Altering the course of schizophrenia: progress and perspectives

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Abstract | Despite a lack of recent progress in the treatment of schizophrenia, our understanding of its genetic and environmental causes has considerably improved, and their relationship to aberrant patterns of neurodevelopment has become clearer. This raises the possibility that 'disease-modifying' strategies could alter the course to — and of — this debilitating disorder, rather than simply alleviating symptoms. A promising window for course-altering intervention is around the time of the first episode of psychosis, especially in young people at risk of transition to schizophrenia. Indeed, studies performed in both individuals at risk of developing schizophrenia and rodent models for schizophrenia suggest that pre-diagnostic pharmacotherapy and psychosocial or cognitive-behavioural interventions can delay or moderate the emergence of psychosis. Of particular interest are 'hybrid' strategies that both relieve presenting symptoms and reduce the risk of transition to schizophrenia or another psychiatric disorder. This Review aims to provide a broad-based consideration of the challenges and opportunities inherent in efforts to alter the course of schizophrenia.

Psychosis

A cluster of clinical signs related to, but not identical to, positive symptoms of schizophrenia: detachment from reality; compromised insight; hallucinations and delusions; psychomotor anomalies, such as catatonia or agitation; and disorganized thought, speech and behaviour. Psychosis is generally used as the operational definition of transition to schizophrenia, despite its (less systematic) occurrence in other disorders.

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Schizophrenia is a chronic, heterogeneous, multi-faceted and debilitating disorder triggered by a panoply of interacting genetic, epigenetic, developmental and environmental factors that collectively interfere with normal brain development and maturation[1,2] (FIG. 1). It has a prevalence of ~1% worldwide and represents a major socio-economic burden, mainly as a result of indirect costs, such as unemployment and social support, but also owing to hospitalisation during crises[1,3,4]. Rare and usually severe cases of early-onset schizophrenia notwithstanding, this disease is usually diagnosed in young adults with the 'first episode of psychosis' (FEP)[2–5] (BOX 1).

Antipsychotics are effective against positive symptoms, but some patients respond poorly to treatment. Furthermore, although clozapine remains the most effective agent for 'resistant' patients, it has haematological and metabolic side effects, and neither clozapine nor second-generation antipsychotics (SGAs) such as risperidone, olanzapine and aripiprazole markedly improve negative symptoms, neurocognitive deficits or impaired social processing and cognition. Thus, although the importance of current treatments must be recognized, and there has been considerable progress in moderating their side effects, there remains a clear unmet need for greater clinical efficacy[6–8]. Recently evaluated glutamatergic agents have not yet proven sufficiently effective for authorization[9,10]. Moreover, numerous mechanisms pursued as 'add-ons' to SGAs have had limited success, possibly because SGAs undermine their ability to relieve cognitive impairment and most studies were undertaken in chronically ill patients[11,12]. Improving the symptomatic treatment of schizophrenia remains an important goal, but progress will likely require a strategic shift in thinking (see Supplementary information S1 (figure)).

By definition, symptomatic treatment does not affect the causes, pathophysiology or course of schizophrenia. However, an improved understanding of the neurobiological substrates of schizophrenia is fostering the notion that the course of schizophrenia might be modified by novel modes of intervention, especially if they are instituted at an early stage of the disorder[13–17]. The challenges and opportunities for the realization of this goal are the central themes of this Review.

REVIEWS

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Positive symptoms
Include delusional thinking, hallucinations, false beliefs, bizarre thoughts, suspiciousness and paranoia. Although usually mild and transient during the prodrome, full-blown positive symptoms during the first episode of psychosis are a diagnostic pillar of schizophrenia. Positive symptoms are reduced in most patients by antipsychotics, but remission may be incomplete, relapses occur and about 20–30% of patients are refractory.

Negative symptoms
Prominent from the pre-diagnostic to the chronic phase of schizophrenia, negative symptoms are poorly controlled by antipsychotics and linked to poor real-world function. There are two sub-clusters: decreased expression (poverty of speech and blunted affect) and avolition (amotivation, asociality and loss of anticipatory pleasure for normally rewarding activities).

Course alteration: general principles

Disease modification as a therapeutic concept. The notion of early, pre-diagnostic disease modification (FIG. 2) has its origins in medical domains such as diabetes, oncology and rheumatoid arthritis, and efforts to develop preventive therapies for multiple sclerosis, Alzheimer disease and Parkinson disease have also intensified over the past decade[18–20]. The more recent application of disease modification to psychiatric states is highlighted by experimental evidence that developmental anomalies and behavioural deficits characterizing autism-related disorders (in particular, those that are monogenic) may be, at least partially, correctible[21]. These observations underscore interest in preventive treatment for bipolar depression[22] and schizophrenia, not least because of the commonalities these disorders have with autism, including symptoms (cognitive and social impairment)[12,21], genetic risk factors (single genes and copy number variants (CNVs))[23,24], epigenetic anomalies (DNA and histone marking)[25,26], environmental triggers (perinatal infection and inflammation)[27,28] and neurobiological substrates (disruption of synaptic plasticity and cerebral connectivity)[21,29,30]. Certain core features are shared between schizophrenia and other disorders, which is important as it implies that course-altering strategies for blocking the onset of psychosis might be of broader therapeutic utility[1,23,31–33].

Course alteration for schizophrenia: core questions. Disease modification refers to interventions that directly target the pathophysiological processes causing a disorder in a manner that enduringly modifies its progression[19], but it is important to clarify the operational meaning of disease modification as applied to schizophrenia. As depicted in FIG. 2, it seems wise to favour a broader and more pragmatic notion of course alteration as a framework for study and therapeutics. Despite several characteristic neurodevelopmental anomalies, no common upstream trigger for schizophrenia is known[1,2,29,30]. Hence, course alteration might target multiple mechanisms, acting in series and in parallel, and either aggravating or counteracting core pathophysiological substrates. Targetable pathological processes may differ between specific clinical dimensions, for example, avolition versus hallucinations versus impaired social cognition[1,12–14,16,33].

The initial diagnosis at the time of the FEP comes relatively late in the neurodevelopmental trajectory of schizophrenia, usually around 25 years of age, and antipsychotic treatment does not normally begin until this FEP. However, course-altering therapy is most likely to succeed when applied early. This is supported by evidence that marked and progressive anomalies in brain structure, neurochemistry and connectivity are already present by the time of diagnosis[30,34–36]. Precocious course-altering therapy for schizophrenia also makes sense in terms of potential cost-effectiveness[37]. Hence, the major focus is currently on prevention of the FEP and the onset of schizophrenia.

A preventive approach to course alteration raises several important questions. First, what is the optimal strategy for identifying people at risk of developing schizophrenia, and who should be treated? Second, which therapeutic strategies would be the most effective for preventing the onset of schizophrenia and/or interfering with its progression? Third, how can the efficacy of course-altering treatments be clinically evaluated and proven? Fourth, is it possible to unite the treatment of symptoms seen in clinically high-risk (CHR) individuals with a reduction in the risk of transition? Indeed, might the control of anomalies and dysfunction in CHR patients of itself impede the onset of schizophrenia?
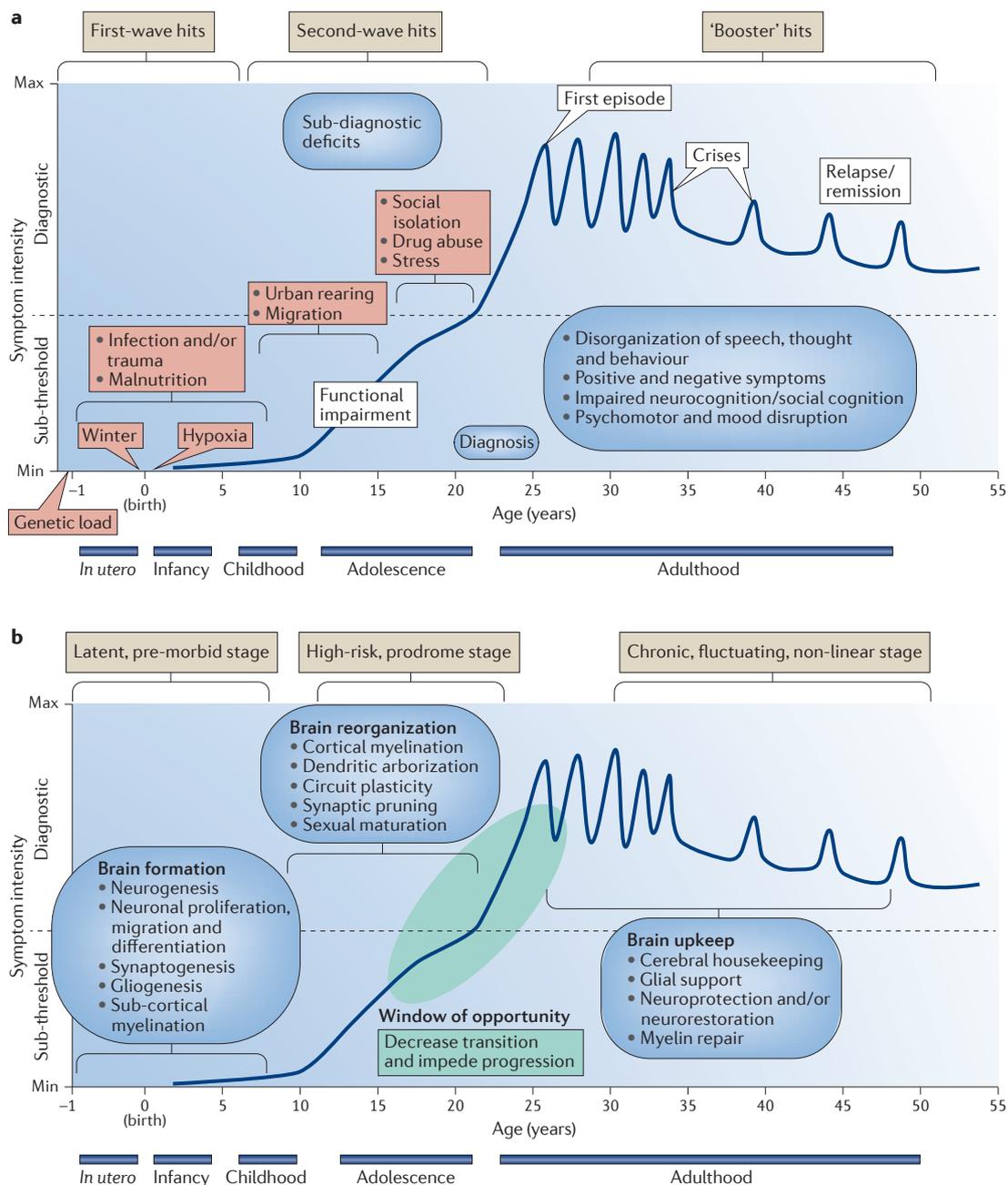
Although current antipsychotics may 'stabilize' patients, this is essentially due to symptomatic effects expressed during treatment. Hence, a basic tenet of the following discussion is the need to identify novel and genuine course-altering therapies. To realize this objective, a broad suite of strategies is being deployed, ranging from cellular studies to therapeutic trials in individuals who are vulnerable to schizophrenia. Accordingly, the discussion herein is structured around three complementary hierarchies of evidence, commencing with the most advanced and direct: clinical trials of pharmacotherapeutic and other interventions for preventing transition to psychosis (also commonly called conversion) in high-risk individuals seeking help. We move on to examine the experimental evaluation of pharmacological agents for blocking the adult appearance of a 'psychosis-like' phenotype in rodent models for schizophrenia. Then we discuss cellular and *in vivo* studies of pathophysiological mechanisms implicated in events leading to the onset of psychosis and their implications for novel therapeutic approaches.

Neurocognitive deficits

Deficits in a range of cognitive domains, including those dependent on frontocortico-striato and frontocortico-parietal circuits: attention; working memory (handling of new and stored information); executive function (planning, decision making and flexible shifting of goals); speed of processing and procedural memory (learning motor tasks); and verbal learning and memory.

Social processing and cognition

Processes used to decode social cues, interpret and predict the mental state, beliefs, desires and intentions of others and hence behave in a socially appropriate, adaptive manner. Signals include facial expression, body posture and hand gestures. Impaired social cognition is seen in the prodrome, interrelated with negative symptoms and linked to poor functional outcome. Deficits are irresponsive to antipsychotics.

Disease modification

Interventions that directly interrupt, decelerate or even reverse the core pathophysiological processes causing a disorder, with the goal of preventing or delaying its onset and/or moderating its severity once it evolves. Effects should, in principal, persist even after treatment has been discontinued and are not necessarily apparent at the onset of, or even during, administration.

Figure 1 | **Onset and progression of schizophrenia in relation to risk factors and developmental processes affected by the disorder. a** | The diagnosis of schizophrenia, which operationally corresponds to the first episode of psychosis (FEP), is usually made in young adults but can (albeit rarely) occur in childhood, adolescence or later in life. Diagnosis generally follows a prodromal, at-risk phase in which sub-threshold psychotic episodes and other characteristic symptoms are apparent. Once diagnosed, schizophrenia follows a fluctuating course punctuated by acute exacerbation of psychotic crises superimposed upon a background of poorly controlled negative, neurocognitive and social cognitive symptoms. Approximately 10–15% of patients recover after their FEP, and a similar proportion display a more severe and unremitting form of the disorder. In addition to inheritance (see Supplementary information S2 (box)), many environmental risk factors have been incriminated during both the perinatal (first wave) period and during adolescence (second wave). Genetic and environmental effects act, at least partially, through the epigenetic misprogramming of neurodevelopment. Throughout the disorder, adverse environmental events can trigger crises (booster hits). **b** | The course to and progression of schizophrenia can be related to three fundamental phases in the 'life' of the brain — although depicted sequentially, these phases are interlinked and there is no absolute demarcation. Each phase is anomalous in schizophrenia, with disruption of brain formation and reorganization implicated in causal pathophysiology. These two phases, as well as brain 'upkeep', embrace a range of processes that could be potentially targeted for therapeutic intervention. Pre- and post-diagnostic course-altering interventions are labelled 'prevention' and 'reversal', respectively, but only relative to the clinical picture: underlying pathophysiological changes will have set in much earlier. Currently, the most compelling 'window of opportunity' is around the FEP, to impede onset or block early progression.

Box 1 | **Schizophrenia and psychosis**

Schizophrenia is a complex and heterogeneous disorder with a broad range of clinical symptoms, as illustrated in FIG. 1. Nonetheless, it is the first episode of psychosis (FEP) that is diagnostic and necessitates rapid treatment[4,35,42,269]. With the exception of a minority of patients who only undergo one episode, those with true schizophrenia will remain at risk of psychotic crises throughout their lives. Furthermore, sub-diagnostic psychotic experiences are common during the prodrome[32,35,40,42].

Psychosis is, therefore, a cardinal and persistent feature of schizophrenia that includes positive symptoms — such as delusions, hallucinations and a loss of insight — with broader conceptualizations, including disorganized thought, speech and behaviour, together with psychomotor retardation or agitation. Moreover, psychosis is enshrined as a core symptom of schizophrenia in the latest (and convergent) editions of the World Health Organization (WHO) International Classification of Diseases (Version 11) and the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association (Version 5). In the latter case, delusions, hallucinations, disorganized thinking and speech and abnormal goal-directed and motor behaviours comprise, together with negative symptoms, the five major pillars for diagnosis of schizophrenia — to which mania, depression and cognitive and/or social impairment may be incorporated to refine diagnostic precision[5,8,269].

The heterogeneity of schizophrenia is reflected in the DSM's recognition of numerous related diagnoses —such as schizoaffective disorder — across the 'schizophrenia spectrum' (REFS 15,33,269). Moreover, some authorities consider that psychosis lies on a continuum with normality: minor psychotic-like episodes may be transiently experienced by 'healthy' individuals without leading to distress or to the individual seeking help[15,33,268,269]. Serious psychotic-like episodes may occur in bipolar disorder and atypical psychotic depression, and such episodes are also associated with recreational use of agents that provoke or mimic certain schizophrenia-like symptoms: cannabis, cocaine, phencyclidine and ketamine[10,33,51,270].

The latter point underlies the increasing recognition that, despite being regarded as distinct diagnostic entities, disorders such as schizophrenia, bipolar depression and autism share certain core symptoms, pathophysiological anomalies and risk factors. These overlapping aetiological, neurobiological and clinical features encourage a more dimensional and pathology-driven approach to the study, treatment and prevention of psychiatric disorders[1,23,28,31,33]. This is of particular significance to efforts for developing course-altering therapies for schizophrenia, which may prove of utility for the control of other disorders, especially those characterized by psychosis.

Finally, the term 'early-onset schizophrenia' is used to cover the individuals that are diagnosed before the age of 18 (approximately 5% of all cases) during adolescence and, even more rarely, in childhood[271]. Diagnostic criteria and symptomatic treatment for these individuals are similar to those used in the usual, adult form, but early-onset schizophrenia tends to be more severe, with a particularly unfavourable long-term outcome[271]. The course-altering strategies discussed herein are mainly directed towards the prevention of young-adult-onset schizophrenia, but they might ultimately be of use for the control of more precocious forms.

First, we consider the characteristics of people at a CHR of developing schizophrenia and the approaches used for assessing the risk of transition.

