Molecular Psychiatry (2015) 20, 84–97

www.nature.com/mp

OPEN

EXPERT REVIEW

The neurobiology and treatment of first-episode schizophrenia

RS Kahn and IE Sommer

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.

Molecular Psychiatry (2015) **20,** 84–97; doi:10.1038/mp.2014.66; published online 22 July 2014

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.[1] 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.[2] 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.[3,4] The growing brain reaches its maximum size at approximately 13 years of age.[5] 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.[2] 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.[6] 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.[7] 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 use[10,11] and psychotic relapses.[12] 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

Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Centre Utrecht, Utrecht, The Netherlands. Correspondence: Professor RS Kahn, Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Centre Utrecht, A01.126 Heidelberglaan 100, Utrecht 3584CX, The Netherlands. E-mail: r.kahn@umcutrecht.nl
Received 11 February 2014; revised 15 April 2014; accepted 12 May 2014; published online 22 July 2014

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.[13,14] In unmedicated first-episode psychosis (FEP) patients reduced fractional anisotropy, a measure reflecting white matter fibre density and myelination, is related to cognitive dysfunction.[15] Pronounced fractional anisotropy reductions in medication-naive FEP patients appear to be predictive of poor response to subsequent antipsychotic treatment.[14] 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.[8] 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.[8,16] 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.[9,17–20] Only few studies have investigated white matter changes over time after the FEP.[21] Two recent studies showed contrasting results with one demonstrating improvement of white matter deficits in FEP patients after antipsychotic treatment[14] and the other showing worsening of these abnormalities.[22] On postmortem examination, decreases in white matter are associated with a reduction in oligodendrocytes in the superior frontal cortex[23] and in the bilateral hippocampus,[24] 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,[25] mood alterations,[26] anxiety,[27] attenuated psychotic symptoms and a decline in social and occupational functioning.[28] 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.[29]

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.[30] 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.[31,32] Progressive reduction in the integrity of frontal white matter has also been reported in ARMS subjects who go on to develop schizophrenia.[33] 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, 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.[27] Indeed, baseline cognitive functioning in ARMS subjects is an adequate predictor of poor outcome, regardless of transition to psychosis.[34–36]

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, postmortem 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 tomogrpahy (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[37–39] (see Table 1A for an overview of DA deviations in ARMS subjects). In medication-naive schizophrenia patients who experience an FEP, increased striatal DA synthesis is a rather consistent finding (an overview is provided in Table 1B). Although increased striatal DA synthesis may be the final common pathway to psychotic symptoms,[40,41] its relation to cognitive symptoms is less clear. In a mouse model, increased postsynaptic striatal DA receptors could evoke cognitive dysfunction in several domains,[42] but this has not been tested directly in humans.

N-methyl-D-aspartate receptor hypofunction

In fact, some of the cognitive dysfunction in schizophrenia may be related to a different neurotransmitter complex, the N-methyl-D-aspartate receptor (NMDAr)/glutamate system.[43] It has been hypothesized that the NMDAr, situated between the primary and secondary glutamatergic cortical neurons, constitutes the main deficit underlying schizophrenia. Poor function of the NMDAr, in turn, renders the gamma-amino-buteric-acid (GABA)-ergic interneuron less effective. This loss of GABA-ergic firing provides insufficient inhibition of the secondary glutamatergic neurons, allowing them to fire more often but with less synchrony, directly causing the excessive firing of DA neurons in the mesolimbic pathway.[44] This 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.[45] Furthermore, patients with an autoimmune encephalitis producing antibodies against the NMDAr can have a clinical picture that is indistinguishable from schizophrenia.[46] Finally, many of the well-known risk genes, such as DISC-1, dysbindin, SHANK and NRG-1,[47,48] but also *de novo* mutations[49] 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.*[50]). NMDAr is a heterotetrameric structure with one obligate 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.[51–53] During pregnancy, fetal NMDAr

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 5 UHR-t, 5 HC	Striatal DA synthesis capacity all UHR = HC, but increased in UHRt
Bloemen *et al.*[156]	[123I]-IBZM SPECT baseline and with α-methyl-para-tyrosine	14 UHR 15 HC	Postsynaptic DA: UHR = HC baseline and after DA depletion
Egerton *et al.*[157]	PET (18)F-DOPA	26 UHR 20 HC	Striatal DA synthesis capacity UHR > HC (ES 0.8)
Fusar-Poli *et al.*[158]	PET (18)F-DOPA	20 UHR, 14 HC[a]	Striatal DA synthesis capacity UHR > HC (ES 0.75)
Fusar-Poli *et al.*[159]	PET (18)F-DOPA	20 UHR, 14 HC[a]	Striatal DA synthesis capacity UHR > HC correlation left inferior frontal activation and striatal dopamine
Hirvonen *et al.*[160]	((11)C)-labelled raclopride PET	11 GHR (of which 5 MZ and 6 DZ unaffected co-twin), 7 HC	Striatal D2 MZ > DZ/HC
Howes *et al.*[161]	PET (18)F-DOPA	24 UHR[a] 7 SCZ, 12 HC	Striatal DA synthesis capacity UHR > HC (ES 0.75) Schiz > > HC (ES 1.25)
Howes *et al.*[37]	PET (18)F-DOPA	20 UHR[a] scanned twice	Striatal DA synthesis↑from UHR to FEP (ES 1.125) in 8 converters
Howes *et al.*[38]	PET (18)F-DOPA	30 UHR[a] 29 HC	Striatal DA synthesis capacity UHR > HC, converters > non-converters
Suridjan *et al.*[162]	PET [11C]-(+)-PHNO	13 CHR, 13 FEP 12 HC	No difference in non-displaceable DA D2/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. [a]Samples overlap.

levels are increased, rendering the infants' brain vulnerable to insults.[54] 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.[50] 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.[55]

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 synchronized neuronal activity leads—again—to impaired cognitive processing.[56] 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 GABA synthesis, 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.[58] 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 symptoms[1] 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.[59] 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.[60] Thus, decreased activation of the NMDAr leads to an increase in striatal DA release and induce psychotic symptoms.[61] This finding provides a biological explanation of the clinical and epidemiological observations that cognitive changes precede the onset of psychosis by many years.[1]

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.[62] 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.[62] 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.*[63] 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 1B. Dopamine in medication-free schizophrenia patients with a first psychotic episode

Study	*Technique and ligand*	*Sample size*	*Main finding*
Abi-Dargham *et al.*[163]	[^{11}C]NNC 112 PET	16 SCZ of whom 7 FEP 16 HC	D1r bp DLPFC patients > HC
Abi-Dargham *et al.*[164]	[^{11}C]NNC 112 PET	30 FEP 15 HC	DAT FEP < HC
Buchsbaum *et al.*[165]	(18)F-fallypride PET	15 FEP 15 HC	bp FEP < HC
Corripio *et al.*[166]	123I-IBZM SPECT	18 FEP[a] 12 HC	D2r bp FEP > HC
Corripio *et al.*[167]	123I-IBZM SPECT	37 FEP[a] 18 HC	D2r striatal/frontal ratios FEP > HC in those with SCZ
Glenthoj *et al.*[168]	123I-IBZM SPECT	25 FEP 20 HC	Extra striatal D2/D3 DAr bp FEP = HC
Graff-Guerrerro *et al.*[169]	[(11)C]-(+)-PHNO PET	13 FEP[a] 13 HC	Nondisplaceable D2/D3 bp FEP = HC
Graff-Guerrerro *et al.*[170]	[(11)C]-(+)-PHNO PET	13 FEP[a] 13 HC	D2/D3 bp FEP = HC
Hietala *et al.*[171]	[18F]-DOPA PET	7 FEP 8 HC	Striatal DA synthesis capacity FEP > HC
Hietala *et al.*[172]	[18F]-DOPA PET	10 FEP 10 HC	Striatal DA synthesis capacity FEP > HC
Hsiao *et al.*[173]	[99mTc]TRODAT SPECT	12 FEP 12 HC	DAT FEP = HC
Karlsson *et al.*[174]	[(11)C]SCH 23390 PET	10 FEP 10 HC	D1r bp FEP = HC
Laakso *et al.*[175]	[18F]CFT PET	9 FEP 9 HC	DAT FEP = HC
Lavalaye *et al.*[176]	[123I]FP-CIT SPECT	36 SCZ of whom 10 FEP 10 HC	DAT FEP = HC
Lehrer *et al.*[177]	(18)F-fallypride PET	33 SCZ of whom 14 FEP 18 HC	bp medial thalamus SCZ < HC (ES = 0.89)
Lindstrom *et al.*[178]	[11C]-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 10 HC	DAT FEP < HC
Mateos *et al.*[180]	[123I]FP-CIT SPECT	30 FEP 15 HC	DAT FEP < HC
Mateos *et al.*[181]	[123I]FP-CIT SPECT	20 FEP 15 HC	DAT FEP < HC
Nozaki *et al.*[182]	[11C]-DOPA PET	18 SCZ of whom 14 FEP 10 HC	bp FEP > HC
Safont *et al.*[183]	(123)I-IBZM SPECT	37 FEP[a] 18 HC	D2r bp cannabis users = non-users
Schmitt *et al.*[184]	([99mTc]TRODAT-1 SPECT	10 FEP 10 HC	DAT FEP = HC
Schmitt *et al.*[185]	([99mTc]TRODAT-1 SPECT	28 FEP 12 HC	DAT FEP = HC
Schmitt *et al.*[186]	[99mTc]TRODAT-1 and [123I]IBZM SPECT	20 FEP 12 HC	DAT FEP = HC D2r bp FEP = HC
Schmitt *et al.*[187]	123I-IBZM SPECT	23 FEP 10 HC	D2r bp FEP < HC
Schmitt *et al.*[188]	[99mTc]TRODAT-1 and [123I]IBZM SPECT	12 FEP 12 HC	DAT FEP > HC D2r bp FEP = HC
Talvik *et al.*[189]	[11C]FLB 457 PET	9 FEP 8 HC	D2/D3 bp right thalamus FEP < HC,
Talvik *et al.*[190]	[(11)C]raclopride PET	18 FEP 17 HC	D2 bp right thalamus FEP < HC,
Yang *et al.*[191]	[99mTc]TRODAT SPECTand ([(123)I]IBZM) SPECT	11 FEP 12 HC	DAT FEP = HC D2/D3 bp FEP = HC
Yasuno *et al.*[192]	[(11)C]FLB 457 PET	10 FEP 19 HC	D2 bp FEP < HC thalamus

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. [a]Samples overlap.

