Psychiatry Research 277 (2019) 17–22

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Review article

Neurobiological approaches to the study of clinical and genetic high risk for developing psychosis

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ARTICLE INFO

Keywords:
Clinical high risk
CHR
MRI
fMRI
ERP
DTI

ABSTRACT

Research on neurobiological impairments in clinical and genetic high risk for developing psychosis individuals (CHR) has identified several brain abnormalities that impact both brain structure and function. The current review will discuss research examining brain abnormalities in clinical and genetic high risk for psychosis using magnetic resonance imaging (MRI) focusing on structural brain abnormalities, diffusion tensor imaging (DTI) focusing on the integrity of white matter tracks, functional MRI focusing on functional brain abnormalities, and EEG and event related potential (ERP) methodologies focusing on indices of cognitive dysfunction in CHR. Studies conducted across these different methodologies sought to identify brain regions and brain processes that would distinguish between those high risk individuals who converted to psychosis versus those who did not. In addition, in some of the studies, the distinction was made between individuals who converted to psychosis, those who did not, and those individuals who remained clinically symptomatic while not converting to psychosis. The brain regions most often identified as abnormal in this subject group were the brain areas often found abnormal in schizophrenia, including frontal and temporal regions. Similarly, several cognitive processes often found to be abnormal in schizophrenia have been also found impaired in CHR.

1. Introduction

It is well established that schizophrenia is associated with a number of brain abnormalities that point to biological underpinnings of clinical and cognitive symptomatology that characterize this serious illness. It has been also recognized that the impairments observed in both first episode schizophrenia and at its chronic stages start long before patients present with frank psychosis. This suggests that they could be identified prospectively, either as indicators of risk, or in those already identified as at-risk as an indication that the early processes leading to psychosis have already begun. However, establishing the point at which pathological changes start in the brain remains difficult and is currently a subject of intense research. In an effort to identify the mechanisms and timetable of these brain pathological changes, interest has turned towards examining individuals at both clinical high risk (CHR) for developing psychosis and at familial or genetic risk. While both of these groups are regarded as being at high risk for developing psychosis, clinical high risk is identified based on clinical features and the genetic high risk is identified based on having a family member diagnosed with schizophrenia. The goal of this research has been to identify mechanisms that distinguish those who are at-risk and later develop psychosis from those who do not develop psychosis. Typically, the distinction is made between endophenotypic traits—observable signs that are believed to be genetically mediated—and specific biomarkers that are associated more with illness progression and are not genetically mediated (e.g., Gottesman and Gould, 2003; Pantelis et al., 2009). Perhaps not surprisingly, the findings from this line of studies have confirmed that structural and functional abnormalities exist before these individuals experience their first psychotic break. In addition, evidence is accumulating that even those individuals who do not convert to psychosis often remain symptomatic clinically and impaired in their neurobiological function. Studies examining the integrity of gray and white matter, and of brain function using both functional magnetic imaging (fMRI) as well as event related potentials (ERPs) methodologies have started to identify such mechanisms and to describe brain states that accompany enduring symptoms without the conversion to psychosis.

In describing the current state of knowledge on the neurobiology of CHR, the evidence was separated into studies that examined the brain structural integrity, including the connectivity between brain regions provided by white matter fibers, or tracts, and studies that examined brain functional integrity in this clinical condition. Brain structural integrity has been examined with structural magnetic imaging (sMRI) to yield measures of regional brain volume and of cortical thickness as well as using diffusion tensor imaging (DTI) to yield measures of white matter tract integrity. Brain functional studies focused on broadly understood cognition as a function of neural processes have been

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https://doi.org/10.1016/j.psychres.2019.02.009
Received 14 December 2018; Received in revised form 4 February 2019; Accepted 4 February 2019
Available online 05 February 2019

investigated with functional MRI (fMRI) methodology that probes activation in brain regions involved in a particular cognitive task and with EEG and ERP studies that probe specific cognitive operations related to activity of neuronal assembles and expressed as either 'brainwaves' or oscillations.

