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Structural and Functional Brain Abnormalities in Schizophrenia

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Abstract

Schizophrenia is associated with changes in the structure and functioning of a number of key brain systems, including prefrontal and medial temporal lobe regions involved in working memory and declarative memory, respectively. Imaging techniques provide an unparalleled window into these changes, allowing repeated assessments across pre- and post-onset stages of the disorder and in relation to critical periods of brain development. Here we review recent directions in structural and functional neuroimaging research on schizophrenia. The view emerging from this work is that schizophrenia is fundamentally a disorder of disrupted neural connectivity, the sources of which appear to be genetic and environmental risk factors influencing brain development both prenatally and during adolescence.

Keywords

schizophrenia; structural MRI; diffusion tensor imaging; connectivity; development; adolescence

Schizophrenia is associated with structural and functional changes in the cortex, as well as in the connections between different cortical regions. Recent advances in neuroimaging technology have enabled an unprecedented window into the nature, sources, and developmental course of these changes. Structural deficits, such as reduced gray matter volume and disrupted white matter integrity, have been observed, and these changes may be progressive during the pre-onset phase of the disorder, as well as in the early post-onset period. Correspondingly, functional imaging techniques show abnormal neural activity when patients are engaged in various cognitive tasks, including those assessing short-term memory, long-term memory, decision making, and emotion processing, and these changes have also been observed across phases of the disorder. In this review, we focus on several recent research trends in the assessment of structural and functional neural abnormalities in schizophrenia, as revealed through the lens of technologies based on magnetic resonance imaging (MRI). We will particularly focus on MRI evidence for the idea that schizophrenia is a disorder of reduced or disrupted connectivity and on the emergence of changes across disease state and across the life span.

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Structural Imaging

Development across disease progression

Gross neural anatomy can be clearly visualized at a resolution of about 1 cubic millimeter with MRI, a technique that measures the effects of strong magnetic fields on different tissue types to create high-resolution images of internal structures. Because MRI techniques are noninvasive and do not involve ionizing radiation, brain images can be acquired repeatedly in awake performing subjects, making well-controlled, large-scale, and longitudinal studies possible. Using this technique, complex patterns of structural abnormalities have been found in schizophrenia patients as well as in those at risk for the disorder.

In MRI studies of schizophrenia, the most consistent findings include reduced gray matter volumes of the medial temporal, superior temporal, and prefrontal areas. These are regions on which episodic memory, processing of auditory information, and short-term memory/decision making, respectively, are critically dependent. Gray matter abnormalities in schizophrenia are partially hereditary, as shown in twin and candidate gene studies, and they are partially modulated by intrauterine risk exposures such as fetal hypoxia (Cannon et al., 2003). Postmortem studies indicate that cortical gray matter reduction does not reflect loss of cell bodies but, rather, reduced dendritic complexity and synaptic density, which may impact interneuronal communication and integration (Glantz & Lewis, 2000).

Further, accumulating longitudinal neuroimaging data suggest that structural abnormalities in schizophrenia may be progressive around the time symptoms first appear and during the early stage of the disorder. In a recent study, longitudinal MRI scanning was performed on a cohort of patients identified as being at risk for the disorder based on clinical symptoms or changes in functioning. Such subjects are thought to be potentially in the prodromal phase of schizophrenia, a period defined by subdiagnostic symptoms and a decline in functioning, and are known as clinical high-risk patients. There was significantly greater brain surface contraction away from the skull in the prefrontal area in individuals who later developed psychosis than in individuals who did not (Fig. 1a; Sun, Stuart, Phillips, et al., 2009). This result largely excludes the possibility that progressive brain volume changes observed in schizophrenia and psychosis are due to medication or to the illness being chronic and strongly suggests that these changes represent a primary pathological process that possibly plays a causal role in the onset of symptoms. A parallel study examined brain surface contraction in first-episode schizophrenia patients relative to the normal developmental profile. In healthy adolescents and young adults, gray matter volume in the prefrontal cortex declines in association with brain developmental processes occurring around the time of adolescence, including synaptic pruning. Interestingly, both first-episode patients and controls demonstrated overall similar anatomical patterns of brain-surface contraction; however, the magnitude of surface contraction in prefrontal regions, reflecting underlying reductions in gray matter, was higher in patients (Fig. 1b; Sun, Stuart, Jenkinson, et al., 2009). Notably, this pattern of changes was also shared by clinical high-risk individuals who later converted to psychosis. Taken together, these findings indicate involvement of developmental deviations in the neuropathophysiology of schizophrenia from prodromal stages to early years of illness. This work supports the hypothesis that the developmental

process itself is abnormal in these subjects, although that does not preclude the possibility that the system on which this process is acting may already be vulnerable and that this developmental process might interact with that vulnerability—something that remains to be fully determined in future studies.

