**EXPERT REVIEW**

The neurobiology and treatment of first-episode schizophrenia

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It is evident that once psychosis is present in patients with schizophrenia, the underlying biological process of the illness has already been ongoing for many years. At the time of diagnosis, patients with schizophrenia show decreased mean intracranial volume (ICV) as compared with healthy subjects. Since ICV is driven by brain growth, which reaches its maximum size at approximately 13 years of age, this finding suggests that brain development in patients with schizophrenia is stunted before that age. The smaller brain volume is expressed as decrements in both grey and white matter. After diagnosis, it is mainly the grey matter loss that progresses over time whereas white matter deficits are stable or may even improve over the course of the illness. To understand the possible causes of the brain changes in the first phase of schizophrenia, evidence from treatment studies, postmortem and neuroimaging investigations together with animal experiments needs to be incorporated. These data suggest that the pathophysiology of schizophrenia is multifactorial. Increased striatal dopamine synthesis is already evident before the time of diagnosis, starting during the at-risk mental state, and increases during the onset of frank psychosis. Cognitive impairment and negative symptoms may, in turn, result from other abnormalities, such as NMDA receptor hypofunction and low-grade inflammation of the brain. The latter two dysfunctions probably antedate increased dopamine synthesis by many years, reflecting the much earlier presence of cognitive and social dysfunction. Although correction of the hyperdopaminergic state with antipsychotic agents is generally effective in patients with a first-episode psychosis, the effects of treatments to correct NMDA receptor hypofunction or low-grade inflammation are (so far) rather modest at best. Improved efficacy of these interventions can be expected when they are applied at the onset of cognitive and social dysfunction, rather than at the onset of psychosis.

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**INTRODUCTION**

When does schizophrenia first manifest itself? Is it at the onset of the first psychosis? Is it at the first signs of psychosis, as in the group of patients referred to as ‘at-risk mental state’ (ARMS)? Or is it even earlier, and not primarily associated with psychosis, but with cognitive decline? This question is not only essential to address the biology of first-episode schizophrenia, but it is at the core of the schizophrenia concept itself.

We have argued that the first signs of schizophrenia already occur in early puberty with a (relative) decline in cognitive dysfunction. It is not until many years later, when psychotic symptoms occur during the ARMS, or more pronounced during the first psychosis itself, that the diagnosis becomes obvious. Thus, we would argue that first-episode schizophrenia is a misnomer, as the core of the illness, that is, the cognitive decline, may not be episodic. Nevertheless, almost all studies into the biology of the first stages of schizophrenia have focused on the psychotic symptoms to define the onset of the illness.

**BRAIN CHANGES AT THE TIME OF FIRST PSYCHOSIS**

It is evident that once psychosis is present in patients with schizophrenia, the underlying biological process of the illness has already been ongoing for many years. This conclusion can be based on the multitude of neuroimaging studies that we recently reviewed in a meta-analysis of over 18 000 subjects, including 771 medication-naive, recent onset patients. These data show a slight, but significant, decrease in intracranial volume in patients with schizophrenia (effect size –0.2), in chronic and recent onset, medication-naive patients. Intracranial volume is driven by brain growth, as it is the enlarging brain that determines the expansion of the skull. Therefore, brain development must be stunted in patients with schizophrenia before that time. From the same meta-analysis, it can be gleaned that there must be additional brain loss, or continued abnormal development, after the age of 13: total brain volume in never-treated patients is decreased to a larger degree (effect size –0.4) than is intracranial volume and this is due to decreases in both white and grey matter. Importantly, while grey matter loss is larger in chronic than in medication-naive patients, white matter volume is decreased to a similar extent in both groups. Indeed, longitudinal studies indicate that loss of white matter volume, while present at psychosis onset, does not progress further after psychosis has emerged. This is consistent with the finding in twin studies that decreased white matter volume in schizophrenia may be related more to the genetic risk to develop the illness than to the effects of illness itself. In contrast, grey matter volume loss (mainly expressed as reductions in cortical thickness) progresses further after the onset of psychosis, and is related to outcome,8 cannabis smoking,9 medication use10,11 and psychotic relapses. Thus, although some of the brain abnormalities in schizophrenia worsen after the onset of psychosis, abnormal development of the brain must have been ongoing for many years before the first psychosis—expressed, as it is, in decreased intracranial volume and even larger decreases in white and grey matter.

What is the nature of the white and grey matter changes that are present at the onset of the first psychosis? Using tract-based...
analysis of white matter fibres in medication-naive schizophrenia patients we, and others, have found differences in the uncinate and arcuate fasciculi, suggestive of axonal or glial damage and/or increased free water concentrations. In unmedicated first-episode psychosis (FEP) patients reduced fractional anisotropy, a measure reflecting white matter fibre density and myelination, is related to cognitive dysfunction. Pronounced fractional anisotropy reductions in medication-naive FEP patients appear to be predictive of poor response to subsequent antipsychotic treatment. While white matter decreases are not evenly dispersed throughout the brain, but instead are most pronounced in association fibres, such as the uncinate and arcuate fasciculi, changes in the grey matter are not uniformly distributed throughout the brain either. Most pronounced grey matter decreases in FEP patients are found in frontal and temporal areas, including the insula, superior temporal gyrus and the anterior cingulate gyrus. As indicated, following the FEP, most (but not all) longitudinal studies suggest that grey matter loss continues, which is most prominent in frontal and temporal areas, and results from cortical thinning (and not surface shrinkage) and is related to clinical and cognitive outcome. Only few studies have investigated white matter changes over time after the FEP. Two recent studies showed contrasting results with one demonstrating improvement of white matter decreases in FEP patients after antipsychotic treatment and the other showing worsening of these abnormalities. On postmortem examination, decreases in white matter are associated with a reduction in oligodendrocytes in the superior frontal cortex and in the bilateral hippocampus, suggesting dysfunction of oligodendrocytes to underlie white matter deficits in schizophrenia.