Predicting the risk of schizophrenia

The CHR state. Mental health problems are highly prevalent in young individuals[3,4], underpinning efforts to set up nationwide structures for the treatment and detection of individuals at risk of psychosis and other psychiatric disorders (BOX 2). Schizophrenia affects young adults who were exposed to multiple risk factors from conception to adolescence[23,24,27,38] (FIG. 1a). Its onset is preceded by a phase known as the prodromal period, during which several sub-diagnostic features progressively emerge, albeit with inter-individual differences. In line with the notion of clinical staging[39], the earliest symptoms may be nonspecific and include anxiety, depressed mood, social withdrawal and educational difficulties, and these early symptoms are followed by the emergence of 'basic symptoms' — subtle disturbances of cognition, perception, language and emotion — and reduced stress tolerance and coping[40,41]. Later, more pronounced abnormalities and disorganized speech become apparent, as well as sub-diagnostic positive symptoms. These 'brief limited intermittent psychotic symptoms' and 'attenuated psychotic symptoms' (APS) are less severe than a fully-fledged psychotic episode[35,42] (BOX 1). During the prodromal period, both negative symptoms and impairment of social cognition are present: these are often pronounced and are linked to poor functioning and a high likelihood of transition to schizophrenia[8,12,40,43,44]. Neurocognitive deficits are also prominent[12,40,43].

Contrasting fates of people at CHR of transition to schizophrenia. The notion of pre-diagnostic disease modification presupposes the reliable identification of individuals at risk. Although the term prodrome implies that schizophrenia is ineluctable, this is not actually the case. In fact, only a minority of CHR individuals will develop schizophrenia or another psychotic disorder[15,17,34,35,40,45] (FIG. 3a). Meta-analyses suggest that the proportion of CHR individuals that do develop such a disorder is ~30%, but this percentage varies across different samples. This variability reflects contrasting criteria for the selection of CHR individuals for study, socio-demographic differences, environmental factors, coping and varying degrees of clinical and family care and support[14,34,35,38,40,46,47]. The latter point supports the 'hybrid' notion that treatment of CHR individuals may reduce their risk of transition to schizophrenia (see below). Nonetheless, complete recovery is rare; some CHR individuals persist in a state of impaired overall functioning and many develop other psychiatric disorders such as depression or anxiety (FIG. 3a). Hence, the need for preventive course-altering therapy remains persuasive, and all of these individuals require treatment and specialized care[17,32,34,35] (BOX 2).

Clinical indices of impending transition. Although all CHR individuals may potentially transition to schizophrenia, certain features are associated with a particularly high risk of this occurring. These include unusual thought content, marked impairment of verbal learning and memory, suspiciousness and paranoid ideation (especially when enduring and denied), low IQ, substance abuse, migrant status, isolation, poor quality of life and comorbidity with other disorders[32,34,35,40,43,45,48]. Inspection of CHR individuals may also reveal 'neurological soft signs', that is, motor and sensory changes provoked by neurodevelopmental abnormalities distributed across widespread cortical regions[49,50].

Such clinical observations are important for assessing vulnerability to psychosis, especially when coupled with information on lifestyle, such as excessive consumption of cannabis[38,51]. Nonetheless, clinical observations alone are insufficient for either predicting the likelihood of transition at the individual level or stratifying subgroups of CHR individuals. Accordingly, more-refined strategies
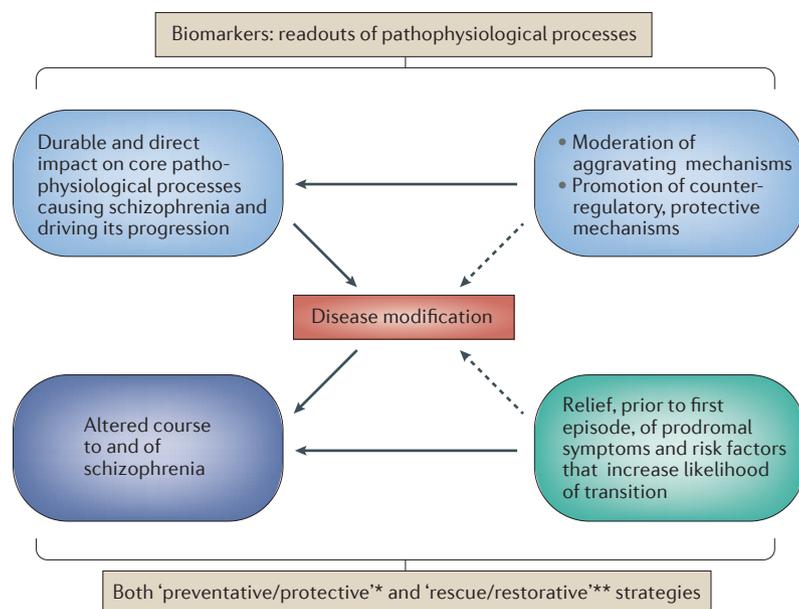
Prodromal period
A high-risk state that precedes the transition to schizophrenia or another psychotic disorder by weeks to years. It is characterized by attenuated and/or brief self-limiting psychotic symptoms, negative, neurocognitive and social cognitive symptoms, depressed mood and other psychological and behavioural abnormalities. Not all individuals showing a prodrome transition to a psychotic disorder, so the term is somewhat misleading.

Figure 2 | **Course alteration and disease modification: core facets.** The notion of disease modification, more familiar for neurodegenerative disorders, refers to a direct and enduring impact on the disease process (that is, on causal pathophysiological mechanisms). This leads to a delay in or halting of the onset or progression of the disorder. Neurobiological substrates of schizophrenia are incompletely defined, multiple and, at least to some extent, symptom-specific. Furthermore, causal processes are subject to modulatory influences, and so a more liberal interpretation of disease-modification incorporates agents that block or promote processes favouring or hindering disease evolution, respectively. This notion can be integrated into the more general concept of course alteration. In addition, precocious relief of certain classes of symptom (such as impaired social cognition) and countering risk factors (such as drug-seeking behaviour and stress) may slow the path to schizophrenia (see Supplementary information S6,S8 (figures)). Although 'prevention' and 'rescue' are relative to diagnosis, the pathophysiological road to schizophrenia begins far earlier (FIG. 1). *These strategies decrease transition to schizophrenia in high-risk individuals. **These strategies decrease disease progression after diagnosis.

Neurological soft signs
A cluster of minor developmental anomalies in motor and sensory integration, motor coordination and motor sequencing. They are present in high-risk individuals before transition to schizophrenia, for whom they represent a useful warning sign.

Neurexin 1
A presynaptically localized adhesion molecule that interacts with the postsynaptic protein neuroligin 1. Neurexin 1 is abundant in inhibitory GABAergic synapses where it controls transmitter release, as well as synaptic formation and transmission. Deletions of the neurexin 1 gene (de novo and inherited) are consistently associated with schizophrenia.

for estimating the risk of conversion are being developed. Such measures of pathophysiological anomalies also provide insights into potential targets for course-altering medication[13,16,35,48,52] (FIG. 3b).

Genetic profile: risk genes and gene 'networks'. The genetics of schizophrenia are complex: it may be associated with a few, very rare variants of large effect or with innumerable variants with small individual effects but a large collective impact. A role for rare CNVs has been shown in schizophrenia, encompassing multiple genes and stretches of DNA; and both inherited and *de novo* anomalies have been observed in this disorder[23,24] (see Supplementary information S2 (box)). Notably, the gene encoding the synaptic protein neurexin 1 (*NRXN1*) has been consistently linked to schizophrenia, and the gene encoding neuregulin 1 (*NRG1*) was specifically associated with a high risk of transition, and gene clusters, pathways and interactions (epistasis) may yield associations with schizophrenia that are more robust than those observed for individual genes[53,54,55]. Thus, no universal genetic biomarker of the risk of transition is currently available, but useful readouts may soon

emerge. Moreover, a family history of psychosis can be readily factored into estimations of risk, as undertaken by the North American Prodrome Longitudinal Studies (NAPLS) Consortium and the European Prediction of Psychosis study[34,43,48].

Biochemical and endocrine measures in the circulation. Increases in leucocyte levels of the pro-inflammatory cytokine interleukin-6 (IL-6) and decreases in brain-derived neurotrophic factor (BDNF) are correlated with a reduced volume of the hippocampus at the time of the FEP, and these observations extend to the CHR state[56]. Furthermore, high plasma levels of pro-inflammatory cytokines correlated with a steep decline in the volume of prefrontal cortex (PFC) grey matter in CHR individuals that progressed to psychosis[57]. More generally, the risk of transition may be associated with a specific molecular signature in blood that involves immune-inflammatory biomarkers[58-60]. Another promising approach focuses on epigenetic readouts, such as patterns of DNA methylation and microRNA (miRNA) profiles in lymphocytes[26,61,62].

Reflecting increased exposure and/or sensitivity to psychosocial stress, altered activity of the hypothalamic–pituitary–adrenocorticotrophic (HPA) axis is common in the CHR state and suggestive of a high risk of conversion; furthermore, HPA axis over-activity is correlated with hippocampal volume loss[63,64]. Although the specificity of stress-related HPA hyperactivation to risk for schizophrenia is debatable, individuals who transitioned to schizophrenia had higher salivary cortisol levels than those who did not in the NAPLS study[48,63]. Moreover, increased circulating cortisol levels are linked to excessive striatal release of dopamine and positive symptoms both in CHR individuals and in people with familial high risk[63,65,66]. Increased cortisol is also related to poor stress-coping, anxiety and suspiciousness, all psychological factors that are themselves associated with conversion[34,35,40,67].

Structural and functional imaging: neurotransmitters and neural circuits. As quantified by magnetic resonance spectroscopy, schizophrenia is associated with altered glutamatergic transmission in several brain regions, and abnormalities are already evident in CHR individuals[68,69]. Changes include increases in glutamate levels in the associative striatum, reductions in glutamate levels in the thalamus and an uncoupling of glutamate levels from functional activation of the medial temporal cortex during an episodic memory task[68,69]. Furthermore, a prodromal hyper-metabolic state of the hippocampus, mimicked in an animal model, was attributed to excess glutamate release; this hyper-metabolic state was associated with GABAergic interneuron dysfunction, neuronal atrophy and spreading to the subiculum upon onset of psychosis[70]. In the CHR state, changes in glutamatergic transmission originating in the cortex seem to drive alterations in subcortical dopaminergic transmission[71,72]. These alterations are exemplified by an increase in the presynaptic synthesis and storage of subcortical dopamine, especially in the associative striatum, which

Box 2 | **Services to improve treatment and prevention of mental health problems in the young**

Major mental health problems frequently (in perhaps 75% of cases) appear before the age of 25 and contribute to a striking 50% of disease burden in individuals between the ages of 10 and 25 (REFS 3,4,272). Growing awareness of this social and public health issue has led to a global call for improved youth mental health services[4,273]. Specialist services are appropriate for several reasons. First, this population is heterogeneous, with clinically varying and uncertain illness trajectories together with a complex and evolving pattern of morbidity and symptom fluctuation. Second, developmentally and culturally appropriate approaches are essential for young people in view of their individual and group identities and their distinctive help-seeking needs and behaviours. Youth-specific services should best be provided in an accessible, community-based, non-judgmental and non-stigmatizing setting, where young people feel comfortable, have a say in how their care is provided and feel a sense of trust[272]. Ideally, this means creating a youth mental health model that overlaps and interacts with, but is distinct from, systems for younger children and adults. One example, named 'Headspace', is an enhanced primary care youth mental health system that was established in 2006 in Australia[272]. It now operates across more than a hundred sites nationally. These centres offer a 'one-stop-shop' service within a youth café-style environment, provide comprehensive assessment and treatment, and propose social and vocational recovery services within an integrated and multidisciplinary primary-care framework. They also offer a youth-focused online counselling service — e-Headspace. Headspace has been highly successful and is broadening its remit to cater for young people experiencing a first episode of psychosis[272]. Innovative models for improving mental health care in the young are increasingly being adopted in other countries, such as the United States (the Portland Identification and Early Referral initiative), the United Kingdom (Outreach and Support in South London), France, Canada and Ireland[274,275]. In addition to specialist centres, educational outreach programmes to identify clinically high-risk individuals and people that have already suffered a psychotic episode are likewise of importance[276].

MicroRNA
(miRNA). A short stretch of non-coding RNA (22–24 nucleotides long) that neutralizes and destabilizes matching mRNAs (in some cases matching hundreds of different mRNAs). When the match is perfect the matched mRNA is degraded. Hundreds of different miRNAs exist in the brain. Many interact with developmentally important proteins, and cerebral levels of diverse classes of miRNA are altered in schizophrenia.

Default mode network
Interconnected cerebral regions in humans that are active in fMRI studies under resting conditions, for example, during introspection and rumination. Conversely, they are deactivated by goal-directed actions such as the performance of a working-memory test. An equivalent network seems to exist in rodents.

Event-related potentials
Negative and positive shifts in the voltage of electro-encephalogram recordings triggered by external stimuli, usually auditory but also visual.

P300
A positive deflection peaking ~300 milliseconds after a deviant ('oddball') stimulus that differs in frequency, duration and strength to a previous sequence.

Mismatch-negativity
A pre-attentional negative response peaking ~100–150 milliseconds after a deviant stimulus.

becomes progressively more pronounced as individuals transition to psychosis[72,73]. Dopamine depletion studies have linked this increased dopamine availability to greater occupation of postsynaptic dopamine D_2 receptors[72–74]. On a different note, reduced levels of a marker of neuronal integrity, N-acetylaspartate, in the fronto-cingulate cortex may be indicative of susceptibility to transition, with decreases intensifying upon diagnosis[75].

Loss of grey matter volume coupled to an increase in lateral ventricle size is highly reproducible in schizophrenia, and MRI of progressive structural changes in CHR individuals can reveal a risk of transition. Indeed, mirroring grey matter loss in patients with a FEP who have never received treatment, CHR individuals display reductions in grey matter in para-hippocampal territories, the cerebellum, the superior and medial temporal lobe, the insular cortex and the PFC[8,57,76–78]. Progression of CHR individuals through various premorbid stages and conversion correlates with incremental grey matter loss[39,73,79]. The precise pattern may even predict the type of psychosis, as reductions in the PFC and the parietal lobe were linked to schizophrenia, and reductions in the PFC and the subgenual cingulate cortex were linked to affective psychosis[80].

Functional MRI (fMRI) of cerebral circuits is likewise instructive[36]. For example, altered activity in cortico-striatal pathways correlated to APS in the prodromal period[81] and parallels the above-mentioned enhancement of presynaptic dopaminergic activity in the associative striatum[72,73]. Furthermore, suppression of the dorsolateral PFC component of the default mode network during a working memory task was blunted both in early schizophrenia and in CHR groups[82]. Deficient working memory in vulnerable individuals has also been related to aberrant coupling of the PFC to the parietal cortex[83]. Finally, altered activity of fronto-temporo-parietal regions has been linked to negative and social cognitive symptoms[8].

To summarize, alterations in dopaminergic, gluta-matergic and GABAergic transmission, loss of grey matter in discrete cortico-limbic regions and disruption of network connectivity are all anomalies that parallel the progressive onset of psychosis (FIG. 1). Collectively, they provide a broad suite of imaging readouts for estimating the risk of transition to psychosis.