2. Structural and functional brain imaging studies

2.1. Gray matter volumetric studies

Several studies, including the early studies examining brain structural changes in individuals with clinical-high risk syndrome identified changes in the temporal and frontal regions to be associated with pre-illness time period. The Pantelis's et al. (2009) review of the early structural findings distinguished between endophenotypes and biomarkers and concluded that most brain regions reported in these early studies were biomarkers rather than endophenotypes. According to Pantelis and co-authors, the frontal regions were likely endophenotypic while the temporal regions were likely biomarkers for psychosis. For example, examining a group of individuals who received special education, Stanfield et al. (2008) reported increased right prefrontal cortical folding in adolescents who later developed psychosis relative to those who did not. The authors suggested that this finding may be related to faulty connectivity in individuals at risk for psychosis development, an important observation that would be followed in several later studies, and pointing to the developmental component of illness. The Edinburgh longitudinal high risk study (McIntosh et al., 2011) further suggested that indeed frontal brain structures are impacted by the disease process both as trait and state features of the illness. In that study, the volumes of the left and right prefrontal lobe and the temporal lobes were smaller in the CHR group relative to healthy controls; in addition, greater volume reductions were observed in the prefrontal lobes in those subjects who converted to frank psychosis. Furthermore, these reductions were positively associated with the severity of psychotic features. Iwashiro et al. (2012) examined the prefrontal brain regions in terms of their possible contributions to the development of psychotic symptoms in more detail by focusing on two structures of the prefrontal lobe: pars opercularis and pars triangularis in a group of CHR, first episode schizophrenia and healthy individuals. Pars triangularis was specifically reduced in both the CHR and the first episode schizophrenia individuals relative to their healthy comparison subjects and the extent of the reduction correlated with the severity of psychosis symptoms. These results suggest that the volume reduction in pars triangularis is already present before the onset of psychosis. Another brain region whose abnormalities seem to precede psychosis development but also continue after the psychosis symptoms onset is the anterior cingulate cortex (ACC) where reduced volumes have been reported (Fornito et al., 2009). Reductions here seemed to be due to the shrinkage of neuronal, dendritic and synaptic densities.

Cortical thickness, another measure of volumetric integrity was also found to be affected in CHR: its reductions were associated with metacognition abnormalities (Buchy et al., 2015), and with the worsening of symptoms (Cannon et al., 2015).

Several recent studies focused on changes in the temporal and limbic structures in those at high risk for psychosis. An early and relatively small sample study of hippocampal volume in a group of 18 CHR individuals, with eight of them transitioning to frank psychosis and 10 not transitioning (Walter et al., 2012), found hippocampal volume reduction in both CHR groups over time but did not find that the volume differences distinguished between converters and non-converters. Similarly, reduced amygdala but not hippocampus was found in CHR (Konishi et al., 2018). A cross-sectional study of hippocampal-amygdaloid complex (Bois et al., 2015) found volume reductions relative to healthy controls in the hippocampus, amygdala, and the nucleus accumbens in those with a first episode of psychosis but not in CHR. The same group reported on the longitudinal results from a cohort of subjects participating in the Edinburgh high risk study (Bois et al., 2016). Here, the results suggested an altered developmental trajectory in CHR individuals in terms of the hippocampal volumetric changes: healthy individuals showed an increase in the hippocampal volume over time while the CHR individuals did not. However, no differences were found between converters and non-converters suggesting that hippocampal volume reductions may be associated with at-risk state but not necessarily with transition to psychosis. A more detailed investigation of the volumetric changes with a focus on CA1 (Ho et al., 2017) revealed that this hippocampal sub-region but not others was sensitive to time-dependent reduction in volume in CHR individuals who either converted to psychosis or remained clinically symptomatic relative to CHR who remitted and to healthy control individuals. However, a meta-analysis of the hippocampal findings (Walter et al., 2016) suggests a lack of hippocampal volume reduction in CHR. It is likely that large, longitudinally designed studies are needed to resolve the issue of the possible contribution of abnormal hippocampal development at the prodromal stage for schizophrenia.

2.2. Structural and functional connectivity studies

In addition to the study of gray matter brain abnormalities in CHR individuals, research focused on brain connectivity abnormalities. The premise behind these studies has been that observed clinical symptoms and cognitive deficits might be due not only to impairments in specific brain regions but be also related to the way these brain regions were connected to each other in functional brain networks. These abnormalities can be discussed in terms of faulty white matter connections between brain regions but also in terms of faulty synchronization of activity between brain regions.