**BRAIN CHANGES BEFORE THE ONSET OF THE FIRST PSYCHOsis**

The ARMS is a prodromal phase of schizophrenia characterized by cognitive impairments, mood alterations, anxiety, attenuated psychotic symptoms and a decline in social and occupational functioning. Although the concept has been useful in understanding the development of schizophrenia, only a small percentage of patients with these symptoms eventually go on to develop the illness—and this percentage further declines as the number of studies increases. A recent review on neurobiological changes in ARMS subjects suggests that volumes of frontal and temporal areas are decreased in a similar fashion—but to a lesser extent—as observed in schizophrenia. Longitudinal studies are scarce, but those available suggest that grey matter deficits present in those subjects that go on to develop schizophrenia, worsen over time and are found mainly in fronto-temporal areas. Progressive reduction in the integrity of frontal white matter has also been reported in ARMS subjects who go on to develop schizophrenia. However, studies in the ARMS period are limited by the fact that the subjects studied are selected on the basis of the presence of mild and incomplete symptoms of psychosis and that outcome, that is, conversion to psychosis, is defined by psychosis as well. It has been argued that a focus on cognitive and negative symptoms in these ARMS subjects may be needed to understand the developmental biology of schizophrenia. Indeed, baseline cognitive functioning in ARMS subjects is an adequate predictor of poor outcome, regardless of transition to psychosis.

**POSSIBLE CAUSES AND EFFECTS OF THE BRAIN CHANGES**

To understand the possible causes of the brain changes in the first phase of schizophrenia, evidence from treatment studies, post-mortem and neuroimaging investigations together with animal experiments needs to be integrated. These studies suggest that schizophrenia is related to at least three interacting pathophysiological mechanisms: dopaminergic dysregulation, disturbed glutamatergic neurotransmission and increased proinflammatory status of the brain. These processes interact with each other and most likely have causal interrelationships.

**Dopamine dysregulation**

Since the discovery of the antipsychotic properties of chlorpromazine in the 1950s, increased dopamine (DA) turnover in the striatum has received much attention as an underlying mechanism of schizophrenia. Although initial studies focused on the postsynaptic DA receptor, more recent positron emission tomography (PET) studies, using (18)F-DOPA as a tracer, show that the major locus of dopaminergic dysfunction is presynaptic rather than postsynaptic in nature, characterized by elevated DA synthesis and release capacity. Increased (18)F-DOPA binding capacity is already present during the ARMS period and is found to be predictive of the further development into full clinical psychosis (see Table 1A for an overview of DA deviations in ARMS subjects). In medication-naive schizophrenia patients who experience an FEP, in the hypothesis is based on studies using NMDAr antagonists, such as ketamine and phencyclidine, which were found to induce the full range of schizophrenia symptoms, including psychosis, negative symptoms, and also cognitive dysfunction. Furthermore, patients with an autoimmune encephalitis producing antibodies against the NMDAr can have a clinical picture that is indistinguishable from schizophrenia. Finally, many of the well-known risk genes, such as DISC-1, dysbindin, SHANK and NRG-1, but also de novo mutations associated with schizophrenia influence glutamatergic neurotransmission.

During brain development the NMDAr has a crucial role in brain maturation by means of synaptic plasticity, which forms the basis for adequate development of higher cognitive functions, such as learning and memory (see Wang et al). NMDAr is a heterotetrameric structure with one obligatory NR1 and two variable NR2 subunits, determining its biophysical and pharmacological properties. During brain development, the subunit composition of this receptor undergoes a switch, in which some subunits are replaced by structurally different ones. The mature receptor composition has different physiological properties, rendering the receptor more suitable for optimal timing of firing, thereby enabling the swift integration of environmental stimuli. The timing of receptor switches differs per brain region, and may coincide with ‘risk windows’ for schizophrenia, that is, developmental phases when the individual is particularly vulnerable to environmental influences such as hypoxia, birth stress, infection or inflammation, drug abuse or social isolation. During pregnancy, fetal NMDAr
levels are increased, rendering the infants’ brain vulnerable to insults. It is conceivable, although largely hypothetical, that environmental risk factors for schizophrenia affect the brain by means of delaying or preventing adequate NMDAr switching in specific brain areas, and an incomplete receptor switch could be related to the onset of cognitive decline in the earliest phases of the illness. Imperfect expression of the mature NMDAr subunit profile is likely to impair the process of long-term depression and potentiation, by which frequently-used connections are strengthened and rarely-used connections are weakened. At early adolescence, pruning will eliminate the weak connections. When a lack of long-term depression and potentiation has resulted in a failure to differentiate the frequently-used from the rarely-used connections, pruning may become a random process, eliminating important as well as less-relevant connections.

