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Neuroimaging Schizophrenia: A Picture Is Worth a Thousand Words, but Is It Saying Anything Important?

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Abstract Schizophrenia is characterized by neurostructural and neurofunctional aberrations that have now been demonstrated through neuroimaging research. The article reviews recent studies that have attempted to use neuroimaging to understand the relation between neurological abnormalities and aspects of the phenomenology of schizophrenia. Neuroimaging studies show that neurostructural and neurofunctional abnormalities are present in people with schizophrenia and their close relatives and may represent putative endophenotypes. Neuroimaging phenotypes predict the emergence of psychosis in individuals classified as high-risk. Neuroimaging studies have linked structural and functional abnormalities to symptoms; and progressive structural changes to clinical course and functional outcome. Neuroimaging has successfully indexed the neurotoxic and neuroprotective effects of schizophrenia treatments. Pictures can inform about aspects of the phenomenology of schizophrenia including etiology, onset, symptoms, clinical course, and treatment effects but this assertion is tempered by the scientific and practical limitations of neuroimaging.

Keywords Neuroimaging · Schizophrenia · Psychosis · Imaging · Structural · Functional · Neuropathology · Endophenotype · Symptoms · Clinical course · Outcome · Neurocognition · Treatment · Psychiatry

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Introduction

The advent of several neuroimaging technologies in the last three decades has allowed researchers to study *in vivo*, brain structure and function in people with schizophrenia and their unaffected relatives in comparison to unaffected individuals. Since Johnstone and colleagues [1] reported the first neuroimaging evidence of enlarged lateral ventricles and decreased cerebral volume in people with schizophrenia using computed tomography (CT) scans, several imaging techniques (Table 1) have elucidated the neuropathological basis of schizophrenia [2–4, 5•, 6–10, 11•, 12–29]. The ubiquitous structural and functional abnormalities (Table 2) have not only supported the neuropathological basis of schizophrenia but provided evidence of both neurodevelopmental and neurodegenerative pathophysiological processes [30].

Despite advances in neuroimaging research, there remains uncertainty about the degree to which neuroimages advance critical knowledge about the phenomenology of schizophrenia and clinically-relevant information such as the emergence of symptoms, features, etiology, or its clinical course. Moreover, the neurological signs that characterize schizophrenia often lack diagnostic specificity, given that such deficits may be shared with other psychiatric disorders —particularly bipolar disorder and other major affective disorders [31]. As such, the relevance of neuroimages to the phenomenology of schizophrenia has to be established through studies that relate neuroimages to the aberrant experiential processes of schizophrenia such as psychotic symptoms, neurocognitive deficits, disability, and developmental bifurcations. Efforts at establishing such links–dubbed construct validation–have potential to advance knowledge about schizophrenia. Several studies have sought to establish neuroimages as part of the nomological network of schizophrenia that includes measures of

