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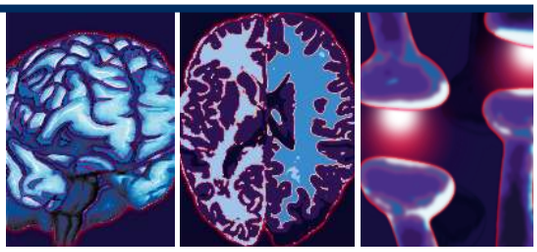

Brain imaging correlates of emerging schizophrenia

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Practice points

- Clinical criteria of the At-Risk Mental State define a population of usually help-seeking young people with a high probability of up to 40% of developing a first episode of psychosis.
- 'At-risk' individuals show early signs of structural and functional brain deficits that predict clinical outcome.
- Early clinical signs and symptoms as well as cognitive impairment in working memory and other executive functions correlate with emerging brain pathology in the prodrome.
- Multimodal brain imaging procedures (i.e., incorporating cognitive tasks and/or physiological measures) are particularly promising research tools.
- Future research should focus more on longitudinal studies to allow for validation of prodromal status.
- Future brain imaging research should also include neurobiological markers of disease liability (i.e., schizophrenia candidate genes) and pathophysiology when investigating 'at-risk' populations and mapping disease processes.

SUMMARY The early detection of the schizophrenia prodrome in young people considered 'at-risk' of developing this severe mental illness has entered mainstream clinical practice despite the limitations in the predictive specificity of the clinical criteria that define the At-Risk Mental State syndrome. These limitations are increasingly addressed by brain imaging research, which has added substantial evidence to the notion of emerging and progressive gray and white matter abnormalities in the early phase of illness. The association of the apparent neuropathology with the clinical signs and symptoms of the disorder – along with cognitive impairment and the underlying pathophysiology – will be reviewed.

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Future Medicine part of fsg

Identifying the prodrome of schizophrenia

The early identification of individuals at a high risk of developing schizophrenia has become a focus of psychiatric research in recent years since it holds the promise of targeting early intervention towards a population at considerable risk of developing a severe mental illness. When exclusively focusing on the predictive criteria of at risk criteria alone, however, the false-positive rates are considerably high at 60–90% and vary depending on the settings where the clinical assessment has taken place (i.e., general versus specialized early psychosis clinics) [1]. Notwithstanding, most young people meeting At-Risk Mental State (ARMS) criteria are help-seeking as a result of experiencing a recent decline in global and/or socio-occupational functioning and often present with a clinically significant behavioral or psychological syndrome that is associated with disability and/or severe distress.

Attenuated or very brief episodes of limited psychotic symptoms and/or a first-degree biological relative with the diagnosis of schizophrenia, together with a recent functional decline, are common ARMS criteria [2,3]. These early clinical signs are usually accompanied by mild-to-moderate cognitive impairment [4] while brain imaging research has provided evidence of emerging brain pathology [5]. Here we review the relationship of morphological and functional abnormalities in the early phase of illness, spanning from the 'at-risk mental state' to the clinical manifestation of the first psychotic episode, in order to identify early disease function/structure signatures of the prodrome. However, a major limitation lies in the cross-sectional design of a number of studies, thus not allowing confirmation of the prodromal status of the at-risk population. With false-positive rates of up to 90%, these samples are considerably heterogeneous with only a minority developing schizophrenia. We attempt to redress this limitation by comparing cross-sectional studies in those at risk with those conducted in first-episode schizophrenia (FES) and evaluating the consistency of findings by assuming a progressive disease process.

Early signs of brain pathology & their association with emerging clinical symptoms

Brain imaging research has provided clear evidence of widespread gray and white matter abnormalities in FES [6,7]. Initial support derives from Crespo-Facorro *et al.* who reported a reduction of whole brain cortical thickness in 142 FES patients when compared with 83 healthy control subjects [8]. Cortical thinning was particularly pronounced in frontal, temporal and parietal cortices, changes that are also well established for more chronic patients diagnosed with schizophrenia [9].

