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Brain Imaging During the Transition from Psychosis Prodrome to Schizophrenia

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Abstract

Neuroimaging studies have identified patterns of brain abnormalities in various stages of schizophrenia, but whether these abnormalities reflect primary factors associated with the causes of illness or secondary phenomena such as medications has been unclear. Recent work conducted within the prodromal risk paradigm suggests that progressive change in brain structure and function occurs around the time when clinically high-risk individuals transition into full-blown psychosis, effects that can not be explained by exposure to medications or illness chronicity. This article reviews recent work bearing on the question of the timing of onset and course of brain changes, focusing on structural MRI, diffusion tensor imaging, and resting state connectivity MRI, in association with the onset and course of psychosis. We conclude with a consideration of potential mechanisms underlying progressive tissue changes during the prodromal phase of schizophrenia and implications for prevention.

Based in part on post-mortem observations of reductions of dendritic branching and spine and synapse density in schizophrenia (Glantz & Lewis, 2000), many schizophrenia researchers now believe that disruptions in cellular connectivity are in some manner involved in the pathophysiology of the disorder. Broadly, reduced cellular connectivity may manifest as reduced neuropil and axonal integrity (e.g., myelination) and altered functional connectivity between local and distal brain regions. Such reductions in connectivity are likely to be present at least in part in some cases from birth, representing a life-long biological vulnerability, but may progress beyond a threshold critical for expression of psychotic symptoms as a function of normal neuromaturational events (i.e., synaptic pruning) during adolescence (McGlashan & Hoffman, 2000). In other cases, reductions in connectivity may emerge during adolescence due to aberrant neurodevelopmental processes (i.e., abnormal pruning (McGlashan & Hoffman, 2000)) and/or environmental insults (e.g., elevated cortisol leading to dendritic atrophy). The contributions of early (pre- and perinatal) and later (adolescent) brain developmental processes to psychosis risk are not mutually exclusive, and both sets of processes may be operative in some cases (Cannon et al., 2003).

Although the theoretical framework just described has existed in some form or another for nearly 30 years, until recently there has been very little in the way of direct empirical tests

bearing on the question of whether a *progressive* change in brain structure and/or function is associated with the emergence of psychosis. Nearly all of the hundreds of neuroimaging studies of schizophrenia to date have utilized patients with established illness. Given that antipsychotic drugs and other factors associated with disease chronicity may account for any differential changes in brain structure and function observed in such patients, there has been lingering doubt about the potential role of these abnormalities in the pathophysiology of the disorder. Recently, it has become possible to track changes in brain structure and function prospectively in individuals with a heightened risk for developing psychosis, termed clinical high-risk (CHR) or prodromal risk syndrome patients. Such cases are considered to be at risk because they have experienced a recent onset of sub-psychotic symptoms; however, only some actually progress to a full-blown psychotic illness such as schizophrenia in the near future. A recent meta-analysis that included 27 studies, with a total sample of over 2500 clinical high-risk patients, revealed that risk for transition to psychosis was about 30% after two years of follow-up, with a decelerating rate of conversion over this period (Fusar-Poli et al., 2012). These observations help to establish the CHR syndrome as the single best predictor of future psychosis, 3-fold higher than for the next best predictor, family history of schizophrenia. Notably, the criteria are shown to be sensitive to conversion to full illness within a fairly circumscribed temporal window, 2 to 3 years from initial ascertainment. The prodromal risk paradigm has thus been validated as an approach that can help address questions of temporal sequencing of brain abnormalities in relation to symptom progression, while minimizing the confounding influences of medication effects and chronicity.

This article reviews recent work bearing on the question of the timing of onset and course of structural brain changes in association with the onset and course of psychosis. These studies make use of magnetic resonance imaging-based techniques, (MRI) and diffusion tensor imaging (DTI), that can be safely and reliably applied repeatedly in the same individuals, allowing for assessment of the dynamically changing brain throughout life (Brown et al., 2012; Cannon et al., 2013). We focus primarily on longitudinal studies of CHR samples, but set the stage for those studies by first considering patterns of brain abnormalities detected in patients with established illness. We conclude with a consideration of potential mechanisms underlying progressive tissue changes during the prodromal phase of schizophrenia and implications for prevention.