Table 1 Summary of neuroimaging techniques

Imaging technique	Description
Computed tomography (CT)	• First imaging technique use to study schizophrenia neuropathology • Involves the use of computers to enhance images formed when X-rays are differentially absorbed by brain tissues • Strengths: Less costly than other techniques; readily available; fewer contraindications than other techniques; • Limitations: Poorer contrast and resolution in the imaging of brain tissues and soft images; exposure to radiation
Magnetic resonance imaging (MRI)	• Capitalizes on the magnetic properties of hydrogen atoms in the brain • MRI alters the energy state of atoms via magnetic fields, radiofrequency energy, and movements during return to resting state • Has been extensively applied to the study of progressive brain change in schizophrenia • Strengths: Good resolution in the imaging of brain structure; can depict 2–3 dimensional images; does not require x-rays or radioactive tracers; non-invasive • Limitations: Costly; impacted by movement; not-indicated for claustrophobic patients and patients with metallic devices
Magnetic resonance spectroscopy (MRS)	• Creates spectrum peaks that correspond to chemical composition of the brain—chemicals generate unique spectrums in the presence of nuclear magnet • Spectral peaks are often generated through magnetization of metabolite such as N-acetyl aspartate (NAA), glutamate, gamma aminobutric acid (GABA) • Strengths: Able to index *in vivo* neurochemistry; non-invasive • Limitations: Poorer contrast/resolution relative to MRI; not adaptable to measuring change due to cognitive activity; limited accessibility of hardware
Position emission tomography (PET)	• First functional neuroimaging technique—detects gamma rays released from the breakdown of radioactive tracers attached to O-labeled water • Produces images by measuring cerebral blood flow using a positron-emitting radio nuclear as its radioactive tracer or fluorodeoxyglucose (FDG) cellular absorption as an index of neural metabolic activity • Has been used extensively in the study of hypo-and-hyperfrontality in schizophrenia and reduced activity in other areas • Strengths: Good temporal and spatial resolution; undisturbed by motion; • Limitations: Costly; invasive set-up; exposure to radioactivity; low time resolution
Single photon emission CT (SPECT)	• Detects gamma rays released from the breakdown of radioactive tracer attached to ethyl cysteamate dimer • Has been applied to the study of hypo-and-hyperfrontality • Strengths: Good temporal and spatial resolution; undisturbed by motion • Limitations: Costly; Poorer spatial resolution relative to PET; exposure to radiation; impractical for longitudinal studies
Functional MRI (fMRI)	• Measures neuronal activity by detecting changes in cerebral blood flow • Its most commonly used display form is the MRI *slice* with Blood Oxygen-Level Dependent (BOLD) signal; other forms are the Glass brain and 3D Render • Has been used extensively in schizophrenia to index abnormal activities in the frontal and temporal areas • Images both functional and structural characteristics • Strengths: Greater spatial and temporal resolution than PET and SPECT; Non-invasive; Cheap; readily available hardware; adaptable to repeated assessments and longitudinal studies • Limitations: Low time resolution; impacted by movement; poor depiction of structure; complex analysis and interpretation
Diffusion tensor imaging (DTI)	• An advancement of MRS that detects the diffusion of water through white matter such as axonal projections through myelin sheaths • DTI creates images by capitalizing on the anisotropic properties of water diffusion through white matter • Strengths: Most effective method for studying white matter architecture and neural connectivity • Limitations: Expertise is not readily available

psychopathology, etiology, and clinical course. In this review, we examine the clinical correlates of neuroimages and evaluate the prospects of neuroimaging for advancing scientific knowledge and clinical practice in schizophrenia.

