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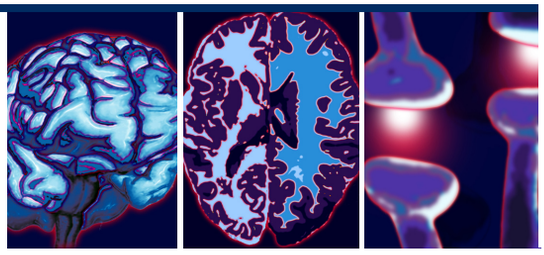

An overview of functional, structural and neurochemical imaging studies in individuals with a clinical high risk for psychosis

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Practice points

- Attenuated psychotic symptoms are present during a prodromal phase that precedes florid psychosis.
- Prodromal psychotics symptoms constitute a clinical high risk (CHR) for psychosis.
- Increasingly, early intervention clinics establish CHR in an attempt to improve the course and outcome of psychosis.
- Neuroimaging techniques are now being investigated to help identify those CHR individuals who are most at risk of developing psychosis.
- Multimodal imaging that combines structural, functional and neurochemical techniques may be better able to identify those with greatest CHR compared with imaging in any single modality.
- This research has shown alterations in brain structure, function and neurochemistry in CHR individuals that are similar to, but less severe than, those in patients with established psychosis.
- Neurochemical imaging has shown alterations in brain dopamine, glutamate and serotonin systems in CHR individuals, suggesting that therapies that target these neurotransmitter systems may be useful in preventing psychosis.
- There is some evidence that the extent of these structural, functional and neurochemical abnormalities may be predictive of psychosis, although further research in larger samples of CHR individuals is required.

SUMMARY In recent years, a growing literature has emerged examining the neurobiological correlates of clinical high risk (CHR) for psychosis. Using a range of neuroimaging techniques, alterations in brain function, structure and chemistry have been reported in CHR subjects. In this article, we provide an overview of studies that have used MRI, PET and multimodal imaging to examine neurobiological abnormalities in CHR subjects. These studies have shown that several abnormalities in brain neurophysiology,

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anatomy and chemistry, which are fundamental to schizophrenia, are also present in people at very high risk of developing the disorder. These abnormalities may represent vulnerability markers that can be used to predict later conversion to psychosis. The future perspectives and limitations of this approach are discussed.

Over the last few decades, early clinical intervention in patients with psychoses has become more widespread. In addition to early onset or first-episode clinics, a number of clinical services aimed at preventative intervention have been established. Such services identify individuals who are experiencing prodromal symptoms characterized by attenuated psychotic symptoms such as hallucinations and delusions, a brief psychotic episode or a decline in social and occupational function coupled with familial risk [1–3]. Individuals meeting one or more of these criteria are considered to have a clinical high-risk (CHR) or an at-risk mental state [2,4]. In addition to putative clinical benefits associated with early identification and intervention, research into early and prodromal phases of the illness may provide important etiological findings that are not confounded by long-term medication and/or chronicity. More importantly, as only approximately 20–30% of CHR subjects go on to develop psychosis and clinical resources are limited, research has attempted to identify definitive markers that distinguish those who go on to develop the illness from those who do not. However, it is difficult to identify the individuals who will later develop psychosis on clinical or symptomatic information alone. One promising approach is to identify biological markers of psychosis risk using neuroimaging techniques such as MRI and PET. In this article, we review the findings of neuroimaging studies in subjects with a CHR for psychosis. We also discuss present and future perspectives and the feasibility of using imaging techniques to aid diagnostic and clinical outcome prediction.

Method

Our aim was to identify all studies fulfilling the following criteria: functional MRI (fMRI) studies of CHR subjects; structural MRI studies of CHR subjects; magnetic resonance spectroscopy (MRS) studies of CHR subjects; PET studies of CHR subjects; and multimodal neuroimaging studies (e.g., MRI and PET in the same subjects) of CHR subjects. To qualify for inclusion, studies had to be original works including a healthy control or other reference group and appear in a peer-reviewed journal. We conducted a systematic literature search of PubMed, Science-Direct and Scopus databases to identify relevant studies published up until March 2011. The following keywords were used for the search: "clinical high risk", "ultra high risk", "at-risk mental state", "prodromal psychosis", "magnetic resonance imaging (MRI)", "positron emission tomography (PET)", "magnetic resonance spectroscopy (MRS)", "neurochemical imaging", "functional imaging", "volumetric" and "gray matter". We also conducted manual searches of the reference sections of the obtained articles. Studies of genetic/familial high risk were not included in the review. A total of 46 suitable studies were identified and included in the current review.

Functional neuroimaging

Over the past two decades, there have been an enormous number of fMRI studies employing a range of cognitive tasks in patients with schizophrenia and other psychoses. Based on the known neuropsychology of schizophrenia, the tasks most frequently used to examine neurofunctional impairment in patients with the illness engage executive, mnemonic (working and episodic memory) and language function. In all of these domains, patients with schizophrenia show altered neurofunctional activation, usually being reduced but sometimes increased, relative to healthy controls (see [5–9]).

To date, there have been 12 published fMRI studies in CHR subjects (see **Table 1**). One further study used perfusion imaging to examine cerebral blood volume (CBV) in prodromal psychosis. The first functional imaging study in CHR subjects used an oddball task to elicit frontostriatal activation and compared CHR subjects with subjects with early psychosis, chronic schizophrenia and healthy controls [10]. The CHR group showed significantly smaller differential activation between task-relevant and task-irrelevant stimuli in frontal regions including the anterior cingulate (ACC), the inferior frontal gyri (IFG) and middle frontal gyri (MFG) relative to control subjects. Patients with early psychosis and chronic schizophrenia showed lower frontostriatal activation than controls, while frontostriatal activation in the CHR group was intermediate

Table 1. Functional imaging studies of subjects at clinical high risk for psychosis.