Although results in ARMS subjects are not consistent, the majority of studies show increased glx,[64–68] whereas a few report decreased[69,70] or normal[71,72] 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,[67,73–75] whereas in medicated FEP patients, glx levels are reported to be normal (Table 2B).[76–79] In the later phases of schizophrenia, glx values appear slightly but

Table 2A. Glutamate and glutamine in ultra-high-risk subjects

Study	*Technique and area*	*Sample size*	*Main finding*
Bloemen *et al.*[193]	^{1}H-MRS hippocampus	11 UHR 11 HC	glu UHR < HC (ES = 0.22)
De la Fuente-Sandoval *et al.*[66]	^{1}H-MRS dorsal-caudate cerebellum	18 UHR[a] 18 medication-naive FEP 40 HC	Dorsal-caudate glu: UHR = FEP > HC cerebellar glu: UHR = FEP = HC
De la Fuente-Sandoval *et al.*[67]	^{1}H-MRS dorsal-caudate nucleus	19 UHR[a] (7 UHR-t) 26 HC	glu UHR-t > UHR-nt UHR-ts > HC (ES = 1.39)
Fusar-Poli *et al.*[194]	^{1}H-MRS thalamus, ACC, hippocampus	24 UHR[a] 17 HC	glu thalamus UHR < HC
Keshavan *et al.*[65]	^{1}H-MRS frontal, occipital, temporal, parietal, basal	40 GHR 46 HC	Inferior parietal/occipital region glx GHR > HC
Natsubori *et al.*[72]	^{1}H-MRS medial prefrontal	24 UHR, 73 HC	glx UHR = HC
Purdon *et al.*[195]	1H-MRS medial frontal	15 GHR 14 HC	glx GHR = HC, but more variability in glx in GHR
Stone *et al.*[69]	^{1}H-MRS, thalamus ACC, hippocampus	27 UHR[a] 27 HC	glu thalamus UHR < HC gln ACC UHR > HC
Tandon *et al.*[68]	^{1}H-MRS thalamus caudate ACC	23 GHR 24 HC	glx thalamus and caudate GHR > HC, ACC glx HR = HC
Tibbo *et al.*[64]	^{1}H-MRS right medial frontal	20 GHR 22 HC	glx GHR > HC
Valli *et al.*[196]	^{1}H-MRS medial temporal, ACC, thalamus	22 UHR 14 HC	glu UHR = HC (trend in thalamus: UHR < HC)
Yoo *et al.*[71]	^{1}H-MRS ACC, DLPFC, thalamus	22 GHR 22 HC	glx HR = 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. [a]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,[62,82,83] 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] Moreover, a nation-wide registry study has shown that both (familial) autoimmune disorders and a history of infection (severe enough to need hospital admittance) increase the risk to develop schizophrenia.[93] 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 illness[101] and, surprisingly, reported strongest indications of increased inflammation in the later stages of the illness. Postmortem literature, which mainly describes the late

Table 2B. 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 10 HC	glu prefrontal FEP > HC
Bartha *et al.*[197]	^{1}H-MRS medial temporal	11 FEP 11 HC	glx FEP = HC
Bustillo *et al.*[75]	^{1}H-MRS AC, frontal white, thalamus	14 FEP 10 HC	gln/glu ratio AC FEP > HC
Bustillo *et al.*[79]	^{1}H-MRS 1 slice parallel to AC-PC above ventricles	30 Medicated FEP 28 HC	glx medicated FEP = HC
De la Fuente-Sandoval *et al.*[66]	^{1}H-MRS precommissural dorsal-caudate cerebellar cortex	18 FEP 40 HC	glu precommissural dorsal-caudate FEP > HC glu cerebellar cortex FEP = HC
De la Fuente-Sandoval *et al.*[198]	^{1}H-MRS striatal cerebellum	24 Medication-naive FEP, 18 HC Scanned twice	Striatal glu: FEP > HC cerebellar glu: FEP > HC after 4 weeks medication: glu FEP = glu HC
Galinska *et al.*[78]	^{1}H-MRS frontal, temporal, thalamus	30 Medicated FEP, 19 HC	glx medicated FEP = HC
Natsubori *et al.*[72]	^{1}H-MRS medial prefrontal	19 FEP, 73 HC, 25 ChSz	glx FEP = HC ChSz < HC
Ohrmann *et al.*[199]	^{1}H-MRS DLPFC	18 FEP, 21 HC, 21 ChSz	glx FEP = HC, ChSz < HC FEP
Ohrmann *et al.*[200]	^{1}H-MRS DLPFC	18 FEP, 20 HC	glx FEP = HC
Olbrich *et al.*[201]	^{1}H-MRS DLPFC hippocampus	9 Medicated FEP 32 HC	Thalamus glu FEP > HC hippocampus same trend
Stanley *et al.*[76]	^{1}H-MRS DLPFC	10 Medicated FEP, 11 FEP, 24 HC	glu FEP > HC (trend) gln FEP = HC
Théberge *et al.*[202]	^{1}H-MRS ACC thalamus	21 FEP 21 HC	gln thalamus and ACC FEP > HC
Théberge *et al.*[203]	^{1}H-MRS ACC thalamus	21 FEP 21 HC	gln thalamus and ACC FEP > HC
Wood *et al.*[77]	^{1}H-MRS temporal	15 FEP, 19 HC 19 medicated FEP,	glx FEP = HC
Wood *et al.*[204]	^{1}H-MRS medial temporal	34 FEP (15 medication-naive), 19 HC	glx 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.

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 antiinflammatory 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 interwoven 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 hypoactivation 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 rodents 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 3. Markers of low-grade inflammation in the brain of patients with schizophrenia

Study	*Technique and ligand*	*Sample*	*Main finding*
Arnold *et al.*[205]	Microglial infiltrates in postmortem brains	23 SCZ 14 HC	No difference
Bayer *et al.*[206]	Microglial activation in postmortem brains	14 SCZ 13 HC	3 SCZ patients with abundant activated microglia density
Bruton *et al.*[207]	Neuropathological examination	56 SCZ 56 HC	More fibrillary gliosis than HC
Busse *et al.*[208]	HLA-DR+ microglial cells in postmortem brains	17 SVZ 11 HC	Microglia activation increased, especially in paranoid group
Doorduin *et al.*[97]	PET PK11195	7 SCZ 8 HC	More activated microglia in SCZ
Falke *et al.*[209]	Microgliosis	11 SCZ 11 HC	No difference
Fillman *et al.*[210]	mRNA expression levels in postmortem brains	20 SCZ 20 HC	40% SCZ: increased microglia density and proinflammatory pathways
Fisman[211]	Neuropathological examination	8 SCZ 10 HC	Microglial nodules in 5 SCZ and 0 HC
Kurumaji *et al.*[212]	PK11195 in postmortem brains	13 SCZ 10 HC	Decrease/no difference in SCZ
Nasrallah *et al.*[213]	Glial counting in corpus callosum	18 SCZ 10 HC	Increased gliosis in SCZ
Radewycz *et al.*[214]	HLA-DR+ microglial numerical density	7 SCZ 10 HC	Increased density of activated microglia in temporal and frontal cortex
Rao *et al.*[215]	Microglial marker CD11b in postmortem brains	10 SCZ 10 HC	Increased microglia activation in SZ
Roberts *et al.*[216]	Antibody to glial fibrillary acidic protein	5 SCZ 7 HC	No difference in gliosis
Roberts *et al.*[217]	Antibody to glial fibrillary acidic protein	18 SCZ 12 HC	No difference in gliosis
Steiner *et al.*[218]	HLA-DR on microglia in postmortem brains	16 HC 16 SCZ	No difference
Steiner *et al.*[219]	HLA-DR+ microglial numerical density	16 SCZ 10 HC	No difference in microglia cell density
Steiner *et al.*[220]	Microglial HLA-DR expression in postmortem brains	16 SCZ 10 HC	No general difference, increased in suicidal (=younger) SCZ patients
Stevens *et al.*[221]	Neuropathological examination	28 SCZ 16 HC	Gliosis in 16 SCZ and in 1 HC
Stevens *et al.*[222]	Postmortem neuropathological examination	5 SCZ 7 HC	No difference in gliosis
Togo *et al.*[223]	Expression of CD40 in postmortem brains	4 SCZ 2 HC	Increased microglia activation
Van Berckel *et al.*[96]	PET PK11195	10 SCZ 10 HC	More activated microglia in SCZ
Wierzba Bobrowic *et al.*[224]	MHC II on microglial cells in postmortem brains	12 SCZ	Degeneration of activated microgial cells
Wierzba Bobrowic *et al.*[225]	MHC II on microglial cells in postmortem brains	9 SCZ 6 HC	More activated microglia cells in SCZ

Abbreviations: HC, healthy controls; PET, positron emission tomography; SCZ, patients with schizophrenia.

similar vein, 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.[44] In parallel, a recent postmortem study indicated signs of low-grade inflammation in 40% patients with schizophrenia.[114] For future research, it will be key to determine deviations in DA synthesis, NMDAr hypofunction and proinflammatory status of the brain on the subject level so that these mechanisms can be targeted on an individual basis. Neuroimaging techniques to visualize striatal DA synthesis, frontal glutamine levels and activation of microglial cells could unravel which underlying neurobiology is relevant in a specific patient.