2.2.1. Structural connectivity

Early studies of white matter changes in CHR suggested pathological processes in white matter integrity. For example, a study focusing on individuals at genetic high risk for psychosis (Hoptman et al., 2008) suggested that fractional anisotropy (FA) might be abnormal in these individuals relative to healthy controls with reductions both in the cingulate and angular gyri bilaterally. The study investigating the FA in genetic high risk individuals, first episode and healthy controls found lower FA in both the patient and high risk individuals in the anterior limb of internal capsule (Maniega et al., 2008). Lower FA was also found in CHR in the inferior longitudinal fasciculus, a fiber bundle connecting frontal and parietal regions (Karlsgodt et al., 2009). Furthermore, CHR did not show increases in FA in either inferior longitudinal fasciculus or medial temporal gyrus (MTG) as a function of age as was observed in the healthy control group. Lower FA in the MTG and in the inferior longitudinal fasciculus at baseline was associated with worse social and role functioning 15 months later. In addition, Bloemen et al. (2010) reported that abnormal local connectivity, as evidenced by lower FA within medial frontal lobes and the left superior temporal gyrus, as well as higher FA in the left MTG distinguished converters from non-converters. These findings suggest that abnormalities in the white matter integrity within the brain structures associated with schizophrenia may be also a contributing factor to the development of psychosis. Evidence for broadly distributed abnormalities in the white matter in individuals at genetic high risk for schizophrenia has been also reported (Francis et al., 2013). Further, a study using several measures of white matter integrity including FA, but also axial, radial and mean diffusivity in a group of 28 individuals at high risk for psychosis, but with a very low conversion rate (4%) (von Hohenberg et al., 2014) pointed to white matter abnormalities in several posterior regions including superior longitudinal fasciculus, posterior corona radiata and posterior parietal lobe. These results suggest that these types of abnormalities are characteristic of CHR irrespective of the conversion rate.

There is also evidence of reduced thalamo-orbitofrontal white

matter connectivity in a study using probabilistic tractography (Cho et al., 2016) in CHR individuals. The altered thalamo-cortical connectivity in that study was also observed in first episode psychosis individuals where it was more pronounced relative to the CHR group. This result suggests that structural thalamo-cortical abnormalities are a common feature of CHR and FE stages which are differentiated by the degree and not by the type of dis-connectivity. Since the conversion in the CHR group was not considered, it is impossible to know if conversion to psychosis confers an additional degree of severity of dis-connectivity.

2.2.2. Functional connectivity

Studies focusing on functional connectivity identified several abnormalities between brain regions associated with compromised function in schizophrenia. For example, reduced functional resting state connectivity between Broca's area and the lateral and medial frontal cortex was found in CHR individuals (Jung et al., 2012), which was associated with positive symptoms. A study of gray matter network properties in a large group of familial high risk individuals ($N = 144$) (Tijms et al., 2015), where size, connectivity, density, path length, degree, clustering coefficient, betweenness centrality and small world properties were examined and showed decreased path length and centrality, and clustering in prefrontal and temporal regions in this group of subjects relative to healthy controls. As described above, the prefrontal and temporal brain regions have been shown to be affected at the clinical high risk stage. Interestingly, the gray matter network properties but not the volumetric measures were a better predictor of schizotypal cognitions (81% vs 48%) in this group of subjects.

Two studies examined functional connectivity in the default mode network (DMN), that includes medial prefrontal cortex and posterior cingulate, in young people with propensity to positive symptomatology (Amico et al., 2017; Clark et al., 2018). The Amico study examined functional connectivity in the DMN as well as in two other networks, salience network (SN) and central executive network (CEN), previously associated with schizophrenia symptomatology (e.g., Whitfield-Gabrieli and Ford, 2012), in young people who experienced auditory hallucinations. Abnormalities were found in all three networks. The Clark study focused on the DMN and fronto-temporal network connectivity in CHR and their relationship to cognitive insight. The DMN, but not the fronto-temporal connectivity, was increased in the CHR individuals and associated with a lack of cognitive insight.

As in the case of structural connectivity impairment, several studies found impaired functional connectivity in the limbic and subcortical structures. For example, a study of whole-brain resting connectivity of amygdala in the CHR, early course and chronic schizophrenia (Anticevic et al., 2014) revealed that the reduced amygdala connectivity with orbitofrontal cortex was a function of developing frank psychosis, while the CHR group was characterized by an exaggerated connectivity to a circuit involved in the stress response. Abnormal connectivity of subcortical areas, and specifically of the thalamus, with several brain regions, was observed in a group of CHR (Anticevic et al., 2015). Individuals at risk for developing psychosis showed reduced resting state functional connectivity with prefrontal and cerebellar regions and, at the same time, an increased connectivity with the sensory motor area. Both types of abnormal connectivity were associated with greater symptom severity and were especially robust in individuals who converted to psychosis. Similarly, abnormal cerebello-thalamo-cortical network development was found in CHR individuals (Bernard et al., 2017) and associated with positive symptom development. The Colibazzi et al. (2017) also reported abnormal connectivity between thalamus and the temporal regions in the CHR individuals.

