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WFSBP CONSENSUS PAPER

Consensus paper of the WFSBP Task Force on Biological Markers: Criteria for biomarkers and endophenotypes of schizophrenia, part III: Molecular mechanisms

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ABSTRACT

Objectives: Despite progress in identifying molecular pathophysiological processes in schizophrenia, valid biomarkers are lacking for both the disease and treatment response.

Methods: This comprehensive review summarises recent efforts to identify molecular mechanisms on the level of protein and gene expression and epigenetics, including DNA methylation, histone modifications and micro RNA expression. Furthermore, it summarises recent findings of alterations in lipid mediators and highlights inflammatory processes. The potential that this research will identify biomarkers of schizophrenia is discussed.

Results: Recent studies have not identified clear biomarkers for schizophrenia. Although several molecular pathways have emerged as potential candidates for future research, a complete understanding of these metabolic pathways is required to reveal better treatment modalities for this disabling condition.

Conclusions: Large longitudinal cohort studies are essential that pair a thorough phenotypic and clinical evaluation for example with gene expression and proteome analysis in blood at multiple time points. This approach might identify biomarkers that allow patients to be stratified according to treatment response and ideally also allow treatment response to be predicted. Improved knowledge of molecular pathways and epigenetic mechanisms, including their potential association with environmental influences, will facilitate the discovery of biomarkers that could ultimately be effective tools in clinical practice.

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Introduction

Biomarkers for schizophrenia: needs and hurdles

The identification of biomarkers clinically useful to psychiatric disorders is one of the most challenging tasks in psychiatric research and of major concern in modern medicine. Dr Thomas Insel, the former Director of the National Institute of Mental Health, insightfully discussed the burden of psychiatric disorders in his 2013 TEDx talk (https://youtu.be/u4m65sbqbhY?t=3m56s). He based all his arguments on World Health Organization (WHO) data concerning disability-adjusted life years (DALYs), a measure of overall disease burden expressed as the number of years lost because of ill-health, disability or early death (Whiteford et al. 2013). The WHO data show that psychiatric disorders are responsible for almost 30 DALYs. This figure is more than double that for cardiovascular disorders, which are claimed to be one of the main disabling human disorders (Liu et al. 2013).

These DALY data prove by themselves the necessity of unravelling biomarkers for psychiatric disorders. In the case of schizophrenia in particular, the search for diagnosis biomarkers – plural and not singular, because it is clear that "the biomarker" for schizophrenia does not exist – evolved exponentially in the 2000s, but then plateaued after several failed attempts. For example, in 2010, on the basis of proteomic findings VeriPsych was proposed as a diagnostic test for schizophrenia (Schwarz et al. 2010). However, after three years of commercialisation in the USA, VeriPsych was discontinued. Those who work in the field understand the difficulty of establishing a biomarker product discovered in a scientific laboratory as a widespread tool for use in a group of clinically heterogeneous patients. The discontinuation of VeriPsych should not be viewed as a failure, but rather as a lesson in the magnitude of the hurdles we are facing when venturing to discover biomarkers. These hurdles are based on the multifactorial characteristics of schizophrenia such as the individual specificity of symptom dimensions and outcome. Many genes contribute to this disorder, each with a small effect, and also interact with environmental factors (Schmitt et al. 2014a, 2014b).

One may argue that nowadays diagnostic biomarkers might not actually be that important as diagnostic tools. Experienced clinicians can make precise diagnoses, despite the subjective nature of symptom-based assessment. On the other hand, psychopharmacological treatment with antipsychotics often is not effective in all symptom dimensions, and side effects are common (Hasan et al. 2012), indicating that treatment biomarkers are urgently needed for schizophrenia (Martins-de-Souza 2013). In the same context, the stratification of patients is also a challenge that can be tackled with biomarkers, in the sense of personalised medicine (Insel and Cuthbert 2015). Schizophrenia is an umbrella of disorders that result in complex dysfunctions at the molecular level and distinct biochemical pathways. Some patients might develop schizophrenia because of metabolic or neurotransmitter disturbances, others because of inflammatory processes (Schwarz et al. 2014). Whatever the root cause of the disorder, most patients show changes in neurophysiological parameters or brain structure and function (see part 1 and 2 of the consensus criteria) (Thibaut et al. 2015; Schmitt et al. 2016). In addition to diagnostic biomarkers, there is a need for biomarkers to identify whether a medication will be successful for specific symptoms, which in turn would require patients to be stratified. These biomarkers will approximate academia to the translational strategies that could be employed in clinical practice.

