18 Structural and Functional Neuroimaging Biomarkers of Antipsychotic Treatment Response in Early-Course and Chronic Schizophrenia

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18.1 Introduction

Schizophrenia spectrum disorders typically emerge during adolescence and early adulthood, severely altering an individual's natural life course (Millan et al. 2016). Characteristic to these disorders are episodes of psychosis that include hallucinations of various modalities, delusional thought processes, and disorganized behavior. Numerous antipsychotic drugs exist to treat these symptoms and primarily target the dopamine D2 receptor, though response to their administration is variable and cannot be predicted (Kapur and Mamo 2003; Carbon and Correll 2014). Treatment decisions are based on trial and error, with no quantitative guidance, unlike in other areas of medicine where precision medicine strategies are integrated. Poor response to antipsychotic treatment, occurring in up to 40% of patients, accounts for a disproportionate amount of disability and health care expenditure (Kennedy et al. 2014).

Outcome trajectories coalesce over time and are unknown at illness onset. Heterogeneity of outcomes in individuals diagnosed with schizophrenia has been described for many decades. Early longitudinal studies, predating the availability of antipsychotic drugs, showed several

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illness courses following the emergence of psychotic symptoms (Bleuler 1968). Subsequent to the advent of antipsychotic drugs, Huber et al. demonstrated 12 treatment trajectories, ranging from persistent and refractory to monophasic illnesses in patients with schizophrenia (Huber et al. 1980). More recent evidence supports this vast degree of variation in outcome (Carbon and Correll 2014).

Many studies have sought to understand the neural mechanisms underlying variation of outcomes in schizophrenia. Neuroimaging methods have emerged as key contributors in this effort (See Chaps. 1, 3 and 5 for more details). Numerous studies have applied both structural and functional neuroimaging to examine the complex phenotypic manifestations and illness trajectories observed in disorders such as schizophrenia (See Chaps. 2, 4 and 6 for more details). While ongoing neuroimaging methods have the capacity to follow and predict treatment outcomes in a noninvasive and applicable manner, the gap between existing findings and clinical practice remains significant.

The following chapter focuses on these efforts by reviewing findings from both structural and functional neuroimaging studies. Both early-course and chronic patients with schizophrenia will be considered, given the importance of markers at both onset and in chronic illness. We will also discuss the potential for structural and functional neuroimaging-related measures to be used as prognostic biomarkers of outcomes. Within this text, various definitions of outcomes and response will be considered. Of note, we emphasize and concentrate on measures associated with efficacy and outcomes to treatment, rather than the effect of medications on brain structure and function.

18.2 Structural Studies of Early-Course Schizophrenia

Structural neuroimaging methods have been used to examine treatment response in individuals with first-episode psychosis or early-course schizophrenia. Patients early in the course of illness offer the advantages of no or limited prior treatment and reduced durations of illness, resulting in potentially less environmental confounds that may serve to decrease study power. Collectively, structural neuroimaging measures, particularly assessments of cortical folding patterns, may reflect developmentally mediated abnormalities that contribute to treatment response.

Initial neuroimaging studies in first-episode and early-course patients with schizophrenia focused on ventricular-brain ratios versus clinical outcomes with magnetic resonance imaging (MRI). Longitudinal studies, using serial MRIs during treatment, reported that in patients with poor outcome to treatment, significant ventricular enlargement was observed over time, whereas the patients with better treatment outcomes and healthy control subjects did not show ventricular enlargements (Lieberman et al. 2001; Ho et al. 2003). Subsequent work focused on ventricular enlargement in relation to antipsychotic type. Lieberman et al. (Lieberman et al. 2005) compared ventricular enlargement between treatment with olanzapine and haloperidol, and found that treatment response, measured by ratings of global psychopathology, correlated with lower increases in ventricular volume in the olanzapine treated group. 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 the second-generation antipsychotic, quetiapine (Ebdrup et al. 2011).