Downstream from the glutamatergic neurons, decreased functioning of the NMDAr leads to hypofunction of the inhibitory GABA-ergic interneurons. Decreased functioning of these fast-spiking GABA-ergic interneurons hampers synchronisation of neuronal firing of the pyramidal neurons. Diminished synchronised neuronal activity leads—again—to impaired cognitive processing. Postmortem studies consistently demonstrate that a subpopulation of the GABA-ergic interneurons, the parvalbumin-containing chandelier cells, is decreased in patients with schizophrenia (for a review see Curley et al.57). Enzymes related to GABA-ergic neurotransmission, such as glutamic acid decarboxylase (GAD)67 and GABA transporter (GAT)1, are consistently reported to be decreased in patients with schizophrenia.57 A large postmortem study involving 240 controls of all age categories and 31 patients with schizophrenia observed that development and maturation in the prefrontal cortex and the hippocampus is characterized by progressive switches in expression from GAD25 to GAD67 and from NKCC1 to KCC2. The former switch leads to L-type calcium channel activation, and the latter leads to switching from excitatory to inhibitory neurotransmission. In the hippocampus, GAD25/GAD67 and NKCC1/KCC2 ratios are increased in patients with schizophrenia, reflecting a potentially immature GABA physiology. This deviation was associated with the risk allele at the promoter region of the GAD-1 gene.58

It remains unclear whether deviations in the GABA-ergic interneurons are secondary to deficits in NMDAr-mediated signalling, or if abnormal NMDAr signalling is compensatory to GABA-ergic aberrations. Either way, hypofunction of the NMDAr and reduced neural synchrony caused by decreased function of the GABA-ergic interneurons may be the converging mechanisms underlying cognitive dysfunction, which—as indicated—starts at least 10 years before the onset of psychotic symptoms1 and remains relatively stable after the FEP, as a 10-year follow-up study of FEP patients showed no clear signs of deterioration as compared with healthy controls. Murine studies show that glutamatergic afferents from the hippocampus to the nucleus accumbens exert a strong excitatory effect on striatal DA neurons, influencing both activity and firing properties of the dopaminergic neurons. Thus, decreased activation of the NMDAr leads to an increase in striatal DA release and induce psychotic symptoms. This finding provides a biological explanation of the clinical and epidemiological observations that cognitive changes precede the onset of psychosis by many years. One of the few available techniques to examine the status of the NMDA/glutamate system in the human brain is the use of magnetic resonance spectroscopy (MRS). This method provides concentrations of several molecules, including glutamate, glutamine and GABA. However, glutamate as measured with MRS does not reflect intrasynaptic glutamate levels, as the MRS signal is derived from glutamate in neurons, blood vessels, white matter, and so on. When glutamate is released into the synapse it is quickly metabolized into the inert glutamine, which may be a better reflection of intrasynaptic glutamate levels and hence of NMDAr hypofunction. Indeed, Rowland et al. found increased glutamine as measured with MRS after infusion of ketamine in healthy subjects. Moreover, with magnetic resonance imaging scanners at a magnetic field strength lower than 4 Tesla, it is difficult to disentangle the peaks from glutamate and glutamine; most studies therefore provide a value of ‘glx’, which is composed of both glutamate and glutamine. Results in schizophrenia suggest that glx concentrations are different for each stage of the illness.

Table 1A. Dopamine in ultra-high-risk subjects

| Study                | Technique and ligand | Sample size | Main finding                                      |
|----------------------|----------------------|-------------|--------------------------------------------------|
| Allen et al.155      | PET (18)F-DOPA       | 16 UHR-nt   | Striatal DA synthesis capacity all UHR = HC, but |
| Bloemen et al.156    | (123)I-BZM SPECT     | 5 UHR-t, 5 HC| increased in UHRt                               |
| Egerton et al.157    | PET (18)F-DOPA       | 14 UHR     | Postsynaptic DA: UHR = HC baseline and after DA  |
| Fusar-Poli et al.158 | PET (18)F-DOPA       | 15 HC       | depletion                                         |
| Fusar-Poli et al.159 | PET (18)F-DOPA       | 26 UHR     | Striatal DA synthesis capacity UHR > HC          |
| Hirvonen et al.160   | (((11)C)-labelled raclopride PET | 20 UHR, 14 HC | Striatal DA synthesis capacity UHR > HC          |
| Howes et al.161      | PET (18)F-DOPA       | 24 UHR* 7 SCZ, 12 HC | Striatal DA synthesis capacity UHR > HC           |
| Howes et al.162      | PET (18)F-DOPA       | 20 UHR* scanned twice | Schiz > HC (ES 1.25) in 8 converters |
| Howes et al.163      | PET (18)F-DOPA       | 30 UHR* 29 HC | Striatal DA synthesis capacity UHR > HC, converters |
| Sundjaj et al.164    | PET (11C)(+-)-PHNO   | 13 CHR, 13 FEP | No difference in non-displaceable DA2/D3 binding potential |