Table 2 Summary of the structural and functional abnormalities in schizophrenia

Brain region	Key findings
Whole brain	• Ventricular enlargement—particularly of the lateral and third ventricles [1, 2]
	• Ubiquitous reduction in cortical volume [1, 2]
Temporal lobe	Structural
	• Reduced gray matter volume in the temporal lobe [2]
	• Reductions in temporal lobe structures–hippocampus, parahippocampal gyrus, superior temporal gyrus [2, 3]
	• Asymmetrically greater reductions in the left hippocampus and parahippocampal gyrus [3, 4]
	• Reduction or reversal of leftward asymmetry of planum temporal [5•]
	• Reduced density of dendritic spines in the temporal cortex [6, 7]
	• Reduced expression of synapsin, synaptophysin, and SNAP-25 in the hippocampus [7, 8]
	Functional
	• Abnormal activation in temporal regions (somewhat mixed) [9]
	• Abnormal activation of the left middle temporal gyrus during facial emotion perception [10]
	• Reduced activation of bilateral amygdala, parahippocampus, and fusiform gyrus during emotion perception [9, 10]
Frontal lobe	Structural
	• Reduced gray and white matter volume in the frontal lobe [2, 11•, 12–17]
	•Reductions in frontal lobe structures
	○ dorsolateral prefrontal cortex
	○ orbitofrontal, and
	○ dorsomedial regions
	• Increased neuronal density
	• Decreased expression of synaptophysin, and lower density of dendritic spines of postsynaptic neurons
	Functional
	• Hypofrontality and hyperfrontality in the bilateral dorsolateral prefrontal cortex [18, 19]
	• Reduced activity in the ventrolateral prefrontal cortex during cognitive challenge
	• Reduced activity in the right ventral premotor cortex during cognitive challenge
	• Reduced activity in the right dorsal anterior cingulated cortex during cognitive challenge
Parietal lobe	Structural
	• Reduced volume of the parietal lobe [20, 21]
	• Reductions in parietal lobe subdivisions—superior parietal gyrus, inferior parietal lobe and the supramarginal gyrus
	Functional
	• Reduced activation in the parietal areas during cognitive challenge [18]
Cerebellum	Structural
	• Mixed findings regarding cerebellar deficits
	• Atrophy in the anterior and posterior superior vermis in both chronic and first episode patients [22–24]
	• Increased vermal white matter volume and discrepant vermal grey/white matter ratio [22–24]
Subcortical regions	Structural
	• Reduced thalamic volumes [25]
	• Reduction in structures of the basal ganglia—caudate nucleus, nucleus accumbens, and the putamen [26]
	Functional
	• Reduced activation of the left thalamus (particularly the mediodorsal nucleus) [18]
	• Reduced activation in the thalamus when the area connecting the thalamus to frontal cortex is activated [27, 28]
	• Reduced activation of the putamen [18]
White matter	Structural
	• Abnormalities in the insulation of fiber tracts
	• Reduced quantity and organization of oligodendrocytes
	• Reduced myelin gene expression
	• Reduced white matter organization in the
	○ Temporal lobe
	○ Frontal lobe

Table 2 (continued)

Brain region	Key findings
	○ Corpus callosum ○ White matter tracts: cingulum, splenium, arcuate fasciculus, thamocorticular tract [29]

The Nomological Network of Images: What do Pictures Tell Us?

A review of neuroimaging studies in schizophrenia is quite an undertaking given the range of abnormalities that includes structural, functional, neurophysiological, and neurochemical alterations that have been the subject of research. We focus our review largely on structural and to a lesser extent functional abnormalities, given that most studies of the correlates of abnormalities have focused on these areas.

Pictures as Candidate Endophenotypes and Predictors of Schizophrenia in at-Risk Individuals

Gottesman and Shields [31] proposed about 40 years ago that overt phenotypes such as verbal self-reported symptoms of schizophrenia are inadequate for deciphering the genetic origins of schizophrenia. Rather, they suggested that the search for candidate genes should focus on indicators that are closer along the causal chain to candidate genes—the identification of such indicators may be informative about the pathway linking etiology with expressed behavioral traits. Gottesman and Gould [32] noted that neuroimaging data are plausible endophenotypes of schizophrenia but also made it a point to distinguish between "biomarker" status and endophenotype status. Pillai and Buckley [33] describe biomarkers as biological signs and indicators that may suggest vulnerability, episode, or treatment response. In contrast, endophenotype status requires that a biomarker be heritable, associated with illness in the population, cosegregrate with illness within families, and exist regardless of the status of the illness [34]. In this context, *all endophenotypes are biomarkers; but not all biomarkers are endophenotypes*. In seeking confirmation of Gottesman and Shields original proposal, Rose and Donohoe [35] conducted a meta-analytic review of studies that investigated schizophrenia risk genes in concert with neurocognitive and neuroimaging data. They determined that greater effect size differences existed between individuals carrying risk genes and individuals not carrying such genes on neuroimaging data than neurocognitive data—suggesting that genes have greater penetrance with neuroimaging data.