We could also argue here that biomarkers are needed for risk assessment and early detection of schizophrenia, both of which are even more challenging than the areas of application described above. However, regardless of the category of biomarkers – diagnosis, treatment or early detection – we need a deeper understanding of the molecular basis and dysregulated signalling pathways in schizophrenia. Improved knowledge of these factors, including their potential association with external and "environmental" influences, will facilitate the discovery of biomarkers that could finally be an effective tool in clinical practice.

The early origin of schizophrenia: when biomarkers emerge

In schizophrenia, susceptibility genes and their interactions with environmental factors play an important role during neurodevelopment and ultimately induce symptoms in early adulthood (Schmitt et al. 2014a). Pre-clinical studies have revealed that stress, drugs and a variety of other environmental factors lead to changes at the level of mRNA in the brain via epigenetic mechanisms, thus contributing to phenotypic differences in genetically identical individuals (such as monozygotic twins). Epigenetics summarises DNA and chromatin modifications that play a critical role in the regulation of various genomic functions and gene–environment interactions. For example, there is increasing evidence that DNA methylation markings could be passed on through the germline, which could imply inheritance without DNA sequence alterations.

However, DNA methylation includes a multitude of complex and intertwined functions, including gene expression, chromosomal integrity and recombinational events. Histone lysine methylation signals at gene promoters could be viewed as markers that differentiate between sites of active and silenced gene expression. In addition, there is increasing evidence that some components of the histone methylation machinery are critical for normal brain function and development. Therefore, histone methylation profiling at promoter regions could provide important clues about mechanisms of gene expression in human brain during development and in brain diseases (for review see Akbarian and Huang 2009).

Epigenetics in schizophrenia

DNA methylation

Methylation of cytosine bases within the genome is a major epigenetic mechanism occurring especially within CG-rich regions, so-called CpG islands. During methylation, DNA methyltransferases add a methyl group at position 5 of cytosine without causing changes in the DNA sequence itself. If this methylation occurs within the promoter region of genes, it results in a functional repression of transcription by altering the accessibility of RNA polymerase and transcription factors (Szyf 2014). DNA methylation enables high plasticity of transcriptional control and thus seems to represent disease-specific patterns. Recent studies emphasise that DNA methylation may contribute to schizophrenia discrepancies in discordant monozygotic twins (Petronis et al. 2003; Dempster et al. 2011; Kinoshita et al. 2013b). Several studies have implied that DNA methylation affects developmental processes, such as cell differentiation contributing to the aetiology of neurodevelopmental disorders (Guidotti et al. 2014; Kubota et al. 2014). Therefore, great effort was taken to investigate methylation patterns in schizophrenia and related disorders that point to their significance in processes affecting the central nervous system (CNS) (Guidotti et al. 2014; Schmitt et al. 2014a). To overcome the limitations of epigenetic studies in brain tissue, such as degradation of molecules during the post-mortem interval and effects of treatment with antipsychotics, there has been a recent focus on studying epigenomic signatures such as altered DNA methylation in peripheral tissue (e.g. blood and saliva) of schizophrenia patients and patients with related disorders (Table 1). Because the epigenomic profile is cell-type specific, it is considered to be different in peripheral tissues than in brain cells. However, certain regions of the periphery and CNS may share some common epigenetic characteristics (Dempster et al. 2011; Lunnon et al. 2014; Stenz et al. 2015). Nevertheless, peripheral tissue samples can be obtained much more easily, permitting larger samples to be collected and longitudinal studies to be performed. An epigenome-wide association analysis in peripheral tissue detected methylation differences at 923 CpGs in the discovery set (false discovery rate <0.2). Of these, 625 showed changes in the same direction, 172 of which were significant in the replication set ($P < .05$). Some of these replicated, differentially methylated positions are located in a top-ranked schizophrenia region identified in genome-wide association studies (GWAS; Montano et al. 2016).

Some caution is required when studying methylation profiles, because the epigenome may be altered also by malnutrition, infection, exposure to chemicals andecological conditions that influence physiological homeostasis. Even experiences related to the familial and social milieu can change the epigenomic landscape and result in neurodevelopmental diseases (Szyf 2015). Nicotine and alcohol abuse or medications (e.g. antipsychotics) may also alter the methylation profile. Nevertheless, identifying peripheral molecular biomarker epigenetic signatures for schizophrenia and related psychiatric disorders could be useful in the early detection and prediction of the disease and its progression or treatment response.

Several studies have already reported promising results for the use of distinct methylation changes as biomarkers to diagnose different psychiatric disorders. For example, the sensitivity, specificity andpositive and negative predictive values of fragile X diagnoses made with new-born blood spots were between 92 and 100% (Inaba et al. 2014). Numata et al. (2015) used methylation profiling of biomarkers in blood to diagnose major depressive disorder and were able to distinguish patients from controls with 100% sensitivity and specificity. Therefore, such approaches, particularly polygenic ones, seem promising, particularly in combination with other biomarkers from fields such as neurophysiology (Thibaut et al. 2015), GWAS, neuroimaging (Schmitt et al. 2016), and gene and protein expression.