Abbreviations: CHR, clinical high risk; DA, dopamine; ES, effect size; FEP, first-episode psychosis; PET, positron emission tomography; Schiz, patients with schizophrenia; UHR-nt, non-transition; UHR-t, transition to psychosis; UHRS, ultra-high-risk subjects. *Samples overlap.
Although results in ARMS subjects are not consistent, the majority of studies show increased glx, whereas a few report decreased or normal values (see Table 2A). Studies differentiating between glutamate and glutamine generally report increased levels of both molecules. In medication-naive FEP patients, studies generally report increased glx concentrations (composed of increased glutamate and increased glutamine) as compared with healthy controls, whereas in medicated FEP patients, glx levels are reported to be normal (Table 2B). In the later phases of schizophrenia, glx values appear slightly but

| Study                          | Technique and ligand       | Sample size | Main finding                                      |
|--------------------------------|----------------------------|-------------|--------------------------------------------------|
| Abi-Dargham et al.163          | [11C]NNC 112 PET           | 16 SCZ of whom 7 FEP; 16 HC | D1r bp DL-PFC patients > HC                      |
| Abi-Dargham et al.164          | [11C]NNC 112 PET           | 30 FEP 15 HC | DAT FEP < HC                                     |
| Buchsbaum et al.165            | (18)F-fallypride PET       | 15 FEP      | bp FEP < HC                                      |
| Corripio et al.166             | [123I]IB2M SPECT           | 18 FEP      | D2r bp FEP > HC                                 |
| Corripio et al.167             | [123I]IB2M SPECT           | 37 FEP      | D2r striatal/frontal ratios                      |
| Glenthoj et al.168             | [123I]IB2M SPECT           | 18 HC       | FEP > HC in those with SCZ                      |
| Graff-Guerrerro et al.169      | [(11)C]-(+)-PHNO PET       | 13 FEP      | Non-displaceable D2/D3 bp                       |
| Graff-Guerrerro et al.170      | [(11)C]-(+)-PHNO PET       | 13 FEP      | D2/D3 bp FEP = HC                               |
| Hietala et al.171              | [18F]-DOPA PET             | 7 FEP       | Striatal DA synthesis capacity FEP > HC         |
| Hietala et al.172              | [18F]-DOPA PET             | 10 FEP      | Striatal DA synthesis capacity FEP > HC         |
| Hsiao et al.173                | [99mTc]TRODAT SPECT        | 12 FEP      | DAT FEP = HC                                    |
| Karlsson et al.174             | [(11)C]SCH 23390 PET       | 10 FEP      | D1r bp FEP = HC                                 |
| Laakso et al.175               | [18F]CFT PET               | 9 FEP       | DAT FEP = HC                                    |
| Lavalaye et al.176             | [123I]FP-CIT SPECT         | 36 SCZ of whom 10 FEP; 12 HC | DAT FEP = HC          |
| Lehrer et al.177               | (18)F-fallypride PET       | 33 SCZ of whom 14 FEP; 12 HC | bp medial thalamus SCZ < HC (ES = 0.89)          |
| Lindstrom et al.178            | [(11)C]-DOPA PET           | 12 SCZ of whom 10 FEP; 10 HC | Striatal DA synthesis capacity FEP > HC         |
| Mateos et al.179               | [123I]FP-CIT SPECT         | 20 FEP      | DAT FEP < HC                                    |
| Mateos et al.180               | [123I]FP-CIT SPECT         | 30 FEP      | DAT FEP < HC                                    |
| Mateos et al.181               | [123I]FP-CIT SPECT         | 20 FEP      | DAT FEP = HC                                    |
| Nozaki et al.182               | [11C]-DOPA PET             | 18 SCZ of whom 14 FEP; 12 HC | bp FEP > HC                                    |
| Safont et al.183               | [123I]-IB2M SPECT          | 37 FEP      | D2r bp                                      |
| Schmitt et al.184              | ([99mTc]TRODAT-1 SPECT     | 18 HC       | D2r bp = HC                                    |
| Schmitt et al.185              | ([99mTc]TRODAT-1 SPECT     | 10 FEP      | DAT FEP = HC                                    |
| Schmitt et al.186              | [99mTc]TRODAT-1 and [123I]IB2M SPECT | 20 FEP | DAT FEP = HC                                    |
| Schmitt et al.187              | [123I]IB2M SPECT           | 12 FEP      | D2r bp FEP = HC                                 |
| Schmitt et al.188              | [99mTc]TRODAT-1 and [123I]IB2M SPECT | 12 FEP | D2r bp FEP < HC                                 |
| Talvik et al.189               | [11C]FLB 457 PET           | 9 FEP       | D2r bp FEP = HC                                 |
| Talvik et al.190               | [(11)C]raclopride PET      | 8 HC        | D2r bp FEP = HC                                 |
| Yang et al.191                 | [99mTc]TRODAT SPECTand     | 12 HC       | DAT FEP = HC                                    |
| Yasuno et al.192               | [(123I)]IB2M SPECT         | 12 HC       | D2r bp FEP = HC                                 |

Abbreviations: bp, binding potential; D1r, dopamine D1 receptor; D2r, dopamine D2 receptor; DAT, striatal dopamine transporter; ES, effect size; FEP, first-episode psychosis; PET, positron emission tomography; SCZ, schizophrenia. *Samples overlap.
significantly decreased, which is the result of decreased glutamate and increased glutamine levels, leading to an increased glutamine-to-glutamate ratio.80,81 The decreased glx levels in chronically medicated patients are most pronounced in the frontal areas and correlate with cognitive deficits.80 GABA levels have been measured less extensively but the few available reports generally indicate decreased GABA levels in medicated FEP as well as in chronic patients, and these are correlated with cognitive dysfunction,82,83 but see Tayoshi et al.84 Detailed information on GABA levels in ARMS subjects and in unmedicated FEP patients is as yet unavailable.