Some studies have examined the prospects of neuroimages as viable endophenotypes of schizophrenia and evaluated the degree to which they predict the onset of psychosis in people classified as ultra-high risk (UHR). These studies have sought to identify abnormalities that may be present in high-risk individuals who have yet to experience a psychotic episode. Several studies have demonstrated that reductions in gray matter, particularly in the prefrontal cortex, are quite common among UHR individuals and have argued that reduced gray matter represents a robust endophenotype [36–38]. There is also evidence of abnormalities in other brain areas when UHR individuals are compared to controls [38–41]. These include abnormalities in frontal lobe structures, the bilateral pars triangularis, bilateral cingulated gyrus, and stria terminalis. The temporal lobe and several structures in this area—right superior temporal gyrus, amygdala-hippocampal complex, right Heschl's gyrus, left supramarginal gyrus, and right angular gyrus—are similarly reduced in UHR individuals. Studies have also shown abnormalities in cerebral dominance in UHR individuals such as reversals in left-right asymmetry of the temporal lobe and pars triangularis [41].

McDonald and colleagues [42] conducted a systematic review of 20 studies that examined brain activation patterns during the performance of cognitive tasks of working memory, long-term memory, cognitive control, and language in first-degree relatives. First-degree relatives demonstrated abnormal activation patterns (usually greater activation) in dorsolateral prefrontal cortex, parietal cortex, thalamus that were associated with cognitive control. Across studies, there was evidence of increased activation of right dorsolateral prefrontal cortex and the bilateral prefrontal cortex, and decreased bilateral activation in the cerebellum all of which were linked to working memory deficits. Linked to long-term memory, they found that increased activation in the parahippocampal gyrus was linked to poorer recognition performance across studies. Increased activity in the right ventral prefrontal cortex and parietal and lateral temporal cortices were linked to language processing deficits in relatives (see also ref [38]).

Clearly, there are structural and functional abnormalities that predate the onset of psychosis and that are found in unaffected relatives. One question of interest is whether there are neuroanatomical differences between UHR individuals who go on to express frank psychosis and individuals who remain relatively compensated. Studies have implicated gray matter reductions in left orbitalfrontal, left parahippocampus, left amygdala, left fusiform gyrus, parietal, and temporal cortex as possible predictors of decompensation [43–47]. Other studies have found that UHR individuals who developed

psychosis had lower white matter volume in their bilateral medial frontal lobe, left medial temporal lobe, left superior temporal lobe, right putamen, and anterior region of their corpus callosum [48, 49]. Functionally, there is some evidence from the Edinburg High Risk Project that UHR individuals who later decompensated demonstrated abnormal activation patterns in the anterior cingulated cortex, parietal, and bilateral temporal regions [38].

Overall, recent studies support the assertion that several neuroanatomic abnormalities revealed through neuroimaging are present in close relatives of people with schizophrenia. Baseline assessments of several structural and functional abnormalities also appear to predict the emergence of schizophrenia at subsequent follow-ups. This suggests that structural and functional alterations identified through neuroimaging may offer a map toward the identification of putative endophenotypes of schizophrenia and assist in the identification of UHR individuals most likely to develop psychosis.

Do Pictures Link with Psychopathology in Schizophrenia?

The possible relationship between neuropathology and psychopathology is viewed as one likely reciprocal — neuropathological abnormality may precede psychopathology including symptoms and functional outcomes; but it is also conceivable that clinical symptoms exert neurotoxic effects. Given that the duration of untreated psychosis has been associated with a more severe clinical profile, including poorer treatment response and long-term outcomes [50, 51], it has been suggested that neuroimages should provide footprints of the neurotoxic effects of psychosis. MRI studies that have examined this association have found links between the duration of untreated psychosis and gray matter reductions in the whole brain, frontal, temporal, parietal, and occipital regions [52, 53]

Neuroimages, Symptoms, and Clinical Course

Some studies have sought to link neuroimaging findings with subsequent clinical course and functional outcomes in people with first episode psychosis. These include studies that obtained baseline neurostructure during the first episode and examined functional outcome at a follow-up period. The follow-up duration for functional outcomes after obtaining neuroimaging data in these studies has ranged from about six months to five years. Another group of studies have examined neuroanatomic changes over time and sought to evaluate the association of progressive brain changes and functional outcomes concurrently in both first-episode and chronic schizophrenia patients. In these studies, the follow-up periods have been even longer, ranging from six months to up to 15 years. The results of these studies differ depending on the brain structure examined and whether baseline volume is designated as the predictor as opposed to actual volumetric change over time.