TREATMENT OF FIRST-EPISODE 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.[35] Interestingly, more recent work in animals (Kato *et al.*)[115,116] and cultured brain cells (Zheng *et al.*)[117] 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;[118] the main challenge then becomes how to keep them well.[119] 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,[118] this rapidly diminishes as episodes increase.[120] 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.*[121] 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.[44,112,113]

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,[122] with little or no impact on cognitive dysfunction.[123] 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.[124]

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.[125] A third option is modulation of the glycine transporter, for example, with sarcosine, which has demonstrated some improvement in negative and cognitive symptoms.[126] 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,[127] but a subsequent larger trial was inconclusive.[128]

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.[129] So far, significant improvement of cognition in patients with schizophrenia by GABA-ergic drugs has not been demonstrated, however.[130] 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.[131] 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.

Antiinflammatory agents for the treatment of schizophrenia

The use of antiinflammatory 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 antiinflammatory properties, such as celecoxib, minocycline, davunetide and polyunsaturated fatty acids.[132] Two EEG studies showed that NAC improved both multivariate phase synchronization and mismatch negativity in patients with schizophrenia.[133,134] A trial in ARMS subjects, however, did show that polyunsaturated fatty acids significantly reduced (or delayed) transition to psychosis.[135] A follow-up study of this RCT showed that a reduction of positive symptoms and a lower mean PANSS positive score in the polyunsaturated 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.[136] 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, antiinflammatory 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.[137] NAC displays a benign side-effect profile and may even have some anti-addictive properties,[138] 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[139] and we recently showed that psychotic and negative symptoms are also reduced by exercise interventions as compared with creative therapy.[140] Interestingly, physical exercise is known to affect gene expression in an antiinflammatory pathway, including the downregulation of monocyte TNF, TLR4 and CD36 genes.[141] In sedentary patients, a fitness programme engaging them in a 1-h daily walk resulted in significant decreases in systemic inflammation parameters.[142] An important advantage of physical exercise is its potential to prevent metabolic side-effects of antipsychotics.[143] Exercise also attenuates progressive grey matter loss in the early stages of

schizophrenia[144] and leads to an increase in hippocampal volume in patients.[145] 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 neuromodulation, using repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation. Theoretically, these interventions can improve GABA-ergic inhibition with minimal side effects.[146,147] 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.[148,149]

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.[112,113] MRS can be performed on most clinical magnetic resonance imaging scanners. Both the peak in glx 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, hypofunction of the GABA-ergic interneurons could be compensated by increasing cortical inhibition with targeted neuromodulation.[147] 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,[49] measurements of proinflammatory cytokines 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.[150,151] Another approach could be to measure the concentration of C-reactive protein, which is a general reflection of heightened (native and adaptive) immune activity,[152,153] but also of metabolic syndrome, stress and even smoking.[154]

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.

ACKNOWLEDGMENTS

We thank Dr C Vinkers, MSc, JL Schutte and Professor Dr P Burbach for their help in preparing this paper.

REFERENCES

1 Kahn RS, Keefe RS. Schizophrenia is a cognitive illness: time for a change in focus. *JAMA Psychiatry* 2013; **70**: 1107–1112.
2 Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophr Bull* 2013; **39**: 1129–1138.
3 O'Rahilly, R Müller, F. *Human Embryology & Teratology*. Wiley-Liss: New York, NY, USA, 1992.
4 Sgouros S, Hockley AD, Goldin JH, Wake MJ, Natarajan K. Intracranial volume change in craniosynostosis. *J Neurosurg* 1999; **91**: 617–625.
5 Blakemore SJ. Imaging brain development: the adolescent brain. *Neuroimage* 2012; **61**: 397–406.
6 Hulshoff Pol HE, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr Bull* 2008; **34**: 354–366.
7 Hulshoff Pol HE, Brans RG, van Haren NE, Schnack HG, Langen M, Baaré WF *et al.* Gray and white matter volume abnormalities in monozygotic and same-gender dizygotic twins discordant for schizophrenia. *Biol Psychiatry* 2004; **55**: 126–130.
8 Cahn W, van Haren NE, Hulshoff Pol HE, Schnack HG, Caspers E, Laponder DA *et al.* Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. *Br J Psychiatry* 2006; **189**: 381–382.
9 van Haren NE, Cahn W, Hulshoff Pol HE, Kahn RS. Confounders of excessive brain volume loss in schizophrenia. *Neurosci Biobehav Rev* 2013; **37**: 2418–2423.
10 van Haren NE, Schnack HG, Cahn W, van den Heuvel MP, Lepage C, Collins L *et al.* Changes in cortical thickness during the course of illness in schizophrenia. *Arch Gen Psychiatry* 2011; **68**: 871–880.
11 Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. *Arch Gen Psychiatry* 2011; **68**: 128–137.
12 Andreasen NC, Liu D, Ziebell S, Vora A, Ho BC. Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: a prospective longitudinal MRI study. *Am J Psychiatry* 2013; **170**: 609–615.
13 Mandl RC, Rais M, van Baal GC, van Haren NE, Cahn W, Kahn RS *et al.* Altered white matter connectivity in never-medicated patients with schizophrenia. *Hum Brain Mapp* 2013; **34**: 2353–2365.
14 Reis Marques T, Taylor H, Chaddock C, Dell'acqua F, Handley R, Reinders AA *et al.* White matter integrity as a predictor of response to treatment in first episode psychosis. *Brain* 2014; **137**: 172–182.
15 Kuswanto CN, Teh I, Lee TS, Sim K. Diffusion tensor imaging findings of white matter changes in first episode schizophrenia: a systematic review. *Clin Psychopharmacol Neurosci* 2012; **10**: 13–24.
16 Radua J, Borgwardt S, Crescini A, Mataix-Cols D, Meyer-Lindenberg A, McGuire PK *et al.* Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medication. *Neurosci Biobehav Rev* 2012; **36**: 2325–2333.
17 Vita A, De Peri L, Deste G, Sacchetti E. Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Transl Psychiatry* 2012; **2**: e190.
18 van Haren NE, Cahn W, Hulshoff Pol HE, Kahn RS. The course of brain abnormalities in schizophrenia: can we slow the progression? *J Psychopharmacol* 2012; **26**: 8–14.
19 van Haren NE, Cahn W, Hulshoff Pol HE, Kahn RS. Schizophrenia as a progressive brain disease. *Eur Psychiatry* 2008; **23**: 245–254.
20 Hulshoff Pol HE, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr Bull.* 2008; **34**: 354–366.
21 Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *Br J Psychiatry* 2006; **188**: 510–518.
22 Wang Q, Cheung C, Deng W, Li M, Huang C, Ma X *et al.* White-matter microstructure in previously drug-naive patients with schizophrenia after 6 weeks of treatment. *Psychol Med* 2013; **43**: 2301–2309.
23 Friedrich VL Jr, Byne W, Buitron C, Perl DP, Davis KL. Loss and altered spatial distribution of oligodendrocytes in the superior frontal gyrus in schizophrenia. *Biol Psychiatry* 2003; **53**: 1075–1085.
24 Schmitt A, Steyskal C, Bernstein HG, Schneider-Axmann T, Parlapani E, Schaeffer EL *et al.* Stereologic investigation of the posterior part of the hippocampus in schizophrenia. *Acta Neuropathol* 2009; **117**: 395–407.