Increased proinflammatory status

The third mechanism that may underlie (some of the) the signs and symptoms of schizophrenia is an increased proinflammatory status of the brain, a hypothesis proposed many years ago, for example, by Stevens,85 who observed signs of low-grade inflammation in postmortem brains of patients with schizophrenia. Interest in inflammation as a possible aetiology of schizophrenia has been bolstered by the simultaneous publication of three genome-wide association studies in 2009 providing compelling evidence for the involvement of the MHC region in the susceptibility of schizophrenia.86–88 MHC class I molecules could also operate through direct effects on brain development as these molecules regulate many aspects of brain development, including neurite outgrowth, synapse formation and function, homeostatic plasticity and activity-dependent synaptic refinement.89–91 However, epidemiological studies consistently show that the risk for schizophrenia is increased following pre and perinatal infections.92 A subset of patients initially diagnosed with schizophrenia is known to suffer from autoimmune encephalitis. A recent study demonstrated anti-NMDAR antibodies in almost 10% patients with schizophrenia as compared with 0.4% in controls,94 but replication of this finding is needed. However, neuroinflammation probably has a role in a larger group of patients, not just in those who can be characterized as suffering from an autoimmune encephalitis. The immature brain can be exposed to inflammation associated with viral or bacterial infection or as a result of sterile brain insults. Microglia are the main immuno-competent cells in the immature brain, and depending on the stimulus, molecular context and timing, these cells will acquire various phenotypes, which are critical regarding the consequences of inflammation.95 Acute inflammation can shift to a chronic inflammatory state and adversely affect brain development.

Support for the putatively increased activation of microglia cells is provided by two studies using 11C-PK11195 PET, reporting increased activation of microglia cells especially in the temporal lobes in patients with early-stage schizophrenia as compared with controls.96,97 A third PET study using another tracer (11C-DAA1106)98 found no differences between schizophrenia patients and controls. Specificity of both tracers for microglia activation is under discussion, however.99 A possible explanation for the difference is that the latter PET study included chronic patients and increased neuroinflammation may be present only in the first years of the disease. If this would be the case, then postmortem studies—usually including only chronic patients—would not be expected to find signs of increased inflammation. However, although results are inconsistent, many postmortem studies, in fact, do report increased numbers of microglia cells in activated states.100 Table 3 provides a summary of these findings. Only one postmortem study analysed brain tissue of patients with long and short duration of illness101 and, surprisingly, reported strongest indications of increased inflammation in the later stages of the illness. Postmortem literature, which mainly describes the late

| Study                      | Technique and area | Sample size | Main finding                      |
|----------------------------|-------------------|-------------|----------------------------------|
| Bloemen et al.193          | 1H-MRS hippocampus| 11 UHR      | glu UHR < HC (ES = 0.22)         |
| De la Fuente-Sandoval et al.68 | 1H-MRS dorsal-caudate cerebellum | 18 UHR 18 medication-naive FEP | Dorsal-caudate glu: UHR = FEP > HC cerebellar glu: UHR = FEP = HC |
| De la Fuente-Sandoval et al.67 | 1H-MRS dorsal-caudate nucleus | 19 UHR 19 medication-naive FEP | glu UHR-t > UHR-nt (7 UHR-t) UHR-ts > HC (ES = 1.39) |
| Fusar-Poli et al.194       | 1H-MRS thalamus, ACC, hippocampus | 24 UHR 24 medication-naive FEP | glu thalamus UHR < HC |
| Keshavan et al.65          | 1H-MRS frontal, occipital, temporal, parietal, basal | 40 GHR | Inferior parietal/occipital region glx GHR > HC |
| Natsubori et al.72         | 1H-MRS medial prefrontal | 24 UHR, 24 medication-naive FEP | gtx UHR = HC |
| Purdon et al.195           | 1H-MRS medial frontal | 15 GHR | gtx UHR = HC, but more variability in glx in GHR |
| Stone et al.69             | 1H-MRS, thalamus ACC, hippocampus | 14 HC | glu thalamus UHR < HC |
| Tandon et al.68            | 1H-MRS thalamus caudate ACC | 23 GHR | glx thalamus and caudate GHR > HC, ACC glx |
| Tibbo et al.64             | 1H-MRS right medial frontal | 24 HC | HR = HC |
| Valli et al.196            | 1H-MRS medial temporal, ACC, thalamus | 22 UHR | glu UHR = HC (trend in thalamus: UHR < HC) |
| Yoo et al.71               | 1H-MRS ACC, DLPFC, thalamus | 22 GHR | glu HC = HC |

Abbreviations: ACC, anterior cingulate gyrus; ES, effect size; FEP, first-episode psychosis; GHR, genetic high risk; gln, glutamine; glu, glutamate; glx, glutamate +glutamine; MRS, magnetic resonance spectroscopy; UHR, ultra-high-risk subjects, UHR-nt, non-transition; UHR-t, transition to psychosis. *Samples overlap.
stages of schizophrenia, may therefore not be representative for the presence (or absence) of increased proinflammatory status of the brain in patients with an FEP. Information on a potential proinflammatory status in FEP patients can be retrieved from peripheral blood markers, which so far show that deviations in pro and anti-inflammatory factors are of the same magnitude in FEP patients as in chronic patients with acute exacerbations.\(^{102}\)