Study (year)	Functions investigated and task	Findings	HC		CHR		CHR-T		CHR-NT		FEP/SZ		Ref.
			n	Age (years)	n	Age (years)	n	Age (years)	n	Age (years)	n	Age (years)	
Fusar-Poli *et al.* (2011)	Prefrontal functioning, VF task	CHR vs HC: ↑ activation in the IFG, ↓ activation in the ACC	15	25	15	24	–	–	–	–	–	–	[12]
Lord *et al.* (2011)	Executive funtioning, VF task	CHR vs HC: ↓ betweeness centrality† of the ACC in CHR subjects with elevated symptoms (PANSS ≥45)	22	25	33	24	–	–	–	–	–	–	[36]
Allen *et al.* (2010)	Sentence completion task	CHR vs HC: ↑ activation in the ACC, ↑ endogenous connection strength between the ACC and middle TG	15	25	15	26	–	–	–	–	–	–	[34]
Broome *et al.* (2010)	Movement generation	CHR vs HC: ↓ activation in the L-IPC. CHR vs FEP: ↑ activation in the L-IPC	15	25	17	24	–	–	–	–	10	25	[22]
Broome *et al.* (2010)	Visuospatial WM task	CHR vs HC: ↓ activation in the medial FC and R precuneus. CHR vs FEP: ↑ activation in the medial FC and R precuneus	15	25	17	24	–	–	–	–	10	25	[18]
Fusar-Poli *et al.* (2010)	Visuospatial WM task	CHR vs HC: ↓ activation L precuneus, L-SPL and R middle TG	15	25	15	24	–	–	–	–	–	–	[21]
Sabb *et al.* (2010)	Language, naturalistic discourse processing	CHR vs HC: ↑ activation in the L/R medial PFC, L-IFG, L middle TG and L-ACC. CHR-T vs CHR-NT: ↑ activation in the STG, caudate and L-IFG	24	18	40	NA	25	17	15	18	–	–	[13]
Allen *et al.* (2011)	Verbal episodic memory, Deese–Roediger–McDermott false-memory task	CHR vs HC: ↓ activation in L middle FG, L/R medial FG and L parahippocampal gyrus during encoding. Altered hippocamal activation during recognition	22	27	18	27	–	–	–	–	–	–	[17]
Benetti *et al.* (2009)	Visuospatial WM task	CHR vs HC: ↓ pattern of effective connectivity from the R posterior hippocampus to the R-IFG. CHR vs HC vs FEP: no difference in the interactions between the IFG and the anterior part of the hippocampus	14	26	16	24	–	–	–	–	10	25	[33]
Broome *et al.* (2009)	Executive functioning and WM, WM task and VF task	CHR vs HC vs FEP: intermediate activation in the IFG and ACC during a VF task and in the DLPFC and PC during a WM task	15	25	17	24	–	–	–	–	10	25	[11]

†'Betweeness centrality' describes a region's importance in the organization of a network (i.e., reduced betweeness centrality = reduced importance of the region in a network).
ACC: Anterior cingulate gyrus; CBV: Cerebral blood volume; CHR: Clinical high risk; CHR-NT: Clinical high risk without transition to psychosis; CHR-T: Clinical high risk with transition to psychosis; C-SZ: Chronic schizophrenia; DLPFC: Dorsolateral prefrontal cortex; E-SZ: Early schizophrenia; FC: Frontal cortex; FEP: First-episode psychosis; FG: Frontal gyrus; HC: Healthy control; IFG: Inferior frontal gyrus; IPC: Inferior parietal cortex; L: Left; NA: Not applicable; OFC: Orbitofrontal cortex; PANSS: Positive and negative syndrome scale; PC: Parietal cortex; PFC: Prefrontal cortex; R: Right; SPL: Superior parietal lobe; STG: Superior temporal gyrus; SZ: Patients with schizophrenia; TG: Temporal gyrus; VF: Verbal fluency; WM: Working memory.

Table 1. Functional imaging studies of subjects at clinical high risk for psychosis (cont.).

Study (year)	Functions investigated and task	Findings	HC		CHR		CHR-T		CHR-NT		FEP/SZ		Ref.
			n	Age (years)	n	Age (years)	n	Age (years)	n	Age (years)	n	Age (years)	
Crossely *et al.* (2009)	WM, N-back test	CHR vs HC: ↑ activation in the STG. CHR vs FEP: ↓ activation in the STG. Effective connectivity between the STG and the medial FG: negative coupling in HC, positive coupling in FEP and intermediate in CHR	13	NA	16	NA	–	–	–	–	10	25	[35]
Schobel *et al.* (2009)	CBV	CHR: baseline CBV abnormalities in the CA1 subfield predicted progression to psychosis. CBV levels in the CA1 subfield differentially correlated with clinical symptoms of psychosis. SZ vs HC: abnormal CBV ↑ in the CA1 subfield and the OFC and abnormal CBV ↓ in the DLPFC	18	31	18	19	7	–	11	–	18	–	[37]
Morey *et al.* (2005)	Executive functioning, oddball task	CHR vs HC: ↓ activation in ACC, IFG and medial FG. SZ vs HC: ↓ activation in frontostriatal areas	16	28	10	23	–	–	–	–	15 E-SZ	–	[10]
			–	–	–	–	–	–	–	–	11 C-SZ	–	

[†]'Betweeness centrality' describes a region's importance in the organization of a network (i.e., reduced betweeness centrality = reduced importance of the region in a network).
ACC: Anterior cingulate gyrus; CBV: Cerebral blood volume; CHR: Clinical high risk; CHR-NT: Clinical high risk without transition to psychosis; CHR-T: Clinical high risk with transition to psychosis; C-SZ: Chronic schizophrenia; DLPFC: Dorsolateral prefrontal cortex; E-SZ: Early schizophrenia; FC: Frontal cortex; FEP: First-episode psychosis; FG: Frontal gyrus; HC: Healthy control; IFG: Inferior frontal gyrus; IPC: Inferior parietal cortex; L: Left; NA: Not applicable; OFC: Orbitofrontal cortex; PANSS: Positive and negative syndrome scale; PC: Parietal cortex; PFC: Prefrontal cortex; R: Right; SPL: Superior parietal lobe; STG: Superior temporal gyrus; SZ: Patients with schizophrenia; TG: Temporal gyrus; VF: Verbal fluency; WM: Working memory.

between controls and the early psychosis group. This was the first functional imaging study to show reduced prefrontal cortex (PFC) activation in CHR subjects that may represent a psychosis vulnerability marker.

Altered PFC function in CHR subjects has also been reported by Broome and colleagues [11]. During executive and working memory tasks, CHR subjects showed intermediate activation relative to controls and first-episode psychosis (FEP) subjects. In CHR and FEP patients, activation in the left IFG was increased during a verbal fluency task, while dorsolateral PFC and parietal activation was decreased during a working memory task relative to control subjects [11]. Moreover, in a follow-up study of the same CHR subjects, the longitudinal normalization of neurofunctional response in the left IFG was positively correlated with an improvement in the severity of hallucination-like experiences after 12 months [12]. In a prospective study that established clinical outcome in a CHR cohort, Sabb and colleagues report that during a discourse processing task, CHR participants showed increased neural activity in a network of language-associated brain regions, including the medial PFC bilaterally, left IFG and middle temporal gyrus (MTG) and the ACC [13]. Furthermore, increased activity in the superior temporal gyrus (STG), caudate and left IFG distinguished those who subsequently developed psychosis.