Histone modifications

More than 100 amino acid residue-specific histone post-translational modifications (PTMs) exist in the vertebrate cell (Tan et al. 2011). These PTMs include mono- (me1), di- (me2) andtri-methylation (me3), acetylation and crotonylation, polyADP-ribosylation

Table 1. DNA methylation as a potential biomarker: summary of DNA methylation findings in peripheral samples from patients with schizophrenia.

Gene/s	Region	Chromosome	Method	DNA source	Sample size (*n*)	Hyper/HypoM	Ethnicity	Sensitivity/ specificity	Reference
DRD2	P	11q23	PCR + Sequencing	Lymphocytes	2 monozygotic twins (1 discordant/1 concordant SZ)	HypoM (SZ)	n.a.	n.a.	Petronis et al. (2003)
GABRB2	In	5q34	Bisulfite sequencing	Whole blood	30 SZ, 30CT	HyperM (SZ)	Chinese	n.a.	Pun et al. (2011)
ST6GALNAC1	P	17q25.1	Illumina Infinium	Whole blood	22 psychosis (SZ, BP) monozygotic discordant twin pairs	HypoM (psychosis)	91% Caucasian (UK)	n.a.	Dempster et al. (2011)
PUS3	U	11q24.2	HumanMethylation27 BeadChip + Sequenom EpiTYPER platform			HyperM (SZ)			
HTR1A	P	5q11.2-q13	HRM- PCR	Blood leukocytes	40 SZ,58 BP, 67 CT	HyperM (SZ & BP)	Swiss	n.a.	Carrard et al. (2011)
MB-COMT	P	22q11.21	qMSP	Saliva	63 SZ, 92 BP, 76 CT	HypoM (SZ & BP)	Iran	n.a.	Nohesara et al. (2011)
HTR2A	P	13q14-q21	qMSP	Saliva	63 SZ, 92 BP, 76 CT	HypoM (SZ)	Iran	n.a.	Ghadirivasfi et al. (2011)
FNDC3B	n.a.	3q26.31	MBD protein-enriched genome sequencing	Whole blood	750 SZ, 750 CT, 75 TR	n.a.	Swedish	n.a.	Aberg et al. (2012)
DCTN		9p13							
GRIA2		4q32.1							
HTRA3		4p16.1							
CAMK2D		4q26							
MAOA	P	Xp11.3	PCR + Sequencing	Whole blood	371 paranoid SZ, 288 CT	HyperM (SZ male)	Han Chinese	n.a.	Chen et al. (2012)
S-COMT	P	22q11.21	Pyrosequencing	Blood leukocytes	47 SZ, 47 CT	HyperM (SZ)	Swedish	n.a	Melas et al. (2012)
SLC6A4	P	17q11.2				No change (SZ)			
BDNF	P	11p13	MSP	Whole blood	80 SZ, 71 CT	HypoM (SZ)	Iran	n.a.	Kordi-Tamandani et al. (2012)
DAT1 (SLC6A3)	P	15p15.3				No change (SZ)			
BDNF	P	11p13	Pyrosequencing	Whole blood	100 SZ, 100 CT	HyperM (SZ) Stonger in male	Japanese	n.a.	Ikegame et al. (2013)
GRM2	P	3p21.1	MSP	Whole blood	81 SZ, 71 CT	HyperM (SZ)	Iran	n.a.	Kordi-Tamandani et al. (2013a)
GRM5	P	11q14.3				HyperM (SZ)			
GRM8	P	7q31.1-q32.1				No Change (SZ)			
GRIA3	P	Xq25				No change (SZ)			
CTLA4	P	2q33	MSP	Whole blood	94 SZ, 99 CT	HyperM (SZ)	Iran	n.a.	Kordi-Tamandani et al. (2013b)
CLDN12	P	7q21	Illumina Infinium	Whole blood	17FESZ, 15 CT	HypoM (FESZ)	Japanese	n.a.	Nishioka et al. (2013)
BCDIN3 (MEPCE)	P	7q22.1	HumanMethylation27 BeadChip array			HypoM (FESZ)			
ADAMTS3	P	4q13.3				HypoM (FESZ)			
COMT	P	22q11.21				Not changed			
HTR2A	P	13q14-q21				Not changed			
HTR1E	P	6q14-q15				HypoM (FESZ)			
COMTD1	P	10q22.2				HypoM (FESZ)			
B3GAT2	P	6q13	Infinium	Whole blood	24 medication free SZ, 23 CT + 3 SZ monozygotic discordant twin pairs	HyperM (SZ)	Japanese	n.a.	Kinoshita et al. (2013b)
HDAC4	P	2q37.3	HumanMethylation450 Beadchips						

