The neurobiology of transition to psychosis: clearing the cache

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The prepsychotic phase of schizophrenia is not only important for indicated prevention strategies, but also crucial for developing mechanistic models of the emergence of frank psychosis (transition). This commentary highlights the work of Dukart and colleagues, published in this issue of the *Journal of Psychiatry and Neurosicence*, who sought to identify MRI-based anatomic endophenotypes of psychosis in a well-characterized sample of patients with at-risk mental state (ARMS) and first-episode psychosis (FEP). Conceptual and translational challenges in clarifying the neurobiology of transitional prepsychotic states are discussed. A role of intracortical myelin in the neurobiology of transition is proposed. Transition may not be an outcome of "progressive structural deficits"; it may occur due to inadequate compensatory responses in the predisposed. The need to revise our current "deficit-oriented" models of neurobiology of psychosis in the wake of burgeoning evidence indicating a dynamic process of cortical reorganization is emphasized.

Introduction

Early intervention services have radically transformed the way treatment is delivered to patients with psychotic disorders, especially schizophrenia.[1] A key component of this success is the accelerated access to clinical care that contributes to reducing the psychosocial impact of the illness. Despite its widespread uptake and optimism, most clinical early intervention services focus on secondary and tertiary prevention (i.e., reducing the impact of the illness) rather than a truly primary prevention (i.e., reducing the incidence of psychosis in the first place). When compared with more common mental disorders, such as depression, the prevalence of psychosis is fortunately lower. As a result, for a cost-efficient prevention (or deferral) of psychosis, we must first develop an approach to identifying a group of high-risk individuals who are about to experience a psychotic episode.

In this pursuit of indicated prevention of psychosis, the concept of at-risk mental state (ARMS) has become popular in recent times. There are numerous operational definitions used to identify ARMS.[2] One commonly used definition is the Personal Assessment and Crisis Evaluation (PACE) criteria[3] that identify individuals with brief limited intermittent psychotic symptoms (< 7 d) or attenuated psychosis present for longer duration, or a first-degree relative with a psychotic disorder plus at least 2 indicators of a clinical change, such as a marked decline in social or occupational functioning. Among patients identified to have ARMS, a variable number, usually around 10%–30%, transition to frank psychosis.[4]

Several groups have attempted to isolate neurobiological features that characterize ARMS samples.[5,6] As ARMS precedes psychosis, there is likely to be a continuum of neurobiology, with the brain alterations that make an individual vulnerable to frank psychosis likely to be present in ARMS samples, albeit in a less pronounced manner than with first-episode psychosis (FEP). Dukart and colleagues[7] test this notion in a fairly large sample of help-seeking individuals with ARMS (n = 59), FEP (n = 59) and healthy controls (n = 26). The authors constructed neuroanatomical contrast maps comparing the 3 groups in terms of grey matter volume and thickness across the whole brain. Contrary to the extant literature highlighting grey matter reduction in psychosis and ARMS samples, Dukart and colleagues found a distributed increase in grey matter volume affecting frontal, insular, temporal and parietal regions in both the ARMS and FEP groups compared with healthy controls, but no differences between the FEP and ARMS groups. When grey matter thickness was examined, again an increase in grey matter tissue content was noted in both the FEP and ARMS groups compared with controls, though the increase in thickness was more localized to the occipitoparietal cortex. Within the FEP group, patients who had the greatest increase in grey matter volume exhibited less symptom severity. Furthermore, both the FEP and ARMS groups showed pronounced age-related reductions in grey matter volume and cortical thickness compared with controls.

Translational challenges in at-risk studies

Before we consider the implications of Dukart and colleagues' observations, it is worth reflecting on the challenges that are

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typical in this area of inquiry. First, while the honing-in strategy using ARMS criteria provides a reliable operationalized means to predict the onset of psychosis, the conversion rates are still too low to meaningfully utilize the ARMS concept in routine clinical care and illness prevention. Second, even in clinical settings with dedicated at-risk services, the use of ARMS criteria captures only 1 in 20 individuals who eventually transition to psychosis.[8] Furthermore, there is a concern that the transition rates reported in the literature may actually be declining with time, especially when adapted to a clinical service that provides early intervention.[9,10]

Moreover, within the group of ARMS individuals, notable heterogeneity is introduced by variable temporal patterns of transition to psychosis and discrepancies in functional status, family history and personality traits. Furthermore, individuals with ARMS experience various diagnostic outcomes in addition to psychosis, introducing the issue of comorbidity when examining the mechanistic basis of ARMS. These issues of variable prognosis and overlapping diagnoses are not specific to the definition of ARMS, but are prevalent across many other disease constructs that we currently use in psychiatry. For this reason, neurobiological features that are shared between ARMS and FEP individuals may not always indicate an intermediate phenotype (as emphasized by Dukart and colleagues), but may relate to shared functional, cognitive and behavioural outcomes or comorbidities.