Gray matter abnormalities in Schizophrenia

Over the past 20 years, hundreds of studies have applied structural MRI techniques cross-sectionally comparing samples at various stages of schizophrenia with healthy controls (Pantelis, 2005). Reductions in prefrontal, medial temporal, and superior temporal gray matter volumes and enlarged ventricles have been among the most consistent findings (Pantelis, 2005; Shenton, Dickey, Frumin, & McCarley, 2001). Several longitudinal imaging studies of patients with schizophrenia have also been conducted. Consistent with cross-sectional studies, regions showing progressive and excessive volume loss in first-episode and chronic patients include prefrontal (Gur et al., 1998; Ho et al., 2003; Mathalon, Sullivan, Lim, & Pfefferbaum, 2001; Thompson et al., 2001) and temporal cortex (Nakamura et al., 2007; J. L. Rapoport et al., 1999). Interestingly, volume loss in the temporal cortex seems to be driven by changes in the superior temporal gyrus, a region that mediates auditory-

language processing and may play a role in hallucinations and formal thought disorder (Kasai et al., 2003; Thompson et al., 2001). However, given that antipsychotic drugs are known to influence anatomical brain imaging parameters (Dazzan et al., 2005; Lieberman et al., 2005), studies of patients with already established illness (whether cross-sectional or longitudinal in design) cannot differentiate whether any abnormalities in the patients reflect primary factors associated with pathophysiology or the accumulating impact of medications or other secondary phenomena.

Progressive gray matter loss as psychosis develops

One strategy to overcome these issues is by ascertaining individuals at imminent risk for onset of psychosis and longitudinally tracking neuroanatomical changes from pre-onset stages through transition into full illness (McGorry, Yung, & Phillips, 2003). Some of the individuals at heightened risk will eventually convert to frank psychosis (converters), and changes in neuroanatomical parameters can be compared to those in a normally developing population and also to those in CHR cases who do not convert to psychosis (non-converters). This prospective longitudinal design can help to elucidate neuromarkers that may underlie increasing symptom severity and deteriorating functioning around the time of onset of the disorder and also help to avoid confounds associated with long-term illness and medications (Cannon et al., 2003).

Several such prospective longitudinal neuroimaging studies have now been published, encompassing multiple independent samples of CHR cases (Borgwardt et al., 2008; Cannon et al., 2015; Pantelis et al., 2003; Sun, Phillips, et al., 2009a; Takahashi, Wood, Yung, Phillips, et al., 2009a; Takahashi, Wood, Yung, Soulsby, et al., 2009b; Walter et al., 2012; Ziermans et al., 2012). All of these studies found that CHR cases who converted to psychosis showed a steeper rate of cortical gray matter loss compared with non-converters. Among the studies that also included a healthy comparison group, the rate of gray matter decline was also greater in converters compared with age- and gender-matched controls. The regions showing *significantly* greater rates of gray matter decline differ somewhat across the studies using whole-brain approaches, with one finding differential change only in prefrontal cortex (Sun, Phillips, et al., 2009a) and the others finding differential change in prefrontal as well as temporal cortical regions (Borgwardt et al., 2008; Pantelis et al., 2003; Ziermans et al., 2012). This variation is not surprising given that most studies included relatively small sample sizes (N's of 8 to 12 converters), employed varying inter-scan intervals (1–2 years), and took different approaches to correcting for multiple comparisons voxel-wise throughout the brain. However, a recent multi-site study, with the largest CHR group reported to date (N=274, including 35 converters), showed that converters experienced a steeper rate of gray matter loss in right superior frontal, middle frontal, and medial orbitofrontal cortex, especially in those individuals with higher level of pre-delusional symptoms (Chung et al., *in press*), even when a stringent multiple correction method was applied at the whole-brain level (Cannon et al., 2015). If the statistical threshold was relaxed, accelerated cortical thinning was also observed in superior temporal cortex, parietal cortex, and parahippocampal gyrus. *Taken together, these findings are remarkably consistent in demonstrating a steeper rate of cortical gray matter decline among CHR cases who convert to psychosis compared with those who do not and with healthy comparison subjects.*