These early morphological deficits are also clinically relevant owing to their correlation with clinical signs and symptoms of the disorder. Lui *et al.* reported a significant decrease of gray matter volume in the superior/middle temporal and cingulate gyrus in the right hemisphere in a sample of 68 antipsychotic-naive FES patients versus 68 matched control subjects [10]. The degree of gray matter volume reduction in these brain regions correlated with clinical outcome as rated on the Global Assessment of Functioning Scale as well as with the severity of a range of positive symptoms, including thought disturbance and paranoia, and impulsive aggression (as rated on the Positive and Negative Syndrome Scale).

Positive symptoms also correlate with reduced fractional anisotropy (FA) – a measure of white matter integrity – in frontotemporal tracts in treatment-naive FES [11], whereas negative symptoms appear to correlate with cerebellar and inferior frontal gray matter volume reduction [12].

Importantly, most of these neuroanatomical abnormalities appear to predate the clinical manifestation of FES and are present in individuals at 'ultra high risk' of developing psychosis [13–15]. Pantelis *et al.* reported less gray matter in the right medial temporal, lateral temporal, inferior frontal and cingulate cortex when comparing ultra high-risk individuals who later did develop psychosis with those who did not [16]. In a longitudinal comparison, follow-up MRIs after at least 12 months also revealed the progressive nature of the neuroanatomical abnormalities in the course of emerging illness with further gray matter reductions in left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and cingulate gyri in those who went on to become psychotic. A recent meta-analysis based on 25 brain imaging studies confirmed small-to-medium volume reductions in prefrontal, cingulate, insular and cerebellar gray matter in high-risk individuals who went on to develop psychosis compared with those who did not [17]. These findings, however, remain somewhat preliminary given methodological limitations in the reviewed literature, which include differences

in scanning parameters and analytical processes across the studies, often small sample sizes that lack appropriate matching for gender, handedness and comorbidities (e.g., substance abuse) as well as potential effects due to antipsychotic pharmacotherapy, which appears to be associated with cerebral gray matter reduction in established schizophrenia [18,19] and also early psychosis [20]. However, Fusar-Poli *et al.* confirmed cerebral gray matter reductions meta-analytically across 14 voxel-based morphometric studies conducted on antipsychotic-naive patients [21]. The authors reported reduced gray matter in temporal, anterior cingulate, cerebellar and insular regions around the onset of psychosis.

There is also corresponding white matter pathology, as indexed by FA, lateral to the right putamen and in the left superior temporal lobe in ARMS individuals who develop psychosis over a follow-up period of 2 years compared with those who did not. Moreover, reduced FA in left middle temporal gyrus has been reported to correlate with the level of positive symptom expression [22]. Peters and colleagues reported reduced FA in superior and middle portions of frontal white matter cross-sectionally in clinical at-risk individuals when compared with healthy control subjects [23]. When analyzing the same cohorts, however, no group differences were found in uncinate and arcuate fasciculi, dorsal and anterior cingulate and subdivisions of the corpus callosum [24]. These findings are to be interpreted with caution given the methodological differences between the two reports. This discrepancy in findings may arise from the differences in diffusion tensor imaging methodology and their respective limitations. Voxel-based analysis allows for automated whole brain analysis without *a prioi* hypotheses [23], but is prone to false-positive findings, whereas fiber tracking [24] seems not to reliably capture some of the early white matter pathology in at-risk and first-episode patients [25].

Finally, emerging cognitive deficits also appear to be associated with prodromal neuroanatomical deficits. For instance, gray matter density measures [26] suggest that impaired semantic fluency performance – which is considered a measure of executive function – is linked to structural abnormalities in task-related brain areas, such as the right insula, right superior/middle temporal cortex and left anterior cingulate in ARMS individuals who go on to develop psychosis versus those who do not. Also, deficits in spatial working memory performance have been reported in high-risk populations [27]. SWM deficits have also been shown to be associated with gray and white matter abnormalities in FES patients [28]. Taken together, these reports lead to the speculation that abnormalities in neural networks involved with SWM may be present prior to the clinical manifestation of psychosis. This is of clinical relevance since SWM performance appears to predict clinical outcome in ARMS, including severity of negative symptom expression in those who go on and develop psychosis [29].