Electroencephalographical readouts: event-related potentials. Electroencephalographic probing of large-scale brain networks can reveal anomalies in cerebral connectivity, neural synchrony and the balance of inhibition and excitation. Accordingly, it is potentially useful for assessing the risk of transition[84,85]. In addition, studies of event-related potentials (ERPs) have shown that two responses to deviant stimuli, one positive (P300) and one negative (mismatch negativity (MMN)), are modified in schizophrenia and in CHR individuals[33,86–88]. Both responses have a strong glutamatergic component and are disrupted by the N-methyl-D-aspartate (NMDA) receptor antagonist and pro-psychotic agent ketamine[87–89]. The attenuation of P300 in CHR individuals that subsequently convert has been related to disruption of grey and white matter in the temporo-parietal cortex and the frontal gyrus, regions implicated in cognitive deficits, impaired language processing and negative symptoms[8,86,90]. Importantly, perturbation of duration-deviant MMN is specific to schizophrenia, and its amplitude is reproducibly blunted in the prodrome[87,88,91]. In longitudinal studies, the amplitude of MMN permitted sub-division of patients into higher- and lower-risk groups[88,91]. Furthermore, meta-analyses suggest that MMN perturbation is the most consistent ERP biomarker of conversion and may be exploitable in a prospective fashion to predict which CHR individuals will convert, with a greater magnitude of reduction correlated to more imminent onset of psychosis[87,88,91]. Another advantage of MMN is its translational
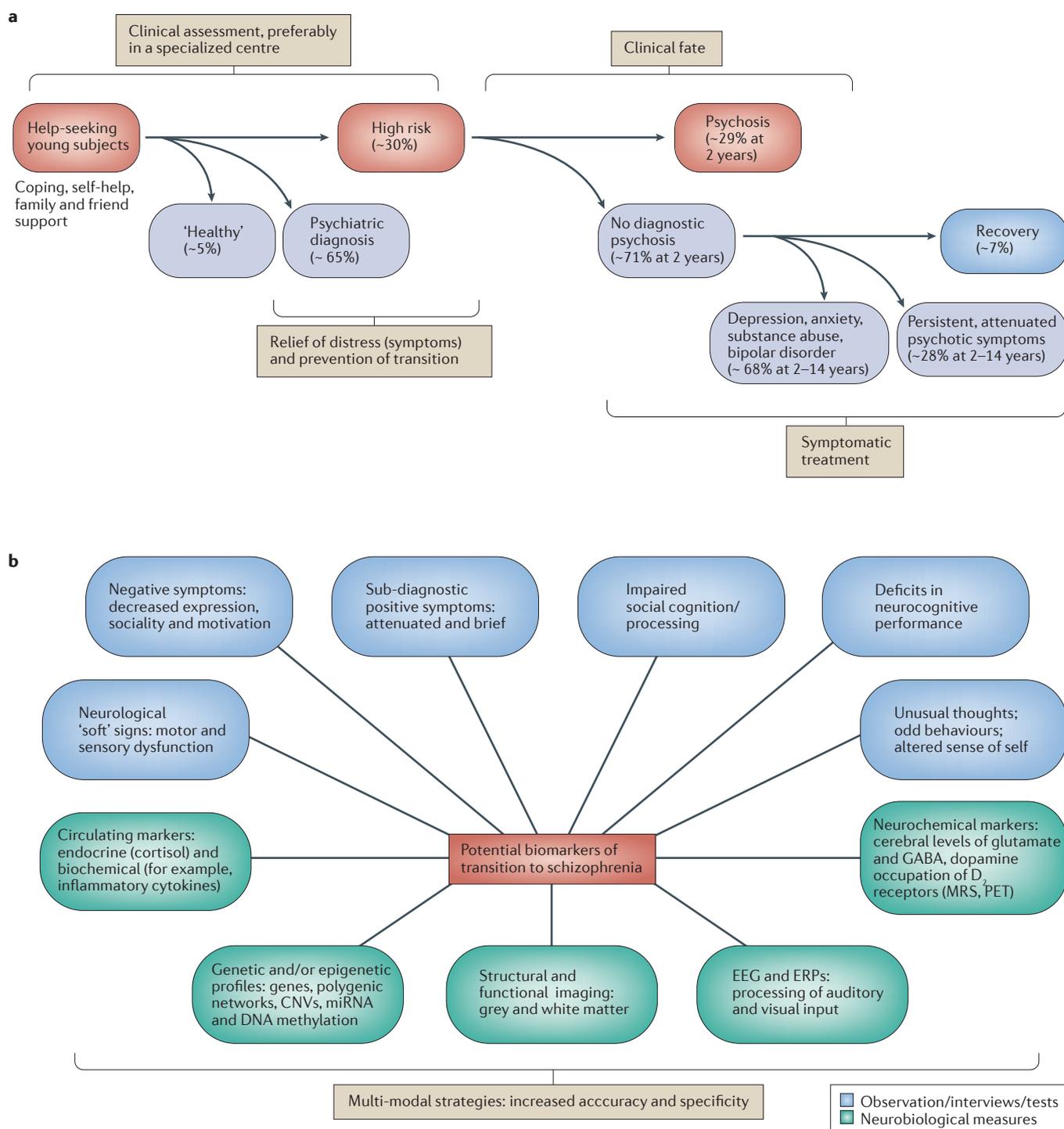
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Figure 3 | **Clinical trajectories of young individuals seeking help who are at high risk for developing schizophrenia: diverse strategies for their detection. a** | Among clinically high-risk (CHR) individuals seeking help, many will need treatment for psychiatric problems such as depression, anxiety and even sub-diagnostic psychotic episodes. Based on observations from specialized centres (BOX 2), about a third of CHR individuals transition to schizophrenia or another psychosis within 2–5 years of seeking help. A minority will remit, some will remain in a comparable state of impairment and others will transition to another psychiatric disorder, not necessarily associated with psychosis. This emphasizes the importance of trans-nosological thinking for strategies designed to reduce transition. The percentages shown are based on a study performed in a sample of CHR individuals in a specialized Australian clinic from 1993 to 2016 (REF. 45). **b** | Comprehensive clinical assessment is crucial for identifying CHR individuals, especially when coupled to information on lifestyle, such as recreational drug abuse and social isolation. A broad variety of measures are also instructive for predicting transition, although no single measure alone has adequate fidelity for reliably predicting the fate of individuals. Multi-modal strategies help to enhance the sensitivity and specificity of predictions, even at the individual level, and are useful for the stratification of subgroups. CNV, copy number variant; EEG; electro-encephalography; ERP, event-related potential; MRS, magnetic resonance spectroscopy; PET, positron emission tomography.

dimension, in that neurobiological substrates are common to animals and humans, and disruption can be measured using similar methods[87–89,91].

Towards the stratification of individuals at risk of transition. By analogy to efforts to better classify sub-classes of patient[33], a major current goal is the sub-categorization of CHR individuals as defined by individual or suites of biomarkers that are preferably linked to a targetable neurobiological anomaly. This should improve the prediction of transition, reduce group heterogeneity and enhance the power and rigour of clinical trials (see below). Despite limitations of genetics (see Supplementary information S2 (box)), deletion of *NRXN1* may define a subset of individuals at risk[52,92], and subgroups may also be revealed by analysis of gene networks[54]. Another potential approach for stratification to sub-classify CHR individuals is a disruption of MMN[88,91] and, when coupled to MMN deficits, cognitive dysfunction may be particularly informative[93,94]. The pattern of grey matter loss also differs between phenotypically distinct patient subgroups[80]. Finally, a blood-borne panel of immune and other biochemical markers has been proposed for at-risk subject sub-classification[59].

Multi-modal strategies for more reliable prediction of transition in individuals. Irrespective of group averages (means), it is imperative to accurately predict the risk of transition to schizophrenia in individuals with as few false positives (preventing stigma, superfluous treatment, unnecessary costs and so on) and false negatives (avoiding a failure to protect) as possible. It is unlikely that any single readout would be fully reliable, specific and of universal utility. Correspondingly, multi-modal strategies are the focus of several ongoing studies[34,52,83]. For example, the NAPLS Consortium has developed a plasma-based, multi-parametric diagnostic predictive of transition that incorporates excess cortisol secretion as well as markers of inflammation, oxidative stress and metabolic anomalies[60]. A similar approach indicated the high predictive performance of an optimized panel of >20 blood protein biomarkers used in parallel with patient interviews[59]. Similarly, a combination of genetic risk, asociality, functional impairment, negative symptoms and/or APS was associated with a particularly high risk of psychosis[48]. Another instance is the coupling of basic cognitive symptoms and standard CHR criteria to improve early detection[94]. Patterns of polygenic risk can be linked to fMRI-documented alterations in cerebral activity[95]. Convergent functional (fMRI) and structural (diffusion tensor imaging to image white matter and MRI to image grey matter) readouts suggest that superior temporal cortex disruption may be a strong warning sign for transition to schizophrenia[8,96]. Finally, machine learning and other multivariate techniques for deciphering complex patterns of data are being developed to refine estimations of the risk of transition for a single individual[97,98].

Overall, multi-modal strategies seem promising both for improving predictions at the individual level and for characterizing subpopulations of patients at differential risk of transition and possessing contrasting neurobiological substrates for intervention.

Clinical studies of course alteration

Therapeutic trials for preventing transition. Despite numerous challenges and a lack of formal guidelines, several controlled clinical trials in CHR individuals have addressed the issue of whether the rate and time of transition can be influenced by potential course-altering therapy[15,16,34] (TABLE 1). Studies focusing on transition have been performed with omega-3 polyunsaturated fatty acids (PUFAs)[99,100], antipsychotics[101], antipsychotics in combination with cognitive-behavioural therapy (CBT)[102–104], and various modes of non-pharmacotherapeutic intervention alone[105–109]. Several independent meta-analyses have concluded that robust clinical trials in CHR individuals seeking help are feasible and that treatment is associated with a significant overall increase in the time to transition and a decrease in the numbers of patients converting[34,110,111]. However, whether transition is merely delayed or permanently halted remains to be clarified. Furthermore, as the trials undertaken to date were modest in size, larger-scale and higher-powered studies are required to confirm observations, refine tools for outcome analysis, and evaluate the significance of additional factors such as gender and co-morbidity (see below)[34,110–113].

Omega-3 PUFAs. Despite the ambivalent efficacy of omega-3 PUFAs in established schizophrenia, levels of PUFAs are reduced both in people diagnosed with schizophrenia and in CHR individuals, supporting interest in trials of preventive treatment[114,115]. In a focused study, the decreased conversion in CHR individuals treated with omega-3 PUFAs (eicosapentaenoic acid, 700 mg per day, plus docosahexaenoic acid, 480 mg per day) was maintained for 1 year despite only 3 months of treatment, and tolerance was excellent[99,100,116]. Patient function, together with both positive and negative symptoms, was improved. Interestingly, those individuals with borderline personality disorder were similarly ameliorated upon treatment with omega-3 PUFAs[117]. Longer-term findings have recently been reported at 6.7 years post-treatment, with treated individuals demonstrating better functioning, a persistent reduction in transition to schizophrenia and a more general decrease in psychiatric morbidity[118]. However, this study had a modest sample size, and another study of omega-3 PUFAs was less positive in its outcome[119] (P. McGorry, unpublished observations). Thus, the course-altering effects of omega-3 PUFAs may depend upon the precise regime and conditions of treatment, and further trials are needed to confirm their potential utility, possibly in distinct patient subgroups. Moreover, whether the preventive effects of omega-3 PUFAs are specific to psychosis remains to be established[120]. Finally, for future progress, it will be important to better understand how omega-3 PUFAs exert their effects, as a multiplicity of mechanisms have been implicated, including anti-inflammatory and antioxidant properties; improved membrane fluidity, mitochondrial performance and synaptic plasticity; inhibition of phospholipase A2; normalization of under- or overactive mesocortical and/or mesolimbic dopaminergic

pathways; promotion of white matter integrity; and restoration of adequate levels of nervonic acid, a major component of the myelin sheath[100,121,122].

Second-generation antipsychotics. In the PRIME study of olanzapine, 11 of 29 placebo-treated patients transitioned to psychosis compared to 5 of 31 patients on medication, but the difference was not significant[101]. In the olanzapine group, psychosis always occurred in the first 4 weeks when doses were relatively low, hence the drug may not have had sufficient opportunity to act effectively[101]. Interestingly, by week 8, prodromal symptoms were significantly lower in individuals receiving olanzapine compared to those receiving the placebo but weight gain was marked — a mean of 8.8 kg in the olanzapine group versus 0.3 kg for the placebo group[101]. Globally, similar observations on transition were made when risperidone was combined with CBT and needs-based interventions, or with cognitive therapy[102,104,123]. In the PACE I study, despite reduced conversion at 6 months for risperidone (3 of 31 individuals) versus placebo (10 of 28 individuals), the difference was no longer significant at 12 months[102]. In the PACE II study, conversion also did not differ, and all groups demonstrated improvement in symptoms and functioning[103].

Thus, to date, there is no clear evidence that antipsychotics can prevent transition (TABLE 1). Furthermore, despite relief of sub-diagnostic psychosis in CHR individuals and the fact that risperidone was relatively well tolerated, CHR individuals are especially susceptible to side effects such as metabolic perturbation and sedation or fatigue[16,32,34,35,102–104]. In practice, many young people will not accept antipsychotics owing to concerns about adverse effects and stigmatization, and antipsychotics are not recommended by many national guidelines for CHR individuals[17,32,34,35,110,111,113]. More generally, there is concern about over-prescription of antipsychotics to young people for reasons other than the control of psychosis[124]. Nonetheless, additional prevention studies with new agents appear warranted. In an open study of a partial D$_2$ receptor agonist, aripiprazole, it improved prodromal symptoms with good tolerance[125], and a larger-scale, controlled study of the influence of aripiprazole on symptoms and conversion is currently underway[126].

Cognitive-behavioural and other non-pharmacotherapeutic interventions. CBT and psychosocial therapy were reported, alone and in association with antipsychotics, to moderate negative, emotional and social symptoms in CHR individuals, as well as reducing the risk of later transition[102–109] (TABLE 1). Carer support promotes the efficacy of CBT, and family-based interventions suggested symptomatic benefits in a sub-set of CHR patients; however, owing to small sample size and the specific trial design, no conclusions can be made concerning conversion[127,128]. Likewise, a pilot study of cognitive remediation therapy suggested improved social function, but conversion was not reported[129].

In a clinical setting, CBT and related therapies are more likely to be accepted by CHR individuals than antipsychotics, and certain national guidelines advise CBT for

CHR patients, mainly as a symptomatic treatment[31,34,35]. Nonetheless, high levels of patient commitment and practitioner training are required for success[110,130]. Thus, further, well-powered studies are required to confirm the efficacy of non-pharmacotherapeutic interventions for diminishing transition[112,113]. Encouragingly, a recent report underpinned the overall cost-effectiveness of CBT for reducing conversion[130].

Preclinical studies of course alteration

Studies of adolescent interventions in rodent models for schizophrenia. Paralleling clinical work, many studies have exploited developmental and genetic models for schizophrenia[131] to determine whether adolescent or early adulthood treatment can prevent a schizophrenia-like phenotype in adult rodents (TABLE 2).

Omega-3 PUFAs and other clinically tested agents with anti-inflammatory and/or antioxidant properties. Administered as a dietary supplement to adolescent rats, omega-3 PUFAs blunted the behavioural, cognitive and biochemical disruption provoked by long-term exposure to ketamine[132,133]. These observations are intriguing, but the data would benefit from extension to more conventional models for schizophrenia. The underlying mechanisms of action also merit further investigation. Nonetheless, omega-3 PUFAs possess anti-inflammatory and antioxidant properties[134–136] and similar effects may be involved in the experimental actions of several other agents that have been clinically tested in established schizophrenia.

Treatment of adolescent rats, which had been gestationally exposed to the viral mimic polyriboinosinic–polyribocytidylic acid (poly(I:C)), with the anti-inflammatory cyclooxygenase 2 inhibitor celecoxib blocked the adult appearance of supersensitivity to the NMDA antagonist dizocilpine[137]. Celecoxib has shown preliminary evidence of utility as augmentation therapy in schizophrenia, but this awaits confirmation[134,135]. Minocycline interacts with microglia and oligodendrocytes to exert a variety of anti-inflammatory, antioxidant and neuroprotective actions on white and grey matter[134–136], and it also promotes NMDA receptor-mediated transmission[138]. Minocycline blocked behavioural deficits and microglial activation in adult rats that had received an intra-hippocampal injection of a pro-inflammatory agent, lipopolysaccharide, just after birth[139]. This is interesting, as minocycline, although not without risks, is well tolerated and has been evaluated as an adjunct in established schizophrenia. Currently, its efficacy awaits corroboration, although it seems to be most active in early schizophrenia and against negative symptoms[8,134–136,140]. Encouragingly, 12-months add-on minocycline in recent-onset schizophrenia reduced symptoms and protected from grey matter loss in the fronto-temporal cortex[141].

N-acetylcysteine, another drug possessing anti-inflammatory properties, promotes the activity of the antioxidant glutathione (which is deficient in early schizophrenia), enhances mitochondrial integrity, acts at the cysteine–glutamate transporter and (similar to minocycline) facilitates NMDA signalling[135,136,142]. In small-scale

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Minocycline

A tetracycline-like antibiotic with anti-inflammatory and antioxidant properties that easily enters the brain. It is under investigation for a number of central nervous system disorders, including adjunctive therapy with antipsychotics for the treatment of schizophrenia, especially negative symptoms soon after diagnosis.

***N*-acetylcysteine**

An analogue of L-cysteine that is rapidly oxidised into cystine in the brain. Cystine is a substrate of glial cystine–glutamate antiporters, so *N*-acetylcysteine elevates extracellular levels of glutamate. In cells, cystine is reduced into cysteine, the rate-limiting component of the antioxidant, glutathione. Hence, *N*-acetylcysteine enhances glutathione activity. *N*-acetylcysteine also exerts anti-inflammatory properties.

Table 1 | **Outcomes of randomized controlled trials in individuals at high risk of conversion to schizophrenia**

Country	Treatment* (group size, n)	Comparison groups (n)	Mean age (range)	Diagnostic tools‡	Treatment duration (time at follow up)	Conversion rate‖	RR	Comment	Refs
Austria	1.2 g omega-3 fatty acids§ (41)	• Placebo (40)	16 (13–25)	SIPS	3 months (12 months)	• 4.9% versus 27.5% at 12 months ($p = 0.007$)	0.18	Reduced symptoms and increased functioning (from 4 weeks). No adverse effects	99, 106
United States	5–15 mg olanzapine (31)	• Placebo (29)	18 (12–36)	SIPS	12 months (24 months)	• 16.1% versus 37.9% at 12 months (NS) • 33% versus 25% at follow-up (NS)	0.42	Reduced prodromal symptoms but pronounced weight gain	101
Australia	1–2 mg risperidone plus CBT and/or NBI (31)	• NBI (28)	20 (14–30)	CAARMS	6 months (12 and 46 months)	• 19.3% versus 35.7% at 12 months (NS)	0.54	Both medication and CBT improved symptoms. Likewise, no difference in conversion at 46 months	102, 104
Australia	0.5–2 mg risperidone plus cognitive therapy (43)	• Placebo and cognitive therapy (44) • Placebo and supportive therapy (28) • Placebo, supportive therapy and monitoring (78)	20 (14–38)	CAARMS	12 months (12 months)	• 10.7% versus 9.6% versus 21.8% versus 8.7% (NS)	0.46	Improved function and reduced negative symptoms in all groups. At 6 months (interim), likewise no significant difference in conversion rates	103
United Kingdom	CBT and monitoring (37)	• Monitoring alone (23)	21 (14–36)	PANSS	6 months (12 and 36 months)	• 6% versus 22% at 12 months ($p = 0.028$)	0.27	Reduced positive symptoms. No difference at 36 months (20% versus 22%)	107
Canada	CBT (27)	• Supportive psychotherapy (24)	21 (14–30)	SIPS	6 months (18 months)	• 0% versus 12.5% at 6 months ($p = 0.059$)	NC	Low transition, all occurred in the first 6 months. Symptoms improved in both groups	105
Netherlands	CBT (98)	• Supportive counselling and treatment as usual (103)	23 (14–35)	CAARMS	6 months (18 months)	• 10.2% versus 21.3% at 18 months ($p = 0.03$)	0.47	Reduction of subclinical psychotic symptoms	109
United Kingdom	Cognitive therapy (144)	• Monitoring and treatment as usual (144)	21 (14–35)	CAARMS	6 months (24 months)	• 6.9% versus 9.0% at 24 months (NS)	0.76	Exclusion of patients transiting to psychosis shortly after CHR diagnosis may have reduced risk of transition in both groups	108
Germany	Integrated psychological intervention (63)	• Supportive counselling (65)	26	EIPS	12 months (24 months)	• 3.2% versus 16.9% at 12 months ($p = 0.008$) • 6.3% versus 20.0% at 24 months ($p = 0.018$)	0.18	High effectiveness of treatment may be related to onset of therapy already in the early phase of the prodrome	106