Moreover, the concept of ARMS hinges on a distinct premise that an episode of frank psychosis has not yet occurred in these individuals. Except for this conjecture, ARMS is a phenomenon that is strikingly similar to psychosis in full or partial remission (i.e., low symptom scores, genetic vulnerability, notable functional deficits). With this in mind, neurobiological differences observed between the symptomatic FEP and ARMS groups should be validated in follow-up studies that seek to compare postepisode (preferably untreated) patients with psychosis and individuals with ARMS. Better yet would be to follow up the same individuals from ARMS to FEP and postepisode states. Given the low conversion rates of individuals with ARMS, such a longitudinal study would need to recruit a large sample of ARMS patients. Cross-sectional studies, such as that of Dukart and colleagues, are critical model-building steps that provide the substrate for challenging longitudinal investigations.

Transition and accelerated brain-aging

Dukart and colleagues report increased age-related reduction in grey matter tissue in both ARMS and FEP samples compared with healthy controls. Historically, the "praecox" aspect of schizophrenia, highlighted by Kraepelin[11] (dementia praecox), emphasizes a dementia-like pathological process that presents in early life, usually around adolescence. On the basis of age-related cognitive, vascular and metabolic dysfunctions seen in patients with schizophrenia, Kirkpatrick and colleagues[12] argued that schizophrenia is a syndrome of accelerated aging. There has been a recent revival of this idea with brain imaging studies estimating an enhanced trajectory of grey matter decline among patients with psychosis.[13–15] Dukart and colleagues contend that their observation of pronounced age-related grey matter reductions in FEP and ARMS samples are in line with an accelerated brain-aging model, though several issues remain unanswered before considering accelerated aging as an indicator of transition.

Large-scale neuroimaging studies of healthy brain development indicate that the cortex shapes itself by reducing its grey matter content steadily from early childhood (i.e., from the fourth year at least, when most of these neuroimaging studies made baseline observations). If accelerated aging underlies the vulnerability to psychosis, we should see a pattern of pronounced age-related grey matter decline alongside grey matter deficits, rather than grey matter excess. The lack of cross-sectional grey matter deficit when compared with controls indicates that accelerated aging is either not prominent enough to cause a notable grey matter deficit, or that it has a finite onset triggered immediately before the acquisition of MRIs selectively in both patient groups. The latter explanation appears somewhat untenable. Unfortunately, this issue cannot be resolved without a longitudinal design with careful control for confounds that can accelerate the aging process (e.g., malnutrition, inactivity, poor vascular health, insomnia and environmental impoverishment).[16]

The issue of grey matter excess in psychosis

To those who are following the neuroimaging literature in psychosis, the observation of diffuse increases in grey matter tissue in both ARMS and FEP samples may appear contradictory to the extant literature published to date. The conventional view of the neuroanatomy of schizophrenia paints a picture of diffuse but subtle reduction of grey matter during the course of the illness. Several studies involving individuals in various stages of schizophrenia have reported a reduction in the amount of grey matter volume and thickness measured using MRI.[17,18] These grey matter deficits are present even in the early stages of illness (i.e., immediately after the onset),[19,20] and to some extent are shared by healthy siblings who carry the genetic risk.[6,21,22] These grey matter deficits appear to intensify following the onset,[23,24] especially in the first few years,[25] but generally slow down with time, irrespective of clinical status.[26] In this context, it is not surprising that Dukart and colleagues' results appear as an outlier.

Consider the meta-analyses of MRI studies that estimate the difference between patients and controls in annualized grey matter loss.[24,27] Given that grey matter loss peaks in the second decade of life (the peak age of FEP) and has been reported even in chronic stages of schizophrenia, about 0.6% per year of loss reported in these studies, when compounded until the age of 60 years, should lead to 21.4% of grey matter lost over 40 years. But postmortem studies estimate that the total volume loss, including all compartments of the brain in schizophrenia, is less than 5%.[28] Assuming that MRI-based measurements are not gross miscalculations of actual tissue changes, we are left with 2 possibilities:

- there is an increase as well as a decrease in tissue volume in individuals with psychosis (either in the same patients or in different subgroups), or

- early deficits are temporally restricted to the first few years but ameliorate with time, probably owing to a reorganization process.