2.3. Functional MRI studies

Finally, functional MRI studies have explored processes found to be impacted by schizophrenia. Cognitive skills such as language (Sabb et al., 2010; Li et al., 2016; Natsubori et al., 2014; Niendam et al., 2014), working memory (Li et al., 2016; Thermenos et al., 2016), theory of mind and social cognition (Marjoram et al., 2006;Takano et al., 2017), as well as emotion have been associated with abnormal brain function in CHR. For example, a functional MRI study of language processing in CHR (Sabb et al., 2010) showed abnormalities in brain regions implicated in different aspects of language processing that included medial prefrontal cortex bilaterally, left inferior frontal gyrus (lIFG), middle temporal gyrus, and the anterior cingulate gyrus. Those individuals who later transitioned to psychosis had higher activation levels in the STG, caudate, and LIFG. Furthermore, signal change in the lIFG, SFG, and MTG correlated with the severity of thought disorder at follow up in the CHR group, while social outcome was correlated inversely with the signal change in the lIFG and ACC.

A study investigating theory of mind in a group of genetic high risk individuals showed activation level differences between HR individuals with positive symptoms and those without them in regions associated with theory of mind processes including prefrontal cortex, precuneus and temporal lobes (Marjoram et al., 2006). Abnormal activation within temporal lobes was also associated with hallucinations (lateral regions) and delusions (medial temporal regions) in a group of genetic high risk individuals (Whalley et al., 2007). The sensitivity to task demands in the working memory paradigm as a function of age was examined by Karlsgodt et al. (2014) in a group of CHR and their age matched typically developing individuals. In the typically developing controls, there was a negative association between activation in the working memory network and age, while in the CHR, there was a positive association. Also, response inhibition, an aspect of cognitive control, was found abnormal in both CHR and first episode individuals in a NoGo/Go fMRI task (Fryer et al., 2018) with both groups showing reduced activation in bilateral dorsal ACC and right inferior frontal cortex. Corticolimbic hypersensitivity to emotional cues was identified in a task involving exposure to neutral and emotional scenes. Both first episode and CHR individuals showed enhanced reaction to emotionally neutral pictures (Modinos et al., 2015). Overall, fMRI studies in CHR individuals suggested that many of the cognitive functions found to be abnormal in schizophrenia are already impacted in the prodromal period, and brain abnormalities as captured by BOLD signal in the brain regions in the prefrontal and temporal cortex contribute to these cognitive impairments.

3. EEG and event related potential studies

Unlike structural and functional imaging studies which have identified which brain regions and their connections are abnormal in the clinical and genetic high risk for developing psychosis group, research using EEG methodology have focused on abnormal neuro-cognitive processes. While localization to brain sources that produce these processes is always somewhat challenging, EEG methodology offers an exquisite temporal resolution and thus allows imaging the unfolding neurocognitions with millisecond resolution and accuracy. As in the study of structural and functional brain abnormalities described above, the strategy for looking at neurocognitive brain abnormalities in the clinical high risk individuals was to focus on these brain processes which were demonstrated to be abnormal in frank psychosis. ERP components are deflections in the brain waveform characterized by the latency at which they appear relative to a stimulus onset and by their amplitude. Different ERP components are associated with different functional properties, i.e., index unique cognitive operations. Reductions in ERP components' amplitude are evidence of an abnormal cognitive process while latency prolongations are interpreted as evidence of a slower but otherwise unaffected cognitive process.