(*continued*)

Table 1. Continued

Gene/s	Region	Chromosome	Method	DNA source	Sample size (*n*)	Hyper/HypoM	Ethnicity	Sensitivity/ specificity	Reference
SLC18A2 GNAL KCNH2 NTNG2	P P n.a. n.a.	10q25 18p11.22 7q36.1 9q34	Infinium HumanMethylation 450 Beadchips	Whole blood	42 male SZ, 42 male CT	HyperM (SZ) HypoM (SZ)	Japanese	n.a.	Kinoshita et al. (2013a)
n.a. (1161 promoter & CpG islands)	n.a.	n.a.	Infinium HumanMethylation 450 Beadchips	Blood leukocytes	63 SZ, 42 CT	n.a.	Japanese	n.a.	Kinoshita et al. (2014)
SLC6A4	P	17q11.2	qMSP	Saliva	30 SZ*, 20 BD, 30 CT	HyperM (SZ*)	Iran	n.a.	Abdolmaleky et al. (2014)
LRRTM1 DLX5	P In	2p12 7q22	454-bisulfite sequencing	Whole blood	41 sibships (99 subjects) with/ out SZ	HypoM (SZ) HypoM (SZ)	n.a.	n.a.	Brucato et al. (2014)
DRD4	In	11p15.5	Pyrosequencing	Whole blood	60 SZ, 30 CT	HyperM (SZ-male)	Han Chinese	AUC=0.832, Se=95%, Sp =70%	Cheng et al. (2014)
GCH1	P	14q22.1-q22.2	Clones and sequencing	Whole blood	51 FEP, 51 CT	HyperM (FEP)	Brazil	n.a.	Ota et al. (2014)
CD244 PRF1 FAM173A CBFA2T3 MPO SLC25A10 CKM H1F0	n.a. n.a. n.a. n.a. n.a. n.a. n.a. n.a.	1q23.3 10q22 16p13.3 16q24 17q23.1 17q25.3 19q13.32 22q13.1	Illumina Infinium Methylation27 Assay	Whole blood	98 SZ, 108 CT Validation- GSE-41037 (325 SZ, 394 CT)	HypoM (SZ) HyperM (SZ) HyperM (SZ) HypoM (SZ) HypoM (SZ) HypoM (SZ) HyperM (SZ) HypoM (SZ)	US ~80% white	n.a.	Liu et al. (2014)**
FAM63B PKDREJ/PPARA CREB1/METTL21A SMAD3 ARNT RELN	Ex, 3′UTR Ex Ex/In In In In	15q21.3 22q13.31 2q33.3-q34 15q22.33 1q21 7q22	Methyl-CpG–binding domain protein-enriched genome sequencing + next-generation DNA sequencing Pyrosequencing	Whole blood	759 SZ, 738 CT Replication 178 SZ, 182 CT 561 SZ, 582 CT	HypoM (SZ) HypoM (SZ) HypoM (SZ) HypoM (SZ) HypoM (SZ) HyperM (SZ)	Swedish	n.a.	Aberg et al. (2014)**
DTNBP1	P	6p22.3	qMSP	Saliva	30 SZ, 30 CT, 15 first-degree SZ	HyperM (SZ)	Iran	n.a.	Abdolmaleky et al. (2015)
n.a.	P, Intergenic & In	n.a.	MBD protein-enriched genome sequencing	Whole blood	Female: 1 Paranoid, 1 undifferentiated SZ, 1 CT	n.a.	Chinese	n.a.	Liao et al. (2015a)
TRIM45 HLA-DPA1 THEM6 C6orf123 Others	P, P P P Intergenic & In	1p13.1 6p21.3 8q24.3 6q27 n.a.	MBD protein-enriched genome sequencing	Whole blood	Male: 34 Paranoid, 22 undifferentiated SZ, 25 CT	HyperM (SZ + Paranoid)	Chinese	n.a.	Liao et al. (2015b)
172 CpG cites e.g. NCOR2 FAM63B	n.a.	n.a. 12q24 15q21.3	Infinium HumanMethylation 450 Beadchips	Whole blood (corrected to cell type)	689 SZ, 645 CT Replication: 247 SZ, 250 CT	n.a. HyperM (SZ) HypoM (SZ-Replication)	US ~37% white (SZ) ~ 65% white (CT) Replication: 100% white	n.a.	Montano et al. (2016)

(*continued*)