Lateral Ventricles Studies that examined baseline volumes have generally found no evidence of a robust association between baseline ventricular size and clinical symptoms or outcomes [54–58]. Studies that examined brain change over time in first episode patients and that obtained data on ventricular size and clinical symptoms at baseline and at follow-up have produced more robust findings [59–62]. Increases in ventricular size are generally associated with increases in both positive and negative psychotic symptoms. In chronic patients, ventricular enlargement has been robustly linked with impairments in self-care and activities of daily living, functional outcomes, risk and length of hospitalization, and clinical symptoms [60, 63].

Temporal Lobe Structures Studies that examined the association between baseline temporal lobe volume and clinical symptoms have generally been mixed with most suggesting no correlation with symptoms and outcomes [57, 64]. In contrast, changes in the volume of temporal lobe structures over time appear to predict symptoms and functional status in most [65–67] but not all studies [68]. Reductions in temporal lobe volumes in childhood-onset schizophrenia predict worse clinical outcomes [69, 70]. Greenstein and colleagues [69] demonstrated that greater baseline cortical thickness in the temporal region as measured by MRI scans was associated with remitted status. In contrast, Thompson and colleagues [70] demonstrated that progressive gray matter reductions in the temporal lobe were associated with greater severity of positive but not negative symptoms. Studies have linked decreased fractional anisotropy (FA) in the medial temporal lobe with increased severity of positive and negative symptoms and decreased FA in the frontal areas with impairments in psychosocial functioning [71]. Functional neuroimaging studies have demonstrated that there are abnormalities in neuronal networks that connect the parietal lobe with other areas such as the temporal cortex and the prefrontal cortex and have linked this network to features of social dysfunction in schizophrenia [72, 73]. Recently, Plaze and colleagues [74] demonstrated that self-reported spatial location of auditory hallucinations (i.e., whether patients reported that auditory experiences came from outside the head or whether they stated that voices were inside) is associated with right temporoparietal junction anatomy. They found that patients who reported outside spatial hallucinations have greater reductions in white-matter volume compared to patients with inside spatial hallucinations.

Frontal Lobe Structures Investigation into the association between baseline frontal cortex volumes and clinical outcomes have generally been mixed. Whereas some studies

have found an association with clinical outcomes [64, 69, 75, 76]; others have found no association [63, 65]. Studies of progressive frontal volume change have been similarly inconsistent with some linking progressive frontal decreases with increased positive and negative symptoms [65], whereas others fail to do so [67]. Several studies have examined the association between frontal hypoactivation and symptoms of schizophrenia. Overall, these studies have demonstrated that there is a robust association between indices of hypofrontality and the severity of psychotic symptoms [77, 78].

Two recent studies also demonstrate that frontal activity induced by a working memory challenge may predict short-term outcome [79, 80]. Van Veelen and colleagues [79] found that patients who remitted following antipsychotic treatment demonstrated a greater practice effect that was indexed by reduced prefrontal activation on exposure to the same task. In contrast, patients who remained decompensated after treatment demonstrated little reduction in prefrontal activation on re-exposure to the same task. Bodnar and colleagues [80] found that patients who failed to remit after one year of treatment had positive activation of the posterior cingulated cortex whereas remitters did not when viewing related images.

Subcortical Structures There have been only a few studies that have examined the association between changes in the volume of subcortical structures and clinical and functional outcomes [54, 56, 81]. These studies suggest that neither baseline nor volumetric changes in the size of the hippocampus or the amygdala predict symptoms or clinical status; although one study found that remitted patients had smaller hippocampal tail volumes [81].

Overall Gray and White Matter Volume Most of the studies that have examined the baseline gray and white matter volumes of patients with schizophrenia have found no association with clinical outcomes [55, 56, 58] with follow-up periods of up to 6 years. In contrast, studies that have examined progressive changes in gray and white matter of first-episode or chronic patients have generally demonstrated an association between reductions in gray matter and increases in white matter over time and clinical outcomes including the severity of psychotic symptoms and hospitalization [61, 62, 67].