3.1. MMN

Mismatch negativity is a negative going component of the waveform

believed to be associated with pre-attentive, automatic processing (e.g., Paavilainen, 2013). It has been used to study the function of both auditory and visual sensory memory functions and more recently it has been used to examine prediction processes. In schizophrenia, auditory MMN has been reliably demonstrated to have reduced amplitude at both chronic and first episode stages. Several studies used frequency and/or duration auditory MMN to examine pre-attentive processing in CHR individuals or specifically looked at MMN as a predictor of conversion to psychosis (Bodatsch et al., 2011; Hsieh et al., 2012; Bruggemann et al., 2013; Nagai et al., 2017; Perez et al., 2014; Solis-Vivanco et al., 2014; Carrion et al., 2015; Light et al., 2015; Erickson et al., 2016; Atkinson et al., 2017; Kim et al., 2017). In several of these studies reduced duration MMN was identified in CHR groups (Bodatsch et al., 2011; Hsieh et al., 2012; Perez et al., 2014; and Solis-Vivano et al., 2014) with some of these studies finding group differences between converters and non-converters. Other studies reported group differences between CHR and HC but not differences between converters and non-converters (e.g., Hsieh et al., 2012 and Solis-Vivano et al., 2014). A meta-analysis of MMN studies suggested that the component is a biomarker for attenuated psychosis syndrome rather than an index of genetic risk for psychosis development (Erickson et al., 2016), with a Light et al., 2015 review and Kim et al. (2017) study pointing out its usefulness in tracking clinical treatment progress. On the other hand, the longitudinal Minds in Transition study results (Atkinson et al., 2017) suggested an absence of group differences in the MMN signal at a prodromal stage.

3.2. Early ERP components

N1 and P1. In addition to processes indexed by MMN, early sensory processes both in visual and auditory modalities have been to be found abnormal in those with APS. This suggests that such early brain processing difficulties could be used as a marker of risk given their likely involvement in the cognitive deficits associated with psychosis. In one of the earliest studies, reduced visual P1 was reported by Yeap et al. (2006). Attenuated speech-related N1 suppression was reported in CHR individuals in a study of corollary discharge mechanism (Perez et al., 2012). The attenuated N1 was intermediate relative to both schizophrenia and HC individuals. Similarly, attenuated N100 repetition suppression was found in CHR (Gonzales-Heydrich et al., 2016. Shin et al. (2012) conducted a magno-encephalography study of early auditory M100 response in CHR in conjunction with the structural study of the Heschl gyrus and planum temporale. Reduced M100 was related to the thinning of these two structures. Similarly, reductions in the N100 distinguished between CHR and first episode individuals in a study examining both sensory driven and attention driven processes (Del Re et al., 2015). Furthermore, the degree of N100 reduction was shown to be associated with severity of positive symptomatology (Gonzales-Heydrich et al., 2015) in CHR.

3.3. P300

P300 oddball and P300 novel are two ERP components that are sensitive to attentional and working memory demands (P300 oddball) and to salience and orienting attention and novelty (P300 novel). They are believed to arise from temporal, limbic, parietal cortices but also cingulate (P300 oddball) and from ACC, frontal and parietal cortices (P300 novel) (Volpe et al., 2007). As in the case of pre-attentive and sensory processes, they have been found abnormal in schizophrenia. Most studies that examine the integrity of these attentional processes in clinical high risk groups have found them to be impacted. In also appears that the P300 can distinguish those individuals who go on to develop psychosis from those who do not when tested at baseline. In an early study of both P300 oddball and novel in a group of genetically vulnerable subjects for developing psychosis as well as schizophrenia patients and healthy controls, the genetically vulnerable subjects showed reductions in the P300 novel suggesting that orienting attention processes are compromised in healthy individuals who are genetically related to schizophrenia patients (Turetsky et al., 2000). The presence of P3 novel reduction in CHR was also reported in the Mondragón-Maya et al. (2013) study even though no group differences were found between CHR and first episode schizophrenia patients. On the other hand, Atkinson et al. (2017) did not find P3 novel group differences between a group of ultra high risk individuals and their healthy controls (Atkinson et al., 2017).

The P300 oddball was also examined in a handful of studies. Frommann et al. (2008) divided their subject groups into early and late prodromal stage and found that late stage prodromal individuals had more widespread P300 oddball abnormalities than early stage individuals. Kim et al. (2015) found that even though there was no group difference in the P300 amplitude between converters and non-converters, the P300 at parietal sites was predictive of clinical improvement. Kim et al. (2017) study pointed out that the feature that distinguished between CHR and individuals genetically related to schizophrenia patients was a trial-to-trial variability which suggested more dysfunction in the processes that contribute to successful deployment of attentional resources in the CHR group.

3.4. Oscillatory processes

It has become apparent that neural oscillations play a critical role in cognition by coordinating activity across brain regions and within brain regions; these processes have been found to be abnormal in schizophrenia (e.g., Ramyead et al., 2015). Alpha, beta, and especially gamma band oscillations have been examined in several research projects involving clinical high risk individuals and suggested impairments in the processes orchestrating cognition (e.g. Kayser et al., 2014). For example, using measures of both spectral power and inter-trial coherence Koh et al. (2011) examined alpha band oscillations which are involved in mediating attentional processes in first episode schizophrenia, CHR and healthy controls. CHR individuals showed reductions in alpha power synchronization relative to HC; it was significantly higher than in the first episode group suggesting that deficits in attentional control exist already in the CHR individuals. Similarly, decreased phase synchronicity in the beta band was identified in at risk mental state for psychosis individuals, especially in those who later transitioned to psychosis relative to HC and those who did not transition (Ramyead et al., 2015).