25 Fusar-Poli P, Deste G, Smieskova R, Barlati S, Yung AR, Howes O *et al.* Cognitive functioning in prodromal psychosis: a meta-analysis. *Arch Gen Psychiatry* 2012; **69**: 562–571.
26 Gajwani R, Patterson P, Birchwood M. Attachment: developmental pathways to affective dysregulation in young people at ultra-high risk of developing psychosis. *Br J Clin Psychol* 2013; **52**: 424–437.
27 Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. *Schizophr Bull* 2014; **40**: 120–131.
28 Simon AE, Grädel M, Cattapan-Ludewig K, Gruber K, Ballinari P, Roth B *et al.* Cognitive functioning in at-risk mental states for psychosis and 2-year clinical outcome. *Schizophr Res* 2012; **142**: 108–115.
29 Simon AE, Borgwardt S, Riecher-Rössler A, Velthorst E, de Haan L, Fusar-Poli P. Moving beyond transition outcomes: Meta-analysis of remission rates in individuals at high clinical risk for psychosis. *Psychiatry Res* 2013; **209**: 266–272.
30 Wood SJ, Reniers RL, Heinze K. Neuroimaging findings in the at-risk mental state: a review of recent literature. *Can J Psychiatry* 2013; **58**: 13–18.
31 Mechelli A, Riecher-Rössler A, Meisenzahl EM, Tognin S, Wood SJ, Borgwardt SJ *et al.* Neuroanatomical abnormalities that predate the onset of psychosis: a multicenter study. *Arch Gen Psychiatry* 2011; **68**: 489–495.
32 Samartzis L, Dima D, Fusar-Poli P, Kyriakopoulos M. White matter alterations in early stages of schizophrenia: a systematic review of diffusion tensor imaging studies. *J Neuroimaging* 2014; **24**: 101–110.
33 Karlsgodt KH, Niendam TA, Bearden CE, Cannon TD. White matter integrity and prediction of social and role functioning in subjects at ultra-high risk for psychosis. *Biol Psychiatry* 2009; **66**: 562–569.
34 Niendam TA, Bearden CE, Johnson JK, McKinley M, Loewy R, O'Brien M *et al.* Neurocognitive performance and functional disability in the psychosis prodrome. *Schizophr Res* 2006; **84**: 100–111.
35 Lin A, Wood SJ, Nelson B, Brewer WJ, Spiliotacopoulos D, Bruxner A *et al.* Neurocognitive predictors of functional outcome two to 13 years after identification as ultra-high risk for psychosis. *Schizophr Res* 2011; **132**: 1–7.
36 van Oel CJ, Sitskoorn MM, Cremer MP, Kahn RS. School performance as a premorbid marker for schizophrenia: a twin study. *Schizophr Bull* 2002; **28**: 401–414.
37 Howes OD, Montgomery AJ, Asselin MC, Murray RM, Valli I, Tabraham P *et al.* Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Arch Gen Psychiatry* 2009; **66**: 13–20.
38 Howes OD, Bose SK, Turkheimer F, Valli I, Egerton A, Valmaggia LR *et al.* Dopamine synthesis capacity before onset of psychosis: a prospective [18F]-DOPA PET imaging study. *Am J Psychiatry* 2011; **168**: 1311–1317.
39 Bonoldi I, Howes OD. The enduring centrality of dopamine in the pathophysiology of schizophrenia: *in vivo* evidence from the prodrome to the first psychotic episode. *Adv Pharmacol* 2013; **68**: 199–220.
40 Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III--the final common pathway. *Schizophr Bull* 2009; **35**: 549–562.
41 Winton-Brown TT, Fusar-Poli P, Ungless MA, Howes OD. Dopaminergic basis of salience dysregulation in psychosis. *Trends Neurosci* 2014; **37**: 85–94.
42 Bach ME, Simpson EH, Kahn L, Marshall JJ, Kandel ER, Kellendonk C. Transient and selective overexpression of D2 receptors in the striatum causes persistent deficits in conditional associative learning. *Proc Natl Acad Sci USA* 2008; **105**: 16027–16032.
43 Anticevic A, Gancsos M, Murray JD, Repovs G, Driesen NR, Ennis DJ *et al.* NMDA receptor function in large-scale anticorrelated neural systems with implications for cognition and schizophrenia. *Proc Natl Acad Sci USA* 2012; **109**: 16720–16725.
44 Schwartz TL, Sachdeva S, Stahl SM. Genetic data supporting the NMDA glutamate receptor hypothesis for schizophrenia. *Curr Pharm Des* 2012; **18**: 1580–1592.
45 Krystal JH, Anand A, Moghaddam B. Effects of NMDA receptor antagonists: implications for the pathophysiology of schizophrenia. *Arch Gen Psychiatry* 2002; **59**: 663–664.
46 Snyder MA, Gao WJ. NMDA hypofunction as a convergence point for progression and symptoms of schizophrenia. *Front Cell Neurosci* 2013; **7**: 31.
47 Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry* 2005; **10**: 40–68, image 5.
48 Hahn CG, Wang HY, Cho DS, Talbot K, Gur RE, Berrettini WH *et al.* Altered neuregulin 1-erbB4 signaling contributes to NMDA receptor hypofunction in schizophrenia. *Nat Med* 2006; **12**: 824–828.
49 Fromer M, Pocklington AJ, Kavanagh DH, William HJ, Dwyer S, Gormley P *et al.* *De novo* mutations in schizophrenia implicate synaptic networks. *Nature* 2014; **506**: 179–184.
50 Wang M, Yang Y, Wang CJ, Gamo NJ, Jin LE, Mazer JA *et al.* NMDA receptors subserve persistent neuronal firing during working memory in dorsolateral prefrontal cortex. *Neuron* 2013; **77**: 736–749.
51 Samuelsson AM, Jennische E, Hansson HA, Holmäng A. Prenatal exposure to interleukin-6 results in inflammatory neurodegeneration in hippocampus with NMDA/GABA(A) dysregulation and impaired spatial learning. *Am J Physiol Regul Integr Comp Physiol* 2006; **290**: R1345–R1356.
52 El-Khodor BF, Flores G, Srivastava LK, Boksa P. Effects of birth insult and stress at adulthood on excitatory amino acid receptors in adult rat brain. *Synapse* 2004; **54**: 138–146.
53 Kaur C, Sivakumar V, Ang LS, Sundaresan A. Hypoxic damage to the periventricular white matter in neonatal brain: role of vascular endothelial growth factor, nitric oxide and excitotoxicity. *J Neurochem* 2006; **98**: 1200–1216.
54 Owen D, Setiawan E, Li A, McCabe L, Matthews SG. Regulation of N-methyl-D-aspartate receptor subunit expression in the fetal guinea pig brain. *Biol Reprod* 2004; **71**: 676–683.
55 Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence. *J Psychiatr Res* 1982–1983; **17**: 319–334.
56 Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. *Nat Rev Neurosci* 2005; **6**: 312–324.
57 Curley AA, Arion D, Volk DW, Asafu-Adjei JK, Sampson AR, Fish KN *et al.* Cortical deficits of glutamic acid decarboxylase 67 expression in schizophrenia: clinical, protein, and cell type-specific features. *Am J Psychiatry* 2011; **168**: 921–929.
58 Hyde TM, Lipska BK, Ali T, Mathew SV, Law AJ, Metitiri OE *et al.* Expression of GABA signaling molecules KCC2, NKCC1, and GAD1 in cortical development and schizophrenia. *J Neurosci* 2011; **31**: 11088–11095.
59 Hoff AL, Svetina C, Shields G, Stewart J, DeLisi LE. Ten year longitudinal study of neuropsychological functioning subsequent to a first episode of schizophrenia. *Schizophr Res* 2005; **78**: 27–34.
60 Floresco SB, Todd CL, Grace AA. Glutamatergic afferents from the hippocampus to the nucleus accumbens regulate activity of ventral tegmental area dopamine neurons. *J Neurosci* 2001; **21**: 4915–4922.
61 Adell A, Jiménez-Sánchez L, López-Gil X, Romón T. Is the acute NMDA receptor hypofunction a valid model of schizophrenia? *Schizophr Bull* 2012; **38**: 9–14.
62 Rowland LM, Kontson K, West J, Edden RA, Zhu H, Wijtenburg SA *et al.* *In vivo* measurements of glutamate, GABA, and NAAG in schizophrenia. *Schizophr Bull* 2013; **39**: 1096–1104.
63 Rowland LM, Bustillo JR, Mullins PG, Jung RE, Lenroot R, Landgraf E *et al.* Effects of ketamine on anterior cingulate glutamate metabolism in healthy humans: a 4-T proton MRS study. *Am J Psychiatry* 2005; **162**: 394–396.
64 Tibbo P, Hanstock C, Valiakalayil A, Allen P. 3-T proton MRS investigation of glutamate and glutamine in adolescents at high genetic risk for schizophrenia. *Am J Psychiatry* 2004; **161**: 1116–1118.
65 Keshavan MS, Dick RM, Diwadkar VA, Montrose DM, Prasad KM, Stanley JA. Striatal metabolic alterations in non-psychotic adolescent offspring at risk for schizophrenia: a (1)H spectroscopy study. *Schizophr Res* 2009; **115**: 88–93.
66 de la Fuente-Sandoval C, León-Ortiz P, Favila R, Stephano S, Mamo D, Ramírez-Bermúdez J *et al.* Higher levels of glutamate in the associative-striatum of subjects with prodromal symptoms of schizophrenia and patients with first-episode psychosis. *Neuropsychopharmacology* 2011; **36**: 1781–1791.
67 de la Fuente-Sandoval C, León-Ortiz P, Azcárraga M, Favila R, Stephano S, Graff-Guerrero A. Striatal glutamate and the conversion to psychosis: a prospective 1H-MRS imaging study. *Int J Neuropsychopharmacol* 2013; **16**: 471–475.
68 Tandon N, Bolo NR, Sanghavi K, Mathew IT, Francis AN, Stanley JA *et al.* Brain metabolite alterations in young adults at familial high risk for schizophrenia using proton magnetic resonance spectroscopy. *Schizophr Res* 2013; **148**: 59–66.
69 Stone JM, Day F, Tsagaraki H, Valli I, McLean MA, Lythgoe DJ *et al.* OASIS. Glutamate dysfunction in people with prodromal symptoms of psychosis: relationship to gray matter volume. *Biol Psychiatry* 2009; **66**: 533–539.
70 Fusar-Poli P, Broome MR, Matthiasson P, Woolley JB, Mechelli A, Johns LC *et al.* Prefrontal function at presentation directly related to clinical outcome in people at ultrahigh risk of psychosis. *Schizophr Bull* 2011; **37**: 189–198.
71 Yoo SY, Yeon S, Choi CH, Kang DH, Lee JM, Shin NY *et al.* Proton magnetic resonance spectroscopy in subjects with high genetic risk of schizophrenia: investigation of anterior cingulate, dorsolateral prefrontal cortex and thalamus. *Schizophr Res* 2009; **111**: 86–93.
72 Natsubori T, Inoue H, Abe O, Takano Y, Iwashiro N, Aoki Y *et al.* Reduced frontal Glutamate + Glutamine and N-Acetylaspartate levels in patients with chronic schizophrenia but not in those at clinical high risk for psychosis or with first-episode schizophrenia. *Schizophr Bull* advance online publication, 10 September 2013; PMID: 24023251 (e-pub ahead of print).
73 Bartha R, Williamson PC, Drost DJ, Malla A, Carr TJ, Cortese L *et al.* Measurement of glutamate and glutamine in the medial prefrontal cortex of never-treated schizophrenic patients and healthy controls by proton magnetic resonance spectroscopy. *Arch Gen Psychiatry* 1997; **54**: 959–965.
74 Théberge J, Jensen JE, Rowland LM. Regarding "Increased prefrontal and hippocampal glutamate concentration in schizophrenia: evidence from a magnetic resonance spectroscopy study". *Biol Psychiatry* 2007; **61**: 1218–1219.