Taken together, these findings support the notion of a progressive gray and white matter pathology in prodromal schizophrenia that particularly affects the frontal, temporal, parietal and cingulate cortex, and possibly the cerebellum. Furthermore, the degree of the morphological deficits is also predictive of clinical outcome (i.e., transition from at-risk mental state to psychosis) along with the severity of clinical symptoms. There is also some evidence that the emerging neuroanatomical deficits in the prodromal phase of illness are closely linked to impaired brain function in a region-specific pattern, which will be further explored below.

Functional & anatomical correlates of impaired working memory & executive dysfunction in the early stages of schizophrenia

Impaired cognition is a robust feature of ARMS [30–32] and FES [33]. Most commonly reported are working memory deficits in schizophrenia when employing the n-back task whilst recording brain activity in response to task-related changes of blood oxygen levels with functional MRI.

A robust finding is aberrant blood oxygenation level-dependent (BOLD) activity in the dorsolateral prefrontal cortex (DLPFC) along with impaired working memory performance in schizophrenia [34]. Broome and colleagues, for instance, reported reduced cortical activation in the inferior frontal, dorsolateral prefrontal and parietal cortex of individuals with first-episode schizophreniform psychosis, and intermediate degrees of activation in ARMS individuals when compared with healthy control subjects [35]. When further differentiating ARMS individuals according to their duration of at-risk status, Smieskova and colleagues found reduced activation in the right inferior frontal gyrus and insula when comparing individuals with higher

transition probability (short-term ARMS) to those with vulnerability but very low transition probability to psychosis (long-term ARMS) [36]. As a putative sign of illness progression, first-episode psychosis patients exhibited decreased activation bilaterally in inferior frontal gyrus and insula, and in the left prefrontal cortex relative to long-term ARMS individuals whereas first-episode psychosis and short-term ARMS individuals presented with reduced activation in parietal and middle frontal brain regions when compared with healthy control subjects.

Crossley *et al.* investigated regional activation and functional connectivity in FES, ARMS and healthy subjects while performing the n-back task [37]. Healthy subjects presented with deactivation of the superior temporal cortex in contrast to FES patients who showed a BOLD increase when performing the task while the ARMS group exhibited a somewhat intermediate activation pattern relative to the other two groups. The authors also reported negative coupling between superior temporal gyrus and middle frontal gyrus in their healthy participants that was reversed in FES and intermediate in ARMS.

Taken together, the reports are consistent in their findings of reduced prefrontal (i.e., DLPFC), parietal, frontal and temporal brain activation when performing the n-back task. The cross-sectional findings also suggest a change in the front-temporal processing of the n-back task around the clinical manifestation of schizophrenia. However, the studies are limited when attempting to map out the working memory deficits and their cortical correlates across a continuum around the early stages of illness. In this respect, longitudinal studies – which ideally also incorporate structural brain measures – are better placed. When following up an ARMS cohort over 1 year with repeated functional MRI, Fusar-Poli *et al.*, for instance, found reduced task dependent activation in the left middle frontal gyrus, supramarginal gyrus and inferior parietal lobule in ARMS individuals at baseline when compared with healthy control subjects [38]. Reduced left middle frontal gyrus volume also correlated with reduced activation in this brain region. Clinical and functional improvement after 1 year was associated with increased activation in anterior cingulate and right parahippocampal gyrus. This study, however, did not report functional/structural correlates that are indicative of a progression towards schizophrenia.