Table 1. Continued

Gene/s	Region	Chromosome	Method	DNA source	Sample size (*n*)	Hyper/HypoM	Ethnicity	Sensitivity/ specificity	Reference
OXTR	P (-934)	3p25	Pyrosequencing	Whole blood	57 SZ, 34 Schizoaffective, 76 BP, 75 CT	HyperM (SZ)	US ∼60% white	n.a.	Rubin et al. (2016)
Combination of GWAS, GWGE, GSEA, imaging & MWAS									
CREB1/METTL21A	Ex/In	2q33.3-q34	See Aberg et al. (2014); Ripke et al. (2013)	Whole blood	See Aberg et al. (2014); Ripke et al. (2013)	HypoM (SZ)	Swedish	n.a.	Kumar et al. (2015)
SDCCAG8	Ex	1q43				n.a.			
ATXN7	In	3p21.1-p12				HyperM (SZ)			
IL-1RAP (rs3796293)	In	3q28	MBD protein-enriched genome sequencing	Whole blood (compared to brain)	712 SZ, 696 CT Replication: 370 SZ, 377 CT	HypoM (SZ)	Swedish	n.a.	van den Oord et al. (2016)
432 CpG sites e.g.	n.a.		Illumina Infinium Methylation27 Assay	Whole blood	260 SZ, 250 CT (including GWAS and GWGE)	n.a.	n.a. (US)	n.a.	van Eijk et al. (2015)
CNNM2		10q24.32				HyperM (SZ)			
CALHM1		10q24.33							
hsa-miR-219a-5p	n.a.	6p21.32	Illumina Infinium Methylation27 Assay (GSEA)	Whole blood (combined with MRI hippocampal WM volume)	103 SZ, 111 CT	n.a.	n.a. (US)	n.a.	Hass et al. (2015)
e.g.			Illumina Infinium Methylation27 Assay	Whole blood (compared to brain)	111 SZ, 122 CT	n.a.	n.a. (US)	n.a.	Walton et al. (2016)
AVPR1A	P	12q14.2							
AVP	P	20p13							

and small protein (ubiquitin, SUMO) modification of specific lysine residues, as well as arginine (R) methylation and citrullination, serine (S) phosphorylation, tyrosine (T) hydroxylation and several others (Kouzarides 2007; Taverna et al. 2007; Tan et al. 2011). Different combinations of site- and residue-specific PTMs show differential enrichment across the genome, and some of the best-studied histone PTMs are defined in the context of transcriptional regulation. Given the relative ease with which histone PTMs could be studied in nearly all somatic tissues, at high resolution and on a genome-wide scale (Maze et al. 2014), this type of epigenetic information could have excellent potential as a biomarker. Any biomarker research studies that explore clinical parameters or treatment response in the context of a genetic risk architecture should consider histone PTMs. This is because histone PTMs such as tri-, di- and mono-methylated histone H3-lysine 4, or H3-lysine 9 and 27 acetylation, which in concert define the functional architecture of many regulatory elements such as promoters and enhancers, show differential regulation at the site of many risk-associated genetic polymorphisms in schizophrenia (Roussos et al. 2014). Thus, epigenomic profiling in patient and control specimens offers the potential opportunity to link genotype to phenotype, including differential gene expression (Glatt et al. 2011). Furthermore, there is very preliminary evidence that histone lysine methylation and acetylation in cultured lymphocytes show a differential response in relation to therapeutic drugs or diagnosis of schizophrenia or both (Gavin et al. 2008, 2009; Chase et al. 2013). If independently confirmed in larger-scale studies, taken together the aforementioned studies could pave the way for a comprehensive biomarker battery based on epigenetic profiling, genotype, and clinical parameters.