75 Bustillo JR, Rowland LM, Mullins P, Jung R, Chen H, Qualls C *et al.* 1H-MRS at 4 tesla in minimally treated early schizophrenia. *Mol Psychiatry*. 2010; **15**: 629–636.
76 Stanley JA, Williamson PC, Drost DJ, Rylett RJ, Carr TJ, Malla A *et al.* An *in vivo* proton magnetic resonance spectroscopy study of schizophrenia patients. *Schizophr Bull* 1996; **22**: 597–609.
77 Wood SJ, Yücel M, Wellard RM, Harrison BJ, Clarke K, Fornito A *et al.* Evidence for neuronal dysfunction in the anterior cingulate of patients with schizophrenia: a proton magnetic resonance spectroscopy study at 3 T. *Schizophr Res* 2007; **94**: 328–331.
78 Galińska B, Szulc A, Tarasów E, Kubas B, Dzienis W, Czernikiewicz A *et al.* Duration of untreated psychosis and proton magnetic resonance spectroscopy (1H-MRS) findings in first-episode schizophrenia. *Med Sci Monit* 2009; **15**: CR82–CR88.
79 Bustillo JR, Chen H, Gasparovic C, Mullins P, Caprihan A, Qualls C *et al.* Glutamate as a marker of cognitive function in schizophrenia: a proton spectroscopic imaging study at 4 Tesla. *Biol Psychiatry* 2011; **69**: 19–27.
80 Marsman A, van den Heuvel MP, Klomp DW, Kahn RS, Luijten PR, Hulshoff Pol HE. Glutamate in schizophrenia: a focused review and meta-analysis of ^{1}H-MRS studies. *Schizophr Bull* 2013; **39**: 120–129.
81 Bustillo JR, Chen H, Jones T, Lemke N, Abbott C, Qualls C *et al.* Increased glutamine in patients undergoing long-term treatment for schizophrenia: a proton magnetic resonance spectroscopy study at 3 T. *JAMA Psychiatry* 2014; **71**: 265–272.
82 Goto N, Yoshimura R, Moriya J, Kakeda S, Ueda N, Ikenouchi-Sugita A *et al.* Reduction of brain gamma-aminobutyric acid (GABA) concentrations in early-stage schizophrenia patients: 3T Proton MRS study. *Schizophr Res* 2009; **112**: 192–193.
83 Yoon JH, Maddock RJ, Rokem A, Silver MA, Minzenberg MJ, Ragland JD *et al.* GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. *J Neurosci* 2010; **30**: 3777–3781.
84 Tayoshi S, Nakataki M, Sumitani S, Taniguchi K, Shibuya-Tayoshi S, Numata S *et al.* GABA concentration in schizophrenia patients and the effects of antipsychotic medication: a proton magnetic resonance spectroscopy study. *Schizophr Res* 2010; **117**: 83–91.
85 Stevens JR. Neuropathology of schizophrenia. *Arch Gen Psychiatry* 1982; **39**: 1131–1139.
86 de Jong S, van Eijk KR, Zeegers DW, Strengman E, Janson E, Veldink JH *et al.* PGC Schizophrenia (GWAS)Consortium. Expression QTL analysis of top loci from GWAS meta-analysis highlights additional schizophrenia candidate genes. *Eur J Hum Genet* 2012; **20**: 1004–1008.
87 Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D *et al.* Common variants conferring risk of schizophrenia. *Nature* 2009; **460**: 744–747.
88 Corvin A, Morris DW. Genome-wide association Studies: Findings at the major histo- compatibility complex locus in psychosis. *Biol Psychiatry* 2014; **75**: 276–283.
89 McAllister AK. Major Histocompatibility Complex I in Brain Development and Schizophrenia. *Biol Psychiatry* 2014; **75**: 262–268.
90 Huh GS, Boulanger LM, Du H, Riquelme PA, Brotz TM, Shatz CJ. Functional requirement for class I MHC in CNS development and plasticity. *Science* 2000; **290**: 2155–2159.
91 Shatz CJ. MHC class I: an unexpected role in neuronal plasticity. *Neuron* 2009; **64**: 40–45.
92 Canetta SE, Brown AS. Prenatal infection, maternal immune activation, and risk for schizophrenia. *Transl Neurosci* 2012; **3**: 320–327.
93 Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. *Am J Psychiatry* 2011; **168**: 1303–1310.
94 Steiner J, Walter M, Glanz W, Sarnyai Z, Bernstein HG, Vielhaber S *et al.* Increased prevalence of diverse N-methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia: specific relevance of IgG NR1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis. *JAMA Psychiatry* 2013; **70**: 271–278.
95 Hagberg H, Gressens P, Mallard C. Inflammation during fetal and neonatal life: implications for neurologic and neuropsychiatric disease in children and adults. *Ann Neurol.* 2012; **71**: 444–457.
96 van Berckel BN, Bossong MG, Boellaard R, Kloet R, Schuitemaker A, Caspers E *et al.* Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C] PK11195 positron emission tomography study. *Biol Psychiatry* 2008; **64**: 820–822.
97 Doorduin J, de Vries EF, Willemsen AT, de Groot JC, Dierckx RA, Klein HC. Neuroinflammation in schizophrenia-related psychosis: a PET study. *J Nucl Med* 2009; **50**: 1801–1807.
98 Takano A, Arakawa R, Ito H, Tateno A, Takahashi H, Matsumoto R *et al.* Peripheral benzodiazepine receptors in patients with chronic schizophrenia: a PET study with [11C]DAA1106. *Int J Neuropsychopharmacol* 2010; **13**: 943–950.
99 Chauveau F, Van Camp N, Dollé F, Kuhnast B, Hinnen F, Damont A *et al.* Comparative evaluation of the translocator protein radioligands 11C-DPA-713, 18F-DPA-714, and 11C-PK11195 in a rat model of acute neuroinflammation. *J Nucl Med* 2009; **50**: 468–476.
100 Monji A, Kato T, Kanba S. Cytokines and schizophrenia: Microglia hypothesis of schizophrenia. *Psychiatry Clin Neurosci* 2009; **63**: 257–265.
101 Narayan S, Tang B, Head SR, Gilmartin TJ, Sutcliffe JG, Dean B *et al.* Molecular profiles of schizophrenia in the CNS at different stages of illness. *Brain Res* 2008; **1239**: 235–248.
102 Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry* 2011; **70**: 663–671.
103 Feigenson KA, Kusnecov AW, Silverstein SM. Inflammation and the two-hit hypothesis of schizophrenia. *Neurosci Biobehav Rev* 2014; **38**: 72–93.
104 Papadia S, Soriano FX, Leveille F, Martel MA, Dakin KA, Hansen HH *et al.* Synaptic NMDA receptor activity boosts intrinsic antioxidant defenses. *Nat Neurosci* 2008; **11**: 476–487.
105 Smith SE, Li J, Garbett K, Mirnics K, Patterson PH. Maternal immune activation alters fetal brain development through interleukin-6. *J Neurosci* 2007; **27**: 10695–10702.
106 Behrens MM, Ali SS, Dugan LL. Interleukin-6 mediates the increase in NADPH-oxidase in the ketamine model of schizophrenia. *J Neurosci* 2008; **28**: 13957–13966.
107 Muller N, Schwarz M. Schizophrenia as an inflammation-mediated dysbalance of glutamatergic neurotransmission. *Neurotox Res* 2006; **10**: 131–148.
108 Mayer ML, Westbrook GL, Vyklický L Jr. Sites of antagonist action on N-methyl-D-aspartic acid receptors studied using fluctuation analysis and a rapid perfusion technique. *J Neurophysiol* 1988; **60**: 645–663.
109 Coyle JT. Nitric oxide and symptom reduction in schizophrenia. *JAMA Psychiatry* 2013; **70**: 664–665.
110 Meyer U, Feldon J. Neural basis of psychosis-related behaviour in the infection model of schizophrenia. *Behav Brain Res* 2009; **204**: 322–334.
111 Pasternak O, Westin CF, Bouix S, Seidman LJ, Goldstein JM, Woo TU *et al.* Excessive extracellular volume reveals a neurodegenerative pattern in schizophrenia onset. *J Neurosci* 2012; **32**: 17365–17372.
112 Egerton A, Fusar-Poli P, Stone JM. Glutamate and psychosis risk. *Curr Pharm Des* 2012; **18**: 466–478.
113 Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD. Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *Am J Psychiatry* 2012; **169**: 1203–1210.
114 Fillman SG, Cloonan N, Miller LC, Weickert CS. Markers of inflammation in the prefrontal cortex of individuals with schizophrenia. *Mol Psychiatry* 2013; **18**: 133.
115 Kato T, Monji A, Hashioka S, Kanba S. Risperidone significantly inhibits interferon- gamma-induced microglial activation *in vitro*. *Schizophr Res* 2007; **92**: 108–115.
116 Kato TA, Monji A, Mizoguchi Y, Hashioka S, Horikawa H, Seki Y, Kasai M, Utsumi H, Kanba S. Anti-Inflammatory properties of antipsychotics *via* microglia modulations: are antipsychotics a 'fire extinguisher' in the brain of schizophrenia? *Mini Rev Med Chem* 2011; **11**: 565–574.
117 Zheng LT, Hwang J, Ock J, Lee MG, Lee WH, Suk K. The antipsychotic spiperone attenuates inflammatory response in cultured microglia *via* the reduction of proinflammatory cytokine expression and nitric oxide production. *J Neurochem* 2008; **107**: 1225–1235.
118 Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP *et al.* Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet* 2008; **371**: 1085–1097.
119 Robinson D. First-episode schizophrenia. *CNS Spectr* 2010; **15**: 4–7.
120 Robinson DG, Woerner MG, Alvir JM, Geisler S, Koreen A, Sheitman B *et al.* Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry* 1999; **156**: 544–549.
121 Agid O, Arenovich T, Sajeev G, Zipursky RB, Kapur S, Foussias G *et al.* An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. *J Clin Psychiatry* 2011; **72**: 1439–1444.
122 Singh SP, Singh V. Meta-analysis of the efficacy of adjunctive NMDA receptor modulators in chronic schizophrenia. *CNS Drugs* 2011; **25**: 859–885.
123 Heresco-Levy U, Javitt DC. Comparative effects of glycine and D-cycloserine on persistent negative symptoms in schizophrenia: a retrospective analysis. *Schizophr Res* 2004; **66**: 89–96.
124 Hashimoto K, Malchow B, Falkai P, Schmitt A. Glutamate modulators as potential therapeutic drugs in schizophrenia and affective disorders. *Eur Arch Psychiatry Clin Neurosci* 2013; **263**: 367–377.