When microglial cells become activated, they abandon their neurotrophic functions (for example, axon guidance and the production of neurotrophins such as BDNF), which leave the neurons in suboptimal condition.\(^{103}\) In addition, activated microglia produce several neurotoxic substances, such as free radicals and proinflammatory cytokines that can damage neuronal and glial cells, leading to cognitive dysfunction and brain volume loss.\(^{100}\) Neuroinflammation and NMDAr dysfunction are intertwined in several ways. For example, activated microglial cells produce high levels of glutamate, whereas NMDAr activity is required for the expression of antioxidant enzymes\(^{104}\) necessary to compensate the toxic effects of microglial activation. Furthermore, deviant brain development and subsequent cognitive alterations in adulthood may be mediated by cytokines, especially by IL-6 induction during infection.\(^{105}\) Activation of the IL-6/Nox2 pathway and consequent increase in superoxide production in the brain can also induce a loss of parvalbumin-containing interneurons in adulthood.\(^{106}\) The increased glutamate levels observed with MRS in the ARMS and early FEP period may thus result from activated microglial cells rather than from NMDAr hypofunction. The increased proinflammatory status can also cause or worsen hypoxia of the NMDAr by means of altered tryptophane catabolism.\(^{107}\) During low-grade inflammation, the catabolism of tryptophane in the brain is shifted away from serotonin as an end product towards kynurenic acid, which inhibits the NMDAr at the glycine site.\(^{108}\) One postmortem study and several studies investigating cerebrospinal fluid indeed showed increased levels of kynurenic acid in patients with schizophrenia as compared with controls (reviewed by Coyle\(^{109}\)). Inflammation can also be linked to DA dysregulation, as animal studies consistently show increased activity of mesolimbic DA neurons in offspring of rats exposed to prenatal inflammatory challenges.\(^{110}\) In fact, the white matter alterations observed in the early stages of schizophrenia, before psychotic symptoms have become apparent, could reflect an increased inflammatory status of the brain.\(^{111}\)

Not all schizophrenia patients have the same pathophysiology. It is highly unlikely that the pathogenesis of all patients with schizophrenia will be uniform. More probable is that some patients will display for example pronounced NMDAr hypofunction, whereas in others this mechanism is hardly affected. Indeed, Egerton et al.\(^{112}\) have found that FEP patients who respond well to antipsychotic medication displayed normal glx levels in the anterior cingulate cortex, whereas those with poor response showed increased glx concentrations, indicating that in the nonresponders, other mechanisms than increased DA synthesis may have a role. Demjaha et al.\(^{113}\) confirmed that patients with intractable psychosis, not responding to various antipsychotic agents, lacked the typical increase in DA synthesis capacity. In a

### Table 28. Glutamate and glutamine in first-episode psychosis subjects

| Study                 | Technique and area                  | Sample size | Main finding                  |
|-----------------------|-------------------------------------|-------------|-------------------------------|
| Bartha et al.\(^{73}\) | \(^1\)H-MRS medial prefrontal        | 14 FEP      | glu prefrontal FEP > HC       |
| Bartha et al.\(^{97}\) | \(^1\)H-MRS medial temporal         | 10 HC       |                              |
| Bartha et al.\(^{75}\) | \(^1\)H-MRS AC, frontal white, thalamus | 11 FEP      | glu FEP = HC                  |
| Bustillo et al.\(^{79}\) | \(^1\)H-MRS AC, frontal white, thalamus | 14 FEP      | gln/gl ratio AC FEP > HC      |
| De la Fuente-Sandoval et al.\(^{66}\) | \(^1\)H-MRS precommissural dorsal-caudate cerebellar cortex | 30 Medicated FEP | glx medicated FEP = HC        |
| De la Fuente-Sandoval et al.\(^{198}\) | \(^1\)H-MRS striatal cerebellum | 24 Medication-naive FEP, 18 HC | Strialt glu: FEP > HC         |
| Galinska et al.\(^{78}\) | \(^1\)H-MRS frontal, temporal, thalamus | 30 Medicated FEP, 19 HC | cerebellar glu: FEP > HC      |
| Natsubori et al.\(^{72}\) | \(^1\)H-MRS medial prefrontal       | 19 FEP, 73 HC, 25 ChSz | glu FEP = HC                  |
| Ohmann et al.\(^{199}\) | \(^1\)H-MRS DLPFC                   | 18 FEP, 21 HC, 21 ChSz | glu FEP = HC                  |
| Ohmann et al.\(^{100}\) | \(^1\)H-MRS DLPFC hippocampus       | 18 FEP, 20 HC | glu FEP = HC                  |
| Olbrich et al.\(^{101}\) | \(^1\)H-MRS DLPFC hippocampus       | 9 Medicated FEP | Thalamus glu FEP > HC         |
| Stanley et al.\(^{76}\) | \(^1\)H-MRS DLPFC                   | 32 HC       | hippocampus same trend         |
| Théberge et al.\(^{202}\) | \(^1\)H-MRS ACC thalamus            | 21 FEP      | glu FEP > HC (trend)          |
| Théberge et al.\(^{203}\) | \(^1\)H-MRS ACC thalamus            | 21 HC       | glu FEP = HC                  |
| Wood et al.\(^{77}\)   | \(^1\)H-MRS prefrontal              | 15 FEP, 19 HC | FEP > HC                      |
| Wood et al.\(^{204}\)   | \(^1\)H-MRS mesial temporal         | 19 medicated FEP | glu FEP = HC                  |

Abbreviations: ChSz, chronic schizophrenia patients; DLPFC, dorsolateral prefrontal cortex; FEP, first-episode psychosis; FEP patients are medication free unless defined otherwise; gln, glutamine; glu, glutamate; glx, glutamate+glutamine; nt, non-transition; t, transition to psychosis.
similar increase, increased proinflammatory status of the brain may be most pronounced in a specific subgroup of patients. Indeed, in 180 medication-naive FEP patients, approximately one-third showed marked increases in serum immunity markers. In parallel, a recent postmortem study indicated signs of low-grade inflammation in 40% patients with schizophrenia. For future research, it will be key to determine deviations in DA synthesis, frontal glutamine levels and activation of microglial cells could unravel which underlying neurobiology is relevant in a specific patient.