Influence of antipsychotics in gray matter development

Given that antipsychotics are the front-line treatment for first-episode psychosis and are known to be associated with gray matter decline in animal models (Dorph-Petersen et al., 2005) and in patients with chronic schizophrenia (Dazzan et al., 2005; Lieberman et al., 2005), antipsychotic drug use represents the most plausible competing explanation for differential gray matter loss among CHR cases who convert to psychosis. Keeping in mind that these factors cannot be controlled in patients for ethical and practical reasons, several lines of evidence argue against this perspective. First, a recent meta-analysis demonstrated that antipsychotic naïve first-episode schizophrenia patients have less cortical gray matter than healthy comparison subjects (Haijma et al., 2013), indicating that at least some amount of gray matter reduction in schizophrenia is independent of antipsychotic drug exposure. Second, in the recent NAPLS2 longitudinal neuroimaging study, CHR converters to psychosis who had not been exposed to antipsychotics during the inter-scan interview showed significantly greater thinning of prefrontal cortex than CHR non-converters (regardless of medication status) and healthy controls (Cannon et al., 2015). Third, longitudinal imaging studies of twins discordant for schizophrenia and other genetically informative samples have observed that a steeper rate of gray matter decline is associated with a genetic diathesis to schizophrenia (Brans et al., 2008; McIntosh et al., 2011).

Neuroinflammation associated with gray matter change

Given that the accelerated gray matter loss associated with psychosis onset is not a secondary phenomenon, it could be due to factors related to the pathophysiology of schizophrenia and related disorders, such as neuroinflammation (Frick, Williams, & Pittenger, 2013; Monji, Kato, & Kanba, 2009). Neuroinflammatory markers are elevated in postmortem neural tissue from patients with schizophrenia (Rao, Kim, Harry, Rapoport, & Reese, 2013), and these same markers are associated with microglial-mediated synaptic pruning and dendritic retraction in animal models (Milatovic, Gupta, Yu, Zaja-Milatovic, & Aschner, 2011), providing a potential mechanistic basis for the reduced neuropil seen in patients (Glausier & Lewis, 2013). Although neuroinflammatory processes initiated during prenatal stress exposures could play a role (Perkins et al., 2014), activation of such processes in association with the synaptic pruning characteristic of adolescent brain development represents an influence more proximal to psychosis onset (Frick et al., 2013; Glausier & Lewis, 2013; McGlashan & Hoffman, 2000; Meyer, 2013). Recently, an elevation in plasma-based markers of inflammation and oxidative stress was found to precede and predict onset of psychosis among CHR cases (Perkins et al., 2014). In the recent longitudinal NAPLS2 imaging study, higher levels of a plasma-based aggregate index of proinflammatory cytokines at BL were strongly predictive of steeper rates of gray matter reduction in right prefrontal cortex among CHR cases who converted to psychosis (Cannon et al., 2015). Given that peripheral cytokines can affect brain function (Besedovsky & del Rey, 2011), and because the cytokines included in the proinflammatory index are potent activators of the M1 cytotoxic phenotype of microglia that result in synaptic pruning and dendritic retraction (Milner & Campbell, 2003; Walker et al., 2014), it is plausible to hypothesize a mechanistic link between neuroinflammation (i.e., microglial activation) and

progressive gray matter loss in individuals who develop psychosis, a hypothesis that should be tested using more direct indicators of neuroinflammatory processes in CHR subjects.