Table 1 (cont.) | Outcomes of randomized controlled trials in individuals at high risk of conversion to schizophrenia

Country	Treatment* (group size, n)	Comparison groups (n)	Mean age (range)	Diagnostic tools‡	Treatment duration (time at follow up)	Conversion rate‖	RR	Comment	Refs
United States	FACT (250 CHR and early FEP)¶	• Community care (87 chronic low risk individuals)	17 (12–25)	SIPS and SOPS	24 months (24 months)	• 6.3% versus 2.3% at 24 months (NA)	NA	FACT improved symptoms, organization and functional outcome in CHR and early FEP group relative to low-risk group. However, the latter did not receive FACT, complicating the study. No conclusions on conversion possible	127
United States	FFT: psychoeducation, problem-solving, stress control and better communication (66)	• EC: psycho-education for symptom prevention (63)	17 (12–35)	SIPS and SOPS	6 months (6 months)	• 1.8% versus 10.6% at 16 months (NA)	NA	FFT produced more pronounced reductions in positive symptoms than EC, but psychosocial improvement with FFT only seen in participants over 20 years old. No conclusions on conversion possible	128

CAARMS, Comprehensive Assessment of the At Risk Mental State; CBT, cognitive-behavioural therapy; CHR, clinically high risk; EC, enhanced care; EIPS, early initial prodromal state; FACT, family-aided assertive community treatment; FEP, first episode of psychosis; FFT, family-focused therapy; NA, not available; NBI, needs-based intervention; NC, not calculated; NS, not significant; PANSS, positive and negative symptom scale; RR, risk ratio; SIPS, Structured Interview of Prodromal Syndromes; SOPS, Scale of Prodromal Symptoms. *For details of the various forms of psychosocial therapy used, see references. For example, there are several variants of CBT with a divergent focus on problem-solving, together with reduction of negative cognitive bias. Integrated treatment refers to a broad-based model of community interactions, home visits, social-skills training and psycho-education for the family. Integrated psychological intervention is similar, but also incorporates elements of CBT and cognitive remediation therapy. ‡Listed are the tools used to determine inclusion. Several procedures have been devised for clinically assessing the prodrome and the risk of conversion, including CAARMS, SIPS and SOPS[35,40]. Numerous meta-analyses have shown a collectively significant reduction in transition to psychosis for interventions undertaken in CHR individuals, though note that the FACT and FFT studies were not analysed[34,35,110,111,123]. §700 mg per day eicosapentaenoic acid plus 480 mg per day docosahexaenoic acid. ‖Treatment group versus comparison groups. The statistical significance of any differences is described in brackets. ¶CHR compared to clinically low risk individuals were distinguished by SIPS scores which were over 7 or under 7, respectively[127].

trials of schizophrenia, adjunctive N-acetylcysteine improved negative symptoms, social functioning and deficits in mismatch negativity, facets that are characteristic of the prodrome[142,143]. Again, confirmation of efficacy is awaited. Nonetheless, using a neonatal ventro-hippocampal lesion (VHL) model, adolescent administration of N-acetylcysteine to rats blocked deficits in pre-pulse inhibition in adults; this action was reproduced by the anti-inflammatory and antioxidant agent ebeselen, underscoring the relevance of these aspects of the activity of N-acetylcysteine[144].

Antipsychotics and their potential mechanisms of action. Upon administration during adolescence, antipsychotics consistently blunt the adult hyperlocomotor response to amphetamine and the disruption of sensorimotor gating. Globally, similar findings have been made in mice and rats using VHL and pro-inflammatory developmental models for schizophrenia[145–151]. What is less clear is how the effects of antipsychotics are expressed. A role for D_2 receptor blockade is supported by clinical data suggesting that subcortical dopaminergic over-activity commences during adolescence (see above). Indeed, D_2 receptor stimulation in adolescent mice disrupts dendritic spine morphogenesis and has a long-term deleterious impact on cortico-hippocampal connectivity[152]. Furthermore, the Sandy mouse strain (which lacks the putative schizophrenia risk gene, dysbindin (*Dbndd1*)), has abnormally high cell-surface levels of D_2 receptors; sustained treatment of adolescent animals with eticlopride prevented both disruption of entorhinal cortex-hippocampal connectivity and impaired working memory in adults[152]. Nevertheless, the observation that low doses of risperidone prevent amphetamine supersensitivity in a rat VHL model suggests a role for its 5-hydroxytryptamine receptor 2A (5-HT_{2A})-antagonist properties, which are likewise implicated in blockade of the actions of phencyclidine (PCP) in rats[145,146,149,151,153]. In addition, 5-HT_{1A} agonism may be involved in the effects of aripiprazole (and clozapine), ostensibly through neuroprotective and/or neurorestorative actions[148,151,154].

Additional studies using a broader range of translatable measures are needed to clarify the clinical relevance of these experimental findings.

Antidepressants, anxiolytics and modulators of neuro-transmission. CHR individuals are frequently treated with antidepressants for the relief of anxiety or depression, and data from clinical audits are consistent with

Table 2 | Influence of pre-symptomatic interventions on adult emergence of behavioural and other deficits in schizophrenia models

Therapy (type)	Experimental model	Treatment regimen (duration)	Period of testing in adults	Major readouts and effects observed*	Comments	Refs
Omega-3 PUFAs (multi-modal and anti-inflammatory)	Treatment of young adult rats with 25 mg per kg per day ketamine on PND 46–52	0.8 g per kg per day on PND 30–45 or on PND 52 (2–3 weeks)	PND 52	Prevention of ketamine-induced: ↑Locomotor activity and deficit in PPI ↓Cognition (working memory) ↓Social interaction ↓Lipid and protein damage	• Omega-3 increased BDNF (mRNA) in plasma but not in the brain: relationship to behavioural actions unclear	132, 133
Celecoxib (COX2 inhibitor and anti-inflammatory agent)	Poly(l:C)‡ treatment of pregnant rats on GD 19	Offspring received 2.5 or 5 mg per kg per day on PND 35–46 (10 days)	PND 90	• Prevention of dizocilpine-induced hyperlocomotion	• Inflammatory state specifically related to a reduction in levels of the endogenous NMDA antagonist kynurenate	137
Minocycline (multi-modal and anti-inflammatory)	Neonatal ventral hippocampus injection of LPS in rats on PND 7	40 mg per kg per day on PND 42–56 (2 weeks)	PND 58–65	↓Deficits in social interaction, PPI and NOR. Reduction of microglial activation in ventral hippocampus and cortex	• Similar observations found with risperidone (see below). Microglial activation is an inflammatory response	139
N-acetylcysteine (anti-inflammatory and antioxidant)	Neonatal ventral hippocampus lesions in rats on PND 7–9	900 mg per L per day in drinking water (estimated dose 50 mg per kg per day) on PND 35–50 (2 weeks)	PND 61	↓Deficit in PPI provoked by apomorphine	• 45 days of treatment starting in juveniles on day 5 (through the dam until weaning at day 23) effective and also prevented neurochemical and electrophysiological deficits	144
Ebselen (antioxidant and glutathione peroxidase mimic)	Neonatal ventral hippocampus lesions in rats on PND 7–9	10 mg per kg per day on PND 35–50 (2 weeks)	PND 61	↓Deficit in PPI provoked by apomorphine	• Ebselen is devoid of the effects of N-acetylcysteine on the cysteine–glutamate transporter	144
Risperidone (antipsychotic)	Neonatal ventral hippocampus lesions in rats on PND 7	0.045 mg per kg per day on PND 35–56 (3 weeks)	PND 57	↓Amphetamine-induced hyperlocomotion	• 5-HT$_{2A}$ receptor blockade may be primary MOA • Higher dose of risperidone is less effective	146
Risperidone (antipsychotic)	Neonatal ventral hippocampus lesions in rats on PND 7	0.045 mg per kg per day on PND 35–100 (7 weeks)	PND 84	↓Open-field hyperlocomotion ↓Increase in 5-HT$_{2A}$ density in the hippocampus	• High dose. No effect on increase in 5-HT$_{2A}$ and D$_2$ receptor density in frontal cortex	149
Risperidone (antipsychotic)	Neonatal ventral hippocampus injection of LPS in rats on PND 7	0.05 mg per kg per day for two weeks on PND 42–56 (2 weeks)	PND 58–65	↓Deficits in social interaction, PPI and NOR. Reduction of microglial activation in ventral hippocampus and cortex	• Similar observations found with minocycline (see above). Microglial activation is an inflammatory response	139
Risperidone or paliperidone (antipsychotics)	Poly(l:C) treatment of pregnant rats on GD 14	Offspring received 0.045 mg per kg per day risperidone or 0.05 mg per kg per day paliperidone on PND 35–70 (5 weeks)	PND 90	↓Amphetamine-induced hyperlocomotion	• Effects of amphetamine at 1.0 mg per kg attenuated; only risperidone attenuated amphetamine at 5 mg per kg • Possible stabilization of dopaminergic transmission	147
Aripiprazole (antipsychotic)	Poly(l:C) treatment of pregnant rats on GD 14	Offspring received 0.66 mg per kg per day on PND 35–70 (5 weeks)	PND 90	↓Amphetamine-induced hyperlocomotion	• Amphetamine at 1 mg per kg attenuated; no influence on higher dose (5 mg per kg) • Possible role for 5-HT$_{1A}$ receptor agonism, and/or increased dopamine release in frontal cortex	148

Table 2 (cont.) | **Influence of pre-symptomatic interventions on adult emergence of behavioural and other deficits in schizophrenia models**

Therapy (type)	Experimental model	Treatment regimen (duration)	Start of testing in adults	Major readouts and effects observed*	Comments	Refs
Risperidone or clozapine (antipsychotics)	Poly(I:C) treatment of pregnant rats on GD 15	Offspring received 0.045–1.2 mg per kg per day risperidone or 7.5 mg per kg clozapine on PND 34–47 (2 weeks)	PND 120	↓Amphetamine-induced hyperlocomotion ↓Deficits in latent inhibition • Prevention of reduction in hippocampal size and of increase in lateral ventricle size (versus PND35)	• Risperidone and clozapine may act via 5-HT$_{2A}$ receptor blockade • High dose risperidone reduced basal locomotion in control rats • Adult administration less effective	145, 151
Clozapine (antipsychotic)	Poly(I:C) treatment of pregnant mice on GD 9	Offspring received 15 mg per kg per day on PND 35–70 (4 weeks)	PND 90	• Disruption of PPI and latent inhibition	• Well tolerated. No interference with behaviour of control groups	150
Haloperidol (antipsychotic)	Poly(I:C) treatment of pregnant mice on GD 9	Offspring received 3 mg per kg per day on PND 35–70 (4 weeks)	PND 90	↓Amphetamine-induced hyperlocomotion ↓MK801-induced hyperlocomotion ↓Disruption of latent inhibition	• Disruption of motor performance in control mice at active doses	150
Eticlopride (dopamine receptor D$_2$/D$_3$ antagonist)	Sandy mice bearing a mutation in the dysbindin gene	5 μg per ml per day in drinking water on PND 21–35 (2 weeks)	PND 56	• Prevents disruption of entorhinal cortex–CA1 hippocampus circuits • Blunts impairment of spatial working memory	• Deficits reflect perturbation of dendritic spines in adolescence that is due to over-expression of D$_2$ receptors • Adult (PND 60) administration ineffective	152
Fluoxetine (antidepressant and 5-HT re-uptake inhibitor)	Poly(I:C) treatment of pregnant mice on GD 9	Offspring received 20 mg per kg per day on PND 35–70 (4 weeks)	PND 90	↓Amphetamine-induced hyperlocomotion ↓Disruption of PPI	• Disruption of latent inhibition in control mice at active doses • Adult administration less effective	150
Fluoxetine (antidepressant and 5-HT re-uptake inhibitor)	Poly(I:C) treatment of pregnant rats on GD 14	Offspring received 10 mg per kg per day on PND 35–70 (4 weeks)	PND 90	↓Amphetamine-induced hyperlocomotion	• Amphetamine at 1 mg per kg. No effect on a higher dose (5 mg per kg) • Possible role for indirect 5-HT$_{1A}$ receptor activation of dopamine release in frontal cortex	148
Diazepam (anxiolytic and benzodiazepine)	MAM§ (20 mg per kg) treatment of pregnant rats on GD 15	Offspring received 5 mg per kg per day, on PND 31-40 (10 days)	PND 62–77 (motor) and 80–140 (electrophy)	↓Amphetamine-induced hyperlocomotion • Prevention of increases in spontaneous activity of dopaminergic neurons	• Anti-stress and anxiolytic properties in adolescence underlie preventive actions seen in adults	156
CDPPB (mGluR5 receptor positive allosteric modulator)	Neonatal treatment of rats with 10 mg per kg PCP on PND 7–11	10 mg per kg per day on PND 35–42 (1 week)	PND 56 and PND 91	• Prevention of deficits in social cognition (social novelty discrimination)	• Diverse mechanisms implicated (including neuroprotective and anti-inflammatory) • Adult (PND 56–63) administration ineffective	157
ADX47273 (mGluR5 receptor positive allosteric modulator)	Neonatal treatment of rats with 20 mg per kg per day PCP on PND 7–11	5 mg per kg per day on PND 28–35 (1 week)	PND 36	↓Disruption of PPI • Normalization of aberrant ion currents in GABAergic and pyramidal cells in frontal cortex	• Findings mirror those of REF. 157 using complementary readouts	158
SSR180711 (α7-nicotinic receptor partial agonist)	Neonatal treatment of rats with 20 mg per kg per day PCP on PND 7–11	5 mg per kg for 1 week, PND 28–35 (1 week)	PND 36	↓Disruption of PPI	• Possible role for receptor desensitization	158

Table 2 (cont.) | **Influence of pre-symptomatic interventions on adult emergence of behavioural and other deficits in schizophrenia models**

Therapy (type)	Experimental model	Treatment regimen (duration)	Start of testing in adults	Major readouts and effects observed*	Comments	Refs
FRAX486 (P21 kinase inhibitor)	*Disc1* knockdown (E14.5, by electroporation *in utero*)	30 mg per kg per day on PND 35–60 (3.5 weeks)	PND 60	• Prevention of further deterioration of dendritic spine loss between PND 35 and 60 • Attention of disrupted PPI	• Well tolerated. Although further hypotrophy of dendritic spines was impeded, a return to normal density was not achieved	161
Cerebrolysin (neurotrophic agent)	Neonatal ventral hippocampus lesion in rats on PND 7	1.075 g per day per rat on PND 30–60 (4 weeks)	PND 60	↓Amphetamine-induced hyperlocomotion and deficits in PPI ↓Cell loss in the PFC and dendritic hypotrophy in the PFC and nucleus accumbens ↓Increase in tyrosine hydroxylase levels in nucleus accumbens	• Possible role for induction of microtubule-associated protein 2, promotion of dendrite repair, suppression of neuroinflammation and/or reduced excitotoxicity	164
Valproic acid (antiepileptic and antibipolar; multiple MOAs, including HDAC inhibition)	MAM (22 mg per kg) treatment of pregnant rats on GD 17	200 mg per kg twice daily on PND 23–29 (1 week)	PND 70	↑Disruption of PPI ↓HDAC (protein) in PFC • No effect on reduction of acetylated H3K9	• Treatment of young adults (PND 63–69) also reduces disruption of PPI, but does not affect HDAC2	166
Valproic acid (antiepileptic and antibipolar; multiple MOAs, including HDAC inhibition)	*Disc-L100P* mutant mice	200 mg per kg per day on PND 50–60 (2 weeks)	PND 84	• Prevention of hyperactivity and deficits in PPI ↑mRNA encoding lipocalin 2 ↑Glia in subventricular zone	• Lipocalin 2 (secreted by astrocytes) regulates glial proliferation • Role of HDAC inhibition in effects of valproate are likely but not proven	165
Sodium butyrate (HDAC inhibitor)	Neonatal ventral hippocampus injection of LPS in rats on PND 7	20 mg per kg per day on PND 8–63 (7 weeks)	PND 64	↓Apomorphine-induced locomotion and disruption of associative learning • Prevention of lesion-induced increases in HDAC activity in frontal cortex	• Effects of early treatment prior to emergence of symptoms not reproduced upon 2-week treatment of adults prior to testing	168
Sodium butyrate (HDAC inhibitor)	Chronic administration of PCP (10 mg per kg per day) to young adult mice on PND 51–65	1 g per kg per day on PND 21–49 (4 weeks)	PND 50–74	• Prevention of hyperlocomotion, social behaviour deficits and impaired cognition (NOR) • Prevention of PCP-induced increase in HDAC activity (H3K9) in frontal cortex	• Suggests that epigenetic strategies may prevent the deleterious effect of environmental risk factors for schizophrenia. Very high dose of sodium butyrate	167
Environmental enrichment	Chronic administration of PCP (10 mg per kg per day) to young adult mice on PND 51–65	12 hours per day on PND 21–49 (4 weeks)	PND 50–74	• Similar behavioural and biochemical profile as sodium butyrate: study performed in parallel	• Social and physical environmental enrichment mimics sodium butyrate and presumably also acts through modulation of histone acetylation	167
Cognitive training	Neonatal ventral hippocampus lesion (PND 14) of rats	PND 35–36 or PND 36–37	Adult (age not specified)	• Normalization of aberrant inter-hippocampal synchrony and field potential oscillations • Improved control (focus on relevant information) in a cognitive task	• May act by favouring neuroplasticity and circuit reconfiguration during a crucial adolescent period of development	169

5-HT, 5-hydroxytryptamine; 5-HT$_{2A}$, 5-HT receptor 2A; BDNF, brain-derived neurotrophic factor; COX2, cyclooxygenase 2; GD, gestational day; HDAC, histone deacetylase; LPS, lipopolysaccharide; mGluR5, metabotropic glutamate receptor 5; MAM, methylazoxymethanol; MOA, mechanism of action; NMDA, *N*-methyl-D-aspartate; NOR, novel object recognition; PFC, prefrontal cortex; PND, postnatal day; poly(I:C), polyriboinosinic–polyribocytidylic acid; PUFA, poly-unsaturated fatty acids; PPI, pre-pulse inhibition. *Amphetamine-induced locomotion is a measure often used as a surrogate for positive symptoms and subcortical dopaminergic overdrive, but some studies have used other readouts. These experimental procedures are instructive for exploring potential course-altering effects of pre-diagnostic treatment, but there remains a need for additional readouts, notably measures related to negative symptoms. ‡Administration of poly(I:C) provokes maternal immune activation. §Administration of MAM disrupts prenatal neurogenesis.