The role of microRNAs in schizophrenia

With the new technologies of next-generation sequencing, it became clear that the mammalian genome encodes for a large number of non-coding RNAs (ncRNAs). Because a biological function is yet to be discovered for most of these novel transcripts, the current classification is mainly based on size: ncRNAs smaller than 200 bases are referred to as "small ncRNAs", while the remaining ones are called "long ncRNAs". Here, we will focus on a group of small ncRNAs, the so-called microRNAs, which are 19–22 nt long and act as key regulators of protein homeostasis (Im and Kenny 2012). They are loaded to the RNA-induced silencing complex (RISC), which catalyses miRNA-mediated gene silencing or inhibition of protein translation. Notably, one miRNA can target multiple mRNAs, and in turn one mRNA can be targeted by more than one miRNA, giving rise to a complex regulatory network of gene expression and protein homeostasis. GWAS studies have implicated microRNAs, such as miR137, in schizophrenia (Willemsen et al. 2011; Forstner et al. 2013; Lett et al. 2013; Ripke et al. 2013). This is interesting because miR137 targets genes linked to schizophrenia, such as Tcf4 or Cacna1c (Forstner et al. 2013; Navarrete et al. 2013). A number of recent studies found several miRNAs to be deregulated in the post-mortem brain samples of schizophrenia and bipolar patients (Banigan et al. 2013; Kolshus et al. 2014; Smalheiser et al. 2014; Pietersen et al. 2014a,b). Of note, there is first evidence that changes in the miR signature may be suitable as a blood biomarker for the prediction of disease pathogenesis and treatment efficacy (de la Morena et al. 2013; Rao et al. 2013b). This is of particular interest, because emerging data suggest that brain-derived microRNAs may play a key role in epigenetic inheritance of cognitive abilities (Gapp et al. 2014). In conclusion, these data suggest that even the analysis of peripheral microRNA signatures may lead to the discovery of novel bio- and surrogate markers that may also point to relevant aetiopathogenic mechanisms (Rao et al. 2013b).

Epigenetic therapies for schizophrenia

Despite the widespread use of antipsychotics, the majority of patients diagnosed with schizophrenia show an incomplete response to treatment (an der Heiden and Häfner 2011), and many of the negative and cognitive symptoms do not respond to pharmacological treatment (Ibrahim and Tamminga 2011). It remains to be seen whether or not the knowledge gained by the field of neuroepigenetics will lead to improved treatment options in the future. Interestingly, both typical antipsychotics acting as dopamine D_2 receptor antagonists and atypicals with broad receptor profiles affect DNA methylation and histone modification levels in various forebrain structures (Li et al. 2004; Dong et al. 2008; Akbarian 2010; Kurita et al. 2012). Conversely, some of the chromatin-modifying drugs, such as the histone deacetylase inhibitors (HDACi), profoundly affect brain metabolism and behaviour in the animal model (Fischer et al. 2007; Schroeder et al. 2007; Vecsey et al. 2007; Abel and Zukin 2008; Kurita et al. 2012; Schroeder et al. 2013). However, as recently discussed, HDACi currently approved for clinical use (with certain types of cancer as the primary indication) exhibit a safety profile that

requires further exploration and testing before one would embark on exploratory studies in psychiatric populations (Hasan et al. 2013). The HDACi are not the only type of chromatin-modifying drugs shown to robustly affect complex behaviours in the animal model. As discussed, a subset of drugs acting as inhibitors of histone or DNA methyltransferases or topoisomerases (DNA-cleaving enzymes involved in transcription and chromatin remodelling (Salerno et al. 2010)) robustly affect brain function and behaviour. In this context, drugs that interfere with regulation of histone H3-lysine 4 (H3K4) methylation – an epigenetic mark often enriched at promoters, enhancers, and other regulatory sequences involved in the regulation of gene expression – are of particular interest, given that regulators of methyl-H3K4 rank prominently among all risk polymorphisms implicated in GWAS involving more than 60,000 participants with psychiatric disease and controls (Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium 2015).

Gene expression

Since its first publication in 2009 (Stefansson et al. 2009), the psychiatric genomics consortium (PGC, http://www.med.unc.edu/pgc) has greatly increased the sample sizes of GWAS: the most recent analysis published in 2014 included 113,075 controls and 36,989 schizophrenia cases (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). The emerging picture is that common genetic variants that individually contribute a small risk for schizophrenia are nearly exclusively located in non-coding, intra- and intergenic regions of the genome (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). Genomic alterations such as copy number variations, however, more frequently affect parts that directly code protein but are rarely found in general or schizophrenia populations (Rees et al. 2011). Thus, it seems likely that common genetic risk variants mainly affect regulatory elements of the genome and thus alter mRNA and microRNA gene expression networks causally implicated in the aetiology of the disease (Sullivan et al. 2012).

ncRNA plays a critical role in regulating the timing and rate of protein translation. As mentioned above, microRNAs regulate gene expression post-transcriptionally by suppressing translation or destabilising mRNAs. Furthermore, they may play a role in brain development. The potential importance of these ncRNAs is suggested by the fact that the complexity of an organism is poorly correlated with its number of protein-coding genes, and that in the human genome only a small percentage (2–3%) of genetic transcripts are translated into proteins (Qureshi and Mehler 2012).