White matter abnormalities in Schizophrenia

In addition to the focus on cortical thinning, summarized above, there is now a widespread interest in investigating neurodevelopmental deviation in white matter tracts as part of the pathophysiology of schizophrenia. White matter in certain regions, particularly prefrontal cortex, shows a protracted pattern of development through adolescence, as increasing myelination facilitates inter-regional connectivity and underpins later cognitive development (Nagy, Westerberg, & Klingberg, 2004; Paus, 2005). Moreover, patients with white matter developmental disorders such as Metachromatic leukodystrophy (MLD), which results in demyelination of prefrontal white matter tracts, exhibit psychotic-like symptoms and cognitive deficits (Hyde, Ziegler, & Weinberger, 1992).

Volumetric MRI studies have consistently observed white matter abnormalities particularly in prefrontal regions, in patients with chronic schizophrenia (Breier et al., 1992; Hulshoff Pol et al., 2002) (Hulshoff Pol et al., 2002). Furthermore, studies examining specific tracts have also found reduction in white matter volumes, for example, in the anterior limb of the internal capsule, which contains the projections from medial dorsal thalamus to the frontal lobes (Suzuki et al., 2002; Zhou et al., 2003). However, these volumetric findings in white matter need to be interpreted with caution, as they do not specifically reveal information about organization of white matter microstructure, myelination and connectivity between different brain regions.

Diffusion tensor imaging is a relatively new MRI-based technique that has been used to quantify organization of white matter microstructure. This technique utilizes water molecules as a probe by exploiting the fact that their motion in white matter is restricted and repelled by fatty myelin sheaths and tends to diffuse along the direction of the axons rather than perpendicular to it (Le Bihan, 2003; Peled, Gudbjartsson, Westin, Kikinis, & Jolesz, 1998). This technique has opened new ways to non-invasively assess the structural integrity of white matter fiber tracts to characterize the architecture of anatomical connections in both normal and diseased tissue (Catani, Howard, Pajevic, & Jones, 2002). Among several indices that represent various characteristics of water diffusivity in brain tissue, fractional anisotropy (FA) is one of the commonly used indices for estimating diffusion anisotropy—this measure is utilized as a proxy for the extent of alignment and organization of cellular microstructure within the white matter projections and is considered to reflect the integrity of structural connectivity.

Many of the early DTI studies extracted diffusivity measures from lobar regions of the brain. These initial studies variously found altered white matter integrity, as measured by FA, in schizophrenia patients compared to controls in frontal (Buchsbaum et al., 1998; Hao et al., 2006; Lim et al., 2006) and parietal lobes (Ardekani, Nierenberg, Hoptman, Javitt, & Lim, 2003; Minami et al., 2003). The variation in regions showing deficits across studies may be due to variation in sample size, image analytic approaches, and/or heterogeneity of the patient samples under study.

Novel tractographic methods have now emerged that allow assessment of structural connectivity in major white matter tracts that connect different regions in the brain. Among the many white matter tracts that have found to be abnormal in patients with schizophrenia, the superior longitudinal fasciculus (SLF) is of particular interest, as this tract primarily consists of white matter projections that link the frontal and parietal lobes (Petrides & Pandya, 2002). Prefrontal and parietal regions show a rapid and coordinated pattern of neuronal responses during working memory tasks (Chafee & Goldman-Rakic, 2000; Paulesu, Frith, & Frackowiak, 1993) and disturbed white matter projections that link these two regions may contribute to the working memory deficits in schizophrenia (Karlsgodt et al., 2008; Szeszko et al., 2007). This circuit may impact a broad array of endpoints, as schizophrenia patients with working memory deficits also show impairments in other cognitive processes and poorer functional outcomes (Goldman-Rakic, 1994; Silver, Feldman, Bilker, & Gur, 2003).