(although not proof of) a decreased likelihood of developing psychosis[32,34,35]. Hence, it is of note that sustained treatment of poly(I:C)-exposed mice with fluoxetine during adolescence and young adulthood decreased both amphetamine hyperlocomotion and disruption of sensorimotor gating, and both indirect recruitment of 5-HT$_{1A}$ and modulation of neurosteroids may be involved[148,150]. However, caution is warranted as fluoxetine disrupted gating in the control group and failed to prevent increased sensitivity to dizocilpine. Another developmental model for schizophrenia, prenatal exposure to methylazoxymethanol acetate (MAM), a mitotoxin and disruptor of neurogenesis, is associated with anxiety[155]. The ability of peri-pubertal diazepam to prevent dopaminergic hyperactivity in adult animals was attributed to its stress-alleviating properties[156]. Further studies of antidepressant and anxiolytic agents appear justified in light of their extensive use in CHR individuals.

Positive allosteric modulators (PAMs) of metabotropic glutamate receptor 5 (mGluR5) and α7-nicotinic receptor possess pro-cognitive properties, attracting interest for symptomatic treatment of established schizophrenia[12]. Accordingly, mGluR5 PAMs, applied acutely, rescued impaired social cognition in adult rats neonatally exposed to PCP. Of greater significance, however, is that chronic administration of mGluR5 PAMs during adolescence prevented the appearance of cognitive deficits throughout adulthood, whereas adult administration was not effective, indicating that prevention was the underlying mechanism[157]. Several mechanisms are implicated in this prevention of cognitive deficits, including anti-inflammatory properties at microglia, recruitment of oligodendrocytes to reduce white matter fibre loss, induction of BDNF, and neuroprotective and anti-apoptotic properties[157]. These data are underpinned by another study in which treatment of adolescent rats with an mGluR5 PAM impeded the adult development of deficits in sensorimotor gating[158]. This action was mimicked by an α7-nicotinic receptor agonist that was proposed to act by a different mechanism, possibly involving receptor desensitization[158].

Modulation of intracellular protein networks and histone acetylation. The scaffolding hub protein, disrupted in schizophrenia (DISC1), is a genetic risk factor for psychosis and several other psychiatric disorders, with DISC1 mutant mice displaying developmental anomalies related to schizophrenia[131,159]. DISC1 is enriched postsynaptically at NMDA receptors, where it interacts with protein partners such as Kalirin 7 to control synaptic plasticity and dendritogenesis[160]. Although direct manipulation of DISC1 may not be feasible, targeting kalirin 7 — which is downregulated in schizophrenia — might counteract deficient synaptic plasticity[159,160]. Other DISC1 protein partners include RAC1 (a Rho-family GTPase). RAC1 modulates p21 kinase, and p21 kinase inhibition during adolescence prevented any further loss of dendritic spines in mice subjected to *Disc1*-knockdown at embryogenesis, possibly by blocking excess synaptic pruning (see below)[161]. These data resemble findings from mouse models of

fragile X syndrome, in which p21 kinase inhibition similarly rescued dendritic deficits[162], and suggest a way of preventing the structural anomalies underlying schizophrenia. Moreover, these results indicate how, through manipulation of interacting proteins, it may be possible to make the transition from anomalous molecular circuits in animal models to tractable targets for development of course-altering medication in CHR individuals.

A rather different approach to course alteration is represented by cerebrolysin, a neurotrophic cocktail under investigation for the treatment of stroke and vascular dementia[163]. When given during adolescence, cerebrolysin decreased the onset of structural, neurochemical and behavioural deficits in adult mice subjected to VHL during the postnatal period[164]. The mechanisms of action of cerebrolysin await further elucidation, and although it is unlikely to be pursued as a clinical option, these data are of interest in supporting the potential utility of neuroprotective interventions.

The ion channel and GABAergic modulator valproate is a candidate for potential clinical trials as, despite risks in pregnant females, it is well tolerated and used in young people as a mood stabilizer[26,33]. Valproate prevented the emergence of hyperlocomotor activity and sensorimotor gating deficits in a mutant DISC1 mouse line when given to young-adult mice, an action related to inhibition of excessive glial proliferation in the hippocampus[165]. Furthermore, valproate blocked the disruption of sensorimotor gating and induction of histone deacetylase 2 (HDAC2) in the above-mentioned mitotoxin model for schizophrenia[166]. Valproate is a pan-inhibitor of HDACs[26]. Although a role for HDAC inhibition in its actions remains to be formally demonstrated, adolescent administration of a more selective HDAC inhibitor, sodium butyrate[26], before chronic PCP treatment impeded the development of behavioural-cognitive deficits[167]. Sodium butyrate also prevented the appearance of cognitive impairment and dopaminergic hypersensitivity when given to adolescent rats that had sustained neonatal inflammatory damage to the hippocampus[168].

Behavioural and environmental interventions. Non-pharmacotherapeutic interventions can also be explored in rodent models. Intriguingly, the preventive effects of sodium butyrate were reproduced by environmental enrichment, consistent with a role for epigenetic mechanisms[167]. Although the therapeutic relevance of environmental enrichment is unclear, this is mechanistically interesting and globally supports the notion that non-pharmacotherapeutic interventions can change outcomes when applied early. Furthermore, mimicking CBT in CHR individuals, cognitive training of neonatal VHL rats during adolescence ameliorated both inter-hippocampal synchrony of field oscillations and cognitive control (the ability to prioritise relevant over irrelevant information) in a test of reversal learning that recruits the PFC[169]. The apparently course-altering effects of early cognitive intervention are, therefore, sustained well into adulthood.

Kalirin 7
A member of a family of brain-specific guanine-nucleotide exchange factors for RAC-like GTPases such as RAC1. Kalirin 7 is located in the postsynaptic density, where it interacts with the actin cytoskeleton to regulate the formation, maturation and stability of dendritic spines, and hence influence synaptic plasticity.

Synaptic pruning
Processes for developmental elimination of 'excess' synaptic connections that are especially prominent during adolescence. Axo-dendritic synapses not stabilized by neural activity in frontocortical, temporocortical and hippocampal regions are particularly affected. Appropriate synaptic pruning optimizes the operation of neural networks, whereas both excessive (schizophrenia) and defective (autism) pruning are deleterious.

REVIEWS

Graph theory
The mathematical analysis of networks of proteins, cells, brain regions or individuals in social groups. These elements are considered as 'nodes' connected by 'edges' (vectors). Brain organization is modular and non-random, incorporating features that enhance integration such as highly connected hubs and a short path length between nodes (a 'small world'). In schizophrenia, this organization is disrupted.

Frontocortical GABAergic interneurons
A subset of fast-firing (gamma frequency, 40–100 Hz), parvalbumin-positive basket (and chandelier) GABAergic interneurons in the prefrontal cortex that synchronises the activity of local, intra-cortical and cortico-subcortical networks of glutamatergic pyramidal neurons. Their dysfunction, which leads to a disruption of the excitation–inhibition balance, network synchrony, cognition and mood, is implicated in events leading to schizophrenia.

Extracellular matrix
Contains proteins such as astrocyte-derived chondroitin sulfate proteoglycans, hyaluronans, neuregulins and reelin. It fills the space between cells in the brain, including the synaptic cleft. 'Perineuronal nets' appear postnatally, are localized perisynaptically, and stabilize neural connections. Their developmental disruption has been related to abnormal plasticity and the genesis of schizophrenia.

The Na–K–Cl co-transporter
Transports Cl⁻ into neurons in the ratio of two Cl⁻ to one each of N⁺ and K⁺. Accumulation of excess Cl⁻ is prevented by extrusion through the K–Cl co-transporter KCC2. In early life, Na–K–Cl co-transporter levels are elevated versus KCC2 so internal Cl⁻ increases and GABA$_A$ receptors mediate depolarisation not hyperpolarisation. Owing to lack of a developmental switch, this may persist in autism and schizophrenia.

Collective preclinical evidence for effectiveness of pre-symptomatic interventions. In conclusion, there is a surprisingly diverse, convergent and robust body of data showing that early intervention in rodent models for schizophrenia can modify the appearance of symptoms in adults. Underlying mechanisms are unlikely to be unitary and only a limited number of agents have been examined. Nonetheless, these observations provide a promising platform for a broader experimental evaluation of novel strategies for altering the course to, and progression of, schizophrenia.

Novel strategies for course alteration

Network-based concepts: multiple hierarchies of intervention. Network thinking and, more specifically, graph theory provide a useful framework for studying the disruption of cerebral circuits in schizophrenia and for devising approaches for course alteration[36,84,170]. Indeed, schizophrenia is a disorder of disconnectivity that reflects progressive disruption of intra-neuronal and cerebral circuits rather than the loss or overactivity of any single cellular signal, neurotransmitter or brain region. Once disrupted, networks may phase-shift to an alternative steady state that is hard to reverse, underpinning the need to intervene as early as possible in the course of the disorder[30,84,170]. From a network perspective, interneurons such as fast-firing GABAergic basket and chandelier cells in the PFC can be considered the nodes (or the hubs, if they are crucial) with longer, inter-connecting projection neurons such as glutamatergic pyramidal cells considered the edges (vectors)[14,36,170–173]. For an individual neuron, the soma might be considered the node and its axon (and dendrites) the edges.

Disruption of either hubs or edges can provoke network failure, and both are legitimate targets for therapy. Although medication interacts with specific proteins rather than networks per se, pharmacotherapy can target specific hubs at many hierarchical levels to improve the operation of dysfunctional networks and hence reduce the risk of schizophrenia (FIG. 4). Drug associations, multi-target agents and non-pharmacotherapeutic interventions such as brain stimulation and psychosocial training may be particularly appropriate for protecting and restoring degraded neural networks[36,170] (FIG. 4).

Deregulated cortico-limbic GABA–glutamatergic circuits: the need for resynchronization. A highly consistent change in patients with schizophrenia and animal models for schizophrenia is a downregulation of fast-spiking frontocortical GABAergic interneurons that reciprocally interact with glutamatergic pathways[14,29,172,173]. The developmental perturbation of GABAergic interneurons is related to several factors, including NMDA receptor hypoactivity; abnormal regulation by astrocytes and neurotrophins (such as BDNF); disruption of the extracellular matrix; insufficient energy supply; and cell-autonomous anomalies[14,29,172–174]. Deregulation of GABAergic interneurons leads to an imbalance between excitatory and inhibitory neurotransmission, desynchronization of cortical and cortical–subcortical circuits, disruption of neural oscillations and gamma-band synchrony and impaired cognition

and mood[12,14,25,29,84,171–173]. Furthermore, perturbation of GABA–glutamatergic coupling in the PFC in turn disrupts subcortical circuits and dopaminergic transmission and is linked to the emergence of psychosis[29,84,88,153,171,172] (FIG. 4). In young CHR individuals, a reduced dynamic range of frontocortical GABA–glutamatergic networks may aggravate cognitive inflexibility, exaggerate sensitivity to stress and increase vulnerability to recreational drugs such as cannabis, which interfere with GABAergic transmission[84,171–173,175].

In view of these observations, the protection of GABAergic–glutamatergic circuits from disturbance, and their restoration following disruption, provides an instructive and integrative framework for the following discussion of potential course-altering mechanisms for schizophrenia.

Restoring normal patterns of GABAergic transmission. One potential strategy to restore normal patterns of GABAergic transmission is direct modulation of GABAergic signalling. Agonist-induced activation of GABA$_A$ receptor subunit α2 (GABA$_A$-α2) on pyramidal cells has been evaluated as an adjunct in chronically ill patients for improving cognition, but results were disappointing[12,14,172]. As discussed below, the network-resynchronization and course-alteration properties of an agent might prove more successful earlier in the disorder. Another possible strategy would be the use of pregnenolone. This neurosteroid acts as a PAM at NMDA receptors and is metabolized into allopregnenolone, a PAM at GABA$_A$ receptors. Supporting such a study, there are encouraging findings with adjunctive pregnenolone, including reduction of negative symptoms and improved functional outcome in newly diagnosed patients[8,176,177].

Recent work has unveiled some other, less familiar ways in which aberrant GABAergic transmission might be normalized to interrupt the path to psychosis.

The Na–K–Cl co-transporter (NKCC1), which is genetically linked to schizophrenia, is involved in expressing the postsynaptic effects of GABA$_A$ receptors, as well as neural circuit formation during brain maturation[178,179]. A developmental decrease in the ratio of NKCC1 to the K–Cl co-transporter explains the gradual transition from depolarizing to hyperpolarizing actions of GABA[178]. Conversely, an aberrantly high level of NKCC1 versus K-Cl co-transporters — together with anomalous *NKCC1* (also known as *SLC12A2*) splicing — is related to network anomalies of developmental disorders[178]. These findings suggest that early inhibition of NKCC1 may restore the balance between excitatory and inhibitory neurotransmission, promote network synchrony and interrupt the path to psychosis. Underpinning interest in modulation of NKCC1, the antagonist bumetanide improved facial processing in autistic children (3–11 years old)[180]. Furthermore, in an experimental model of autism, prenatal treatment of mother rats with bumetanide precluded the emergence of behavioural deficits in their offspring[181]. Although the ability of bumetanide to cross the blood–brain barrier is limited, more-brain-penetrant and more-selective ligands might be an option for preventive treatment of CHR patients[178]. One caveat is that most
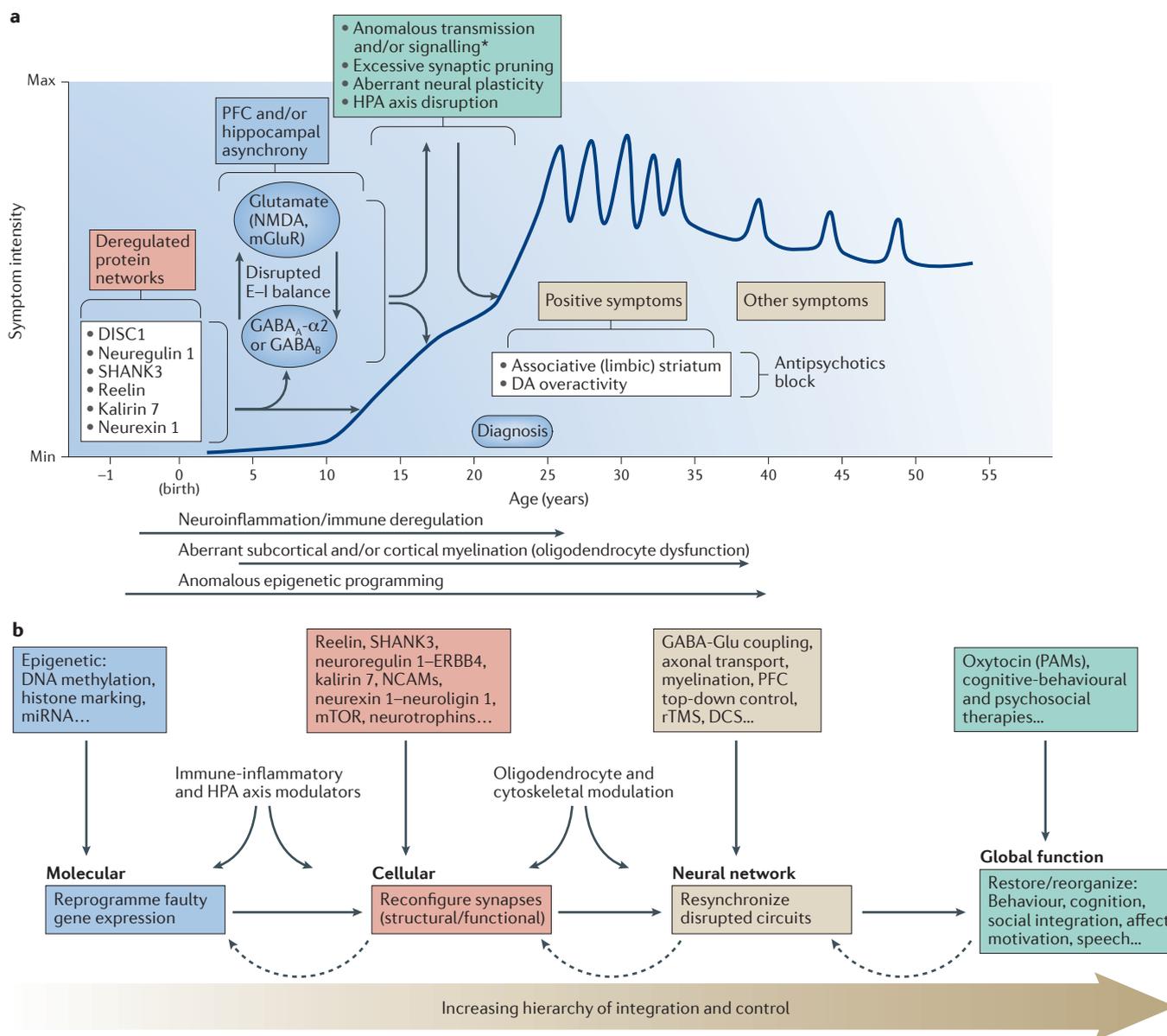
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Figure 4 | **Overview of core pathophysiological mechanisms implicated in the genesis of schizophrenia: potential targets for course-altering intervention. a** | Several potentially targetable mechanisms are implicated in the genesis of schizophrenia. The antipsychotic-sensitive hyperactivity of subcortical dopaminergic projections is a comparatively late repercussion of other (upstream) pathophysiological events, and the high-risk phase is characterized by several anomalies, such as enhanced cortisol secretion, perturbed activity of several classes of neurotransmitter and, probably, anomalous pruning of synapses. Anticipating such changes is a disruption of GABAergic–glutamatergic networks in corticolimbic regions, including a hypoactivity of N-methyl-D-aspartate (NMDA) receptors on GABAergic interneurons. Even earlier, cellular modulators of neural differentiation, migration and plasticity are deregulated. Finally, three other global mechanisms playing a part in the genesis of schizophrenia are indicated: neuroinflammation, epigenetic misprogramming and aberrant patterns of cortical myelination. **b** | Anomalies are apparent at several interacting levels of regulation, from molecules to cells to cerebral circuits to social networks. All present opportunities for intervention. Although drugs engage with molecular targets, they influence higher echelons of this hierarchy. G protein-coupled receptors and ion channels (not shown) are relevant at all levels. Epigenetic mechanisms exert a broad-based influence upon networks of proteins. Mitigation of 'stress' would have multifarious, beneficial effects in protecting circuits from disruption. Agents that normalise GABAergic interneuron activity should re-coordinate perturbed cortico-subcortical networks controlling mood and cognition. Protecting oligodendrocytes may reconfigure neural networks in which myelin has been damaged by inflammation or other insults. Axons themselves are disrupted in schizophrenia, and so promoting their structural and functional integrity would be of interest. Agents acting in the prefrontal cortex (PFC) to favour top-down control of neurocognition and social function could be effective, whereas cognitive-behavioural therapy and stimulation techniques engage widespread cortical circuits. Drug associations and multi-target drugs with complementary mechanisms of action may also be especially effective for network reconstitution and course-alteration. CRT; cognitive-remediation therapy; DA, dopamine; DCS, direct current stimulation; DISC1, disrupted in schizophrenia 1; E–I, excitatory–inhibitory; Glu, glutamate; HPA, hypothalamic–pituitary–adrenocorticotrophic; miRNA, microRNA; mGluR, metabolic Glu receptor; mTOR; mammalian target of rapamycin; NCAM, neural cell adhesion molecule; PAMs, positive allosteric modulators; rTMS, rapid transcranial magnetic stimulation; SHANK3, SH3 and multiple ankyrin repeat domains protein 3. *Signalling molecules include cannabinoids, serotonin, oxytocin and neurosteroids.

