learning for precision psychiatry: opportunities and challenges. Biol. Psychiatry Cogn. Neurosci. Neuroimaging. 3, 223–230.
Cahn, W., et al., 2006. Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. Br. J. Psychiatry 189, 381–382.
Carbon, M., Correll, C.U., 2014. Clinical predictors of therapeutic response to antipsychotics in schizophrenia. Dialogues Clin. Neurosci. 16, 505–524.
Crossley, N.A., et al., 2017. Connectomic correlates of response to treatment in first-episode psychosis. Brain 140, 487–496.
Dazzan, P., et al., 2015. Magnetic resonance imaging and the prediction of outcome in first-episode schizophrenia: a review of current evidence and directions for future research. Schizophr. Bull. 41, 574–583.
de la Fuente-Sandoval, C., et al., 2013. Glutamate levels in the associative striatum before and after 4 weeks of antipsychotic treatment in first-episode psychosis: a longitudinal proton magnetic resonance spectroscopy study. JAMA Psychiatry. 70, 1057–1066.
Demjaha, A., et al., 2014. Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. Biol. Psychiatry 75, e11–e13.
Ebdrup, B.H., et al., 2011. Progressive striatal and hippocampal volume loss in initially antipsychotic-naive, first-episode schizophrenia patients treated with quetiapine: relationship to dose and symptoms. Int. J. Neuropsychopharmacol. 14, 69–82.
Egerton, A., et al., 2012. Anterior cingulate glutamate levels related to clinical status following treatment in first-episode schizophrenia. Neuropsychopharmacology 37, 2515–2521.
Emsley, R., et al., 2007. Remission in early psychosis: rates, predictors, and clinical and functional outcome correlates. Schizophr. Res. 89, 129–139.
Ertugrul, A., et al., 2009. The effect of clozapine on regional cerebral blood flow and brain metabolite ratios in schizophrenia: relationship with treatment response. Psychiatry Res. 174, 121–129.
Fahim, C., et al., 2005. Differential hemodynamic brain activity in schizophrenia patients with blunted affect during quetiapine treatment. J. Clin. Psychopharmacol. 25, 367–371.
Ford, J.M., et al., 2014. Studying hallucinations within the NIMH RDoC framework. Schizophr. Bull. 40 (Suppl. 4), S295–S304.
Friedman, L., et al., 1992. The relationship of structural brain imaging parameters to antipsychotic treatment response: a review. J. Psychiatry Neurosci. 17, 42–54.
Fung, G., et al., 2014. MRI predicts remission at 1 year in first-episode schizophrenia in females with larger striato-thalamic volumes. Neuropsychobiology 69, 243–248.
Fusar-Poli, P., et al., 2013. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci. Biobehav. Rev. 37, 1680–1691.
Garver, D.L., et al., 2000. Heterogeneity of response to antipsychotics from multiple disorders in the schizophrenia spectrum. J. Clin. Psychiatry. 61, 964–972 (quiz 973).
Garver, D.L., et al., 2008. Compromised myelin integrity during psychosis with repair during remission in drug-responding schizophrenia. Int. J. Neuropsychopharmacol. 11, 49–61.
Goghari, V.M., et al., 2013. Effects of eight weeks of atypical antipsychotic treatment on middle frontal thickness in drug-naive first-episode psychosis patients. Schizophr. Res. 149, 149–155.
Goldstein, M.E., et al., 2015. Glutamatergic neurometabolites in clozapine-responsive and -resistant schizophrenia. Int. J. Neuropsychopharmacol. 18.
Guo, J.Y., et al., 2015. Longitudinal regional brain volume loss in schizophrenia: relationship to antipsychotic medication and change in social function. Schizophr. Res. 168, 297–304.
Guo, W., et al., 2017a. Olanzapine modulates the default-mode network homogeneity in recurrent drug-free schizophrenia at rest. Aust. N Z J Psychiatry. 51, 1000–1009.
Guo, W., et al., 2017b. Treatment effects of olanzapine on homotopic connectivity in drug-free schizophrenia at rest. World J. Biol. Psychiatry. 1–9.