It is also likely that the published rates of decline in grey matter are grossly exaggerated, representing a reporting bias in favour of demonstrating anatomic deficits. An unfortunate view widely prevalent across the field is that psychosis in general, and schizophrenia in particular, is a condition where neurobiological/neurocognitive faculties change in the direction of showing deficits in patients. Gold and colleagues[28] made a case for turning the catalogues of documented impairments upside down and reported on relatively spared neurocognitive domains in patients with schizophrenia. Zipursky and colleagues[29] took this further, and used Cohen and Cohen's concept of clinician's illusion to highlight the pessimism that prevails among clinicians who mostly see the neediest and the most unwell individuals in the psychosis spectrum. They argue that it is a myth to consider schizophrenia as a progressive illness in a substantial number of patients.[29] It is important to keep these arguments in mind when interpreting neurobiological observations in individuals with schizophrenia.

A closer examination of the neuroanatomical literature in psychosis indeed suggests that in contrast to older studies that favoured reporting grey matter deficits, many recent studies report conflicting results.[30] Grey matter increase in patients with psychosis has now been reported in both cross-sectional studies of treated[31–33] and neuroleptic-naive patients[34,35] and in longitudinal studies[36–41] in which patients were treated with antipsychotics. Dukart and colleagues report that a medium to large effect size of increase in grey matter tissue can occur even before the onset of psychosis in individuals with ARMS. In this regard, Dukart and colleagues provide a refreshing extension to our current understanding of the neuroanatomy of psychosis.

The role of myelin in morphometry

If MRI-based grey matter thickness and volume increases in some individuals with ARMS and FEP, what are the likely pathological explanations? As rightly pointed out by Dukart and colleagues, the estimate of grey matter volume and thickness using MRI depends directly on where the grey matter–white matter boundary lies in the cortex. Image intensity–based estimation of this boundary is contingent upon the amount of myelin present in the deeper layers of grey matter. A pathological aberration (delay or deficient) myelination could contribute to apparently higher grey matter volume and thickness. Intriguingly, observations reported by Bartzokis and colleagues[41] using inversion recovery– and proton density–based boundaries of tissue intensity indicate that intracortical myelination is reduced in patients with schizophrenia and certain antipsychotic agents can restore this defect.[41] If this is true, then increased grey matter in ARMS and FEP samples could indeed be a reflection of delayed or deficient myelination in those with schizophrenia.

Several lines of evidence suggest a critical role for dysmyelination in patients with schizophrenia.[42–44] First, postmortem studies have reported that significant reduction (14%–22%) in the density and the quantity of oligodendrocytes (cells producing myelin)[44–56] is seen alongside signs of apoptotic damage to myelin sheaths,[52,55,57] especially in the grey matter, and downregulation of myelin-related genes and proteins.[58–64] Arguably, of all the expressed brain proteins with recorded abnormalities, astrocytic and oligodendrocytic proteins appear to be the most consistently affected in patients with schizophrenia.[65] Second, recent genomic studies indicate a cardinal role for oligodendrocyte-related genetic polymorphisms in patients with schizophrenia.[66–68] Neuregulin-1, a well-established candidate marker for schizophrenia, results in a schizophrenia-like phenotype (increased dopamine transmission and reduced social interaction), possibly through oligodendrocyte dysfunction and defective myelination.[69] Several other myelin-related candidate genes have been identified in patients with schizophrenia (for a review see the work of Takahashi and colleagues[58]). Third, dysmyelination is consistently noted in neurodevelopmental models that reproduce behavioural features reminiscent of negative symptoms of schizophrenia. This includes perinatal and subchronic administration of phencyclidine,[70–74] maternal immune activation (polyinosinic–polycytidylic acid [polyI:C],[75,76] lipopolysaccharide [LPS],[77,78] influenza[79]), early social isolation,[80] and excitotoxic developmental lesion models (medial prefrontal[81]). Cuprizone, a copper chelating agent that actively disrupts myelination, results in diminished social interaction in mice,[81–86] but only when dysmyelination occurs before adult life.[83] Guest and colleagues[87] have recently shown that dizocilpine (also known as MK-801, an *N*-methyl-D-aspartate receptor [NMDAr] antagonist and pharmacological model of schizophrenia[88]), primarily affects the metabolic processes of oligodendrocytes rather than neurons in vitro. Clozapine, a drug with some therapeutic effect on negative symptoms,[89] counters the metabolic effects of MK-801, but again, preferentially in oligodendrocytes rather than neurons/astrocytes.[87,90,91] A number of myelin gene knockout mice models exhibit schizophrenia-like behaviours.[92–94] Consistent with this notion, using 7 T magnetization transfer imaging in conjunction with 3 T diffusion tensor imaging, we reported significant reduction in myelin affecting both white matter and cortical grey matter in the occipitotemporal cortex in a medicated group of patients with schizophrenia.[95] Interestingly, Dukart and colleagues and others who observed increased grey matter in individuals with psychosis[30,31,32] report increased grey matter in overlapping occipitotemporal regions.