125 Goff DC, Lamberti JS, Leon AC, Green MF, Miller AL, Patel J *et al.* A placebo-controlled add-on trial of the Ampakine, CX516, for cognitive deficits in schizophrenia. *Neuropsychopharmacology* 2008; **33**: 465–472.
126 Lane HY, Liu YC, Huang CL, Chang YC, Liau CH, Perng CH *et al.* Sarcosine (Nmethylglycine) treatment for acute schizophrenia: a randomized, double-blind study. *Biol Psychiatry* 2008; **63**: 9–12.
127 Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andregv BV *et al.* Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. *Nat Med* 2007; **13**: 1102–1107.
128 Kinon BJ, Zhang L, Millen BA, Osuntokun OO, Williams JE, Kollack-Walker S *et al.* A multicenter, inpatient, phase 2, double-blind, placebocontrolled dose-ranging study of LY2140023 monohydrate in patients with DSM-IV schizophrenia. *J Clin Psychopharmacol* 2011; **31**: 349–355.
129 Gill KM, Grace AA. The role of α5 GABAA receptor agonists in the treatment of cognitive deficits in schizophrenia. *Curr Pharm Des* advance online publication, 15 December 2013 (e-pub ahead of print).
130 Vinkers CH, Mirza NR, Olivier B, Kahn RS. The inhibitory GABA system as a therapeutic target for cognitive symptoms in schizophrenia: investigational agents in the pipeline. *Expert Opin Investig Drugs* 2010; **19**: 1217–1233.
131 Insel TR. Rethinking schizophrenia. *Nature* 2010; **468**: 187–193.
132 Sommer IE, van Westrhenen R, Begemann MJ, de Witte LD, Leucht S, Kahn RS. Efficacy of Anti-inflammatory Agents to Improve Symptoms in Patients With Schizophrenia: An Update. *Schizophr Bull* 2014; **40**: 181–191.
133 Carmeli C, Knyazeva MG, Cuénod M, Do KQ. Glutathione precursor N-acetyl-cysteine modulates EEG synchronization in schizophrenia patients: a double-blind, randomized, placebo-controlled trial. *PLoS One* 2012; **7**: e29341.
134 Lavoie S, Murray MM, Deppen P, Knyazeva MG, Berk M, Boulat O *et al.* Glutathione precursor, N-acetyl-cysteine, improves mismatch negativity in schizophrenia patients. *Neuropsychopharmacology* 2008; **33**: 2187–2199.
135 Amminger GP, Schäfer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM *et al.* Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2010; **67**: 146–154.
136 Mossaheb N, Schäfer MR, Schlögelhofer M, Klier CM, Cotton SM, McGorry PD, Amminger GP. Effect of omega-3 fatty acids for indicated prevention of young patients at risk for psychosis: when do they begin to be effective? *Schizophr Res* 2013; **148**: 163–167.
137 Berk M, Malhi GS, Gray LJ, Dean OM. The promise of N-acetylcysteine in neuropsychiatry. *Trends Pharmacol Sci* 2013; **34**: 167–177.
138 Schmaal L, Berk L, Hulstijn KP, Cousijn J, Wiers RW, van den Brink W. Efficacy of N-acetylcysteine in the treatment of nicotine dependence: a double-blind placebo-controlled pilot study. *Eur Addict Res* 2011; **17**: 211–216.
139 Schneider ML, Kwan BM. Psychological need satisfaction, intrinsic motivation and affective response to exercise in adolescents. *Psychol Sport Exerc* 2013; **14**: 776–785.
140 Scheewe TW, Backx FJ, Takken T, Jörg F, van Strater AC, Kroes AG *et al.* Exercise therapy improves mental and physical health in schizophrenia: a randomised controlled trial. *Acta Psychiatr Scand* 2013; **127**: 464–473.
141 Radom-Aizik S, Zaldivar FP Jr, Haddad F, Cooper DM. Impact of brief exercise on circulating monocyte gene and microRNA expression: Implications for atherosclerotic vascular disease. *Brain Behav Immun* 2014; **39**: 121–129.
142 Di Raimondo D, Tuttolomondo A, Buttà C, Casuccio A, Giarrusso L, Miceli G *et al.* Metabolic and anti-inflammatory effects of a home-based programme of aerobic physical exercise. *Int J Clin Pract* 2013; **67**: 1247–1253.
143 Abdel-Baki A, Brazzini-Poisson V, Marois F, Letendre E, Karelis AD. Effects of aerobic interval training on metabolic complications and cardiorespiratory fitness in young adults with psychotic disorders: a pilot study. *Schizophr Res* 2013; **149**: 112–115.
144 Scheewe TW, van Haren NE, Sarkisyan G, Schnack HG, Brouwer RM, de Glint M *et al.* Exercise therapy, cardiorespiratory fitness and their effect on brain volumes: a randomised controlled trial in patients with schizophrenia and healthy controls. *Eur Neuropsychopharmacol* 2013; **23**: 675–685.
145 Pajonk FG, Wobrock T, Gruber O, Scherk H, Berner D, Kaizl I *et al.* Hippocampal plasticity in response to exercise in schizophrenia. *Arch Gen Psychiatry* 2010; **67**: 133–143.
146 Daskalakis ZJ, Möller B, Christensen BK, Fitzgerald PB, Gunraj C, Chen R. The effects of repetitive transcranial magnetic stimulation on cortical inhibition in healthy human subjects. *Exp Brain Res* 2006; **174**: 403–412.
147 de Jesus DR, Favalli GP, Hoppenbrouwers SS, Barr MS, Chen R, Fitzgerald PB *et al.* Determining optimal rTMS parameters through changes in cortical inhibition. *Clin Neurophysiol* 2013; **124**: 1309–1320.
148 Luber B, Kinnunen LH, Rakitin BC, Ellsasser R, Stern Y, Lisanby SH. Facilitation of performance in a working memory task with rTMS stimulation of the precuneus: frequency- and time-dependent effects. *Brain Res* 2007; **1128**: 120–129.
149 Luber B, Steffener J, Tucker A, Habeck C, Peterchev AV, Deng ZD *et al.* Extended remediation of sleep deprived-induced working memory deficits using fMRI-guided transcranial magnetic stimulation. *Sleep* 2013; **36**: 857–871.
150 Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. *Biol Psychiatry* 2008; **63**: 801–808.
151 Zakharyan R, Boyajyan A. Inflammatory cytokine network in schizophrenia. *World J Biol Psychiatry* 2014; **15**: 174–187.
152 Dickerson F, Stallings C, Origoni A, Boronow J, Yolken R. C-reactive protein is associated with the severity of cognitive impairment but not of psychiatric symptoms in individuals with schizophrenia. *Schizophr Res* 2007; **93**: 261–265.
153 Dickerson F, Stallings C, Origoni A, Vaughan C, Khushalani S, Yang S *et al.* C-reactive protein is elevated in schizophrenia. *Schizophr Res* 2013; **143**: 198–202.
154 Vuksan-Cusa B, Sagud M, Jakovljevic M, Peles AM, Jaksic N, Mihaljevic S *et al.* Association between C-reactive protein and homocysteine with the subcomponents of metabolic syndrome in stable patients with bipolar disorder and schizophrenia. *Nord J Psychiatry* 2013; **67**: 320–325.
155 Allen P, Chaddock CA, Howes OD, Egerton A, Seal ML, Fusar-Poli P *et al.* Abnormal relationship between medial temporal lobe and subcortical dopamine function in people with an ultra high risk for psychosis. *Schizophr Bull.* 2012; **38**: 1040–9.
156 Bloemen OJN, de Koning MB, Gleich T, Meijer J, de Haan L, Linszen DH *et al.* Striatal dopamine D2/3 receptor binding following dopamine depletion in subjects at Ultra High Risk for psychosis. *Eur Neuropsychopharmacol* 2013; **23**: 126–132.
157 Egerton A, Chaddock CA, Winton-Brown TT, Bloomfield MAP, Bhattacharyya S, Allen P *et al.* Presynaptic striatal dopamine dysfunction in people at ultra-high risk for psychosis: findings in a second cohort. *Biol Psychiatry* 2013; **74**: 106–112.
158 Fusar-Poli P, Howes OD, Allen P, Broome M, Valli I, Asselin MC *et al.* Abnormal frontostriatal interactions in people with prodromal signs of psychosis: a multimodal imaging study. *Arch Gen Psychiatry* 2010; **67**: 683–691.
159 Fusar-Poli P, Howes OD, Allen P, Broome M, Valli I, Asselin MC *et al.* Abnormal prefrontal activation directly related to pre-synaptic striatal dopamine dysfunction in people at clinical high risk for psychosis. *Mol. Psychiatry* 2011; **16**: 67–75.
160 Hirvonen J, van Erp TGM, Huttunen J, Aalto S, Någren K, Huttunen M *et al.* Increased caudate dopamine D2 receptor availability as a genetic marker for schizophrenia. *Arch Gen Psychiatry* 2005; **62**: 371–378.
161 Howes O, Bose S, Turkheimer F, Valli I, Egerton A, Stahl D *et al.* Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: a PET study. *Mol Psychiatry* 2011a; **16**: 885–886.
162 Suridjan I, Rusjan P, Addington J, Wilson AA, Houle S, Mizrahi R. Dopamine D2 and D3 binding in people at clinical high risk for schizophrenia, antipsychotic-naive patients and healthy controls while performing a cognitive task. *J Psychiatry Neurosci* 2013; **38**: 98–106.
163 Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y *et al.* Prefrontal dopamine D1 receptors and working memory in schizophrenia. *J Neurosci* 2002; **22**: 3708–3719.
164 Abi-Dargham A, Xu X, Thompson JL, Gil R, Kegeles LS, Urban N *et al.* Increased prefrontal cortical D_1 receptors in drug naive patients with schizophrenia: a PET study with [^{11}C]NNC112. *J Psychopharmacol (Oxford)* 2012; **26**: 794–805.
165 Buchsbaum MS, Christian BT, Lehrer DS, Narayanan TK, Shi B, Mantil J *et al.* D2/D3 dopamine receptor binding with [F-18]fallypride in thalamus and cortex of patients with schizophrenia. *Schizophr Res* 2006; **85**: 232–244.
166 Corripio I, Pérez V, Catafau AM, Mena E, Carrió I, Alvarez E. Striatal D2 receptor binding as a marker of prognosis and outcome in untreated first-episode psychosis. *Neuroimage* 2006; **29**: 662–666.
167 Corripio I, Escartí MJ, Portella MJ, Pérez V, Grasa E, Sauras RB *et al.* Density of striatal D2 receptors in untreated first-episode psychosis: an I123-IBZM SPECT study. *Eur Neuropsychopharmacol* 2011; **21**: 861–866.
168 Glenthoj BY, Mackeprang T, Svarer C, Rasmussen H, Pinborg LH, Friberg L *et al.* Frontal Dopamine D2/3 Receptor Binding in Drug-Naive First-Episode Schizophrenic Patients Correlates with Positive Psychotic Symptoms and Gender. *Biological Psychiatry* 2006; **60**: 621–629.
169 Graff-Guerrero A, Mamo D, Shammi CM, Mizrahi R, Marcon H, Barsoum P *et al.* The effect of antipsychotics on the high-affinity state of D2 and D3 receptors: a positron emission tomography study With [11C]-(+)-PHNO. *Arch Gen Psychiatry* 2009a; **66**: 606–615.
170 Graff-Guerrero A, Mizrahi R, Agid O, Marcon H, Barsoum P, Rusjan P *et al.* The dopamine D2 receptors in high-affinity state and D3 receptors in schizophrenia: a clinical [11C]-(+)-PHNO PET study. *Neuropsychopharmacology* 2009b; **34**: 1078–1086.
171 Hietala J, Syvälahti E, Vuorio K, Räkköläinen V, Bergman J, Haaparanta M *et al.* Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. *Lancet* 1995; **346**: 1130–1131.