Structural connectivity

Many theories have framed schizophrenia as a disorder of reduced or disrupted neural connectivity, in which impaired communication between brain regions leads to the associated symptoms and cognitive changes. White matter forms the structural connections between brain regions, and thus, not surprisingly, in addition to the previously described gray matter changes, disruptions in white matter integrity have been implicated in schizophrenia. Supporting evidence includes neuroimaging studies of first-episode and chronic patients that find white matter volume reductions and structural abnormalities (Wright et al., 2000). Further, myelination, the maturational process in which the myelin sheath encases neural fibers to increase efficiency and speed of conduction, continues up into late adolescence and early adulthood. Given that this is the same time period most associated with the onset of psychosis, deficiencies in white matter development may have a special importance.

Diffusion tensor imaging (DTI) is a powerful MRI-based tool for examining the structural integrity of white matter based on patterns of water diffusion in neural tissue. Fractional anisotropy (FA) is the primary DTI measure and uses the shape of the area in which water is diffusing (basically, how constricted the area it moves in is) to index neuronal integrity, potentially reflecting both myelination and organization of white matter tracts. DTI studies in schizophrenia have shown decreased FA in many major tracts, including the superior longitudinal fasciculus, cingulate bundle, uncinate fasciculus, inferior longitudinal fasciculus, and hippocampus (Kyriakopoulos, Vyas, Barker, Chitnis, & Frangou, 2008). These tracts serve as long connection fibers facilitating inter-regional communication, and thus their disruption has the potential to affect a wide range of cognitive abilities. DTI changes have been observed in tracts associated with both working memory (Karlsgodt et al., 2008) and long-term memory (Karlsgodt, Niendam, Bearden, & Cannon, 2009), and FA changes are directly correlated with working memory performance (Karlsgodt et al., 2008), indicating that structural connectivity deficits have behavioral implications.

The developmental origins of the deficits in connectivity observed in schizophrenia are of great interest. Similarly to the gray matter changes, white matter changes are present by the time of the first episode and are present in subjects at risk for the disorder, indicating that they are not secondary to the later progression of the disease or to treatment effects but may be a core contributor to the disease's onset. This makes the developmental trajectory particularly interesting—particularly the question of whether there are pre-existing neural differences that may leave at-risk individuals more vulnerable to later insults or whether observed changes result from a disruption in developmental processes around the time of adolescence, such as myelination. Recent work has shown that high-risk subjects may indeed show an abnormal pattern of white matter development across adolescence, as indexed by DTI (Karlsgodt, Niendam, et al., 2009). This may indicate that, in parallel to the

patterns observed in gray matter development, there is a difference in the developmental process itself in these subjects.

New structural approaches

It is tantalizing to think that structural MRI abnormalities may be used for diagnosis of schizophrenia or prediction of outcome. To these ends, one approach has been to assess whether baseline structural changes are predictive of later functional outcome; for instance, it has been shown that white matter changes in temporal regions predict functional outcome and possibly serve as an early marker of risk (Karlsgodt, Niendam, et al., 2009). However, there is considerable overlap on individual brain measures between patients and controls, and examining isolated individual structures may not be the most powerful diagnostic approach. Accordingly, work using machine-learning methods has attempted to differentiate patients from unaffected people by taking into account the whole pattern of changes across the brain simultaneously. Machine learning (or pattern classification) is a technique in which the factors that differentiate groups are carefully examined and a statistical algorithm is developed that can determine which group (i.e., patients or controls) a subject resembles most and use that to predict which one he or she belongs to. Encouraging initial results from this approach show that schizophrenia patients can be differentiated from healthy subjects with high accuracy based on MRI scans (Davatzikos et al., 2005), and there has also been a report that clinical high-risk people who later convert to psychosis can potentially be differentiated from those with the same risk factors who do not convert (Koutsouleris et al., 2009). In a study using a sophisticated cortical matching method in combination with a novel pattern classification algorithm, an accuracy of 86% was achieved in differentiating patients who had a recent onset of psychosis from healthy control subjects (Sun, van Erp, et al., 2009). These techniques show promise to aid early prediction and diagnosis of schizophrenia in the future.

Functional Imaging

Development across disease progression

In addition to structural changes, functional activation changes, as measured by both functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have been well documented in patients with schizophrenia. Among the domains that have been prominently investigated are working memory and episodic memory. These processes are particularly interesting because they represent areas of cognition that are disrupted in patients with schizophrenia and are known to rely on gray matter regions (frontal lobes and hippocampus) that are compromised in these patients.

Deficits in working and long-term memory tasks and physiological changes during functional imaging have been shown not only in chronic schizophrenia patients, but also in subjects at genetic and clinical risk for the disorder and those in the first episode. This indicates that, like the gray matter and white matter structural changes, functional differences are not a result of the long-term effects of the disorder or of treatment for the disorder. Individuals at high genetic risk, such as siblings and unaffected co-twins of schizophrenia patients (who share the genetic liability for the disorder but not the disorder

itself) can serve as an indication of the effect of the genetic components of schizophrenia in the absence of disease progression, symptoms, or medication. Genetic high-risk subjects have shown changes in functional activation similar to those seen in the patients themselves across a number of studies (MacDonald, Thermenos, Barch, & Seidman, 2009).