Dysfunction of the medial temporal lobe (MTL) is also widely reported in patients with schizophrenia (for reviews, see [6,7]). Similar but less severe dysfunction in hippocampal and parahippocampal regions may underlie the verbal memory impairment reported in CHR subjects [14–16], although evidence for MTL dysfunction in CHR subjects is mixed. Allen and colleagues used a verbal encoding and recognition task to examine MTL function in CHR and healthy control subjects [17]. During the encoding phase, CHR subjects showed less activation than controls in the left MFG, parahippocampal gyrus and bilateral medial frontal gyrus. During the recognition phase, correctly recognized trials were associated with increased bilateral hippocampus activation compared to false-alarm trials (trials in which foil words are misrecognized as having previously been presented during an encoding phase) in control subjects, but this activation difference was absent in the CHR group [17]. Broome and colleagues used fMRI to

examine spatial working memory in CHR subjects [18]. Despite robust evidence of hippocampal involvement in spatial working memory processing [19,20], CHR subjects did not show altered hippocampal activation relative to a control group, although reduced activation was observed in the left precuneus, left superior parietal lobule and right MTG [18]. Longitudinal follow up of these CHR subjects revealed that symptom improvement was associated with a compensatory increase in occipitoparietal regions [21,22]. Reduced activation in the parietal cortex in CHR subjects relative to controls was also observed during a movement-generation task [22].

In addition to regional dysfunction, disordered brain connectivity, or dysconnectivity, is thought to be a central pathophysiological feature of schizophrenia [23–25]. Dysconnectivity is an "abnormal (rather than decreased) integration" between anatomically distinct brain regions [26,27]. fMRI studies investigating connectivity usually do so in one of two ways. By investigating 'functional connectivity', inferences can be made about how activation in functionally and anatomically distinct brain regions covary. Studies using 'effective connectivity' techniques such as dynamic causal modeling [28] examine the influence that one neural system exerts over another, either at a synaptic or a cortical level (for a detailed review of connectivity studies in schizophrenia and psychosis, see [29]). In particular, abnormal patterns of connectivity between prefrontal and temporal lobe regions have been reported in patients with schizophrenia [30–32], and subsequent experimental evidence based on fMRI studies has been largely consistent with this hypothesis [29]. Recently, a handful of studies have begun to investigate dysconnectivity in CHR subjects. Benetti and colleagues examined frontal–hippocampal connectivity using a visuospatial working memory task in CHR, FEP and healthy control subjects [33]. The normal pattern of effective connectivity from the right posterior hippocampus to the right IFG was significantly decreased in both FEP and CHR subjects, although interactions between the IFG and the anterior part of the hippocampus did not differ across the three groups. This finding suggests that reduced frontohippocampal connectivity may be a correlate of increased vulnerability to psychosis and that it is not attributable to an effect of chronic illness or its treatment [33]. Allen and colleagues used a sentence-completion task to examine prefrontal–lateral temporal interactions in CHR subjects [34]. Although CHR subjects did not differ from controls in terms of frontotemporal activation they did demonstrate increased ACC activation, during the inhibitory phase of the task. CHR subjects also showed increased connection strength between the ACC and the MTG relative to healthy controls. Although task-related frontotemporal integration in the CHR subjects was intact, this may depend on increased engagement and coupling of the ACC, which was not observed in healthy control subjects [34]. Crossley and colleagues also examined frontotemporal connectivity in CHR, FEP and control subjects [35]. During a working memory task, activation in the STG and its relationship to frontal activation was examined. There was deactivation of the STG during the working memory task in controls, whereas subjects with FEP showed increased activation. CHR subjects demonstrated intermediate activation relative to the two other groups. There were corresponding differences in connectivity between the STG and the MFG across the three groups, with a negative coupling between these areas in controls, a positive coupling in the FEP group and an intermediate value in the CHR group. The authors conclude that a failure to deactivate the STG during tasks that engage the PFC is evident at the onset of schizophrenia and may reflect a disruption of frontotemporal connectivity [35]. Lord and colleagues examined between-group differences in total network connectivity and global network compactness/efficiency during a verbal fluency task, focusing on the ACC [36]. While global network connectivity and efficiency were maintained in CHR patients relative to the controls, there was a significant decrease in the contribution of the ACC to task-relevant network organization in CHR subjects with elevated symptoms relative to both control and less symptomatic CHR subjects [36].

Finally, one study used MRI to measure regional CBV in patients with schizophrenia, healthy controls and CHR subjects who were followed clinically for 2 years [37]. In a prospective analysis, baseline CBV in the hippocampal CA1 subfield was higher in CHR subjects who subsequently developed a psychotic disorder compared with patients at similar high clinical risk who did not develop psychosis. Higher CA1 CBV was also reported in patients with schizophrenia compared with controls, and positively correlated with severity of positive and negative

symptoms. These results suggest that hyperperfusion of the CA1 subfield of the hippocampus may be predictive of transition to psychosis in CHR individuals.

In summary, functional imaging studies in CHR subjects have employed a range of cognitive paradigms engaging memory, executive and language function. Relative to healthy control subjects, these studies report both increased and decreased activation in PFC and ACC regions. It is not clear why both increased and decreased activations are reported by different studies, but these inconsistencies may be due to the different functional tasks used. A closer inspection of these studies suggests that, broadly speaking, increased PFC activation in CHR subjects is seen during tasks involving language/executive function [13,34,38], while decreased PFC activation is apparent during mnemonic tasks [11,17,18]. The basis of the increased PFC activation in these regions is unclear, but it may reflect an inefficient prefrontal function [39,40] or a compensatory response to impaired executive function [41]. Decreased activation in PFC and MTL regions during memory paradigms are widely reported in patients with established schizophrenia [6,7] and, in CHR subjects, may underpin subtle memory impairments [14,15]. Studies that also include early psychosis or chronic schizophrenia comparison groups reveal abnormalities of regional brain function in CHR subjects that are qualitatively similar to, but less severe than, patients with established psychosis. A small number of studies have examined connectivity using functional imaging and report altered connectivity between PFC regions and lateral temporal and MTL regions, thus implicating dysconnectivity as a vulnerability factor. One study assessing global connectivity reports a significant decrease in the contribution of the ACC to task-relevant network organization in CHR subjects with elevated symptom levels. Only two studies have prospectively compared CHR subjects according to clinical outcome. While these studies employed different MRI techniques (functional and perfusion imaging), they report increased function in frontal, temporal and hippocampal regions in CHR individuals who develop psychosis relative to those who do not. However, in both studies, the number of CHR subjects who made a transition to psychosis during the follow-up period was small.