Along with changes in ventricular size, structural neuroimaging studies have shown response-related morphological findings in the prefrontal cortex. Reductions in negative symptoms were found to be related to increased thickness of middle frontal gyrus following treatment with atypical antipsychotics (Goghari et al. 2013). Poorer overall functioning after 1 year of treatment in a small cohort of patients with first-episode schizophrenia was associated with reduced prefrontal grey matter volume (Kasparek et al. 2009). Prasad and colleagues demonstrated that a larger

dorsolateral prefrontal cortex volume after 1 year of treatment predicted better functional outcome based on a score that incorporated social contacts, employment, and symptomatology (Prasad et al. 2005).

Multiple findings related to treatment outcome have been reported in medial temporal regions. In a study where first-episode psychosis patients were categorized as responders or non-responders by the Schizophrenia Working Group remission criteria, responders were found to have larger parahippocampal cortex volumes in both left and right hemisphere (Bodnar et al. 2011; 2012a). An analysis of cortical gyrification in first-episode psychosis revealed that non-response to antipsychotic treatment was associated with decreased gyrification in regions of the insula, frontal, and temporal cortices (Palaniyappan et al. 2013). Moreover, responders to antipsychotic treatment displayed more asymmetry between left and right frontal cortices and greater thickness of temporal regions relative to patients with poor response to antipsychotic treatment (Szeszko et al. 2012).

Structural neuroimaging findings associated with treatment response have also been reported outside of fronto-temporal areas. Greater total cortical grey matter was shown to be associated with a percent reduction in psychotic symptoms following antipsychotic treatment (Zipursky et al. 1980). Likewise, a greater decrease in total grey matter volume after 1 year of treatment was associated with a greater need for psychosocial support after long term follow-up 5 years later (Cahn et al. 2006). Findings have been described in non-cortical regions as well. In white matter, a smaller baseline volume of the left anterior limb of the internal capsule was noted in patients with first-episode psychosis who showed a greater clinical deterioration after 1 year of treatment relative to those with more stable measures of psychopathology (Wobrock et al. 2009). In the basal ganglia, increased striatal volume was observed in relation to treatment efficacy after 6 weeks of medications (Li et al. 2012). Sex differences have also been noted in the striatum and thalamus. Larger volumes of these structures at baseline predicted remission after 1 year of treatment in females, but not males (Fung et al. 2014). Recent work has combined structural neuroimaging with graph theoretical measures to examine response to antipsychotic treatment. In a large cohort of patients undergoing treatment for 12 weeks, patterns of structural covariance across the brain were examined that focused on gyrification (Palaniyappan et al. 2016). Treatment non-responders showed increased segregation and impaired integration of structural relationships, possibly resulting in unstable information flow throughout the brain. It should be noted that relationships between structure and treatment response are not universally described, with several non-significant results reported (Molina et al. 2014; van Haren et al. 2003; Robinson et al. 1999).

In addition to studies of grey matter and volumetric analyses, efficacy of antipsychotic treatment has been examined along with white matter integrity. Diffusion tensor imaging (DTI) allows for the measurement of fractional anisotropy (FA), which characterizes water diffusion to provide a proxy measure of the white matter myelination. While most published studies examine changes in DTI measures in relation to antipsychotic exposure (Szeszko et al. 2014; Bartzokis et al. 2011; Samartzis et al. 2014), a few report state-dependent changes in white matter related to the amelioration of psychotic symptoms in early-course patients with schizophrenia. Reduced FA was reported within the uncinate and superior longitudinal fasciculi in first-episode psychosis patients who were characterized by poor treatment outcomes (Luck et al. 2011). Consistent with this report, FA increase in the superior longitudinal fasciculi was associated with more efficacious treatment over the course of 8 weeks of antipsychotic treatment (Zeng et al. 2016). Reis Marques et al. (2014) reported findings from a longitudinal study of 63 first-episode psychosis patients with stringent response criteria (Andreasen et al. 2005). While no change was observed in FA following 12 weeks of antipsychotic treatment, a negative correlation was observed between baseline psychopathology and

FA. Other studies in first-episode psychosis patients reported whole-brain increases in fractional anisotropy in patients with greater reductions in ratings of psychopathology (Serpa et al. 2017). More recent work has merged DTI tractography with network-based statistics to examine antipsychotic treatment in a cohort of first-episode patients. Responders to 12 weeks of treatment had more efficient DTI-derived connectomes at baseline, reflecting a higher capacity for information flow throughout the brain (Crossley et al. 2017).