rodent studies of NKCC1 have been undertaken in early postnatal life. Nevertheless, bumetanide enhanced social cognition in adolescents and young adults with autism, supporting the relevance of NKCC1 to events occurring around the time of conversion to schizophrenia[182]. Furthermore, polymorphisms in *NKCC1* affect PFC function and cognition in adults with schizophrenia[179].

Like their GABA$_A$ receptor counterparts, pre- and postsynaptic GABA$_B$ receptors are involved in the establishment, operation and integration of cortical networks. Their actions are partially mediated through BDNF and include the control of neural migration, synaptogenesis and neurite growth[183]. Suggesting a link to schizophrenia, activation of GABA$_B$ receptors counters the imbalance between excitatory and inhibitory neurotransmission, the gamma-asynchrony and deficits in sensorimotor gating, cognition and behaviour seen in mice with genetic NMDA receptor hypofunction[184] and in rodents exposed to psychostimulants; these actions are expressed at least partly in the PFC[185]. In addition, the GABA$_B$ agonist arbaclofen improved social behaviour in children with fragile X syndrome[186]. Small-scale clinical trials of baclofen in established schizophrenia were unsuccessful, but GABA$_B$ receptor stimulation would justify evaluation in the CHR phase for reduction of transition.

Another potential target could be K$_v$3 potassium channels, which rapidly repolarize GABAergic interneurons following excitation. This action permits precise patterns of high-frequency firing, coordination of cortical networks and synchronization of gamma-oscillations in relation to goal-related behaviour and cognition[29,84,171,172]. K$_v$3.1b and K$_v$3.2 expression peaks during early development but persists through adolescence into adulthood, and levels of the former were decreased in the PFC of individuals with chronic schizophrenia[187]. This decrease was countered by antipsychotics[187]. Information on K$_v$3 channel levels in the brain is lacking for CHR individuals, but direct K$_v$3 ligands are an intriguing prospect for symptom relief and prevention of transition in CHR individuals. Indeed, K$_v$3 channel inducers alleviated cognitive and negative symptoms in a rodent, sub-chronic PCP model of schizophrenia in which K$_v$3 channel expression was reduced[188,189]. It would be important to determine whether K$_v$3 channel inducers, applied during adolescence, can impede the appearance of symptoms in animal models for schizophrenia.

There are also intracellular targets for the restoration of normal GABAergic transmission, including neuregulin 1 and its receptor tyrosine-protein kinase ERBB4, although such targets are challenging. Neuregulin 1–ERBB4 signalling has an important role in the differentiation and migration of cortical GABAergic interneurons and in other developmental processes such as axon myelination[29,159,190] (FIG. 4a). Moreover, neuregulin 1 is strongly linked to schizophrenia based on genetic association; changes in its levels in the brain (and lymphocytes) of people with schizophrenia; and the schizophrenia-like phenotype of its manipulation in rodents, including deletion solely in PFC populations of GABAergic interneurons where it is enriched[29,53,159,190]. Furthermore, neuregulin 1 overexpression in pyramidal

neurons triggers synaptic and behavioural anomalies that are relieved by extinction of its expression, suggesting that the effects of aberrant ERBB4 signalling and a schizophrenic phenotype might be reversible after emergence[191]. Finally, neuregulin 1–ERBB4 signalling recruits the DISC1 partner kalirin 7 to influence the plasticity and morphology of dendrites in interneurons[159,160,190].

However, neuregulin 1 illustrates the challenges of trying to therapeutically manipulate a cellular hub protein[159]. Early intervention to prevent abnormal neuronal migration is not yet feasible. Increases and decreases in neuregulin 1–ERBB4 signalling have been reported in schizophrenia, and both are deleterious in animal models, meaning that medication would need to be tightly regulated around a 'set point' (REF. 190). In addition, neuregulin 1 has multifarious (and partly sex-specific) actions across many cells types[159]. Finally, administration of neuregulin 1 to rodents is not consistently favourable: for example, early-life exposure results in persistent over-stimulation of mesolimbic dopaminergic transmission[190,192]. Thus, although the focused manipulation of neuregulin 1–ERBB4 signalling in GABAergic interneurons might be favourable, it would be hard to specifically realize as a strategy for course alteration.

One potential solution may be to target proteins downstream of neuregulin 1. Overexpression of an ERBB4 isoform (CYT1) in schizophrenia recruits the phosphoinositide 3-kinase (PI3K)–AKT signalling cascade[190,193]. Pharmacological inhibition of the p100δ subunit of PI3K countered anomalies in a VHL model of schizophrenia, and so study of these inhibitors before the emergence of symptoms is warranted[193].

Finally, it might be possible to act at inhibitory GABAergic synapses through the modulation of the risk gene neurexin 1 (*NRXN1*) in interaction with its postsynaptic partner, neuroligin 1 (NLGN1)[55,53,92].

Thus, there are several targets for manipulating GABAergic, glutamatergic and other modes of transmission through actions at intracellular networks disrupted in schizophrenia, but this currently remains challenging.

Epigenetic strategies for normalizing faulty neurodevelopment leading to schizophrenia. Anomalous control of gene transcription by DNA methylation and histone post-translational marking, together with aberrant regulation of mRNA translation by miRNAs, lie at the interface of genetic and environmental triggers for schizophrenia[25,26,194,195]. Disrupted epigenetic mechanisms may be inherited, provoked by *de novo* CNVs and mutations and/or triggered by diverse environmental events, ranging from perinatal infection to adolescent drug abuse, that increase the risk for schizophrenia[25,26,66,191,195,196]. Interestingly, the best-documented link between aberrant epigenetic mechanisms and the onset of schizophrenia has been found with GABAergic interneurons. Thus, hyper-methylation of DNA promoters and aberrant patterns of histone acetylation and/or methylation in PFC and hippocampal populations of GABAergic interneurons lead to reduced synthesis of GABA and reelin, together with concomitant downregulation of mGluR2 receptors and BDNF[25,26,196–198].

Reelin
A developmentally regulated glycoprotein that controls neuronal migration, corticogenesis and synaptic plasticity. Reelin is enriched in and secreted by GABAergic interneurons in adult prefrontal cortex where it is co-regulated with GABA by epigenetic mechanisms. It is a component of the extracellular matrix.

With regard to strategies for reviving GABAergic interneurons, reducing promoter hyper-methylation may be feasible by: interfering with DNA methyltransferases; inducing endogenous demethylases such as growth arrest and DNA damage-inducible protein-β (GADD45β); or using engineered constructs to mimic their activity and enhance demethylation. However, in all cases, safe and brain-penetrant agents will be required for clinical use[25,26,198,199]. More accessibly, GABA promoter demethylation can be elicited upstream using agonists at mGluR2s, which rekindle GABA, reelin and BDNF expression through induction of GADD45β[25,26]. Furthermore, nicotinic α2β4 agonists harness GABA synthesis by reducing the expression of DNA methyltransferases and disrupting repressive activity of the DNA-binding protein, MECP2 (REF. 25).

Approaches other than demethylation might also be used to revive genes repressed in GABAergic interneurons. By interfering with histone deacetylation (aberrant in schizophrenia), valproate re-activates GABA synthesis both directly and indirectly through the recruitment of mGluR2 receptors[25,26,200]. Although modulators of acetylation affect numerous genes, agents modifying histone methylation (which is similarly disrupted in schizophrenia) act at a more restricted set; these agents are well advanced in oncology and could be experimentally tested for GABAergic interneuron revival and course alteration in schizophrenia[26,201].

Another possibility to promote GABAergic transmission may be by targeting miRNAs, which fulfil diverse regulatory roles in neurodevelopment and interact with DNA and histone methylation. miRNAs are highly dynamic during puberty, are affected by risk factors ranging from CNVs to peri-natal inflammation to adolescent stress, and are deregulated in schizophrenia[26,194,202,203]. Interestingly, GABAergic interneurons possess a distinctive complement of miRNAs[204] and their activity is under the control of several miRNAs including miR-137 (genetically linked to schizophrenia), miR-132 (a controller of synaptic plasticity) and miR-34a (modulated by NMDA receptors) (see Supplementary information S3 (box))[26,194,203].

More broadly, epigenetic anomalies in schizophrenia are not restricted to GABAergic interneurons. For example, a suite of changes in miRNA expression affects many mediators, such as glutamate, D_2 receptors, kalirin–p21 kinase and ERBB4 (REFS 25,26,194,203,205) (see Supplementary information S3 (box)). Epigenetic medication for course alteration would be especially attractive as it acts at the network level to modulate entire clusters of proteins. Furthermore, such agents could have beneficial symptomatic effects on cognition and mood in CHR individuals[26]. The major focus is currently on better understanding of the functional roles of epigenetic mechanisms and harnessing them as biomarkers. For therapeutic exploitation, it will be necessary to establish which epigenetic factors drive (versus oppose or merely accompany) the pathophysiological processes leading to schizophrenia and to determine the optimal mode, timing and duration of therapy.

Promoting the connectivity of neural circuits. Although less well documented than GABAergic mechanisms, there are several other potential approaches for enhancing cerebral connectivity and hence reducing the risk of transition. One of these approaches focuses on cytoskeletal microtubules, as their disruption in schizophrenia perturbs the structural support of neurons, impedes axonal transport and compromises synaptic plasticity (see Supplementary information S4 (box)). Two further strategies are outlined below, and both are particularly relevant during the therapeutic window of adolescence and young adulthood.

The first strategy is targeting oligodendrocytes to counter aberrant patterns of myelination. In comparison to extensive subcortical myelination during childhood, intra-cortical and cortico-subcortical myelination intensifies during adolescence and young adulthood (that is, at the time of transition to psychosis)[206,207]. Myelin requires continuous renewal in the face of damage by trauma, nutritional deficits, hypoxia, stress and inflammation[206,208,209]. These are all risk factors for schizophrenia, and the white matter disruption seen before and following diagnosis of psychosis reflects both the impact of these factors and faulty oligodendrocyte-controlled programmes of myelination[206,208,209]. Cortical white matter (myelin) deficits and oligodendrocyte abnormalities have been related to the onset of network asynchrony, negative symptoms, hallucinations, impaired sensory processing, cognitive decline and perturbed dopaminergic and glutamatergic transmission[204,206,208,210,211].

Therefore, myelin and oligodendrocytes are potential targets for course-alerting therapy. It has been speculated that antipsychotics (possibly through the inhibition of glycogen synthase kinase 3β) exert transient neuroprotective properties for white matter[212]. Furthermore, the anti-inflammatory and antioxidant actions of pregnenolone, minocycline and omega-3 PUFAs (see above) have a trophic, neuroprotective influence on myelin[100,134–136,175,176] that might also benefit from neutralization of retroviruses (see below). Several other concepts are emerging for opposing the developmental deregulation of oligodendrocytes and myelination that accelerates the course to schizophrenia[206,213,214]. For example, valproate and lithium promote myelination and oligodendrocyte function[214,215], and the anti-parkinson agent benztropine exerts myelin-repairing activity by a mechanism involving M_1/M_3 muscarinic receptor antagonism[18]. In addition, the pro-myelination and neuroprotective G protein-coupled oestrogen receptor 1 (GPER1, also known as GPR30) is enriched in oligodendrocytes[216].

The second strategy is countering excessive synaptic pruning during adolescence. Corticolimbic synaptic density peaks in infancy at ~2–4 years and is followed by the pruning of superfluous synapses, a process occurring most intensely during adolescence and continuing until the third decade of life. Surviving synapses are stabilized and so network connectivity is globally improved[217,218]. There is evidence that synaptic pruning in the dorsolateral PFC and hippocampus is disproportionate in schizophrenia, which would aggravate the abnormal coupling of glutamatergic–GABAergic neurons and

compromise the operation of neural circuits[71,171,217–219]. For example, in interaction with kalirin–RAC, the actin-related protein 2 (ACTR2)–ACTR3 complex promotes actin polymerization and spine formation. Disruption of ACTR2–ACTR3 mirrors excess pruning, with a loss of synaptic contact on pyramidal cells leading to over-activity and, through a long-range projection to the ventrotegmental area, activation of mesolimbic dopaminergic pathways and psychosis[71]. Furthermore, together with reduced neuronal size, over-pruning may help to account for the reduction in cortico-hippocampal spine density and grey matter volume that anticipates and characterizes schizophrenia[71,76,77,217,219].

Several pathways that are disrupted in schizophrenia might provide therapeutically accessible opportunities to modify the aberrant synaptic pruning and spine dynamics thought to anticipate psychosis, including the DISC1–kalirin–RAC axis, neuregulin–ERBB4 and oestrogen signalling, BDNF and NMDA receptors (see above)[159,161,220–223]. Other opportunities might emerge from the role of cytokines in anomalous astrocytic and microglial sculpting of synapses[218,222], and, based on studies of defective synaptic pruning in autism, from mammalian target of rapamycin (mTOR)-regulated autophagy, which also controls pruning[223].

The latter observation underpins the relevance of pruning to developmental disorders in general and indicates that an optimal 'degree' of pruning (neither too much nor too little) is needed for normal development. However, as discussed elsewhere[217], any causal link between aberrant pruning and psychosis remains to be further confirmed, and evidence that normalization of pruning impedes appearance of psychosis in animal models for schizophrenia is awaited.

Countering neuro-inflammation, immune deregulation and the impact of infections. Genetic studies have found an association of schizophrenia with the major histocompatibility complex[224], and people with schizophrenia and CHR individuals display robust evidence for inflammatory and neuroimmune disruption (see above)[134,135,225]. Furthermore, bacterial or viral infection of the mother during pregnancy elicits an immune-inflammatory response (maternal immune activation) that deleteriously affects cerebral development of the fetus, and postnatal infection likewise compromises normal maturation of the brain[27,28,225]. Inflammation is linked to microglial release of pro-inflammatory cytokines such as IL-1β, IL-6 and tumour necrosis factor, as well as release of kynurenate (an NMDA and α7-nicotinic receptor antagonist). Collectively, these molecules exert deleterious effects on neurons, astrocytes and oligodendrocytes, leading to anomalous neural proliferation and/or differentiation, disrupted synaptic plasticity and myelin formation and, later in life, interference with GABA–glutamatergic networks[28,34,135,137,226]. Importantly, perinatal inflammatory events provoke long-lasting changes in immune status (such as an upregulation of IL-6 expression) that persist into young adulthood both in human patients and animal models for schizophrenia. These enduring changes render individuals more sensitive to second-wave risk factors such as stress, which likewise perturb immune function and unveil latent structuro-functional deficits[28,227–229]. Of particular interest, early-life immune disruption leads to abnormal PFC levels of inflammatory mediators and anomalous GABAergic transmission in adult mice[230].