Structural imaging

Structural neuroimaging studies clearly indicate that schizophrenia is associated with neuroanatomical abnormalities, with the most replicated findings being ventricular enlargement and reductions in frontal and medial temporal gray matter volume (GMV) [42,43]. Structural neuroimaging studies during the first episode of psychosis indicate reductions in regional GMVs at initial presentation [44,45]. However, the extent to which these are related to a vulnerability to schizophrenia, as opposed to the disorder *per se*, is less certain. During the previous decade, studies reported qualitatively similar abnormalities that were also evident in the first-degree relatives and co-twins of patients with schizophrenia [46–52]. Twin studies suggest that structural abnormalities [48,53,54] in the dorsolateral PFC and superior temporal cortex [55], the hippocampus [56] and white matter [52] are at least partially genetically determined. Currently, it is not clear at what stage of the developing psychosis these brain abnormalities occur. Neurodevelopmental models of schizophrenia propose that brain abnormalities are present before the onset of psychosis, but there is also evidence that at least some structural abnormalities progress over the course of the disorder [57,58]. MRI studies of nonpsychotic subjects who are at genetic high risk of psychosis indicate that regional volumetric abnormalities comparable to those seen in schizophrenia are evident in these cohorts [49,59].

Relatively little is known about the nature of the abnormalities in CHR subjects. To date, 16 studies examining structural changes in CHR subjects have been published (see **Table 2**; note that many of these studies report findings in overlapping samples). Studies using a region of interest (ROI) approach report that, relative to healthy controls, CHR subjects show GMV reductions in the bilateral hippocampus [60], planum polare/temporale, insula/STG [61,62] and an increase in pituitary volume [63]. However, other ROI studies have failed to find volumetric differences between CHR and healthy control subjects [64,65].

Using a voxel-based approach in CHR subjects it was found that, relative to healthy controls, CHR subjects, regardless of outcome, showed reduced GMV in the frontal lobe and lateral and medial temporal regions [66]. More interestingly, relative to those subjects who did not develop the illness, those who later became psychotic had

Table 2. Structural imaging studies of subjects at clinical high risk for psychosis.

Study (year)	Analysis	Findings	HC		CHR		CHR-T		CHR-NT		FEP/SZ		Ref.
			n	Age (years)	n	Age (years)	n	Age (years)	n	Age (years)	n	Age (years)	
Koutsouleris *et al.* (2010)	Deformation-based morphometry, partial least squares	CHR vs HC: morphometric changes in R-PFC, perisylvian, parietal and periventricular structures. CHR-T vs CHR-NT: same changes as above, but more pronounced in CHR-T group	28	25	25	23	12	22	13	24	–	–	[84]
Koutsouleris *et al.* (2009)	Multivariate neuroanatomical pattern classification	HCs vs all other participants: accuracy 86%; second analysis accuracy 90%. E-CHR vs all other participants: accuracy 91%. L-CHR vs all other participants: accuracy 86%. CHR-T vs all other participants: accuracy 88%. CHR-NT vs all other participants: accuracy 86%	25	25	20 E-CHR	25	15	22	18	26	–	–	[83]
			–	–	25 L-CHR	–	–	–	–	–	–	–	
Fornito *et al.* (2008)	ACC morphometry	CHR-T vs CHR-NT: thining of rostral paralimbic ACC region in CHR-T group	33	21	70	–	35	19	35	19	–	–	[69]
Takahashi *et al.* (2009)	ROI	CHR-T vs HC: ↓ GMV in PT (males only); longitudinally: ↓ GMV in L/R-PT and STG. CHR-T vs CHR-NT: no difference in STG GMV; longitudinally: ↓ in L-PT	22	–	35	–	12	–	23	–	23	–	[62]
Takahashi *et al.* (2009)	ROI	CHR-T vs HC: ↓ GMV in R insula. CHR-T vs CHR-NT: ↓ in L/R insula	55	–	97	–	31	–	66	–	–	–	[61]
Borgwardt *et al.* (2008)	VBM analysis of GMV	CHR-T vs CHR-NT: ↓ in OG, R-SFG, ITG, medial and superior parietal cortex, cerebellum, L precuneus and rectal gyrus	–	–	–	–	10	25	10	24	–	–	[74]
Meisenzahl *et al.* (2008)	VBM	CHR-T vs HC: ↓ GMV frontal and lateral/medial temporal lobe	75	25	40	25	–	–	–	–	–	–	[66]
Sun *et al.* (2008)	Brain surface contractions, cortical pattern matching	CHR-T vs CHR-NT: ↑ brain surface contraction in the R-PFC	–	–	–	–	12	19	23	20	–	–	[75]
Walterfang *et al.* (2008)	WM VBM	CHR-T vs CHR-NT: ↑ WM in left frontal lobe; longitudinal analysis: ↓ WM in L fronto–occipital fasiculus	–	–	75	14–30	23	–	52	–	–	–	[70]
Borgwardt *et al.* (2007)	VBM analysis of GMV	CHR vs HC: ↓ L insula, STG, CG, precuneus and L-MTC. CHR vs FEP: no difference. CHR-T vs CHR-NT: ↓ R insula, IFG and STG	22	23	35	24	12	25	23	23	25	27	[68]

ACC: Anterior cingulate gyrus; CG: Cingulate gyrus; CHR: Clinical high risk; CHR-NT: Clinical high risk without transition to psychosis; CHR-T: Clinical high risk with transition to psychosis; E-CHR: Early clinical high risk; FEP: First-episode psychosis; GMV: Gray matter volume; HC: Healthy control; IFC: Inferior frontal cortex; IFG: Inferior frontal gyrus; ITG: Inferior temporal gyrus; L: Left; L-CHR: Late clinical high risk; LTC: Lateral temporal cortex; MTC: Medial temporal cortex; OFC: Orbitofrontal cortex; OG: Orbital gyrus; PFC: Prefrontal cortex; PT: Planum temporale; R: Right; ROI: Region of interest; SFG: Superior frontal gyrus; STG: Superior temporal gyrus; SZ: Patient with schizophrenia; VBM: Voxel-based morphometry; WM: White matter.

Table 2. Structural imaging studies of subjects at clinical high risk for psychosis (cont.).