Neuroimages and Neurocognition in Schizophrenia

While not used as formal diagnostic criteria, neurocognitive deficits have been considered critical phenotypes of schizophrenia given their ability to predict functional disability in the illness [82]. Several neurocognitive deficits have been identified in people with schizophrenia that include deficits in memory, attention, processing speed, problem solving, planning, and other executive functions [82]. The impact of neuropathology on neurocognitive functioning in people with schizophrenia has garnered much interest in neuroimaging research. Functional neuroimaging of the frontal regions has linked hypofrontality in the dorsolateral prefrontal cortex with deficits in working memory, attention, and executive functions [19]. In these studies, individuals with schizophrenia demonstrate reduced prefrontal activation relative to healthy controls while performing demanding cognitive tasks, and hyperfrontality (greater activation relative to controls) during the performance of simple tasks—a state of affairs that has been attributed to inefficient information processing [83]. Some studies have linked polymorphisms in specific genes to neuroimages and neurocognition. Specifically, they have implicated Catechol-O-Methytransferase (COMT) Val-Met polymorphisms and their interactions with genes coding for other receptors such as metabotropic glutamate receptor (GRM3) and methylenetetrahydrofolate reductase (MTHFR) to deficits in prefrontal processing [84].

Temporal areas and their link to neurocognitive deficits have similarly received attention but findings in this area are slightly less robust. Neuroimaging studies have linked reductions in the volume of temporal lobe structures to deficits in some neurocognitive functions. Reductions in the medial temporal lobe have been consistently shown to predict deficits in episodic and autobiographical memories in people with schizophrenia [85]. Similarly, functional neuroimaging studies have linked reduced activation in regions such as the superior temporal region to poor performance in tasks that demand auditory selective attention, automatic, and controlled attentional processes [86]. Several functional neuroimaging studies have demonstrated that people with schizophrenia have reduced activation in structures of the midbrain region—the basal ganglia, ventral tegmentum, thalamus, ventral striatum, and the anterior cingulated cortex [87]. These midbrain structures play a role in particular aspects of neurocognition—reward learning and reward-value representation—that are relevant to motivating behavior for incentives [88•]. It appears that abnormal activation in midbrain structures may be associated with deficits in distinguishing between antecedent stimuli for which certain actions may lead to reinforcement [87, 88•]. This breakdown in stimulus–response-outcome contingency learning may explain difficulties that schizophrenia patients have in inhibiting actions that may be irrelevant to completing a task and eliciting actions that may be germane to task completion. Some of the structures of the midbrain including the thalamus, cingulate cortex, caudate nucleus, and the basal ganglia appear to play a role in attention and concentration [89].

In the limbic system, the most attention has been paid to the amygdala and the hippocampus with regard to their role in neurocognition. Structural and functional neuroimaging has shown that people with schizophrenia have reductions

and decreased activation in these areas that are associated with deficits in memory encoding and retrieval [90]. Deficits in amygdala and hippocampal functioning have in tandem with other brain areas (e.g., the visual cortex, midbrain, and frontal areas) been linked to deficits in sociocognition [91]. Reduced neural activity in the right amygdala appears to be linked to difficulties with emotional processing, whereas reduced activity in the cingulate gyrus have been linked to difficulties in theory-of-mind [91, 92]. Compared to people with bipolar disorder, people with schizophrenia demonstrate reduced activation of neural areas relevant to facial affect processing including the parahippocampus/amygdala and the thalamus but a greater activation of the visual processing area [93•]. Thus, neuroimaging data provides evidence that the poorer overall integration of visual and emotional information may be a characteristic that particularly distinguishes schizophrenia from bipolar disorder and may have diagnostic value.