172 Hietala J, Syvälahti E, Vilkman H, Vuorio K, Räkköläinen V, Bergman J *et al.* Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. *Schizophr Res* 1999; **35**: 41–50.
173 Hsiao MC, Lin KJ, Liu CY, Tzen KY, Yen TC. Dopamine transporter change in drug-naive schizophrenia: an imaging study with 99mTc-TRODAT-1. *Schizophr Res* 2003; **65**: 39–46.
174 Karlsson P, Farde L, Halldin C, Sedvall G. PET study of D(1) dopamine receptor binding in neuroleptic-naive patients with schizophrenia. *Am J Psychiatry* 2002; **159**: 761–767.
175 Laakso A, Vilkman H, Alakare B, Haaparanta M, Bergman J, Solin O *et al.* Striatal dopamine transporter binding in neuroleptic-naive patients with schizophrenia studied with positron emission tomography. *Am J Psychiatry* 2000; **157**: 269–271.
176 Lavalaye J, Linszen DH, Booij J, Dingemans PM, Reneman L, Habraken JB *et al.* Dopamine transporter density in young patients with schizophrenia assessed with [123]FP-CIT SPECT. *Schizophr Res* 2001; **47**: 59–67.
177 Lehrer DS, Christian BT, Kirbas C, Chiang M, Sidhu S, Short H *et al.* 18F-fallypride binding potential in patients with schizophrenia compared to healthy controls. *Schizophr Res* 2010; **122**: 43–52.
178 Lindström LH, Gefvert O, Hagberg G, Lundberg T, Bergström M, Hartvig P *et al.* Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-11C) DOPA and PET. *Biol Psychiatry* 1999; **46**: 681–688.
179 Mateos JJ, Lomeña F, Parellada E, Font M, Fernandez E, Pavia J *et al.* Decreased striatal dopamine transporter binding assessed with [123I] FP-CIT in first-episode schizophrenic patients with and without short-term antipsychotic-induced parkinsonism. *Psychopharmacology (Berl)* 2005; **181**: 401–406.
180 Mateos JJ, Lomeña F, Parellada E, Font M, Fernández E, Pavia J *et al.* Striatal dopamine transporter density decrease in first episode schizophrenic patients treated with risperidone. *Rev Esp Med Nucl* 2006; **25**: 159–165.
181 Mateos JJ, Lomeña F, Parellada E, Mireia F, Fernandez-Egea E, Pavia J *et al.* Lower striatal dopamine transporter binding in neuroleptic-naive schizophrenic patients is not related to antipsychotic treatment but it suggests an illness trait. *Psychopharmacology (Berl)* **191**: 805–811.
182 Nozaki S, Kato M, Takano H, Ito H, Takahashi H, Arakawa R *et al.* Regional dopamine synthesis in patients with schizophrenia using L-[beta-11C]DOPA PET. *Schizophr Res* 2009; **108**: 78–84.
183 Safont G, Corripio I, Escartí MJ, Portella MJ, Pérez V, Ferrer M *et al.* Cannabis use and striatal D2 receptor density in untreated first-episode psychosis: an in vivo SPECT study. *Schizophr Res* 2011; **129**: 169–171.
184 Schmitt GJE, Meisenzahl EM, Frodl T, La Fougère C, Hahn K, Möller HJ *et al.* The striatal dopamine transporter in first-episode, drug-naive schizophrenic patients: evaluation by the new SPECT-ligand[99mTc]TRODAT-1. *J Psychopharmacol (Oxford)* 2005; **19**: 488–493.
185 Schmitt GJE, Frodl T, Dresel S, la Fougère C, Bottlender R, Koutsouleris N *et al.* Striatal dopamine transporter availability is associated with the productive psychotic state in first episode, drug-naive schizophrenic patients. *Eur Arch Psychiatry Clin Neurosci* 2006; **256**: 115–121.
186 Schmitt GJE, la Fougère C, Dresel S, Frodl T, Hahn K, Möller HJ *et al.* Dual-isotope SPECT imaging of striatal dopamine: first episode, drug naïve schizophrenic patients. *Schizophr Res* 2008; **101**: 133–141.
187 Schmitt GJE, Meisenzahl EM, Frodl T, La Fougère C, Hahn K, Möller HJ *et al.* Increase of striatal dopamine transmission in first episode drug-naive schizophrenic patients as demonstrated by [(123)I]IBZM SPECT. *Psychiatry Res* 2009; **173**: 183–189.
188 Schmitt GJE, Dresel S, Frodl T, la Fougère C, Boerner R, Hahn K *et al.* Dual-isotope SPECT imaging of striatal dopamine: a comparative study between never-treated and haloperidol-treated first-episode schizophrenic patients. *Eur Arch Psychiatry Clin Neurosci* 2012; **262**: 183–191.
189 Talvik M, Nordström AL, Olsson H, Halldin C, Farde L. Decreased thalamic D2/D3 receptor binding in drug-naive patients with schizophrenia: a PET study with [11C]FLB 457. *Int. J Neuropsychopharmacol* 2003; **6**: 361–370.
190 Talvik M, Nordström AL, Okubo Y, Olsson H, Borg J, Halldin C *et al.* Dopamine D2 receptor binding in drug-naïve patients with schizophrenia examined with raclopride-C11 and positron emission tomography. *Psychiatry Res* 2006; **148**: 165–173.
191 Yang YK, Yu L, Yeh TL, Chiu NT, Chen PS, Lee IH. Associated alterations of striatal dopamine D2/D3 receptor and transporter binding in drug-naive patients with schizophrenia: a dual-isotope SPECT study. *Am J Psychiatry* 2004; **161**: 1496–1498.
192 Yasuno F, Suhara T, Okubo Y, Sudo Y, Inoue M, Ichimiya T *et al.* Low dopamine d (2) receptor binding in subregions of the thalamus in schizophrenia. *Am J Psychiatry* 2004; **161**: 1016–1022.
193 Bloemen OJN, Gleich T, de Koning MB, da Silva Alvis F, de Haan L, Linszen DH *et al.* Hippocampal glutamate levels and striatal dopamine D(2/3) receptor occupancy in subjects at ultra high risk of psychosis. *Biol Psychiatry* 2011; **70**: e1–2, author reply e3.
194 Fusar-Poli P, Stone JM, Broome MR, Valli I, Mechelli A, McLean MA *et al.* Thalamic glutamate levels as a predictor of cortical response during executive functioning in subjects at high risk for psychosis. *Arch. Gen. Psychiatry* 2011; **68**: 881–890.
195 Purdon SE, Valiakalayil A, Hanstock CC, Seres P, Tibbo P. Elevated 3T proton MRS glutamate levels associated with poor Continuous Performance Test (CPT-0X) scores and genetic risk for schizophrenia. *Schizophr Res* 2008; **99**: 218–224.
196 Valli I, Stone J, Mechelli A, Bhattacharyya S, Raffin M, Allen P *et al.* Altered medial temporal activation related to local glutamate levels in subjects with prodromal signs of psychosis. *Biol Psychiatry* 2011; **69**: 97–99.
197 Bartha R, al-Semaan YM, Williamson PC, Drost DJ, Malla AK, Carr TJ *et al.* A short echo proton magnetic resonance spectroscopy study of the left mesial-temporal lobe in first-onset schizophrenic patients. *Biol Psychiatry* 1999; **45**: 1403–1411.
198 De la Fuente-Sandoval C, León-Ortiz P, Azcárraga M, Stephano S, Favila R, Díaz-Galvis L *et al.* Glutamate levels in the associative striatum before and after 4 weeks of antipsychotic treatment in first-episode psychosis: a longitudinal proton magnetic resonance spectroscopy study. *JAMA Psychiatry* 2013; **70**: 1057–1066.
199 Ohrmann P, Siegmund A, Suslow T, Spitzberg K, Kersting A, Arolt V *et al.* Evidence for glutamatergic neuronal dysfunction in the prefrontal cortex in chronic but not in first-episode patients with schizophrenia: a proton magnetic resonance spectroscopy study. *Schizophr Res* 2005; **73**: 153–157.
200 Ohrmann P, Siegmund A, Suslow T, Pedersen A, Spitzberg K, Kersting A *et al.* Cognitive impairment and in vivo metabolites in first-episode neuroleptic-naive and chronic medicated schizophrenic patients: a proton magnetic resonance spectroscopy study. *J Psychiatr Res* 2007; **41**: 625–634.
201 Olbrich HM, Valerius G, Rüsch N, Buchert M, Thiel T, Hennig J *et al.* Frontolimbic glutamate alterations in first episode schizophrenia: evidence from a magnetic resonance spectroscopy study. *World J Biol Psychiatry* 2008; **9**: 59–63.
202 Théberge J, Bartha R, Drost DJ, Menon RS, Malla A, Takhar J *et al.* Glutamate and glutamine measured with 4.0 T proton MRS in never-treated patients with schizophrenia and healthy volunteers. *Am J Psychiatry* 2002; **159**: 1944–1946.
203 Théberge J, Williamson KE, Aoyama N, Drost DJ, Manchanda R, Malla AK *et al.* Longitudinal grey-matter and glutamatergic losses in first-episode schizophrenia. *Br J Psychiatry* 2007; **191**: 325–334.
204 Wood SJ, Berger GE, Wellard RM, Proffitt T, McConchie M, Velakoulis D *et al.* A 1H-MRS investigation of the medial temporal lobe in antipsychotic-naïve and early-treated first episode psychosis. *Schizophr Res* 2008; **102**: 163–170.
205 Arnold SE, Trojanowski JQ, Gur RE, Blackwell P, Han LY, Choi C. Absence of neurodegeneration and neural injury in the cerebral cortex in a sample of elderly patients with schizophrenia. *Arch. Gen. Psychiatry* 1998; **55**: 225–232.
206 Bayer TA, Buslei R, Havas L, Falkai P. Evidence for activation of microglia in patients with psychiatric illnesses. *Neurosci. Lett* 1999; **271**: 126–128.
207 Bruton CJ, Crow TJ, Frith CD, Johnstone EC, Owens DG, Roberts GW. Schizophrenia and the brain: a prospective clinico-neuropathological study. *Psychol Med* 1990; **20**: 285–304.
208 Busse S, Busse M, Schiltz K, Bielau H, Gos T, Brisch R *et al.* Different distribution patterns of lymphocytes and microglia in the hippocampus of patients with residual versus paranoid schizophrenia: further evidence for disease course-related immune alterations? *Brain Behav Immun* 2012; **26**: 1273–1279.
209 Falke E, Han LY, Arnold SE. Absence of neurodegeneration in the thalamus and caudate of elderly patients with schizophrenia. *Psychiatry Res* 2000; **93**: 103–110.
210 Fillman SG, Cloonan N, Catts VS, Miller LC, Wong J, McCrossin T *et al.* Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia. *Mol Psychiatry* 2013; **18**: 206–214.
211 Fisman M. The brain stem in psychosis. *Br J Psychiatry* 1975; **126**: 414–422.
212 Kurumaji A, Wakai T, Toru M. Decreases in peripheral-type benzodiazepine receptors in postmortem brains of chronic schizophrenics. *J Neural Transm* 1997; **104**: 1361–1370.
213 Nasrallah HA, McCalley-Whitters M, Bigelow LB, Rauscher FP. A histological study of the corpus callosum in chronic schizophrenia. *Psychiatry Res* 1983; **8**: 251–260.
214 Radewicz K, Garey LJ, Gentleman SM, Reynolds R. Increase in HLA-DR immunoreactive microglia in frontal and temporal cortex of chronic schizophrenics. *J Neuropathol Exp Neurol* 2000; **59**: 137–150.
215 Rao JS, Kim H-W, Harry GJ, Rapoport SI, Reese EA. Increased neuroinflammatory and arachidonic acid cascade markers, and reduced synaptic proteins, in the postmortem frontal cortex from schizophrenia patients. *Schizophr Res* 2013; **147**: 24–31.