Treatment could not realistically be instigated at the time of immune disruption or infection if these occur during pregnancy or infancy. Conversely, owing to the above-mentioned longer-term repercussions of perinatal infection — and to pro-inflammatory events in adolescence and young adulthood — interventions could be undertaken in CHR individuals. In fact, anti-inflammatory properties may well be implicated in the clinical influence of omega-3 PUFAs on conversion and in the preventive actions of omega-3 PUFAs, minocycline, N-acetylcysteine and celecoxib in animal models for schizophrenia[100,134,135] (TABLES 1,2). The latter agents and aspirin (which was similarly evaluated for efficacy as an adjunct in schizophrenia[135]) merit consideration for trials of course alteration. Another candidate would be the neurosteroid and GABA modulator, pregnenolone, which displays complementary anti-inflammatory properties[176,177]. These and other agents directly targeting anti-inflammatory mechanisms (for example, cytokine modulators) warrant experimental exploration in models of course alteration.

Another approach that could be explored is neutralizing retrovirus triggers of neuro-inflammation. One consequence of infection with bacteria and viruses (such as herpes virus 2) and parasites (such as *Toxoplasma gondii*) is the revival of dormant human endogenous retroviruses[231,232]. Neutralization of their pro-inflammatory protein envelopes by passive immunization is under investigation for the treatment of multiple sclerosis, and a comparable course-altering strategy might be applicable to schizophrenia[232] (see Supplementary information S5 (box)).

In addition, the intestinal microbiome is important for mental and physical health, and its disruption is related to anomalous neurodevelopmental processes leading to disorders such as autism and schizophrenia[28,233]. Various opportunities for course-altering intervention are presented by an interrelated suite of developmental anomalies triggered by early-life intestinal infection-inflammation: an abnormal gut microflora; structural damage to the gut; increased intestinal permeability; and excessive penetration of bacteria and their metabolites or toxins into the circulation[234,235]. Potentially benign ways of reducing the risk of psychosis include the use of pro-biotic, non-pathogenic bacteria such as bifidobacteria that affect central GABAergic transmission and of agents that prevent bacterial translocation to the circulation[201,234–236]. With regard to antimicrobial agents, it might be asked whether minocycline exerts its putative actions in schizophrenia at least partially through an effect on the gut microbiome. Nonetheless, it is unclear just how specific microbiotic interventions would be for reducing the risk of schizophrenia compared to a broader influence on mental and physical health[234]. Further rigorous experimental and clinical

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Human endogenous retroviruses
Viral elements within the genome that encode a protein envelope, reverse transcriptase and other proteins needed for replication. They are relics of ancient infections that survived by integration into the genome where multiple gene copies occur owing to amplification and re-infection. They comprise ~8–10% of the human genome, mostly in non-coding regions. Revival may trigger disorders like multiple sclerosis and, possibly, schizophrenia.

studies are required to confirm any causal relationship between an abnormal gut microbiome and pathophysiological changes that ultimately result in schizophrenia and to identify potential therapies for their control.

Protecting young CHR individuals from lifestyle and environmental risk factors. The transition to schizophrenia occurs at a time when the adolescent and young adult brain is undergoing a major structural and functional reorganization. More generally, the brain is enduring the onslaught of gender-specific hormones; facing increased energy demands; experiencing shifts in processes of decision-making, behavioural control and reward mechanisms; and confronting an increasingly complex social, cultural, cognitive and emotional environment[63,237,238]. Accordingly, the brain is especially vulnerable to disruption. However, rather than an inevitable or stochastic progression to schizophrenia, conversion is probably triggered by a new wave of risk factors, including a triad of mutually aggravating 'hits': poor resistance to psychological stress; social isolation; and excessive consumption of drugs of abuse, especially cannabis (see Supplementary information S6 (figure)). Although primary prevention (avoidance) and education are desirable, there is considerable interest in psychosocial, cognitive-behavioural and pharmacotherapeutic interventions to counteract these risk factors and decrease conversion (BOX 3).

Accelerating progress towards course alteration
Novel cellular models for probing pathophysiology and identifying new targets. A major challenge for developing course-altering medication is the limited understanding of cellular anomalies involved in transition. One way of addressing this would be to use induced pluripotent stem cells (iPSCs) for the characterization of perturbed developmental processes underlying schizophrenia; analysis of its genetic, cellular and molecular substrates; and identification of novel mechanisms for prevention and rescue[239,240]. iPSCs from people with schizophrenia and CHR individuals could be differentiated into networks of GABAergic, glutamatergic and/or dopaminergic neurons, permitting exploration of both intra- and intercellular communication and the identification of potential course-altering strategies[241]. Compared to monogenic diseases, iPSC models for schizophrenia present a major challenge, but considerable progress is now being made (BOX 4).

Optimizing the use of animal models for schizophrenia. Despite the availability of many well-characterized animal paradigms for studying schizophrenia, all have limitations and none has, as yet, been specifically designed to study course-alteration[131]. The important issue of which animal models, procedures and readouts are best adapted to this goal is considered in BOX 5.

Improved linking of experimental with clinical studies of course-altering therapies. To enhance the predictive validity of animal models, it would be instructive to integrate 'translational' measures that are exploitable in clinical investigations. To this end, current procedures for characterizing CHR individuals and monitoring treatment efficacy should be more systematically applied to studies of prevention in rodents. Endocrine, immune and biochemical readouts from the circulation are accessible, and quantification of GABAergic, glutamatergic and dopaminergic transmission, as well as MMN interrogation of sensory processing, is readily performable. Recent technical advances now make it feasible to analyse structuro-functional changes in small animals that trigger and signal the onset of psychosis — using grey and white matter imaging, fMRI studies of cerebral connectivity and EEG analyses of neural networks[242–244].

Mirroring work in animals[131,153], one promising translational approach in humans is the use of ketamine at sub-psychotic doses to mimic the perturbation of glutamatergic and GABAergic transmission seen before the FEP[245]. fMRI and cognitive testing can be undertaken in parallel, and this procedure would be useful for early clinical exploration of novel strategies for course alteration.

Biomarkers for tracking and predicting clinical efficacy of course-altering therapies. It is desirable to: first, link a risk factor to a pathophysiological mechanism favouring onset or progression of schizophrenia; second, identify a strategy for rectification; and third, develop biomarkers both for identifying individuals to treat and for predicting therapeutic efficacy of the intervention in question[33,52]. Such biomarkers should serve to track and predict medication efficacy from the inception of treatment, as a clinical reduction in transition might only become apparent years later. The goal is to find a surrogate biomarker that directly reflects the pathophysiological mechanism that is targeted by treatment, with changes coupled to and predictive of an eventual reduction of transition. Many procedures would be similar to those used to detect and stratify CHR individuals (FIG. 3b) but the details and application would differ. Furthermore, during medication, biomarkers should be coupled to measures of drug exposure and target engagement.

The NAPLS study of CHR individuals exemplifies the multi-pronged approach that can be used[48] and surrogate readouts of efficacy include (depending on the medication used): cortisol levels for drugs countering HPA axis overdrive, circulating levels of cytokines for anti-inflammatory agents, changes in lymphocyte patterns of histone marking for epigenetic modulators[26,190], and GABA and/or glutamate levels in PFC for therapies designed to re-coordinate GABA–glutamatergic networks[10,59,61,63,69]. More generalist strategies would be estimation of extracellular dopamine release and/or D_2 receptor occupation in striatum, MMN measures of neural processing and structural MRI of the ventricles and hippocampus[57,84,88,93]. As a general rule, it would be important to use multiple biomarkers at both the initiation of clinical trials and throughout their duration.

Finally, in tracking the efficacy of course-altering therapies, the influence of several variables not yet factored into clinical trials, such as age of onset, potential placebo effects of treatment, gender and cultural differences, also deserve consideration (see Supplementary information S7 (box))[246–248].

A hybrid concept: symptom relief coupled to a reduction of transition. Care of CHR individuals necessitates the relief of presenting symptoms — usually of greater concern to patients at consultation than an increased risk of transition. In principle, a separate treatment might be instituted to impede transition. However, control of symptoms in the CHR state may reduce the risk of progression to psychosis and other disorders, either by itself

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Box 3 | Protecting high-risk young individuals from transition to psychosis

Several factors that may provoke transition to psychosis in young individuals at clinically high risk could provide opportunities for intervention.

Improving resilience to stress. Deregulation of the hypothalamic–pituitary–adrenocorticotrophic (HPA) axis is associated with deleterious central actions of glucocorticoids and corticotropin-releasing factor (CRF). In addition to anxiety, depressed mood, cognitive deficits and drug-seeking behaviour, stress and HPA axis over-activity triggers neuronal changes characteristic of the clinically high-risk (CHR) state: perturbation of prefrontal cortex (PFC)–hippocampal circuits; reductions in brain volume and brain-derived neurotrophic factor (BDNF) secretion; anomalous synaptic pruning; excitotoxic damage to neurons; exacerbation of the impact of infection and inflammation; and increased responsiveness of subcortical dopaminergic pathways, especially in the associative striatum[63–66].

Glucocorticoid receptor antagonists have proved to be of limited efficacy in psychotic depression and questions of safety persist; hence, they are unlikely candidates for use in CHR individuals[66,277]. As for corticotropin-releasing factor 1 (CRF_1) receptors, together with vasopressin V_{1B} receptors, they synergistically contribute to stress-induced HPA axis overdrive and are incriminated in stress-related anxiety, depressed mood and cognitive impairment[250]. CRF_1 receptor antagonists and V_{1B} receptor antagonists had ambivalent efficacy in major depression and anxiety disorders[250,270]. Nonetheless, they are well tolerated and might be effective in CHR individuals both for interrupting the progression to psychosis and for alleviating stress-related symptoms. Stress-management variants of cognitive-behavioural therapy and psychosocial therapy may also be useful for decreasing the increased risk linked to stress[38,47,259].

Palliating recreational drug abuse and its consequences. Stress can provoke the relapse of drug-seeking behaviour, and CRF_1 antagonists remain candidates for controlling stress-induced rekindling of drug misuse: this action would contribute to a decrease in the risk of transition in CHR individuals[270]. The major drug consumed by the young is cannabis[51]. Its use may partially reflect self-medication for anxiety and social stress, which are common in CHR individuals. Cannabis intake may also compensate for the deficient cannabinoidergic signalling implicated in asociality[51,278]. However, prolonged recreational abuse of stronger formulations of cannabis from early adolescence can provoke subcortical dopamine release and psychosis when superimposed upon a vulnerable genetic or developmental background[51,270,279]. Long-term detrimental effects are also related to an interference with experience-dependent synaptic remodelling, GABAergic transmission, and neural synchrony in the PFC[175,280].

Protective psychotherapeutic and pharmacotherapeutic strategies to control cannabis consumption are of considerable interest[38,51,281]. In contrast to delta-tetrahydrocannabinol (the staple ingredient of cannabis), another constituent, cannabidiol, behaves as an antagonist at CB_1 receptors and it also acts at orphan G protein-coupled receptor 55 (GPR55) receptors: these actions are linked to a reduction of drug-seeking behaviour and, potentially, clinical alleviation of psychosis[51,279,282]. Cannabidiol is thus a candidate for trials in CHR individuals. Based on experimental data, neuropeptide Y receptor agonists, α_2-adrenoceptor partial agonists, dopamine D_3 receptor antagonists, neurokinin 1 (NK_1) receptor modulators and κ-opioid receptor antagonists all justify consideration for countering recreational and stress-induced drug-taking and hence for reducing the risk of conversion to schizophrenia[270,283–285].

Finally, long-term detrimental actions of cannabis might be opposed by pre-diagnostic administration of 5-hydroxytryptamine receptor 6 ($5-HT_6$) antagonists, which modulate GABAergic and glutamatergic transmission and prevent adult-onset of cognitive dysfunction in rats exposed to cannabis during adolescence[286] (P. Marin, unpublished observations). They seem to act by suppressing over-activation of mammalian target of rapamycin, a developmentally important controller of synaptic plasticity, although other mediators such as neural cell adhesion molecule may also be involved[286,287].

Promoting social integration and social cognition. Social isolation is a risk factor for conversion that reciprocally interacts with and exacerbates stress and drug abuse[288]. Furthermore, social isolation may partly be ascribed to impaired social cognition that itself aggravates or provokes positive symptoms (such as delusions and paranoia owing to false attribution) and negative symptoms (such as social withdrawal and apathy)[8,12,43,44] (see Supplementary information S8 (figure)).

Accordingly, an improvement of social cognition might promote social integration and reduce the progression to schizophrenia. Complementary to psychosocial training and other behavioural interventions, the most promising pro-social mechanism characterized so far is oxytocin[289]. Indeed, disruption of oxytocinergic transmission may contribute to social withdrawal, impaired social cognition and negative symptoms in schizophrenia[8,289,290]. Accordingly, oxytocin promotes social behaviour through actions in the nucleus accumbens, amygdala, PFC, insula and other structures[289,290]. Its intra-nasal administration favoured social cognition and social motivation in individuals with schizophrenia and also facilitated social skills therapy[249,291,292]. These data suggest that, by countering deficits in social cognition and motivation, oxytocin or small-molecule positive allosteric modulators at oxytocin receptors[290] may impede the progression of psychosis (see Supplementary information S8 (figure)). Note, however, that positive actions of oxytocin have not yet been demonstrated in CHR individuals, its actions may not be invariably favourable, gender differences have been described and long-term effects remain to be further characterized[293]. Although pharmacological control of social cognition is not well characterized in humans, a range of neuromodulators have been implicated in other species, including vasopressin V_{1A} receptors and D_3 receptors mentioned above[12,290]. As antagonists at D_3 receptors promote social cognition via actions mediated in the PFC, they might counter social isolation in CHR individuals and hence reduce the risk of conversion, a hypothesis justifying experimental exploration[251,294,295].

Box 4 | Stem-cell models for characterizing course-altering strategies

Induced pluripotent stem cells (iPSCs) can be generated using reprogramming factors from patient-derived somatic cells, such as keratinocytes and fibroblasts. iPSCs can subsequently be converted into different classes of cell, including GABAergic and dopaminergic neurons and pyramidal cells with a glutamatergic phenotype. iPSC-derived neurons display synaptic signalling, form networks and can integrate into neural circuits upon transplantation into the mouse brain[239–241,296,297]. Intriguingly, iPSC-derived neurons correspond more to immature neurons than to those in adult brain; this underscores their use for modelling (within a human genetic background) early developmental events that ultimately culminate in schizophrenia[240,296,297].

In fact, modelling diseases through iPSCs presents formidable challenges, including erasure of epigenetic signatures; inter-cell-line variability; genetic drift, mosaic single-nucleotide polymorphisms (SNPs) and copy number variants (CNVs); loss of phenotype; the difficulty of generating inhibitory GABAergic forebrain neurons (which have a more extended period of maturation); and differences between autonomous iPSC-derived networks *in vitro* and neurochemically diverse neuronal circuits in human brain[297]. Furthermore, compared to more tractable monogenic diseases, the utility of small-scale iPSC studies for modelling polygenic disorders with a strong epigenetic component might be questioned.

Nonetheless, progress is rapid and several studies have exploited iPSCs to gain insights into the pathophysiology of schizophrenia and to explore potentially novel medication[239–241,296,297]. In an early study, iPSCs from patients with schizophrenia were differentiated into neurons that displayed aberrant cAMP and WNT signalling as well as reduced neuritic extension — a phenotype partially reversed by the antipsychotic loxapine[239]. More recently, defective cytoskeletal remodelling and oxidative stress were reported in iPSC models, as well as deficient neurogenesis following the transformation of iPSCs into hippocampal-like cells[298,299]. iPSCs were reprogrammed from patients possessing a frame-shift mutation in disrupted in schizophrenia 1 (*DISC1*). These iPSCs revealed broad-based transcriptional deregulation, defective vesicular release and abnormal synaptic connectivity, a phenotype possibly caused by a dominant-negative effect of the mutant form of DISC1 (REF. 240).

Insights can also be gleaned using human iPSC cells bearing CNVs such as 15q11.2, a risk factor for schizophrenia[300]. Furthermore, the 22q13.3 CNV associated with Phelan–McDermid syndrome encompasses the schizophrenia risk gene *SHANK3* — deficient excitatory transmission in patient iPSC-derived neurons was restored by SHANK3 itself or by application of insulin-like growth factor 1, suggesting a novel therapeutic strategy[301]. Very recently, iPSCs were used to model idiopathic autism, revealing a developmental imbalance between inhibitory and excitatory circuitry that is reminiscent of schizophrenia but caused by exuberant production of GABAergic neurons[296].

Finally, a 3D organoid approach to iPSC differentiation seems to be more robust and reproducible than traditional 2D approaches: it allows for more advanced stages of cell differentiation, including production of glial cells, and hence an environment closer to that in the brain[302].

Insights into course-altering strategies for schizophrenia could also be gained — avoiding some of the caveats of iPSCs — by using other sources of cells from CHR individuals and patients[241]. Possibilities include neurons derived from the nasal olfactory epithelium of people with schizophrenia or CHR individuals, a 'window' to the brain, which have revealed a disorganization of microtubule networks and a disruption of signalling pathways controlling the cell cycle in these individuals[303]. Furthermore, olfactory neurons may permit the study of aberrant epigenetic mechanisms implicated in schizophrenia. These neurons have revealed both anomalous patterns of histone methylation[304] and an elevation in microRNA 382 (miR-382) levels linked to impaired fibroblast growth factor signalling, which is essential for normal brain development[305].

or perhaps causally (FIG. 5). Such a hybrid strategy would have advantages compared to pure disease-modification. First, alleviation of symptoms provides a functionally relevant, patient and/or regulator-valued readout of target engagement and potential course-altering efficacy before longer-term measures of transition, hence de-risking clinical trials of course-altering therapy[16,32,34]. Second, a single therapy for symptom control and course alteration would minimize poly-pharmacy. Third, interventions may similarly reduce conversion to other disorders such as bipolar depression[23,34]. Last, medication would not be considered an antipsychotic, improving acceptability.