Study (year)	Analysis	Findings	HC		CHR		CHR-T		CHR-NT		FEP/SZ		Ref.
			n	Age (years)	n	Age (years)	n	Age (years)	n	Age (years)	n	Age (years)	
Velakoulis *et al.* (2006)	ROI of hippocampus and amygdala	CHR-T vs HC: no difference in hippocampal/amygdala volume. CHR-T vs CHR-NT: no difference in hippocampal/amygdala volume	87	27	135	–	39	19	96	20	162	21	[65]
Garner *et al.* (2005)	ROI	CHR-T vs HC: ↑ pituitary volume; CHR-T vs CHR-NT: ↑ pituitary volume	49	20	94	–	31	19	63	20	–	–	[63]
Wood *et al.* (2005)	ROI	CHR vs HC: no difference in hippocampus/ACC. CHR-T vs CHR-NT: no difference in hippocampal/ACC volume	49	23	79	–	35	19	44	26	–	–	[64]
Pantelis *et al.* (2003)	VBM analysis of GMV	CHR-T vs CHR-NT at baseline: ↓ in R-MTC, R-LTC, R-IFC and L/R-ACC; CHR-T progressive changes: L parahippocampal, fusiform, OFC and cerebellum; CHR-NT progressive changes: cerebellum	–	–	75	20	23	19	52	21	–	–	[67]
Philips *et al.* (2002)	ROI	CHR vs HC: ↓ L/R hippocampal volume. CHR-T vs HC: no difference in hippocampal volume. CHR-T vs CHR-NT: ↑ L hippocampal volume. CHR-T vs FE: ↑ L hippocampal volume	139	30	60	20	20	20	40	19	32	21	[60]

ACC: Anterior cingulate gyrus; CG: Cingulate gyrus; CHR: Clinical high risk; CHR-NT: Clinical high risk without transition to psychosis; CHR-T: Clinical high risk with transition to psychosis; E-CHR: Early clinical high risk; FEP: First-episode psychosis; GMV: Gray matter volume; HC: Healthy control; IFC: Inferior frontal cortex; IFG: Inferior frontal gyrus; ITG: Inferior temporal gyrus; L: Left; L-CHR: Late clinical high risk; LTC: Lateral temporal cortex; MTC: Medial temporal cortex; OFC: Orbitofrontal cortex; OG: Orbital gyrus; PFC: Prefrontal cortex; PT: Planum temporale; R: Right; ROI: Region of interest; SFG: Superior frontal gyrus; STG: Superior temporal gyrus; SZ: Patient with schizophrenia; VBM: Voxel-based morphometry; WM: White matter.

reduced volumes in the IFG and ACC [67] and right insula, inferior frontal and superior frontal gyrus [68]. ACC morphometry also reveals thinning of the rostral ACC in CHR subjects who later became psychotic [69]. These volumetric differences within the CHR group were associated with the subsequent development of psychosis and could be related to a process which underlies a progression from a high-risk state towards the illness. One study examining white matter volume reports that CHR subjects who later develop psychosis show increased white matter volume in the left frontal lobe and a longitudinal decrease in the left fronto–occipital faciculus [70].

The actual transition [71] from the prodromal phase into frank psychosis [67,72] and the first 2 years of the first episode [73] has been associated with frontal and temporal decreases in GMV. Volumetric studies in CHR subjects found that subjects with 'prodromal' symptoms who developed psychosis showed a longitudinal reduction in GMV in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyri [67], a decrease of cortical volumes in the orbitofrontal cortex that included the right orbital and left rectal gyrus, as well as in the right inferior temporal, superior frontal and superior parietal lobule, the left precuneus and the right hemisphere of the cerebellum [74]. In another longitudinal study, greater brain contraction was found in right prefrontal regions in recent-onset psychosis patients compared with CHR subjects who did not develop psychosis [75]. These findings are consistent with prospective studies in patients with established schizophrenia, which indicate that longitudinal reductions in regional GMV also occur in chronic patients [76–81]. Individual structural imaging studies report contrasting findings and are unable to definitively characterize which brain regions are associated with an increased liability to psychosis. However, a recent meta-analysis in a large sample of 920 high-risk subjects reports structural alterations in the bilateral prefrontal and limbic cortex and in the temporoparietal cortex [82]. High-risk subjects who later become psychotic show additional volumetric reductions in superior temporal and inferior frontal areas relative to those who do not. This meta-analysis confirmed that brain structural changes in these areas may be crucial to the development of psychotic illness. Recent studies using multivariate methods have indicated that pattern recognition techniques may also facilitate

an accurate prediction of these structural brain dynamics, potentially allowing for an early recognition of individuals at risk of developing psychosis-associated neuroanatomical changes over time [83,84].

In summary, people at high risk of psychosis show qualitatively similar volumetric abnormalities (usually reductions) to patients with schizophrenia. Studies comparing CHR subjects according to outcome report reduced GMV in the PFC, lateral and MTL regions, rostral cingulate gyrus, insula and cerebellum, and changes in frontal WMV in those subjects who develop psychosis. However, a small number of ROI studies have failed to find volumetric differences between subjects grouped according to outcome. Recent evidence has indicated short-term as well as long-term treatment with antipsychotics can affect both the function [85] and the structure [86,87] of the human brain. Antipsychotic treatment is thus a potential confounding factor in studies of patients with schizophrenia. An advantage of studies examining GMV in CHR cohorts is that subjects have no or limited exposure to antipsychotic medication. As such, any GMV reduction seen in CHR subjects cannot be attributed to the effects of antipsychotic medication. However, it is still unclear which MRI abnormalities are specific to psychotic illness as opposed to vulnerability to psychosis. Structural studies using techniques that measure cortical thickness [88], gyrification [89] and magnetization transfer ratio [90] may allow for the detection of subtle anatomical changes not seen using standard voxel-based morphometry and ROI methods.

Neurochemical imaging: proton MRS

Proton MRS (^{1}H-MRS) can used to measure the concentration of brain metabolites in a predefined voxel of interest. Depending on the field strength of the MRI scanner and the acquisition sequence applied, metabolite concentrations quantifiable in ^{1}H-MRS spectra can include glutamate, the glutamate metabolite glutamine, N-acetyl-aspartate (NAA), choline-containing compounds, creatine and myo-inositol. Of these metabolites, glutamate and glutamine, along with NAA, are probably of greatest interest to studies of psychosis; glutamate dysfunction is thought to be one of the primary neurochemical abnormalities in schizophrenia, which may lead to excitotoxic processes and dysregulation of downstream neurotransmitter systems [91–93], while NAA is thought to provide a marker of neuronal integrity [94]. To date, there are seven published ^{1}H-MRS studies (see **Table 3**) of regional brain metabolites in CHR subjects compared with control subjects [95–101].