216 Roberts GW, Colter N, Lofthouse R, Bogerts B, Zech M, Crow TJ. Gliosis in schizophrenia: a survey. *Biol Psychiatry* 1986; **21**: 1043–1050.
217 Roberts GW, Colter N, Lofthouse R, Johnstone EC, Crow TJ. Is there gliosis in schizophrenia? Investigation of the temporal lobe. *Biol Psychiatry* 1987; **22**: 1459–1468.
218 Steiner J, Mawrin C, Ziegeler A, Bielau H, Ullrich O, Bernstein H-G *et al*. Distribution of HLA-DR-positive microglia in schizophrenia reflects impaired cerebral lateralization. *Acta Neuropathol* 2006; **112**: 305–316.
219 Steiner J, Bernstein H-G, Bielau H, Farkas N, Winter J, Dobrowolny H *et al*. S100B-immunopositive glia is elevated in paranoid as compared to residual schizophrenia: a morphometric study. *J Psychiatr Res* 2008a; **42**: 868–876.
220 Steiner J, Bielau H, Brisch R, Danos P, Ullrich O, Mawrin C *et al*. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. *J Psychiatr Res* 2008b; **42**: 151–157.
221 Stevens CD, Altshuler LL, Bogerts B, Falkai P. Quantitative study of gliosis in schizophrenia and Huntington's chorea. *Biol Psychiatry* 1988a; **24**: 697–700.
222 Stevens J, Casanova M, Bigelow L. Gliosis in schizophrenia. *Biol Psychiatry* 1988b; **24**: 727–731.
223 Togo T, Akiyama H, Kondo H, Ikeda K, Kato M, Iseki E *et al*. Expression of CD40 in the brain of Alzheimer's disease and other neurological diseases. *Brain Res* 2000; **885**: 117–121.
224 Wierzba-Bobrowicz T, Lewandowska E, Kosno-Kruszewska E, Lechowicz W, Pasennik E, Schmidt-Sidor B. Degeneration of microglial cells in frontal and temporal lobes of chronic schizophrenics. *Folia Neuropathol* 2004; **42**: 157–165.
225 Wierzba-Bobrowicz T, Lewandowska E, Lechowicz W, Stepień T, Pasennik E. Quantitative analysis of activated microglia, ramified and damage of processes in the frontal and temporal lobes of chronic schizophrenics. *Folia Neuropathol* 2005; **43**: 81–89.