18.3 Functional Studies of Early-Course Schizophrenia

Task-based functional neuroimaging has been used to examine treatment outcomes in patients with schizophrenia. While some studies describe negative findings relating treatment outcome and neural activation (Snitz et al. 2005; Blasi et al. 2009), others reported treatment-related findings, primarily in decreased engagement of prefrontal and striatal regions with poor response. In treatment-naive first-episode psychosis patients, nonresponse to a 10-week trial of antipsychotic treatment was associated with greater dysfunction of dorsolateral prefrontal activation during a working memory task (van Veelen et al. 2011). Supporting this finding, decreased engagement of executive regions and increased activation of the default mode network has been reported in non-remitters relative to patients who responded to treatment during memory encoding (Bodnar et al. 2012b). Two studies examined longitudinal changes in activation of the striatum during treatment with second-generation antipsychotic drugs. One reported that recruitment of the ventral striatum during reward processing was normalized only in first-episode patients who responded to treatment (Nielsen et al. 2012), while the second study found that activation of the striatum corresponded with drug-related weight gain, suggesting a link between neural engagement and metabolic outcomes to treatment (Nielsen et al. 2016).

Along with activation studies, findings show changes in resting-state functional connectivity during antipsychotic treatment. Resting-state scans are a convenient method for examining the intrinsic functional architecture of the brain. Analytic approaches to resting-state connectivity range from hypothesis-driven inter-regional assessments to more data-driven global connectivity measure that capture small-world network clustering throughout the brain. Recent work, including resting-state findings, has conceptualized schizophrenia as a 'dysconnectivity' syndrome, consisting of abnormalities in large-scale functional networks (van den Heuvel and Fornito 2014; Nejad et al. 2012). Supporting this theory, multiple reports characterize functional interactions between subcortical and prefrontal regions across antipsychotic treatment. Treatment-induced increases in functional connectivity of the striatum with important limbic and prefrontal regions, including the hippocampus, the anterior cingulate, and the dorsolateral prefrontal cortex, corresponded with efficacy of treatment in a randomized controlled trial between two second-generation drugs in a cohort of patients with first-episode schizophrenia (Sarpal et al. 2015). In addition, an index of striatal connectivity at treatment initiation predicted ultimate response to treatment in two independent cohorts (Sarpal et al. 2016). Functional interactions of brain regions including the striatum, hippocampus, and the anterior cingulate cortex are additionally implicated in the mechanism of response by other longitudinal, treatment-based studies (Anticevic et al. 2015; Kraguljac et al. 2016a).

Together, the fMRI studies described above suggest that when antipsychotic treatment works, there is an associated increase in either activation or synchronization of neural activity in brain regions important for cognition and emotional processing. Additional studies use more novel connectivity methods and report either negative findings or normalization of fMRI signals with treatment response (Lui et al. 2010; Guo et al. 2017, 2018; Wang et al. 2017). It is worth noting that analytic approaches vary

across these fMRI studies, introducing heterogeneity in reported findings. Multisite studies with a uniform analytic approach may yield more conclusive results.

18.4 Structural Studies of Chronic Schizophrenia

In addition to studies focused on patients early in the course of illness, multiple studies have assessed more chronically ill subjects. These study groups, though perhaps more heterogeneous that early phase patients, represent the vast majority of patients seen in treatment settings, and therefore predictors of response in this group of patients would be of potentially enormous clinical utility.

The first studies to use neuroimaging to examine treatment response examined ventricular-brain ratios with computed tomography imaging (CT scans). Larger ventricles were observed in patients who were poorer responders to treatment (Weinberger et al. 1980; Schroder et al. 1993; Kaplan et al. 1990). Later studies continued to examine ventricular volumes with MRI scans. In a comparison of percent time hospitalized in the previous year and ventricular-brain ratios, smaller frontal lobe volumes and larger ventricles were observed in patients who spent more time hospitalized (Staal et al. 2001). Supporting this finding that gross measures of outcome and structure may be useful markers, Jääskeläinen and colleagues showed that in a large voxel based morphological analysis, individuals with better functional and clinical outcomes following treatment had "denser" frontal and limbic grey matter, relative to those with worse treatment outcomes (Jaaskelainen et al. 2014).