The first ^{1}H-MRS study at 3 T in CHR subjects was performed by Stone and colleagues [98]. Compared with healthy controls, CHR subjects had significantly lower levels of glutamate in the thalamus and higher levels of glutamine in the ACC. Increased levels of glutamine in the ACC of CHR subjects are consistent with findings in FEP patients [102]. Due to overlapping resonances, high field strengths (3 T or above) are required to separate glutamate and glutamine peaks in the ^{1}H-MRS spectra, so studies at lower field strengths (1.5 T) generally report glutamate and glutamine in combination (as Glx). At 1.5 T, Glx levels in the ACC or thalamus did not differ significantly between CHR and healthy control subjects [99]. In the hippocampus, no difference in glutamate or glutamine levels has been observed in control compared with CHR subjects at 3 T [97,98]. In summary, glutamatergic abnormalities may be present in CHR patients, particularly in the thalamus and ACC, but further confirmation is required at high field strengths in independent cohorts. Prospective and longitudinal studies are required to determine whether the extent of glutamatergic abnormality is predictive of psychosis.

Recent meta-analyses of the several studies of NAA in psychosis have found lower levels of NAA in the frontal and temporal lobes and in the thalami of patients with either FEP or schizophrenia [103,104]. There is also evidence that NAA may be reduced in CHR patients: lower levels of NAA have been reported in the thalami [98] and corpus callosum [105], and lower NAA:creatine or NAA:choline ratios are reported in the frontal lobe and ACC [95]. In contrast to these studies, a higher NAA:creatine ratio has also been reported in the dorsolateral PFC of CHR subjects compared with control [96], but as the ratio of choline:creatine was also elevated, the higher NAA:creatine ratio was interpreted as a decline in creatine in frontal areas, indicative of hypometabolism [99]. Other investigations have found no difference in NAA (or NAA:creatine ratio) in regions including frontal cortical areas, the thalamus or hippocampus in the CHR state [96,98,100,106]. Finally, in a subgroup of CHR subjects with major depressive disorder, ^{1}H-MRS has shown elevations in myo-inositol, which may indicate glial cell dysfunction [99].

Table 3. Neurochemical imaging studies of subjects at clinical high risk for psychosis.

Study (year)	Modality	Findings	HC		CHR		CHR-T		CHR-NT		FEP/SZ		Ref.
			n	Age (years)	n	Age (years)	n	Age (years)	n	Age (years)	n	Age (years)	
^{1}H-MRS studies													
Uhl *et al.* (2011)	^{1}H-MRS (1.5 T)	CHR vs HC: ACC, MPFC and L hippocampus; no differences	31	25	30	25	-	–	–	–	24	26	[100]
Wood *et al.* (2010)	^{1}H-MRS (3 T)	CHR vs HC: R- and L-TL: no group differences	29	–	66	–	7	–	59	–	–	–	[106]
Byun *et al.* (2009)	^{1}H-MRS (1.5 T)	CHR (MDD) vs HC: L thalamus ↑ mi; ACC and L-DLPFC: no group differences	20	22	11 with MDD	21	–	–	–	–	–	–	[99]
		CHR (no MDD) vs HC: L thalamus, ACC and L-DLPFC: no group differences	–	–	9 without MDD	–	–	–	–	–	–	–	
Stone *et al.* (2009)	^{1}H-MRS (3 T)	CHR vs HC: L thalamus: ↓ glutamate, ↓ NAA; ACC: ↑ glutamine; L hippocampus: no group differences	27	25	27	25	–	–	–	–	–	–	[98]
Aydin *et al.* (2008)	^{1}H-MRS (1.5 T)	CHR vs HC: CC: ↓ NAA. CHR and FEP: levels of CC NAA correlate with the severity of negative symptoms	30	20	17	20	–	–	–	–	14	25	[101]
Jessen *et al.* (2006)	^{1}H-MRS (1.5 T)	CHR vs HC: ACC and L-FL: ↓ NAA:Cr and NAA:Cho. L-TL: no group difference. CHR-T vs CHR-NT: ACC: ↑ Cho:Cr, ↓ NAA:cho; L-FL and L-TL: no group difference	31	35	10 E-CHR	27	3	–	16	–	21	33	[95]
			–	–	9 L-CHR	–	–	–	–	–	–	–	
Wood *et al.* (2003)	^{1}H-MRS (1.5 T)	CHR vs HC: L-MTL: no difference. L-DLPFC; ↑ NAA:Cr, ↑ Cho:Cr. CHR-T vs CHR-NT: L-MTL and L-DLPFC: no differences. CHR vs FEP: L-MTL and L-DLPFC: no differences	21	34	30	19	6	–	24	–	56	21	[96]
PET studies													
Howes *et al.* (2011)	^{18}F-DOPA PET	CHR-T vs CHR-NT: ↑ ^{18}F-DOPA in the striatum	–	–	20	25	8	–	12	–	–	–	[110]
Howes *et al.* (2009)	^{18}F-DOPA PET	CHR vs HC vs SZ: intermediate ↑ ^{18}F-DOPA in the striatum	12	24	24	25	–	–	–	–	7	–	[109]
Hurlemann *et al.* (2008)	^{18}F-altanserin PET	CHR vs HC: ↓ 5-HT$_{2A}$ in cortical areas. CHR-T vs CHR-NT: ↓ 5-HT$_{2A}$ in R caudate	21	27	6 E-CHR	26	5	–	9	–	–	–	[111]
			–	–	8 L-CHR	–	–	–	–	–	–	–	

^{1}H-MRS: Proton magnetic resonance spectroscopy; ACC: Anterior cingulate cortex; CC: Corpus callosum; Cho: Choline; CHR: Clinical high risk; CHR-NT: Clinical high risk with no transition to psychosis; CHR-T: Clinical high risk with transition to psychosis; Cr: Creatine; DLPFC: Dorsolateral prefrontal cortex; E-CHR: Early clinical high risk; FEP: First-episode psychosis; FL: Frontal lobe; HC: Healthy control; L: Left; L-CHR: Late clinical high risk; MDD: Major depressive disorder; mi: Myo-inositol; MPFC: Medial prefrontal cortex; MTL: Medial temporal lobe; NAA: N-acetyl aspartate; PFC: Prefrontal cortex; R: Right; SZ: Patient with schizophrenia; TL: Temporal lobe.