Neuroimages as Plausible Biomarkers of Treatment Effects

Another question is the degree to which neuroimages can serve as possible markers of treatment effects in schizophrenia. Two forms of treatment effects are of interest—neuroanatomical changes that reflect the deleterious footprints of medication management and those that denote treatment-related clinical improvements. Studies suggest differential effects of first-versus-second generation antipsychotics on gray matter volume, neuronal integrity, neurotrophic factor expression, glial functioning, and other CNS characteristics that are critical to optimal neuronal functioning [94, 95]. Overall, it appears that whereas first generation antipsychotics such as haloperidol and chlorpromazine may cause deleterious effects on the CNS, second generation antipsychotics such as risperidone, paliperione, and olanzapine may improve and reverse the deleterious effects of first generation antipsychotics [94, 95]. One meta-analytic review showed that the neuroanatomic impact of antipsychotics may be regional and specific rather than global [96•]. Whereas first generation antipsychotics tended to increase the size of the basal ganglia, atypical antipsychotics tended to decrease the size of the basal ganglia; in contrast, the impact of antipsychotics on the thalamus and cortex appeared to be mixed.

Studies of cognitive remediation as a behavioral intervention for ameliorating neurocognitive deficits in schizophrenia have examined the meditational role of neuroanatomic changes in neurocognitive improvements following cognitive training. These studies have documented improvements in fMRI activations in the frontal and visual cortical areas, cingulate gyrus, and inferior parietal lobe following cognitive remediation [97]. A recent study also linked up-regulated gray matter in the left amygdala, and preserved hippocampal, parahippocampal, and fusiform gyral volumes at two-year follow-up to cognitive remediation, thereby suggesting neuroprotective benefits [98•].

Prospects and Problems of Pictures: Are Pictures Worth a Thousand Words?

Synthesizing neuroimaging findings in schizophrenia, there are a number of important conclusions that can be drawn from this review:

1. Endophenotypes: Neuroimaging offers a means of identifying candidate endophenotypes that may ultimately contribute to efforts at explicating the etiology of schizophrenia. The neuroimaging of endophenotypes confer the advantage of greater measurement precision over phenotype measurement (e.g., psychometric assessment) and may be underpinned by a more parsimonious genetic architecture that allows more precise identification of *schizogenes*. Recent technological advancements in molecular imaging and neuroimaging genomics would contribute substantially to linking the etiology of schizophrenia to its phenomenological expression.
2. Prediction: Structural and functional neuroimaging in UHR individuals may contribute to the finer distinction between individuals who develop schizophrenia and those who remain fairly compensated. There is some evidence from our review that some neuroanatomic deviations may characterize UHR individuals that go on to develop schizophrenia. This area of investigation is in relative infancy but the identification of neuroanatomical deviations that best predict schizophrenia onset may enhance prodromal classification and assist in early identification and prevention.
3. Symptoms and Course: Neuroimaging has linked neuropathology in areas such as the temporal lobe, frontal lobe, and midbrain structures to neurocognitive deficits and clinical symptoms of schizophrenia but findings have often been mixed. Baseline neuroimaging assessment in first-episode patients offers a poor prediction of clinical course and functional outcome; in contrast, longitudinal assessments of brain change over time appear to be robust predictors of clinical course and functional status. There have been very few studies of the correlates of neurofunctional abnormalities but two studies demonstrated that activation patterns in the prefrontal cortex and the cingulated cortex may predict remission in the short-term. The question of whether neuroimages (along with other biomarkers) can be incorporated into the diagnostic algorithm of schizophrenia is one that remains of interest. Unfortunately, comparisons between people with schizophrenia and other psychotic and mood disorders suggest that neuropathological differences are quantitative rather than qualitative. Certain functional

characteristics (e.g., those shown to be associated with the integration of visual and emotional information) may reliably distinguish people with schizophrenia from those with affective disorder. However, the utility of neuroimages as diagnostic measures hinges on a demonstration that they improve the accuracy of diagnoses over and above clinician ratings of diagnostic criteria.