**TREATMENT OF FIRST-EPIODE SCHIZOPHRENIA**

For obvious reasons, treatment of schizophrenia has focused almost exclusively on the stage when patients present with clear-cut clinical symptoms, that is, psychosis. Although an increasing number of studies are now developing treatment at the earlier stages of the illness, such as the ARMS, or focus on the alleviation of cognitive dysfunction in chronic patients, the bulk of studies still focus on the treatment of psychosis.

**Antipsychotic treatment**

The best-known mechanism of action of antipsychotic medication is the correction of increased striatal DA turnover. Interestingly, more recent work in animals (Kato et al.) and cultured brain cells (Zheng et al.) suggest that inhibition of microglial activation may be an additional aspect of the efficacy of antipsychotics. Although we have had effective antipsychotic treatments for nearly 50 years, the application and implementation of these treatments is far from optimal. Many of the elementary questions in the treatment of schizophrenia have remained unanswered. Fortunately, first-episode patients do often respond reasonably well; the main challenge then becomes how to keep them well. Once it has been decided that antipsychotic...
treatment is to be initiated, the question arises on how to prioritize the currently available treatments in a rational and optimal manner. No one treatment will be adequate for all patients. Prospective, sequential studies are necessary to develop treatment algorithms for schizophrenia, but these are almost completely missing. Although every year hundreds of studies on schizophrenia are published (the register of the Cochrane Schizophrenia Group currently includes 12,000 controlled clinical trials), most of the studies focus on the question of whether a specific drug or psychotherapeutic intervention works or not. However, lacking are the mechanism-based, rational, sequential studies that address how to deal with treatment nonresponse. Although schizophrenia patients with an FEP are highly responsive to antipsychotic medication, this rapidly diminishes as episodes increase. Whether switching of antipsychotics is helpful in such patients has hardly been studied, although several large trials are currently under way (OPTiMiSE trial and SWITCH). Agid et al. used an algorithm in which 244 FEP patients were randomized to risperidone or olanzapine. After 4 weeks, as much as 75% had responded to medication (82% in the olanzapine group and 66% in the risperidone group). Nonresponders were switched to the other arm. In this second trial, response rate dropped dramatically to only 17% and again significantly more patients in the olanzapine than in the risperidone group responded. This study illustrates the high response rate in FEP patients, but also shows that patients who do not respond to the first antipsychotic medication have a low probability of responding to a second antipsychotic drug. In these nonresponders, non-dopaminergic mechanisms may be important and when a first trial of antipsychotic medication has failed, treatments to correct NMDAr hypofunction, or increased proinflammatory status of the brain, are expected to be more effective.

Glutamatergic treatments

There are several routes that can potentially improve, or compensate, NMDAr hypofunction in schizophrenia. First, the availability of glycine or D-serine at the glycine site can be increased by the administration of glycine or D-serine. Some studies suggest that glycine and D-serine modestly improve positive and negative symptoms, with little or no impact on cognitive dysfunction. D-serine levels can also be increased by inhibiting its cataboliser D-amino acid oxidase (DAAO), which so far showed no efficacy on symptom severity.

Modulations of AMPA receptors, which are colocalized in synapses near NMDA receptors, provide another avenue for treatment. Several compounds such as CX-516, piracetam cyclothiazide and LY404187 have been tested but so far have not shown clear benefits. A third option is modulation of the glycine transporter, for example, with sarcosine, which has demonstrated some improvement in negative and cognitive symptoms. Finally, modulation of the metabotropic glutamate receptor (mGluR) has been studied: in a phase II study, one of these substances (LY354740), was comparable in efficacy to olanzapine, but a subsequent larger trial was inconclusive.

Influencing GABA-ergic interneurons—the downstream relays of the glutamatergic neurons—offers an alternative strategy. Two classes of selective GABA-ergic drugs have been proposed to enhance cognition in schizophrenia, α5-selective inverse agonists and α2/3-selective agonists. There is compelling evidence from animal models of schizophrenia that allosteric modulation of the α5 subunit of the GABA-A receptor can correct underlying deviations and lead to improvements in cognition. So far, significant improvement of cognition in patients with schizophrenia by GABA-ergic drugs has not been demonstrated, however. The disappointing results with agents targeting NMDAr-mediated or GABA-ergic signalling may not come as a surprise given the fact that dysfunction within these circuits is likely to take place far earlier than does the onset of psychosis. At the time of frank psychotic symptoms many years of NMDAr and GABA-ergic hypofunction may already have caused irreversible deficits in brain maturation and synaptic plasticity. Therefore, treatment for schizophrenia may only be truly effective during the critical developmental window, after which the brain is hard-wired. For treatment, or better prevention, of cognitive decline, it will be key to diagnose at-risk subjects much earlier than the FEP or even the ARMS stage so that glutamatergic or GABA-ergic medication can be given before the window of opportunity has closed.