Abnormal gamma band auditory steady state response (ASSR), especially to 40 Hz auditory stimuli, is one of the best documented oscillatory abnormalities in schizophrenia suggesting GABAergic interneuron dysfunction. It appears that this abnormality exists already in individuals at high risk for psychosis albeit to a much lower degree. Abnormalities of late but not of early latency gamma band ASSR were found in the ultra high risk for psychosis individuals (Tada et al., 2016). The Perez et al. (2013) study of the gamma band response in a group of young early psychosis, clinical high risk individuals, and healthy controls suggested a marginal reduction in the gamma band response in the CHR group, with no significant distinction between these individuals who converted to psychosis and those who did not. Of note, an EEG-fMRI study employing high cognitive load auditory task identified lower activation in the CHR individuals in the network of regions involved in the generation of the gamma-band response that included bilateral auditory cortices, the thalamus, frontal brain regions and the ACC as well as dlPFC (Leicht et al., 2016). It will be recalled that these regions were identified as abnormal in several sMRI studies reviewed above.

4. Overview of biological risk factors for developing psychosis

Imaging studies reviewed above clearly demonstrate that the brains of individuals at clinical and genetic risk for psychosis are different

from those of matched comparison individuals. Most studies reviewed above focused on clinical high risk group with only a handful of studies focusing on genetic high risk. Therefore, it is not possible to make a principled comparison of neurobiological profiles of these two groups. Rather, they are typically discussed under the rubric of high risk for psychosis.

The discussion above delineated brain level differences between high risk for psychosis individuals and their healthy comparisons. These differences are multiple. For example, they manifest as reduced gray matter volume reflecting neuronal, axonal and dendritic loss in the impacted regions. The brain regions affected by these changes are most consistently localized to the frontal and temporal areas, but also subcortical structures such as thalamus are impacted. As reviewed above, the nature of these impairments is complex: some appear in all individuals diagnosed with high risk for psychosis and are not sensitive to conversion while others distinguish between those who transition to psychosis and those who do not. There are also marked differences in white matter tracts that connect particular brain regions in high risk individuals relative to healthy controls. Again, the two tracts most prominently impacted by the disease process are those that connect the frontal and temporal as well as parietal brain regions, particularly those involved in language function, e.g., STG, IFG, and inferior parietal gyrus.

In addition to the structural brain differences, a number of functional brain abnormalities have been identified. Functional MRI studies point to cognitive abnormalities that are already at the pre-psychosis stage that include language, working memory, social cognition, and theory of mind. The brain regions that are primarily involved include again the frontal and temporal regions. ERP and EEG studies add to this evidence by pointing to sensory, pre-attentive, short term memory and attentional processes impacted in this group of individuals. While the neural sources of these processes are harder to identify, several lines of evidence suggest the involvement of temporal and frontal brain regions.

Cognitive processes depend on the integrity of both gray and white matter, their connections but also on neurotransmitter levels, again in turn dependent partly on the integrity of the brain tissue. Considered together, these results suggest interactions between tissue integrity and possible neurochemical imbalance as well as abnormal structural and functional connectivity in key brain structures including the temporal and frontal regions that produce abnormal cognitions and clinical symptoms characteristic of individuals at high clinical and genetic risk for psychosis. As reviewed, above some of these impairments are sensitive to conversion to psychosis while others do not. It appears that large, well powered studies in addition to comprehensive statistical approaches are needed to establish the clinical significance of these neurobiological indicators of pre-psychotic stage. Currently, a diagnosis of a high risk for psychosis state is largely rendered based on clinical symptoms. Developing strong associations among clinical and cognitive profiles as well as specific neurobiological indices would allow for a more nuanced understanding of an individual's unique symptomatology and thus help craft better treatments.

Finally, in spite of the overwhelming evidence for the contribution of neurobiological factors to the development of clinical symptoms described as clinical and genetic high risk, the specific phenomenological manifestation of clinical symptoms will ultimately unfold in concrete circumstances of family, culture and society.

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