4. Treatment Effects: Our review suggests that neuroimages may serve as additional outcome indicators for treatment studies of schizophrenia. Neuroimages have successfully indexed the neuroprotective benefits of SGAs and cognitive remediation as well as the neurotoxic effects of substantially dosed FGAs. The enthusiasm to incorporate neuroimaging in treatment outcome studies however says little about its practicality in clinical settings as part of routine psychiatric examination to evaluate the effects of ongoing treatment.

Several limitations of the prospects of neuroimaging in schizophrenia are noteworthy. Neuroimaging has mostly remained a research endeavor and has yet to impact the clinical care of schizophrenia. Neuroimaging findings generally "play the odds" as they compare people with schizophrenia to other groups and may in some cases have very little relevance to an individual patient. Most neuroimaging studies involve the use of small samples of patients that are highly clinically homogeneous. This limits the generalizability of neuroimaging findings to clinical settings where patients often present with comorbid psychiatric and substance use problems, traumatic brain injury, and long histories of medication use that may impact their neuroanatomy and neurofunction. The prospect of neuroimaging in the clinical arena is limited by the difficulty of interpreting neuroimaging data, which may require expertise that is not readily available in clinical settings. One interpretive challenge that limits the diagnostic prospects of neuroimaging is defining the range that constitutes "normal" structure and function—characteristics that may be highly heterogeneous within subpopulations of patients and controls. Specialized training would likely be required to collect, manage, integrate, and interpret the often complex imaging data. Coupled with the cost of purchasing imaging technology, clinical settings may be reluctant to invest in such an endeavor. The prediction of outcome and assessment of treatment effects based on neuroimaging data would currently require the repeated assessment of brain structure and function, and may say little about short-term outcomes or immediate treatment effects (although a few studies are promising in functional neuroimaging). In addition, neuroimaging is to an extent, a "moving target" and frequent improvements in resolution and interpretive algorithms may limit the interpretability of longitudinal assessments.

Our current knowledge of the neuroanatomical and neurofunctional aberration in schizophrenia and their correlates is limited by the preponderance of mixed findings especially in the prediction of symptom severity, outcome, and clinical course. As such, there are very few reliable biomarkers of response, relapse, and clinical course of schizophrenia in the neuroimaging arena. Methodologically, many neuroimaging studies may have lacked adequate power to detect effects (given their small sample sizes). The heterogeneity of schizophrenia as a diagnostic entity also poses problems to the detection of effects and their replicability. Functional neuroimaging studies may be plagued by the heterogeneity of task performance among patient and control groups that may be influenced by factors such as intellectual functioning, motivation, response to success/failure, and personality traits that are usually not controlled for in research studies.

The frontiers for neuroimaging are numerous. The integration of neuroanatomical and neurofunctional findings with neurophysiological and neurochemical findings in schizophrenia has potential to inform the etiology, pathophysiology, and pathogenesis of schizophrenia [20]. Improvements in neuroimaging technology have potential to inform a finer articulation of the nature of neurobiological disturbances and their correlates in schizophrenia. To our knowledge, no studies have attempted to combine neuroimaging with techniques such as mismatch negativity (MMN), P300 event-related potential (ERP), P50 mid-latency auditory evoked response, and prepulse inhibition (PPI), and other neurophysiological techniques that have identified abnormal electrical activity in people with schizophrenia. The combination of several techniques may improve the prediction of clinically meaningful variables; however, the complexity of analyzing, interpreting, and integrating neuroimaging data is no doubt a daunting endeavor.

Conclusions

The need to understand the neuropathological basis of schizophrenia has led to the application of several neuroimaging technologies that have advanced our understanding of brain architecture and functioning in people with schizophrenia. Neuroimaging measures have been demonstrated as possible endophenotypes of schizophrenia, and have been shown to predict schizophrenia in UHR individuals. Neuroimaging data may also predict long-term clinical course and functional outcome (when examined longitudinally), and index neuropsychological functioning, and treatment effects. As such, neuroimaging has something to say about the phenomenology of schizophrenia but several scientific and practical issues temper its prospects in clinical practice.

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