A more recent pathway-oriented follow-up analysis of GWAS data supports these assumptions because the most significant pathways are comprised of gene sets that control histone methylation, synapse development and immune functions (Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium 2015). These observations are congruent with the hypotheses that complex epistatic interactions of risk alleles are implicated in the control of gene expression to alter transcription networks affecting foetal brain development. Ca^{2+}-mediated synapse-to-nucleus signalling (Bading 2013), however, appears to be associated with postnatal stages that modulate aspects of neuronal plasticity (Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium 2015). The association of immune function-related gene sets with schizophrenia may add evidence to the immunological hypothesis of the disease (Benros et al. 2012), although it may also be interpreted as a non-inflammatory deregulation of microglia gene expression networks that control microglial functions implicated in synaptic and axonal pruning processes and ultimately fine tune neuronal networks during young adulthood (Prinz and Priller 2014). Another observation from a recent GWAS pathway analysis supports the implication that oligodendrocyte-/myelin-associated gene expression networks are associated with schizophrenia (Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium 2015). This finding is congruent with a series of globally scaled gene expression studies in post-mortem brain samples that have most consistently identified synaptic and immune genes (Schmitt et al. 2011, 2012) as well as oligodendrocyte/myelin genes to be deregulated in schizophrenia (Takahashi et al. 2011). Although these findings strongly implicate alterations at the level of gene expression as a central and causal aspect of schizophrenia, neither the available genetic information nor post-mortem brain gene expression studies provide immediate progress towards translational biomarker discovery. Nonetheless, the enormously complex genetic architecture implicating regulatory genetic elements in schizophrenia makes it highly likely that gene expression networks in extra-brain tissues may be altered in at-risk individuals compared to controls and may in consequence carry diagnostic and potentially also prognostic information. In accordance with this assumption and for reasons of practicability, gene expression-based biomarker research has nearly exclusively focussed on blood-derived samples. A PubMed survey revealed a steady increase since 2000

of publications on gene expression in blood samples from schizophrenia patients (Figure 1). Despite more than 300 publications on the topic, diagnostic biomarkers with clinical value that are based on gene expression profiles have not yet been identified. However, cross-comparing data sets generated by different laboratories is usually challenging because of the use of different experimental designs, the diversity across and within cohorts, the limited sample sizes, the effects of disease treatments before death on gene expression, the comorbidity with other disorders, and the risk of type II errors. The specificity of the findings is also questionable. In addition, the question of the primary or secondary origin of these gene expression alterations is difficult to answer. Finally, there is a low concordance between proteomic and transcriptomic data sets. Unfortunately, these important translational and post-translational events are key biological regulatory mechanisms that are not assessed by any of the methods used to investigate the transcriptome.

Proteomics

The term "proteome" was coined in 1995 (Wilkins et al. 1996) and comprises the whole set of proteins produced by a biological system, be it a cell, a tissue or an organism, in a particular state, at a given time. Proteomics, the science that studies the proteome, is a suitable tool to study multifactorial diseases, such as schizophrenia, because it deals with both integration of molecular pathophysiology and identification of biomarkers (Martins-de-Souza et al. 2012). The complexity of schizophrenia reinforces the need to unravel its molecular mechanisms. These mechanisms are essential for the identification and validation of biomarkers for diagnosis, prognosis, and medication monitoring, and of drug targets that provide the basis for clinical trials (Hyman 2014). Several proteomic platforms have been employed in schizophrenia research, such as two-dimensional gel electrophoresis (2DE and 2D-DIGE), mass spectrometry-based shotgun proteomics, and antibody-based multiplex profiling approaches (Martins-de-Souza 2011). The use of these techniques rendered proteins that could not only provide new insights into the disease's pathophysiology but also reveal proteins that may serve as diagnostic biomarker candidates (Table 2). Prognosis and medication-monitoring biomarkers remain to be explored more deeply by proteomics (Martins-De-Souza et al. 2010a).

Post-mortem brain is the most frequently studied tissue in schizophrenia proteomic research (Martins-De-Souza et al. 2010a, 2010b; Föcking et al. 2011, 2015; Martins-de-Souza 2012; Wesseling et al. 2013). The main findings of such research include major effects on neuronal structure, signalling, and energy metabolism (Martins-de-Souza et al. 2012). Some of the proteins of neuronal transmission and synaptic plasticity, which include several cytoskeletal constituents, are neuroreceptors such as *N*-methyl-D-aspartate (NMDA) receptors; glial fibrillary acidic protein; and glutamatergic signalling molecules, e.g. neurofilaments (light polypeptide and medium polypeptide), glutamate-ammonia ligase, and dihydropyrimidinase-related protein 2. Other proteins associated with dysfunction of glucose metabolism, energy production, and oxidative stress are aldolase c (ALDOC), lactate dehydrogenase B (LDHB), superoxide dismutase (SOD1) and peroxiredoxins (PRDX 2, 4, 6) (Martins-de-Souza et al. 2011). Proteomic studies in brain tissue have contributed to the comprehension of the pathophysiology of schizophrenia from the molecular point of view. However, when considering applications that can be brought closer to the bedside, diagnostic biomarkers that might be useful for classifying diseases and monitoring medication response are needed (Oliveira et al. 2013). Studies were conducted to reveal biomarker candidates in cerebrospinal fluid (CSF; Huang et al. 2006, 2007; Martins-de-Souza et al. 2010b; Albertini et al. 2012), blood serum and plasma (Domenici et al. 2010; Levin et al. 2010; Schwarz et al. 2010, 2012a; Jaros et al. 2012), liver (Huang et al. 2007; Prabakaran et al. 2007), fibroblasts (Wang et al. 2010), among others (Herberth et al. 2011; Iavarone et al. 2014). On the other hand, studies in saliva and urine are still scarce (Iavarone et al. 2014).