The progressive nature of working memory deficits in the early phase of illness is also reflected by other working memory tasks. Fusar-Poli *et al.* assessed longitudinal changes in ARMS individuals and healthy control subjects with the Paired Associate Learning Task [39]. At baseline, ARMS subjects showed reduced activation in the left precuneus/occipital gyrus, left superior parietal lobule and in the right middle temporal gyrus when compared with healthy control subjects. After a year, the general clinical status of the ARMS cohort had improved. This was accompanied by greater activation in the left lingual and in the left superior parietal lobule relative to baseline which, however, did not correlate with changes in the clinical measures.

The previous studies are limited in adapting task difficulty to performance levels of study participants. This may result in ceiling or floor effects in the BOLD dynamics, thereby trivializing the relevance of any group differences. A preferred approach is therefore incorporating graded task difficulty as an independent variable when analyzing BOLD differences between groups. Rasser *et al.* adopted a visuo-spatial working memory/planning task [40,41] and recorded functional MRI in remitted FES patients and closely matched healthy control subjects while performing the Tower of London task in the scanner. FES showed less task difficulty-dependent BOLD activity in the DLPFC and parietal lobule as well as less deactivation in the superior temporal cortex compared with the control group. Moreover, these differences in the BOLD activation pattern were also correlated with gray matter reduction in the respective areas of the cerebral cortex in FES, thus establishing a direct link between impaired executive function and apparent brain pathology in FES.

Other visuo-spatial working memory tasks have also confirmed a similar pattern of deficits in the emerging illness. Broome *et al.*, for instance, employed an object–location paired-associate memory task, which progressively activates the medial frontal and medial posterior parietal cortex with increasing task difficulty [42]. The authors reported a reduced BOLD response in ARMS individuals in medial frontal cortex and right precuneus that was more profound in FES when compared with healthy subjects, respectively.

The neural network subserving working memory processes overlaps with other executive functions. Hence, the regional pattern of

structure/function deficits is usually very similar. For instance, ARMS subjects consistently show abnormal activation in the prefrontal, frontal, temporal and cingulate cortex when performing verbal fluency tasks and thereby often show intermediate activation patterns somewhere between healthy control subjects and FES patients [35,43,44].

Performance on response inhibition tasks (e.g., measured as Go/No-Go procedure) is also impaired in ARMS subjects along with reduced BOLD activity in right frontal and bilateral temporal cortex when compared with healthy subjects [45]. The same study also revealed an aberrant activation pattern in the anterior cingulate, insula and middle frontal gyrus for error-related processing in the at-risk group. By contrast, no differences in fronto-temporal BOLD activation were reported between ARMS and healthy subjects when investigating response inhibition with the Hayling Sentence Completion Task [46]. The authors reported increased BOLD in caudate and anterior cingulate in their at-risk cohort, which may reflect increased processing load due to cognitive impairment.

This selective review of functional brain imaging studies clearly demonstrates that those brain areas emerging with gray matter deficits in the early phase of illness are also functionally compromised. While longitudinal studies are unfortunately sparse, the overall picture is consistent with an emerging neuroanatomical deficit that apparently drives the early cognitive deficits in a brain region-specific pattern as they are identified in the early phase of illness.

The final section of this review will focus on electrophysiological findings in early psychosis and how they relate to structural and functional deficits. This line of research may further our understanding of the underlying pathophysiology of the emerging illness and potentially holds clues regarding the neurobiology of the disorder.

Electrophysiological correlates of early psychosis & their association with neuroanatomical abnormalities

One of the most robust findings in schizophrenia is a reduced event-related potential termed mismatch negativity (MMN), which is recorded during a passive auditory listening oddball task [47–50]. Psychopharmacological research has linked reduced MMN to impaired *N*-methyl-D-aspartate receptor function [51,52], which, in turn, has been implicated in the neuropathology of schizophrenia [53,54].