Hadley, J.A., et al., 2014. Ventral tegmental area/midbrain functional connectivity and response to antipsychotic medication in schizophrenia. Neuropsychopharmacology 39, 1020–1030.
Ho, B.C., et al., 2003. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. Arch. Gen. Psychiatry 60, 585–594.
Howes, O.D., Kapur, S., 2014. A neurobiological hypothesis for the classification of schizophrenia: type a (hyperdopaminergic) and type B (normodopaminergic). Br. J. Psychiatry 205, 1–3.
Howes, O.D., et al., 2017. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. Am. J. Psychiatry 174, 216–229.
Huber, G., et al., 1980. Longitudinal studies of schizophrenic patients. Schizophr. Bull. 6, 592–605.
Insel, T.R., 2014. The NIMH research domain criteria (RDoC) project: precision medicine for psychiatry. Am. J. Psychiatry 171, 395–397.

Jaaskelainen, E., et al., 2014. Associations between brain morphology and outcome in schizophrenia in a general population sample. Eur. Psychiatry. 29, 456–462.
Kane, J.M., Correll, C.U., 2010. Past and present progress in the pharmacologic treatment of schizophrenia. J. Clin. Psychiatry. 71, 1115–1124.
Kani, A.S., et al., 2017. Converging effects of diverse treatment modalities on frontal cortex in schizophrenia: a review of longitudinal functional magnetic resonance imaging studies. J. Psychiatr. Res. 84, 256–276.
Kapur, S., Mamo, D., 2003. Half a century of antipsychotics and still a central role for dopamine D2 receptors. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 27, 1081–1090.
Kasparek, T., et al., 2009. Gray matter morphology and the level of functioning in one-year follow-up of first-episode schizophrenia patients. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 33, 1438–1446.
Kennedy, J.L., et al., 2014. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. Int. Clin. Psychopharmacol. 29, 63–76.
Kraguljac, N.V., et al., 2016a. Abnormalities in large scale functional networks in unmedicated patients with schizophrenia and effects of risperidone. Neuroimage Clin. 10, 146–158.
Kraguljac, N.V., et al., 2016b. Aberrant hippocampal connectivity in Unmedicated patients with schizophrenia and effects of antipsychotic medication: a longitudinal resting state functional MRI study. Schizophr. Bull. 42, 1046–1055.
Kumari, V., et al., 2009. Dorsolateral prefrontal cortex activity predicts responsiveness to cognitive-behavioral therapy in schizophrenia. Biol. Psychiatry 66, 594–602.
Lawrie, S.M., et al., 1995. Magnetic resonance imaging and single photon emission tomography in treatment-responsive and treatment-resistant schizophrenia. Br. J. Psychiatry 167, 202–210.
Li, M., et al., 2012. Volume increases in putamen associated with positive symptom reduction in previously drug-naive schizophrenia after 6 weeks antipsychotic treatment. Psychol. Med. 42, 1475–1483.
Lieberman, J., et al., 2001. Longitudinal study of brain morphology in first episode schizophrenia. Biol. Psychiatry 49, 487–499.
Lieberman, J.A., et al., 2005. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch. Gen. Psychiatry 62, 361–370.
Lottman, K.K., et al., 2017. Risperidone effects on brain dynamic connectivity-a prospective resting-state fMRI study in schizophrenia. Front. Psychiatry. 8, 14.
Luck, D., et al., 2011. Fronto-temporal disconnectivity and clinical short-term outcome in first episode psychosis: a DTI-tractography study. J. Psychiatr. Res. 45, 369–377.
Lui, S., et al., 2010. Short-term effects of antipsychotic treatment on cerebral function in drug-naive first-episode schizophrenia revealed by "resting state" functional magnetic resonance imaging. Arch. Gen. Psychiatry 67, 783–792.
McClure, R.K., et al., 2006. Regional change in brain morphometry in schizophrenia associated with antipsychotic treatment. Psychiatry Res. 148, 121–132.
Mcnabb, C.B., et al., 2018. Functional network dysconnectivity as a biomarker of treatment resistance in schizophrenia. Schizophr. Res. 195, 160–167.