In fact, as discussed above, omega-3 PUFAs and psychosocial/cognitive-behavioural interventions may both alleviate symptoms and reduce progression in CHR individuals, but it is unclear whether these actions are mechanistically linked. For novel strategies, counteracting the adolescent risk factors — psychosocial stress, drug-seeking and/or cannabis abuse, social isolation and impaired social cognition — is particularly attractive (BOX 3) (see Supplementary information S8 (figure)).

Pharmacotherapeutic strategies include the pro-social modulator oxytocin[249]; corticotropin-releasing factor 1 (CRF$_1$) receptor antagonists for relieving anxiety and moderating stress-induced relapse of drug-seeking behaviour[250]; and dopamine D$_3$ receptor antagonists for countering drug abuse and promoting cognition[251] (BOX 3). 5-HT$_{2A}$ receptor blockade may also be of interest as it is well tolerated, counters hallucinations and is implicated in the preventive actions of risperidone in rats[153,252]. As a final example, 5-HT$_{2C}$ receptor antagonism is associated with anxiolytic and antidepressant properties and increased frontocortical dopaminergic transmission, which may counter negative symptoms[8,253].

The most effective hybrid treatment for schizophrenia and related disorders may well be the judicious association of psychosocial/cognitive-behavioural strategies with appropriate pharmacotherapy.

Re-orienting agents evaluated in chronic schizophrenia for early course alteration. It could be valuable to re-evaluate certain classes of agent that are ineffective at treating the symptoms of chronic schizophrenia as

Box 5 | **Improving the use of animal models for studying course alteration**

Diverse animal models for schizophrenia. A persistent question concerning animal models for (rather than models of) schizophrenia is their validity in terms of construct, face and predictive ability. This issue has been comprehensively discussed elsewhere[130,153,306–308] so the following comments specifically focus on use of animal models for studies of course-altering strategies.

Although no dedicated paradigm has as yet been described, several developmental procedures used to test course-altering interventions (such as polyriboinosinic–polyribocytidylic acid (poly(I:C)), neonatal phencyclidine (PCP), ventrohippocampal lesion (VHL) and others; see TABLE 2) have been widely used for studies in adult animals, and these models have solid construct and face validity in terms of the pattern of pathophysiological and phenotypic changes seen[131,307,309] (see citations in TABLE 2). The pharmacological, sub-chronic PCP model is also well established and well recognized[153]. Conversely, the Sandy mouse is not a conventional model, and it is unclear to what extent disrupted in schizophrenia 1 (*DISC1*)-knockdown or mutations truly represent a model for schizophrenia.

Thus, despite the interest of findings using these paradigms (TABLE 2), studies could profitably be repeated using better-established developmental and pharmacological procedures. In fact, it would seem wise to confirm the actions of all putative course-altering interventions across several models. In a complementary manner, it would be instructive to directly compare several mechanisms of action in each model, as there is no 'standard' clinically established agent available for pharmacological validation.

Multi-hit models mimicking cumulative risk factors for schizophrenia. Multi-hit animal models are of special interest for characterizing course-altering therapies. They are of greater construct value than single-factor models and tend to provoke a broader range of impairment[306,309]. For example, a genetic or early-life environmental insult might sensitize for a subsequent adverse event during adolescence, such as neonatal PCP exposure followed by post-weaning isolation, adolescent cannabis in neuregulin 1 mutant mice, or a combination of poly(I:C) with a *DISC1* mutation[306,310,311]. Furthermore, adolescent stress unmasks latent immune hypersensitivity provoked by prenatal poly(I:C)[228].

Studying the immediate effect of interventions during adolescence. A lack of information on the actions of medication before adulthood in animal models for schizophrenia is one factor limiting their clinical testing for symptomatic relief and prevention of transition in clinically high-risk (CHR) individuals[34,268]. Study of drug effects during administration to adolescent rodents before onset of symptoms would also provide insights into their use for relief of distress in CHR individuals[312].

One instructive paradigm would be VHLs, in which cognitive impairment, social disruption and negative-like symptoms start to emerge during puberty and a mild hyperlocomotor response to amphetamine is already apparent[313]. Furthermore, structural and cellular anomalies begin to appear during adolescence in mice with a deletion of *Grin1*, the gene encoding *N*-methyl-D-aspartate receptor subunit NR1 (NMD-R1, also known as GluN1)[314], and adolescent spine loss — which worsens in adults — is seen in *Disc1*-knockdown mice[161].

In such models, the influence of pharmacotherapy upon behavioural symptoms and underlying biochemical–structural anomalies could be evaluated during adolescence and then through 'transition' into adulthood, and both longer-term course-altering and symptomatic actions could be characterized. It would also be interesting to characterize course-altering interventions that are applied immediately following the appearance of symptoms in adults, mirroring the evaluation of novel drugs after the FEP in patients.

Integration of a broader range of variables and readouts. Important variables to consider in future work on putative course-altering interventions are gender, age of testing and co-morbid symptoms such as depression[246–248] (see Supplementary information S7 (box)). Furthermore, there is a need to systematically incorporate measures of core pathophysiology such as GABAergic interneuron integrity, glutamatergic transmission, hippocampal volume and hypothalamic–pituitary–adrenocorticotrophic axis activity. Other translatable readouts of function, such as mismatch negativity, gamma oscillations and cognitive performance, would also be instructive, as would measures of negative symptoms and social processing, as very little information regarding these readouts is currently available[88,130,244,290,312–315].

course-altering therapies for CHR individuals. As discussed above, this option has already been evoked for anti-inflammatory agents, but there are several other intriguing possibilities.

The effects of GABA$_A$-α2 subunit agonists were disappointing in association with SGAs for amelioration of neurocognitive deficits in patients with chronic schizophrenia; however, when administered to CHR individuals, these agonists might reduce conversion (and improve symptoms) by resynchronizing cortico-subcortical glutamatergic circuits[14,29,171–173]. Recruitment of hypoactive NMDA receptors upstream of GABAergic interneurons by agonists and inhibitors of glycine reuptake has yielded varied results in schizophrenia, but the most compelling hints of efficacy were against negative symptoms,

which are present in the prodromal phase[8,9,10]. Hence, agents promoting the activity of NMDA receptors might be repositioned in CHR individuals. Supporting this idea, a 24-week pilot study[254] reported beneficial effects of glycine in CHR patients, but work on conversion remains to be undertaken. Intriguingly, D-serine rather than glycine gates dysfunctional NMDA receptors in the PFC[255], and D-serine improved negative symptoms in a controlled study of CHR individuals, with larger-scale studies that include measures of conversion anticipated[256]. D-amino-acid oxidase inhibitors for blocking D-serine metabolism would be another therapeutic option[257], as would drugs that block the generation of the endogenous NDMA antagonist kynurenate[10,134]. Levels of kynurenate are elevated by inflammatory states that
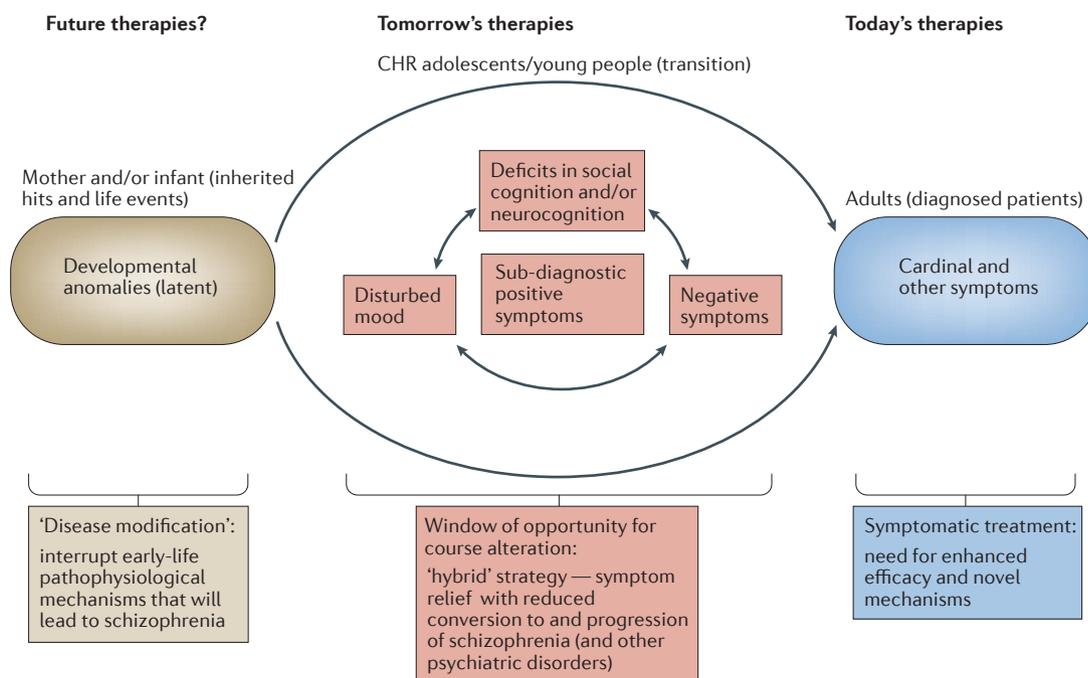
Figure 5 | Schematic representation of a 'hybrid' strategy as compared to other therapeutic approaches for treating schizophrenia and its genesis. Currently, we are limited to symptomatic control of schizophrenia. However, treatment needs to be improved, in particular with regard to resistant patients and symptoms other than positive symptoms (see Supplementary information S1 (figure)). Early-life 'disease-modifying' therapy to interrupt the path to schizophrenia presents formidable problems of validation, clinical development and safety. Accordingly, therapeutic exploitation is not yet a viable proposition. Nonetheless, one pragmatic strategy would be to target the pathophysiology and symptoms presented by young, clinically high-risk people seeking help. For example, palliating stress-induced hypothalamic–pituitary–adrenocorticotrophic (HPA) axis overdrive and promoting social cognition both alleviates symptoms and, at least partly as a consequence, may reduce the risk of conversion (see Supplementary information S8 (figure)). Inasmuch as certain pre-diagnostic symptoms and neurobiological substrates are not unique to schizophrenia, the transition to other psychiatric disorders may likewise be impeded. A dual, 'hybrid' strategy would have advantages in terms of developability and therapeutic utility over pure course-alteration. CHR, clinically high risk.

enhance the risk of schizophrenia[134,135]. Valproate is also of interest as an epigenetic regulator, despite a lack of evidence for efficacy in chronic schizophrenia[26].

There is, therefore, scope for re-orienting certain agents that were largely unsuccessful in chronic schizophrenia (usually as add-on therapies) to an earlier time-point in CHR individuals, when they may interrupt progress of the disorder and be of symptomatic benefit — either alone or in association with psychosocial/cognitive-behavioural therapies.

Evaluation of course-altering therapy after the first episode. Although the above discussion has focused on preventive interventions in CHR individuals, an alternative point for the administration of course-altering therapy is just after the FEP. In reality, some CHR individuals will already have had a 'pre-diagnostic' psychotic event (FIG. 3), and their treatment is urgent, as duration of untreated psychosis correlates with unfavourable short- and long-term outcomes, a lower chance of remission, more-severe symptoms and poor social integration[34,35,83,258]. In this sense, rapid intervention with antipsychotics might nominally be considered to be course altering[259]. However, evidence for their protective effects against

pathophysiological changes associated with psychosis is limited and of uncertain clinical relevance[154,212,260–264]. Moreover, in certain patients, decreases in brain volume may be aggravated by long-term exposure to high doses of antipsychotics[76,78].

Promoting recovery and course alteration with novel or existing therapies in the crucial phase after the FEP would certainly be cost effective[37]. One important study is RAISE (Recovery After Initial Schizophrenia Episode), which proposes a range of treatments, pharmacotherapeutic and otherwise, to enhance quality of life, patient function and long-term outcome. Whether this strategy directly engages with neural substrates underlying progression of schizophrenia is unclear, and the lack of a formal control group makes it hard to be sure of the specificity of treatment effects. Nonetheless, preliminary findings are promising, this study will be of considerable interest to follow, and it has led to enhanced government funding of early psychosis programmes[265–267].

In the use of course-altering agents after the FEP, there is no dilemma of whom to treat, unlike treatment of CHR individuals who may not convert. Full recovery — sustained functional and symptomatic remission — after the FEP is only seen in 10–15% of individuals, remission

RAISE
A National Institute of Mental Health initiative to alter the course and prognosis of the first episode of psychosis. A well-trained, multidisciplinary team offers up to two years of pharmacotherapeutic and psychosocial treatments together with family education, resiliency training and supported employment in a patient-centric and real-world fashion to improve function and promote recovery.

is often incomplete and relapse is common (up to 80% of individuals at 5 years post-FEP)[262,264]. Hence, delayed appearance of a second episode, reduced symptom intensity and recuperation of real-world function would be suggestive of course alteration if accompanied by structural and other biomarkers of normalized pathophysiology. Success would be favoured by well-tolerated medication with high adherence, as relapse after the FEP is coupled to non-compliance[263]. Substance abuse, negative symptoms and poor social functioning suggest a poor prognosis and, therefore, agents that also acted on these symptoms might, by analogy to hybrid CHR agents, particularly improve long-term outcome[8,38,263] (BOX 3).

On the downside, following the FEP, novel drugs may well have to be given with SGAs, and so differentiating genuine course alteration versus symptom relief would be difficult[263]. Moreover, once the threshold to psychosis has been transgressed, course alteration may be harder to achieve owing to a network phase-shift and more-pronounced structural and functional changes in the brain[170]. Finally, although adult rescue of behavioural deficits is under study for monogenic forms of autism, the duration of relief is uncertain and clinical proof is awaited[21,26].

For novel agents, one pragmatic strategy may be to perform an initial trial with patients in remission after a FEP and then to 'work backwards in time' to evaluate efficacy in earlier phases of the disorder, including prevention of conversion in CHR individuals. Dose reduction might also be progressively achieved by combining therapeutic agents with psychosocial/cognitive-behavioural treatments.

Collaborative ventures promoting discovery and development of course-altering therapies. Governments, regulators, academia, industry and national associations are collectively searching for solutions to complex and overarching socio-medical challenges, such as orphan diseases, epidemics and mental health disorders[52,268]. One example relevant to this discussion is the European Union Innovative Medicines Initiative 'NewMeds' — a programme for refining the translational tools needed to validate improved treatments for schizophrenia and depression[268]. Another initiative — PsyScan — is developing multi-modal strategies for more reliably predicting transition in individuals and is sufficiently well powered to deal with factors such as gender[52]. As preventive medicine and adolescent health are now high on the agenda, such programmes should accelerate progress towards course alteration for schizophrenia and other psychiatric disorders[1–4,17,40,268] (BOX 2). Furthermore, prophylactic medicine for cardiovascular and inflammatory disorders is widely accepted. Nevertheless, in light of costs to health services and the fact that CHR individuals do not yet have a psychotic diagnosis, it will be important to minimize risk and ensure the support of patients, carers, regulators and reimbursers for early interventions to prevent transition to schizophrenia or other psychiatric disorders (see Supplementary information S9 (box)). This support should be boosted by the fact that the majority of CHR individuals will have enduring

psychiatric problems (FIG. 4); the current focus on young people that are actively seeking help; and undertaking initial clinical studies of new drugs in patients who have just undergone a FEP (BOX 2).

Concluding comments

Sustained efforts to improve the symptomatic treatment of schizophrenia have yielded little major progress over the past 2–3 decades[268]. It is important that this work continues within a revised framework focusing on novel mechanisms of action and real-world measures of outcome (see Supplementary information S1 (figure)). However, driven by an improved understanding of the underlying pathophysiology, there is now scope for a complementary strategy that aims to alter the course to schizophrenia.

Much progress is being made in the identification of CHR individuals, and a substantial body of clinical and, predominantly, preclinical data suggest that pre-emptive interventions may interrupt (or at least delay) the emergence of a schizophrenia-like phenotype (TABLES 1,2). Evidence from clinical studies is of particular significance, although, as emphasized above, much work remains to confirm promising observations, increase the power and size of trials, take account of many complicating variables and expand studies to novel therapeutic mechanisms. The latter enterprise is being driven by cellular studies and work with rodent models for schizophrenia. Despite their limitations, a broad range of interventions administered during adolescence can reduce the appearance of schizophrenia-related anomalies in adult rodents. Certain treatments, such as those interacting with GABAergic transmission, inflammatory processes and the response to stress, have a solid conceptual and experimental foundation, whereas others, such as those targeting intracellular proteins, epigenetic marking and synaptic pruning, require further characterization. In any event, recent progress in the field is encouraging.

Hybrid strategies are particularly appealing for both relief of symptoms in CHR individuals and — partly as a consequence — reduction of transition and improved functional outcome. Challenges remain in terms of identifying whom to treat and when best to start treatment, with interventions after the FEP an option for drugs as yet untested in humans. Furthermore, only a handful of potential approaches have been clinically evaluated, and so the issue of how best to treat remains to be resolved. A one-size-fits-all unitary answer appears improbable, and the judicious combination of distinct modes of pharmacotherapy and psychosocial/cognitive-behavioural therapy appears the most likely route to success. Finally, a crucial issue is how to rapidly predict and demonstrate efficacy over a reasonable timescale in the course of clinical trials. These issues are under intense scrutiny and progress should be rapid over the coming years.

Thus, in addition to improved alleviation of the symptoms of schizophrenia, it may eventually become possible to target the underlying pathophysiology and delay, prevent or moderate its progress. In view of the huge personal and socio-economic burdens of schizophrenia and other psychoses, this would seem a worthy goal.

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