Across analyses, larger volumes of various structures have been associated with response to antipsychotic treatment in chronic patients with schizophrenia. This includes hippocampal volumes in both cross-sectional and longitudinal studies (Savas et al. 2002; Panenka et al. 2007), temporal grey matter volumes compared with reductions of psychotic symptoms (McClure et al. 2006), the thalamic volume after 4 weeks of treatment (Strungas et al. 2003), and cerebellar volume after a 7 year follow-up (Wassink et al. 1999). In addition, a decline in social and occupational functioning was associated with a corresponding decrease in supramarginal gyrus volume (Guo et al. 2015).

Studies focused on white matter in chronic patients with schizophrenia are limited. As with early-course patients, most studies concentrate on the effect of antipsychotic drugs on DTI-based measures, rather than correlates of treatment efficacy. Mitelman et al. (2006) reported widespread increases in FA, driven by treatment response. One additional report found an increase in DTI-based mean diffusivity in patients who demonstrated reduced psychotic symptoms following 1 month of antipsychotic treatment (Garver et al. 2008).

Neuroimaging findings of chronic patients with schizophrenia have also centered on treatment-refractory patients who are often treated with clozapine. Non-responders to clozapine treatment showed reduced grey matter volumes in the middle frontal gyrus, bilaterally, and in the medial temporal cortex (Quarantelli et al. 2014; Arango et al. 2003). In a comparison with cohort of responders, treatment-resistant patients, many treated with clozapine, showed reduced cortical thickness in the dorsolateral prefrontal cortex, perhaps suggesting a neurobiological marker for illness severity (Zugman et al. 2013).

Despite this pattern of larger brain volumes in responders, several structural studies with negative findings have also been reported (Friedman et al. 1992; Lawrie et al. 1995; Roiz-Santianez et al. 2012; Scheepers et al. 2001). Likewise, meta-analyses of treatment-associated changes in both grey matter and ventricular volume did not replicate the results described in individual studies, including ones outlined above (Fusar-Poli et al. 2013). Reasons for this may be due to a lack of overlapping results secondary to variation in treatment approaches and definitions of response, as well as disparate neuroimaging and analytic approaches.

18.5 Functional Studies of Chronic Schizophrenia

Functional neuroimaging has been used to examine treatment response in chronic patients with schizophrenia spectrum disorders, largely reporting findings in the prefrontal cortex and striatum. Significantly increased activation of the dorsolateral prefrontal cortex, anterior cingulate cortex, and striatum was reported during passive viewing of stimuli with a negative emotional valance in the context of successful antipsychotic treatment over 22 weeks (Fahim et al. 2005). Refractory patients who responded to clozapine showed increased activation of dorsomedial prefrontal regions (Potvin et al. 2015). Furthermore, increased dorsolateral prefrontal activity during working memory paradigm was also noted to predict successful response to cognitive behavioral therapy for psychotic symptoms (Kumari et al. 2009). In addition to prefrontal findings, reward paradigms have been applied in chronic patients. Vanes et al. (2018) reported that responders to treatment failed to functionally engage the striatum during reward processing, compared to both treatment-resistant patients and healthy volunteers. This work differentiates antipsychotic treatment response by a reward-related mechanism, supporting the hypothesis that nonresponders to treatment may exhibit a non-dopaminergic pathophysiology.

Functional connectivity analyses have also been applied to capture treatment response in chronic schizophrenia. The connectivity strength between dopaminergic regions, such as the ventral tegmental area and midbrain to the anterior cingulate cortex, positively correlated with good response to a 6-week course of risperidone (Hadley et al. 2014). Moreover, successful treatment with olanzapine was associated with increases in connectivity within the default mode network (Sambataro et al. 2010), and aberrant intra-network connectivity within the dorsal attention network was normalized with successful antipsychotic treatment (Kraguljac et al. 2016b). Like the early-course literature, novel methods for examining large-scale functional connectivity shows both normalization of functional networks with antipsychotic treatment, as well as negative findings (Lottman et al. 2017; Bai et al. 2016).