Millan, M.J., et al., 2012. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat. Rev. Drug Discov. 11, 141–168.
Millan, M.J., et al., 2016. Altering the course of schizophrenia: progress and perspectives. Nat. Rev. Drug Discov. 15, 485–515.
Mitelman, S.A., et al., 2006. White matter fractional anisotropy and outcome in schizophrenia. Schizophr. Res. 87, 138–159.
Molina, V., et al., 2014. Greater clinical and cognitive improvement with clozapine and risperidone associated with a thinner cortex at baseline in first-episode schizophrenia. Schizophr. Res. 158, 223–229.
Mouchlianitis, E., et al., 2016. Treatment-resistant schizophrenia patients show elevated anterior cingulate cortex glutamate compared to treatment-responsive. Schizophr. Bull. 42, 744–752.
Mourao-Miranda, J., et al., 2012. Individualized prediction of illness course at the first psychotic episode: a support vector machine MRI study. Psychol. Med. 42, 1037–1047.
Nejad, A.B., et al., 2012. Brain connectivity studies in schizophrenia: unravelling the effects of antipsychotics. Curr. Neuropharmacol. 10, 219–230.
Nielsen, M.O., et al., 2012. Improvement of brain reward abnormalities by antipsychotic monotherapy in schizophrenia. Arch. Gen. Psychiatry 69, 1195–1204.
Nielsen, M.O., et al., 2016. Striatal reward activity and antipsychotic-associated weight change in patients with schizophrenia undergoing initial treatment. JAMA Psychiatry. 73, 121–128.
Palaniyappan, L., et al., 2013. Cortical folding defects as markers of poor treatment response in first-episode psychosis. JAMA Psychiatry. 70, 1031–1040.
Palaniyappan, L., et al., 2016. Globally efficient brain organization and treatment response in psychosis: a connectomic study of gyrification. Schizophr. Bull. 42, 1446–1456.
Panenka, W.J., et al., 2007. A longitudinal study on the effects of typical versus atypical antipsychotic drugs on hippocampal volume in schizophrenia. Schizophr. Res. 94, 288–292.
Petrides, G., et al., 2015. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. Am. J. Psychiatry 172, 52–58.
Potvin, S., et al., 2015. Emotion processing in treatment-resistant schizophrenia patients treated with clozapine: an fMRI study. Schizophr. Res. 168, 377–380.
Prasad, K.M., et al., 2005. Dorsolateral prefrontal cortex morphology and short-term outcome in first-episode schizophrenia. Psychiatry Res. 140, 147–155.
Quarantelli, M., et al., 2014. Patients with poor response to antipsychotics have a more severe pattern of frontal atrophy: a voxel-based morphometry study of treatment resistance in schizophrenia. Biomed. Res. Int. 2014, 325052.
Reis Marques, T., et al., 2014. White matter integrity as a predictor of response to treatment in first episode psychosis. Brain 137, 172–182.
Remington, G., et al., 2015. What does schizophrenia teach us about antipsychotics? Can. J. Psychiatr. 60, S14–S18.
Remington, G., et al., 2016. Treating negative symptoms in schizophrenia: an update. Curr. Treat. Options Psychiatry. 3, 133–150.
Robinson, D.G., et al., 1999. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. Am. J. Psychiatry 156, 544–549.
Roiz-Santianez, R., et al., 2012. Effect of antipsychotic drugs on cortical thickness. A randomized controlled one-year follow-up study of haloperidol, risperidone and olanzapine. Schizophr. Res. 141, 22–28.
Samartzis, L., et al., 2014. White matter alterations in early stages of schizophrenia: a systematic review of diffusion tensor imaging studies. J. Neuroimaging 24, 101–110.
Sambataro, F., et al., 2010. Treatment with olanzapine is associated with modulation of the default mode network in patients with schizophrenia. Neuropsychopharmacology 35, 904–912.
Sarpal, D.K., et al., 2015. Antipsychotic treatment and functional connectivity of the striatum in first-episode schizophrenia. JAMA Psychiatry. 72, 5–13.