Structural connectivity deficits in prodrome

Given the relative novelty of DTI compared with other MRI-based techniques, only a few DTI studies have thus far been conducted in the CHR population. Two recent studies reported differences in diffusivity parameters between CHR and healthy controls, suggesting white matter alteration before onset of full psychosis (Bloemen et al., 2009; Clemm von Hohenberg et al., 2014). Despite some variability in the regions found to be affected, inconsistencies that could be due to different sensitivities of tract-based versus voxel-wise approaches, the superior frontal area was affected in both studies. In another cross-sectional investigation by Karlsgodt and colleagues, CHR individuals showed lower FA than healthy controls in SLF, and the prodromal group failed to show increasing FA as a function of age (Karlsgodt, Niendam, Bearden, & Cannon, 2009), which is typically observed in normal white matter development (Brown et al., 2012; Lebel & Beaulieu, 2011). Moreover, lower FA in the patient group was predictive of poorer functional outcomes at follow-up. The only longitudinal DTI study of CHR to date revealed abnormalities in a number of white matter tracts, including SLF, and further showed FA reduction in CHR individuals who later converted to psychosis in a cluster surrounding the left anterior limb of the internal capsule and in the anterior body of the corpus callosum, while non-converting CHR individuals did not show such reductions at follow-up scan (Carletti et al., 2012). However, these aberrant developmental trajectories need to be replicated, as only 5 converters and 17 non-converters were assessed at follow-up.

These preliminary results suggest that disrupted white matter development during late adolescence and early adulthood may be associated with onset of psychosis. While the results of these studies are provocative in this regard, they are limited primarily by the small numbers of cases included, by the uncontrolled nature of treatments received by the patients, and by heterogeneity of outcomes among converters. In sum, DTI provides a non-invasive, repeatable procedure that enables studying development of white matter microstructure around the time of psychosis onset, and future studies should implement this relatively new method to establish whether there are progressive changes in connectivity in CHR persons as psychosis develops and whether any such changes precede and predict gray matter loss or vice versa.

Functional neuroimaging

A handful of studies have utilized functional MRI to investigate whether altered patterns of functional connectivity precede and predict the onset of psychosis among CHR cases (Anticevic et al., 2014a; Anticevic et al., 2014b; Fryer et al., 2013; Wotruba et al., 2014). These studies are notable in finding patterns of anomalous functional connectivity during the prodrome phase of psychosis that resemble patterns seen in studies of patients with established schizophrenia. Most recently, the NAPLS project observed aberrant functional connectivity in prefrontal-thalamic network among 243 clinical high-risk individuals, with most pronounced alteration in those who later convert to full psychosis (Anticevic et al., 2014a). This observation is strikingly consistent with the altered thalamo-cortical connectivity observed in chronic schizophrenia (Anticevic et al., 2013). However, because no such study has evaluated fMRI parameters longitudinally, it remains to be determined whether there is deteriorating functional connectivity during the ramp-up to full psychosis in CHR cases.

Classification and machine learning

In addition to its role in investigating dynamic changes in brain structure and function around the time of psychosis onset, neuroimaging may be useful in predicting future psychosis among CHR individuals based on profiles of neuroimaging parameters assessed at baseline. Most clinical neuroimaging studies to date have utilized either an *a priori* hypothesis approach using pre-defined regions of interest or performed mass independent univariate statistics at each voxel level in attempt to reveal clusters that may reflect markers of regional neurovulnerability. Although these initial approaches were successful in showing regional differences at a group level, they are of limited utility for diagnostic application because there is considerable overlap between cases and non-cases even in voxels/clusters with pronounced neuroanatomical difference at the group level (Friston & Ashburner, 2004). In order to address these limitations, application of multivariate classification methods using neuroanatomical measures has gained interest. These methods attempt to discern patterns in the underlying data, including consideration of inter-regional or voxel dependencies across the entire brain, that help to differentiate cases from controls at the individual subject level (Lao et al., 2004).