18.6 Discussion

In the studies described above, there is evidence that neuroimaging parses the heterogeneity of response to treatment of psychotic symptoms with antipsychotic medications while elucidating potential mechanisms. Relatedly, neuroimaging may assist in clinical treatment by serving as a prognostic assay.

Some important clinical considerations should be noted. Across studies, definitions of response vary. An assortment of outcomes and groupings of patients are represented by the studies described, reflecting the complexity of schizophrenia and the various methods for characterizing outcomes to treatment. Standardization of response criteria has been suggested (Andreasen et al. 2005; Emsley et al. 2007), including a rigorous and uniform definition of nonresponse (Howes et al. 2017). In addition, it should be noted that antipsychotic treatments do not significantly impact the negative and cognitive symptoms of schizophrenia, which may result in the severe functional and social impairments characteristic of the illness (Remington et al. 2016; Kane and Correll 2010). As described above, some studies examined response to clozapine or focused on treatment refractory illness. Clozapine is uniquely efficacious for patients who have failed other antipsychotic drugs and plays an important role in treatment algorithms. For ultra-refractory patients who fail clozapine, electroconvulsive therapy is often delivered, which has long demonstrated efficacy for psychotic symptoms (Petrides et al. 2015). The classification of patients based on responsiveness to these therapies may become standard of care as our knowledge of the neurobiology underlying treatment improves, and if replicable biomarkers are identified (Remington et al. 2015).

Results described in this chapter show that there is an overall convergence of findings from neuroimaging studies in both early-course patients and chronic patients. These results suggest that variation in neural circuitry may encode

the potential for response to treatment, preceding the onset of psychosis, and may have its roots in neurodevelopment. Structural neuroimaging findings suggest that non-responders to treatment exhibit greater ventricular volumes, along with decreased grey matter density in regions important for cognitive functioning, including frontal and medial temporal regions, as well as other limbic and subcortical structures. Greater dysfunction within these regions that confer importance for cognition is also observed in functional MRI studies, though the variance of reported results is considerable. Though some evidence suggests that non-responders to antipsychotic treatment display overall decreased white matter integrity, DTI studies are limited in numbers, and distinct conclusions cannot be drawn for early-course and chronic illness. Of note, it is unknown how findings from structural and functional imaging modalities are related to each other and whether neurodevelopmentally encoded structural deficits in patients with poor outcomes precede functional observations.

Existing studies also indicate that the heterogeneity in clinical outcomes to antipsychotic treatment in patients with schizophrenia may be driven by neurobiologically distinct subtypes of illness. The development of novel therapeutic approaches may depend on stratifying our approaches to clinical trials on subgroupings of patients with distinct biological profiles. This approach may maximize the efficacy of therapeutic interventions. Progress in this effort may lead to more efficacious and personalized treatments. Efforts will require consistency across study designs, stringent and uniform outcome criteria, as well as consolidation of neuroimaging datasets via multisite studies. In addition, further integration of clinical trials with neuroimaging will bridge clinical care with neurobiology. Future work may also integrate neuroimaging-derived markers with combinations of demographic, neurocognitive, and pharmacogenomic markers to enhance our prognostic capabilities. While this chapter focuses on antipsychotic drugs, other treatment modalities for psychosis should be examined with neuroimaging, including electroconvulsive therapy, transcranial magnetic stimulation, and evidence-based psychosocial interventions. Future directions for the field include the incorporation of neuroimaging with data-driven, machine learning approaches to transition, from descriptions of differences between groups of patients, to prognostic inferences that can be made for individuals, to usher the field in the direction of precision medicine approaches for schizophrenia treatment.

Summary

- Overall, there is convergence of findings from studies of treatment response in both early-course and chronic patients with schizophrenia.
- Early studies focused on ventricular enlargement in first-episode psychosis found greater ventricular size in patients with poorer outcomes to treatment.
- Morphologic findings in patients with schizophrenia, ranging from first-episode psychosis to chronic, treatment-refractory illness, largely report decreased frontal and temporal gray matter volumes.
- Functional studies of treatment response via task and resting-state imaging report abnormalities in regions important for cognition within the prefrontal cortex and the striatum.
- DTI studies suggest that non-response to antipsychotic treatment is associated with overall decreased white matter integrity.

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