Two of these ^{1}H-MRS studies subsequently followed the CHR subjects clinically to determine whether ^{1}H-MRS measures at baseline differed between subsequent converters and nonconverters to psychosis [95,96]. In the study of Wood and colleagues, there was no difference in NAA:creatine ratios in the dorsolateral PFC in the six subjects who developed psychosis compared with those who did not [96]. In the study of Jessen and colleagues, three of the 19 CHR subjects developed psychosis during the follow-up period, and the NAA:choline ratios in the ACC were lower in these converters than in nonconverters [95]. Further studies in larger samples are therefore required to determine whether baseline levels of ^{1}H-MRS metabolites can predict subsequent conversion to psychosis.

Neurochemical imaging: PET

PET imaging with the radiotracer ^{18}F-DOPA has consistently shown elevated dopaminergic function in the striatum of patients with established psychosis [107]. Uptake of ^{18}F-DOPA reflects presynaptic dopamine synthesis capacity, as DOPA is converted to dopamine by aromatic acid decarboxylase in presynaptic terminals [108]. Howes and colleagues have recently shown that ^{18}F-DOPA uptake is increased in the striata of CHR subjects to levels that are intermediate to those observed in controls and schizophrenia patients **(Table 3)** [109]. This provides compelling evidence that dopaminergic abnormalities precede the onset of frank psychosis. Moreover, in a subsequent follow-up study 2 years later, eight of these CHR subjects had developed psychosis, and this was accompanied by a longitudinal increase in ^{18}F-DOPA uptake in the sensorimotor striatum [110]. While confirmation is required in larger and independent samples, these data provide the first evidence that conversion to psychosis may be associated with progressive striatal dopaminergic dysfunction, and provide *in vivo* neurochemical data in support of the use of treatments that act on the dopamine system in preventing the development of psychosis.

The serotonin 5-HT$_{2A}$ receptor is also implicated in the pathogenesis of schizophrenia. Using ^{18}F-altanserin PET, reductions in 5-HT$_{2A}$ receptor availability have been observed in early and late prodromal states across several cortical areas [111]. Furthermore, decreases in 5-HT$_{2A}$ receptor availability in the caudate were apparent in five subjects who subsequently converted to psychosis compared with nine subjects who had not converted during the clinical follow-up period [111]. This indicates that 5-HT$_{2A}$ receptor availability may also provide a surrogate marker of psychosis risk in CHR individuals.

In summary, PET studies have revealed dopaminergic and serotonergic abnormalities in CHR subjects, which may worsen as symptoms progress. Conformation of these findings in new cohorts of CHR subjects is required.

Multimodal imaging

There are now a small number of investigations that have combined different imaging modalities in cross-sectional studies of the CHR state (see **Table 4**). In addition to providing information about disease processes, and thereby informing strategies for intervention, it is possible that the additional information provided by multimodal data may have greater value in predicting psychosis risk in CHR individuals.

As stated earlier, it has been suggested that glutamatergic dysfunction may be one of the primary neurochemical abnormalities in psychosis, which could lead to reductions in GMV, abnormal brain activation and dysregulation of downstream neurotransmitter systems [91–93]. The relationships between brain glutamate levels and several of these processes have been explored in studies by Stone and colleagues, combining ^{1}H-MRS data obtained in the CHR state [98] with data available in the same subjects across several different imaging modalities. First, Stone and colleagues found that, in CHR subjects but not controls, levels of glutamate in the thalamus were directly correlated with GMV in several brain areas including the medial temporal cortex, left PFC and insula. This suggests that glutamatergic dysfunction in the thalamus of CHR individuals may lead to structural abnormalities, possibly via disinhibition of thalamocortical glutamatergic projections [98]. Similar findings have also been reported in FEP [112]. The consequences of thalamic glutamate abnormality in CHR subjects have also been investigated using mismatch negativity (MMN) [113]. MMN is a neurophysiological biomarker for schizophrenia that indexes deviance or oddball detection, and is known to relate to thalamic function [114]. In CHR subjects, lower levels of thalamic Glx were associated with lower MMN amplitudes in frontal areas, indicating thalamic glutamate may be associated with abnormal sensory filtering in the CHR state, in particular in deviance detection [113].

Animal studies have shown that hippocampal glutamate is critically involved in memory encoding [115]. Combining fMRI data acquired during memory encoding and ^{1}H-MRS glutamate measures, Valli and colleagues have recently shown that MTL activation during memory encoding is positively correlated with hippocampal glutamate levels in control but not CHR subjects [116]. This finding suggests that reduced activation of the MTL during encoding in the CHR state may be attributable to glutamatergic abnormality.

Contemporary theories and data from animal studies propose that striatal hyperdopaminergia in psychosis may be driven by upstream changes in hippocampal glutamate function [93,117,118]. Combining results of ^{1}H-MRS and ^{18}F-DOPA PET in the same individuals,

Table 4. Multimodal imaging studies of subjects at clinical high risk for psychosis.

Study (year)	Modalities	Findings	HC		CHR		Ref.
			n	Age (years)	n	Age (years)	
Allen *et al.* (2011)	fMRI (episodic memory task) and ^{18}F-DOPA PET	CHR: positive correlation between hippocampal activation during memory task and ^{18}F-DOPA uptake. HC: negative correlation between hippocampal activation during memory task and ^{18}F-DOPA uptake	14	26	20	26	[122]
Fusar-Poli *et al.* (2011)	fMRI (VF task) and ^{18}F-DOPA PET	CHR: positive correlation between striatal dopamine synthesis capacity and activation in the IFC. HC: no correlation	14	25.4	20	27	[121]
Valli *et al.* (2011)	^{1}H-MRS and fMRI (episodic memory task)	HC: positive correlation between MTL activation during episodic encoding and MTL glutamate. CHR: no correlation with glutamate	14	26	22	26	[116]
Fusar-Poli *et al.* (2010)	fMRI (WM task) and ^{18}F-DOPA PET	CHR: negative correlation between striatal dopamine synthesis capacity and activation in R middle FG. HC: opposite correlation	14	25	20	27	[120]
Stone *et al.* (2010)	^{1}H-MRS and ^{18}F-DOPA PET	CHR: negative relationship between hippocampal glutamate levels and striatal dopamine synthesis capacity. HC: no correlation	12	NA	16	NA	[119]
Stone *et al.* (2010)	EEG and ^{1}H-MRS	CHR: ↓ levels of Glx in the thalamus is associated with ↓ MMN amplitude in frontal areas	–	–	11 MRS and MMN	27	[113]
			–	–	8 MRS and P300	29	
Stone *et al.* (2009)	^{1}H-MRS and sMRI	CHR: level of thalamic glutamate positively correlated with GMV in the MTL and insula. HC: no correlation	27	25	27	25	[98]

^{1}H-MRS: Proton magnetic resonance spectroscopy; CHR: Clinical high risk; FG: Frontal gyrus; fMRI: Functional MRI; Glx: Glutamate plus glutamine; GMV: Gray matter volume; HC: Healthy controls; IFC: Inferior frontal cortex; MMN: Mismatch negativity; MTL: Medial temporal gyrus; NA: Not applicable; R: Right; sMRI: Structural MRI; VF: Verbal fluency; WM: Working memory; WMV: White matter volume.