When applied to neuroanatomical images from patients with established schizophrenia and healthy controls, such multivariate classification algorithms generally achieve about 80% classification accuracy with both high sensitivity and specificity (Davatzikos et al., 2005; Kawasaki et al., 2007; Sun, van Erp, et al., 2009b). Koutsouleris and colleagues applied support vector machine algorithms to baseline neuroanatomical data in a prodrome sample; the algorithm was able to discriminate those who later convert to psychosis from non-converters and healthy controls with reasonable accuracy (Koutsouleris et al., 2009). However, the ultimate utility of such classification algorithms awaits confirmation of diagnostic/predictive accuracy in completely independent samples. Some factors that represent challenges for these approaches to overcome include the fact that any schizophrenia-promoting changes in brain structure occur against the backdrop of the gradual decline in gray matter that is part of normative adolescent brain development and

may thus be obscured by sample differences in age, sex and other factors that influence brain maturation. Given the converging evidence that accelerated longitudinal changes in neuroanatomical measures are associated with conversion to psychosis (Cannon et al., 2015), multivariate analysis incorporating the rate of change in neuroanatomical parameters may produce a much more robust signal than the cross-sectional absolute measures for classification purposes. Koutsouleris et al. also have applied their methods on longitudinal imaging data and showed promising initial results. However, a small number of prodrome cases (n=25) were utilized in this study, and hence future studies should aim to replicate the findings with larger samples for both training the classifier and confirmation to assess generalizability.

Conclusions and Future Directions

Overall, the psychosis prodrome provides a unique window on the unfolding pathophysiology of illness, without the clouding effects of disease chronicity and long-term treatment that plague studies of patients with established illness. Neuroimaging studies of the psychosis prodrome have proven valuable in showing dynamic changes in brain structure around the time of psychosis onset that may participate in the up-ramp in symptom severity leading to full illness. Nevertheless, it is important to note that all longitudinal MRI studies of CHR cases used follow-up intervals of 12-months or more, and for the vast majority of converters in these studies, the follow-up scans occurred *after* the point of conversion. In the NAPLS2 study, the amount of tissue loss in prefrontal cortex over 1 year was comparable among those whose follow-up scan occurred before conversion compared with those whose follow-up occurred after this point, which is reassuring on this question. Nevertheless, this finding requires confirmation in a larger sample. In addition, the shape of the function relating change in gray matter decline to time to conversion is not known, but whether this function is stable or accelerating has implications critical for the design of future intervention trials and for the minimal period of monitoring required to use rate of change in a predictive classifier. Therefore, future neuroimaging studies of CHR cases are encouraged to conduct assessments at more frequent time points (e.g., 2 to 3 month intervals) to elucidate brain trajectories that predict a course of worsening clinical symptoms. The suggested longitudinal design could also potentially reveal critical information about the temporal relationships between various biomarkers. For example, we could gather evidence on whether aberrant white matter development or neuroinflammation precede gray matter loss or are a consequence of it.

Improving prospective prediction of psychosis is an additional goal of prodromal research. Initial evidence suggests that adjunctive use of risk factors including family history of schizophrenia, poor social functioning, and history of drug abuse may improve positive predictive power to a range (i.e., 70–80%) that may be at the threshold required for ethical justification of early interventions that carry some risk of side effect burden (Cannon et al., 2008). Neurobiological measures may or may not lead to an enhancement of psychosis prediction over and above that associated with clinical and demographic risk indicators. However, even if the contribution to the prediction of psychosis contributed by biological measures is ultimately shown to overlap entirely with that of clinical and demographic measures, such knowledge would in itself be valuable. Biological measures would then be

validated as predictive biomarkers in prodromal populations. Such findings, in turn, would be likely to generate future research to determine if biological measures could be used to ascertain individuals at risk, independently of prodromal symptoms and before substantial clinical and functional deterioration has occurred. Given the heterogeneity of the prodromal population in terms of risk factors and outcomes, testing the unique predictive roles of multiple biological and clinical predictors simultaneously requires very large samples and systematically acquired data, which will only be possible in multi-site collaborative studies.

These results may ultimately aid in the development of preventive interventions. Specification of rational preventive interventions requires knowledge of the mechanisms underlying the progression from prodromal to fully psychotic symptoms (Insel & Scolnick, 2006). Considering the evidence reviewed above of dynamic changes in brain structure and connectivity around the time of psychosis onset, new molecular targets may be identifiable in the signaling cascades driving these neural changes.

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