With increasing access to quantitative myelin imaging in the human brain, the time is now ripe to undertake more detailed examination of the role of intracortical myelin in individuals with psychosis. Quantitative MRI methods, such as T_1-based inversion recovery,[96] are highly correlated with spatial[97] and age-related variations[98] in myelin content, can quantify both intracortical and white matter myelin,[99] and appear to be sensitive to even subtle dysmyelination.[100,101] Furthermore, T_1-based methods are cross-validated with histological myelin staining[102] and postmortem myeloarchitecture[103] and

show robust longitudinal reproducibility.[104,105] To our knowledge, this method is yet to be applied in the study of ARMS and other prepsychotic states.

Cortical reorganization in psychosis

One of the intriguing findings of Dukart and colleagues is their observation that in patients with FEP, grey matter increases correlate with reduced symptom burden, indicating a role for an ameliorative reorganization process that may underlie the physiology of compensation and resilience. In this context, the observed grey matter increase in individuals with ARMS, the majority of whom may not become frankly psychotic despite the risk they carry, could also be an indicator of resilience rather than risk. Nevertheless, as rightly pointed out by Dukart and colleagues, this cannot be resolved using the cross-sectional design in their study.

A number of observations reported elsewhere indeed suggest that an increase in grey matter could reflect the process of reducing illness severity in psychosis. Schauffenberger and colleagues[39] reported no significant grey matter loss in nonremitting patients with FEP, but those who remitted showed a pattern of grey matter increase in regions that showed baseline deficits (insula, superior temporal gyrus). Lappin and colleagues[37] noted that 29% of medicated patients with FEP showed a bilateral hippocampal volume increase over a 6-year period; this was associated with better clinical and functional outcome. A more directly relevant observation is the association between higher occipital grey matter tissue and a favourable treatment response in individuals with psychosis.[31]

In a cross-sectional sample of 93 antipsychotic-treated patients at various clinical stages of schizophrenia, we previously reported that the brain regions showing pronounced grey matter deficits in medicated early-stage patients had notably reduced deviation from controls in medicated later-stage samples, thus having the effect of "closing the gap."[30] We also noted a higher than expected covariance between regions with reduced thickness and regions with increased thickness, suggesting that the processes leading to grey matter loss in some regions and grey matter increase in the others are intricately linked in schizophrenia. This observation indicates that the cortical grey matter, given its plasticity, may be constantly reorganizing itself, either due to the "primary insult" that produces clinical features of psychosis or in response to dysfunctional processes that result from this insult. This issue, reviewed elsewhere in more detail,[106] needs further critical examination given the emerging results of grey matter increase in individuals with psychosis.

Clearing the cache

For the last 2 decades, neuroimaging has promised a great deal in aiding our understanding of the mechanistic basis of psychosis. With constant technological advances and increasing accessibility of scanners, testing neuroanatomical hypotheses has become much more feasible in recent times.[107] Nevertheless, the optimism raised on the basis of novel and more precise technology cannot be sustained without evidence for concrete progress.[108] Given this tipping point in our pursuit of the mechanistic basis of psychosis, studies such as the one by Dukart and colleagues challenge the conventionally accepted neurobiological models and serve to "clear our cache." The emergent mechanistic frameworks should be put to rigorous testing through multicentre neuroimaging studies that cover the prepsychotic, psychotic and postpsychotic course of schizophrenia and hold the wherewithal to recruit and retain sufficient number of at-risk individuals.

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