If at all, MMN amplitude reduction shows only very weak associations with clinical symptoms of the disorder. Rather, it appears to be associated with clinical outcome, such as global function levels [55], but also with the course of illness (i.e., progressive MMN reduction with chronicity [56]) and the prediction of treatment response to clozapine in chronic schizophrenia [57]. Some further research suggests an association of reduced MMN amplitudes with some of the cognitive deficits found in FES, such as poor performance on the Trail-Making Test, the Mental Control Subtest of the Wechsler Memory Scale III, and the Rey Auditory Verbal Learning Test [58]. Although largely generated in the primary auditory cortex with possibly a second generator in prefrontal cortex [59,60], reduced MMN amplitudes – particularly in response to pitch oddballs – correlate with widespread gray matter deficits in frontal, temporal and parietal cortices in schizophrenia [61]. MMN amplitudes recorded in ARMS subjects usually tend to fall in the intermediate range between FES and healthy control subjects [62], with some recent studies suggesting that at-risk individuals who later develop FES have smaller MMN amplitudes than those who will not [63–65].

A few further studies suggest impaired sensory gating of the P50 auditory event-related potential in at-risk populations. For instance, Brockhaus-Dumke *et al.* reported impaired P50 suppression in prodromal ARMS subjects who developed psychosis within a clinical follow-up period of 2 years [66]. By contrast, no such deficit was observed in ARMS subjects who did not develop psychosis within the follow-up period. The authors also reported less N100 suppression in their prodromal sample similar to FES. Again, no such deficit was found in ARMS individuals who did not develop psychosis within the follow-up period. A previous study also found impaired P50 suppression in prodromal individuals but not in at-risk individuals who were solely defined by genetic risk such as having a first-degree biological relative diagnosed with schizophrenia [67].

Disrupted sensorimotor gating has also been closely linked to schizophrenia and abnormal dopamine neuromodulation in concert with other neurotransmitters [68–70]. Usually the electromyographic eye blink response to startling noises is recorded with and without a nonstartling acoustic prepulse (prepulse inhibition). 'Sensorimotor gating' refers to the inhibition

of the eye blink response when the startling noise is preceded by a prepulse at short lead intervals (i.e., 601–620 ms). When compared with healthy subjects, ARMS individuals show impaired sensorimotor gating, which tends to improve along with clinical improvement [71].

Reduced P300 amplitudes are also robustly linked to schizophrenia [72]. Fusar-Poli *et al.* reported reduced P300 amplitude and reduced brain volumes in prefrontal and parietal areas in 39 ARMS individuals at their first clinical presentation versus 41 healthy control subjects [73]. Parietal brain volumes correlated with P300 amplitudes at baseline. However, neither parietal brain volumes nor P300 amplitudes changed longitudinally. On the other hand, parietal (as well as parahippocampal) brain volumes predicted transition to psychosis while progressive gray matter changes were only reported for prefrontal and some subcortical areas.

This selective review of electrophysiological findings in the early phase of illness suggests impaired auditory information processing occurring in the prodrome. These findings may assist in improving the early identification of at-risk individuals, particularly when psychophysiological measures are combined with clinical ARMS criteria.

Conclusion & future perspective

The identification of early stages of a severe mental illness such as schizophrenia is currently our best option to implement targeted intervention to alleviate or even prevent the transition to psychosis. While the research data are promising, the early diagnosis still lacks the specificity to unequivocally justify, for instance, the introduction of antipsychotic pharmacotherapy in the at risk mental state. Notwithstanding, brain imaging research is probably our best tool for the time being to further our understanding of the emerging illness. Future research, however, should address some of the limitations discussed in the current review, such as the need for larger sample sizes and the replication of findings. Future research must also include the rapidly increasing knowledge about the molecular genetics of schizophrenia in order to comprehensively investigate the biological pathways from gene and gene products to brain pathology. Brain imaging research has already shown how and where early signs of illness emerge in the brains of young people developing schizophrenia, whereas psychophysiological and cognitive research has informed us about the impaired processes and functions in the affected brain areas. It is only a matter time before these lines of research eventually merge to open up novel approaches to early detection, intervention and perhaps illness prevention.

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