Sarpal, D.K., et al., 2016. Baseline striatal functional connectivity as a predictor of response to antipsychotic drug treatment. Am. J. Psychiatry 173, 69–77.
Sarpal, D.K., et al., 2017. Relationship between duration of untreated psychosis and intrinsic corticostriatal connectivity in patients with early phase schizophrenia. Neuropsychopharmacology 42, 2214–2221.
Savas, H.A., et al., 2002. Hippocampal volume in schizophrenia and its relationship with risperidone treatment: a stereological study. Neuropsychobiology 46, 61–66.
Scheepers, F.E., et al., 2001. The effect of clozapine on caudate nucleus volume in schizophrenic patients previously treated with typical antipsychotics. Neuropsychopharmacology 24, 47–54.
Serpa, M.H., et al., 2017. State-dependent microstructural white matter changes in drug-naive patients with first-episode psychosis. Psychol. Med. 47, 2613–2627.
Snitz, B.E., et al., 2005. Lateral and medial hypofrontality in first-episode schizophrenia: functional activity in a medication-naive state and effects of short-term atypical antipsychotic treatment. Am. J. Psychiatry 162, 2322–2329.
Staal, W.G., et al., 2001. Structural brain abnormalities in chronic schizophrenia at the extremes of the outcome spectrum. Am. J. Psychiatry 158, 1140–1142.
Stip, E., et al., 2009. Increased grey matter densities in schizophrenia patients with negative symptoms after treatment with quetiapine: a voxel-based morphometry study. Int. Clin. Psychopharmacol. 24, 34–41.
Strungas, S., et al., 2003. State-related thalamic changes during antipsychotic treatment in schizophrenia: preliminary observations. Psychiatry Res. 124, 121–124.
Szeszko, P.R., et al., 2012. Magnetic resonance imaging predictors of treatment response in first-episode schizophrenia. Schizophr. Bull. 38, 569–578.
Szeszko, P.R., et al., 2014. White matter changes associated with antipsychotic treatment in first-episode psychosis. Neuropsychopharmacology 39, 1324–1331.
Szulc, A., et al., 2011. Proton magnetic resonance spectroscopy study of brain metabolite changes after antipsychotic treatment. Pharmacopsychiatry 44, 148–157.
van den Heuvel, M.P., Fornito, A., 2014. Brain networks in schizophrenia. Neuropsychol. Rev. 24, 32–48.
van Haren, N.E., et al., 2003. Brain volumes as predictor of outcome in recent-onset schizophrenia: a multi-center MRI study. Schizophr. Res. 64, 41–52.
van Veelen, N.M., et al., 2011. Prefrontal lobe dysfunction predicts treatment response in medication-naive first-episode schizophrenia. Schizophr. Res. 129, 156–162.
Vanes, L.D., et al., 2018. Differential neural reward mechanisms in treatment-responsive and treatment-resistant schizophrenia. Psychol. Med. 1–10.
Wang, Y., et al., 2017. Resting-state functional connectivity changes within the default mode network and the salience network after antipsychotic treatment in early-phase schizophrenia. Neuropsychiatr. Dis. Treat. 13, 397–406.
Wassink, T.H., et al., 1999. Cerebellar morphology as a predictor of symptom and psychosocial outcome in schizophrenia. Biol. Psychiatry 45, 41–48.
Wobrock, T., et al., 2009. Internal capsule size associated with outcome in first-episode schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 259, 278–283.
Yue, Y., et al., 2016. Regional abnormality of Grey matter in schizophrenia: effect from the illness or treatment? PLoS One 11, e0147204.
Zeng, B., et al., 2016. Abnormal white matter microstructure in drug-naive first episode schizophrenia patients before and after eight weeks of antipsychotic treatment. Schizophr. Res. 172, 1–8.
Zipursky, R.B., et al., 1998. MRI correlates of treatment response in first episode psychosis. Schizophr. Res. 30, 81–90.
Zugman, A., et al., 2013. Reduced dorso-lateral prefrontal cortex in treatment resistant schizophrenia. Schizophr. Res. 148, 81–86.