Changes in functional activation exist not only in those at risk for schizophrenia but also in patients experiencing their first episode. Subjects in the first episode have been shown to have differences in functional activation during a variety of tasks, including working memory (Karlsgodt, Sanz, et al., 2009), which is particularly interesting given that regions associated with working memory, such as the frontal lobe, also show underlying gray matter changes in schizophrenia. Knowing that such changes exist early on can inform our understanding of what other factors might contribute to them, because these subjects meet full diagnostic criteria and yet have relatively short medication histories and are free from the effects of disease progression that might confound studies in older subjects. Further probing functional activation differences in clinical high-risk, first-episode, and chronic patients may provide valuable information on neural changes across disease progression.

Functional connectivity

Given the likelihood that some of the symptoms of schizophrenia might arise out of a dyscoordination of brain regions, directly observing the interaction between regions during cognitive tasks has been the focus of a number of investigations (Ragland, Yoon, Minzenberg, & Carter, 2007). However, with recent developments in fMRI, it is now possible to noninvasively assess baseline functional connectivity, something previously only possible using PET. There has been a resulting surge of investigations of functional connectivity during the “resting state,” when subjects are not performing an explicit cognitive task but simply relaxing with eyes open or shut. Such investigations are thought to have the potential to inform our understanding of the connectivity between brain regions independently of confounds such as differences in attention or task performance.

Briefly, during periods of rest, there is activation and increased functional connectivity of a “default mode network” (DMN) that includes ventromedial prefrontal cortex, posterior cingulate, and angular gyrus/inferior parietal lobe (Raichle et al., 2001). Activity in the DMN, assessed at rest, can be referred to as “task negative” and has been shown to be negatively correlated with activity in “task positive” networks associated with cognitive task performance; these two systems can be thought of as having a competitive, interactive relationship (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). In healthy subjects, greater suppression of DMN activity during task performance is associated with better performance and greater task-related activity and functional connectivity on working memory and other tasks (Kelly et al., 2008). Schizophrenia patients, as well as their first-degree relatives, may show a lack of the normal suppression of DMN activity during a working memory task (Whitfield-Gabrieli et al., 2009). This pattern may potentially explain their poorer performance and altered pattern of task-related activity and functional connectivity compared with controls. This failure to disengage the DMN may provide an additional angle from which to explain behavioral and physiological deficits on tasks assessing neuro-cognition and emotion.

New functional approaches

Now that general differences in fMRI function in patients with schizophrenia have been established, an important goal is to assess what types of factors may influence these measures and contribute to the observed differences. For example, behavioral performance is interesting, as recent work has shown that the discrepancy in the working memory literature between findings of prefrontal hypoactivation and hyperactivation may be in part related to differences in the ability of low- and high-performing patients to recruit their working memory circuitry (Karlsgodt, Sanz, et al., 2009). In addition, incorporating symptomatology or indices of disease severity may be informative, such as in recent work showing that fMRI activation may co-vary with level of symptoms (Sanz et al., 2009). Future work exploring the interplay between these types of measures and fMRI activation can help us gain further insights into the neural basis of this complex disorder.

As with structural imaging, it is exciting to consider that fMRI measures might be capable of predicting diagnosis or outcome or of differentiating subgroups of patients. To pursue these possibilities, a number of recent investigations have applied machine-learning techniques to functional data. This technique has been used with standard fMRI data, and it seems that, just as focusing on individual brain structures might not be the most powerful approach for structural imaging pattern classification, due to task variability, single tasks might not be the most powerful approach for functional imaging. Recent data indicate that combining data across multiple tasks may improve classification abilities (Michael, Calhoun, Andreasen, & Baum, 2008). Machine learning has also been used to classify subjects based on patterns observed in resting-state scans (Shen, Wang, Liu, & Hu, 2010). This area of research is a promising direction for future studies.

General Conclusions

Overall, the body of knowledge that has been assembled in neuroimaging studies of schizophrenia bring us to an exciting place. We are gaining an ever-more-sophisticated understanding of the structural changes associated with schizophrenia and of the functional changes that accompany them. Moving forward, an important step is to determine the specific molecular bases of these changes, such as changes in neurotransmitter systems and cellular signaling. In addition, the possibility that structural and/or functional changes as measured by MRI can be used diagnostically and prognostically is under active investigation, as we try to identify those people who are at greatest risk for onset of schizophrenia and learn to target treatments to different subgroups of patients.

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Fig. 1.

Maps of the average annual rates of brain surface contraction in (a) individuals at ultra-high risk for developing psychosis who converted to psychosis (converters) versus those who did not convert (nonconverters), and (b) schizophrenia patients versus healthy controls.

Converters and schizophrenia patients showed significantly greater brain-contraction rates compared with nonconverters and healthy individuals, respectively. A similar pattern of prominent prefrontal surface contraction was shared across groups. For the top two rows, bluer areas indicate regions of higher surface motion (in mm/year), while red and pink areas indicate areas of negative motion, or contraction; in the bottom row, red indicates regions that show statistically significant differences in the rate of contraction between groups.

Based on data in Sun, Stuart, Phillips, et al. (2009) and Sun, Stuart, Jenkinson, et al. (2009).