Antinflammatory agents for the treatment of schizophrenia

The use of antinflammatory agents to improve symptoms of schizophrenia is still in its infancy. A recent meta-analysis has shown some efficacy in schizophrenia for aspirin, n-acetylcysteine (NAC) and estrogens (the latter only in females), but not for other agents with antinflammatory properties, such as celecoxib, minocycline, davunetide and polysaturated fatty acids. Two EEG studies showed that NAC improved both multivariate phase synchronization and mismatch negativity in patients with schizophrenia. A trial in ARMS subjects, however, did show that polysaturated fatty acids significantly reduced (or delayed) transition to psychosis. A follow-up study of this RCT showed that a reduction of positive symptoms and a lower mean PANSS positive score in the polysaturated fatty acids group were apparent after 8 weeks, whereas the significant drop in negative symptoms and the higher mean scores in global functioning occur later at 12 weeks. More studies are needed, however, before this treatment can be considered an effective intervention. As increased proinflammatory status may also affect the brain in an early stage of the illness, augmentation with these agents during the ARMS or FEP stages may be less effective than earlier interventions, that is, several years before psychosis starts. As the diagnosis of schizophrenia is currently based on the onset of the psychotic symptoms, irreversible damage to neurons and glia cells, reflected in brain volume loss, may already be present at the time of diagnosis (as has been argued above and has been repeatedly shown in magnetic resonance imaging studies). Thus, to treat the earliest phases of the illness, antinflammatory agents with high numbers-needed-to-harm are the best candidates. NAC may be of particular interest, as this component targets not only a diverse array of factors including glutamatergic neurotransmission, the antioxidant glutathione, neurotrophins, apoptosis, mitochondrial function, but also the inflammatory pathways. NAC displays a benign side-effect profile and may even have some anti-addictive properties, which would make this component a valuable substance for prevention of brain volume loss, cognitive deterioration and subsequent transition to psychosis in individuals at (genetic) risk for schizophrenia.

Non-pharmacological treatments

Among the many non-pharmacological interventions recently developed to treat patients in the ARMS and FEP period, exercise interventions, such as aerobic interval training, seem especially appealing. The beneficial effects of exercise on mood and self-esteem have long been acknowledged and we recently showed that psychotic and negative symptoms are also reduced by exercise interventions as compared with creative therapy. Interestingly, physical exercise is known to affect gene expression in an antinflammatory pathway, including the downregulation of monocyte TNF, TLR4 and CD36 genes. In sedentary patients, a fitness programme engaging them in a 1-h daily walk resulted in significant decreases in systemic inflammation parameters. An important advantage of physical exercise is its potential to prevent metabolic side-effects of antipsychotics. Exercise also attenuates progressive grey matter loss in the early stages of
schizophrenia and leads to an increase in hippocampal volume in patients. Whether exercise is effective in FEP or ARMS has not been tested, but may show particular promise in view of the absence of harmful side-effects.

Other non-pharmacological interventions consist of neumo- 
dulation, using repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation. Theoretically, these interventions can improve GABA-ergic inhibition with minimal side effects.

Recent advances in spatial and temporal precision of these neuromodulation techniques allow for specific enhancement of neural synchrony in a particular brain area (for example, the dorsolateral prefrontal cortex), which can improve cognitive functions, such as working memory.

Towards personalized medicine for patients with schizophrenia Schizophrenia most likely develops from several different mechanisms, among which are increased DA synthesis, NMDAR hypofunction and increased proinflammatory status of the brain. Neuroimaging techniques may help to tailor treatments to the needs of individual patients. Given that the vast majority of FEP patients respond well to an antipsychotic agent, it does not seem worthwhile to use invasive and expensive PET scans for selection before a first medication trial. In the FEP patients who fail to respond to a first antipsychotic trial, however, further investigations may be valuable. MRS can be performed on most clinical magnetic resonance imaging scanners. Both the peak signal observed during ARMS and FEP and the subsequent decrease observed in more chronic stages of the illness could be targeted with glutamatergic drugs. Likewise, decreases in GABA could be compensated with selective GABA-agonists. Alternatively, hypo- 
function of the GABA-ergic interneurons could be compensated by increasing cortical inhibition with targeted neuromodula- 
tion. Increased proinflammatory status of the brain, in particular increased microglia cell activation, can be detected with PET scans using the PK11195 tracer, but this is an invasive and expensive technique. As increased proinflammatory status may not be restricted to the brain, but may be systemic in a subset of patients with schizophrenia, measurements of proinflammatory cyto- 
kines in peripheral blood, such as the IL-1 receptor antagonist, IL-6 and sIL-2R could provide a simple screening method to select patients for augmentation with antiinflammatory drugs.

Another approach could be to measure the concentration of C-reactive protein, which is a general reflection of heightened (native and adaptive) immune activity but also of metabolic syndrome, stress and even smoking.

CONCLUSION

At the time of first psychotic symptoms, neurobiological processes underlying schizophrenia have already been ongoing for many years. Although increased DA synthesis may be the final common pathway to psychosis, hypofunction of the NMDAr, associated decreased GABA-ergic signalling and increased proinflammatory status of the brain may be important mechanisms underlying cognitive dysfunction. The contribution of these pathophysiological pathways to the clinical picture of schizophrenia most likely varies per individual. If we aim to intervene before the window of opportunity is closed and deviations in the brain have become hard-wired, it will be key to include cognitive deterioration in the diagnosis of schizophrenia instead of postponing diagnosis until the onset of psychotic symptoms many years later. Meanwhile, effective interventions, with high numbers-needed-to-harm, should be considered for at-risk groups.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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