Stone and colleagues detected a negative relationship between hippocampal glutamate and striatal dopaminergic function in CHR subjects that is absent in controls and is most marked in CHR subjects that subsequently developed psychosis [119]. This suggests that abnormal relationships between hippocampal glutamate and striatal dopamine may be present during the prodrome, and worsen as psychosis progresses.

Taken together, these studies have provided preliminary evidence that glutamatergic abnormalities in the CHR state may be associated with abnormalities in brain structure and function. While confirmation in larger independent samples is required, these studies suggest that drugs that modulate glutamatergic transmission may be beneficial in preventing the development of psychosis in those most at risk for the disorder.

Another line of work has investigated the relationship between striatal dopaminergic function in the CHR state (as measured with ^{18}F-DOPA PET) and abnormalities in prefrontal activation assessed with fMRI during task performance [120,121]. The first of these studies combined fMRI data acquired while subjects performed a working memory task (N-back). While ^{18}F-DOPA uptake in the associative striatum was positively correlated with activation of the right MFG in controls, these variables were negatively correlated in CHR subjects [120]. In the second study, fMRI data were acquired while subjects performed a verbal fluency task. Striatal ^{18}F-DOPA uptake was positively correlated with the degree of activation of the inferior frontal cortex in CHR but not control subjects [121]. Both of these studies provide evidence that increased striatal dopamine synthesis capacity is associated with abnormal prefrontal activation during cognitive task performance and link deficits in executive processing to striatal hyperdopaminergia in CHR individuals. Finally, Allen and colleagues used the same verbal memory task reported previously [17] to examine the relationship between MTL and dopaminergic function [122]. In CHR subjects, the relationship between striatal dopamine function and MTL activation during both verbal encoding and verbal recognition was significantly different in CHR subjects compared with controls. An altered relationship between MTL function and dopamine storage/synthesis capacity exists in at-risk mental state individuals and may be related to psychosis vulnerability.

In summary, multimodal imaging studies have begun to establish associations between altered neurotransmission and neurofunction/anatomy. Dysfunction in dopamine and glutamate systems, both widely implicated in the pathogenesis of psychosis, has been shown to correlate with altered PFC and MTL dysfunction in CHR subjects. However, the causal direction of these associations is unclear and the possibility that they may be epiphenomenal cannot be ruled out.

Conclusion & future perspective

These neuroimaging studies have shown that several abnormalities in brain neurophysiology, anatomy and chemistry that are fundamental to schizophrenia are also present in people at very high risk of developing the disorder, and may therefore represent vulnerability markers. Studies that have included control, CHR and first-episode patients show that the CHR phenotype is usually intermediate to controls and first-episode patients [6,10,29,33,109], which suggests that the extent of abnormality may either be predictive of psychosis or worsen as symptoms progress. Indeed, there is already evidence from structural [67,68], functional imaging studies [13] and a study of CBV [37] that the extent of abnormality at baseline is predictive of subsequent conversion to psychosis, and there is evidence from ^{18}F-DOPA PET studies that conversion to psychosis is accompanied by longitudinal increases in dopaminergic function in the striatum [110]. While further prospective and longitudinal studies are required, these recent findings provide some evidence that neuroimaging methods may have additional predictive value for identifying psychosis risk. Of the CHR subjects included in these studies, only approximately 20–30% will go on to develop psychosis. This implies that, at a group level, several neurobiological changes are present in people who, while currently at CHR, will never develop psychosis. This may indicate that the presence of more than one neurobiological abnormality, together with the presence of additional factors such as genetic or environmental risks, is required for clinical psychosis. Future studies, which combine multimodal imaging data together with additional risk factors, may therefore have greater predictive value for psychosis. Existing multimodal data provide empirical evidence that abnormalities in brain neurotransmitters, structure and activation may be related [98,113,116,119,120–122]. However, in these cross-sectional studies, it cannot be determined which abnormality is primary, but future longitudinal studies may help to determine the direction of causality.

To date, two functional, 14 structural and five neurochemical imaging studies have compared CHR subjects according to outcome. Many of the structural studies report findings in overlapping datasets and the power of these studies to detect predictive changes will depend on conversion base rates, which vary considerably across time and across clinical centers using different diagnostic instruments [123]. Many of these studies report modest effect sizes at a group level, and as such, their ability to predict conversion to psychosis in an individual case is questionable. In addition, the reviewed literature notoriously differs in their definitions of 'psychosis', which is not a diagnostic category, but rather a syndrome that can occur in various disorders such a bipolar and some affective disorders. As such, these studies are often not directly comparable. The age of CHR subjects also varies considerably across studies. Although the mean age of CHR subjects in the studies reported here is approximately 20 years, some studies include subjects as young as 14 years, while others include subjects aged >30 years. It is worth noting that because older CHR subjects are towards the latter stages of the maximum risk period, their symptomology may be indicative of disorders other than schizophrenia.

Despite these caveats, research in CHR groups is a potentially powerful means of investigating the mechanisms underlying the onset of psychosis, as subjects can be studied prospectively, before the onset of the disorder. Moreover, comparison of those who do and do not develop psychosis can reveal which risk factors are critical for the onset of illness, in the absence of the potentially confounding effects of antipsychotic treatment. An overarching aim of future studies should be to maximize the translational benefits of research in CHR groups. Clinical trials suggest that intervention in CHR subjects can reduce the risk of later transition to psychosis [124]. However, it is difficult to predict which CHR individuals will later develop psychosis on the basis of their clinical presentation [125]. Consequently, at present, potentially preventative clinical interventions have to be delivered to all CHR subjects, including many

who will never develop psychosis, which is clinically inefficient and ethically problematic. Thus, there is a pressing need to identify biomarkers that can identify those CHR subjects who are most likely to become psychotic, so that clinical resources can be focused on this subgroup. A recent study by Koutsouleris and colleagues applied multivariate methods to imaging data to facilitate accurate outcome prediction in a CHR cohort [83]. Although promising, more studies using multivariate and pattern classification techniques will be needed before their predictive utility can be accurately assessed. As healthcare provision moves towards preventative and early intervention strategies, methods to enhance outcome prediction will become increasingly important and sought after.

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