Because of its closeness to the brain and periphery, CSF was investigated in several proteomic studies in schizophrenia patients (Huang et al. 2006, 2007; Zougman et al. 2008; Martins-De-Souza et al. 2010a; Albertini et al. 2012; Maccarrone et al. 2013). Maccarrone et al. (2013) proposed a list of biomarker candidates that combine new and previous proteomic analyses of CSF from psychiatric patients (Maccarrone et al. 2004; Ditzen et al. 2012). As concerns schizophrenia, the list of potential candidates includes proteins such as CHGA, FN1, GPX1, HSPA12A, IGSF8, MAP2, NFASC and PTPRZ1. In addition, differential expression of proteins such as APOA1, APOE and PGD2 was observed in the CSF from schizophrenia patients, confirming the hypothesis of disturbed cholesterol and phospholipid metabolism in the disorder (Huang et al. 2008; Martins-De-Souza et al. 2010d). PGD2 plays a role in the arachidonic acid (AA) pathway, which was previously associated with the disorder (Condray and Yao 2011; Rao et al. 2013a). Furthermore, altered levels of MBP and MOG were detected in the CSF of schizophrenia patients (Martins-

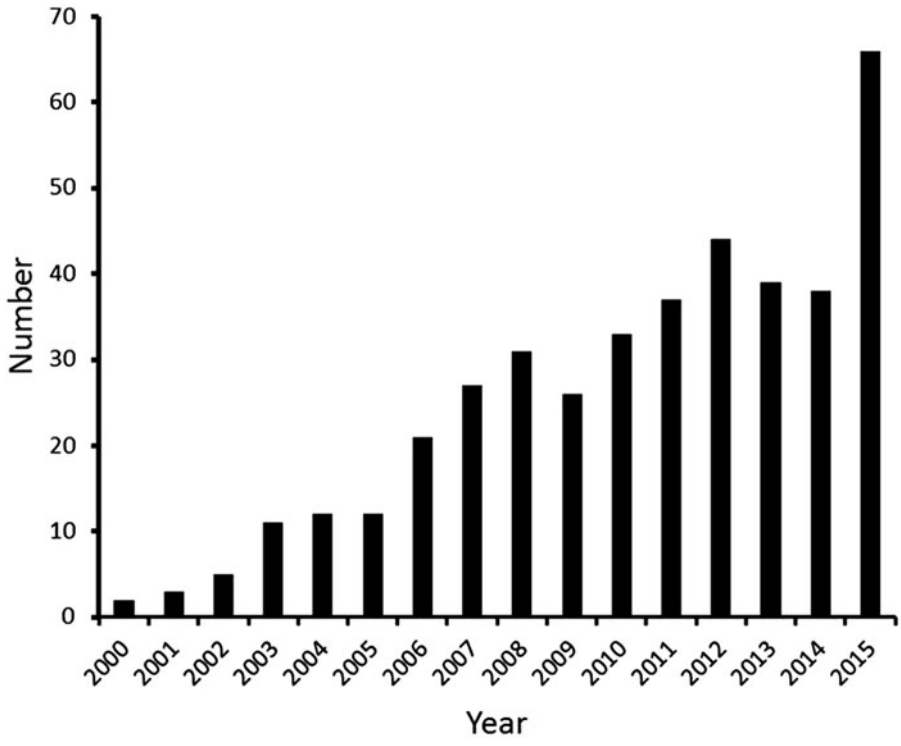

Figure 1. PubMed literature survey of gene expression studies in schizophrenia that used blood samples. The search terms "gene" AND "expression" AND "blood" AND "schizophrenia" AND "year" were used to identify the numbers of corresponding publications from 2000 to 2014. In 2000, only two publications were found, whereas an average of 40 publications per year were found for 2011–2014 and even more in 2015.

De-Souza et al. 2010a), supporting the importance of oligodendrocytes in the disease (Haroutunian et al. 2014; Nave and Ehrenreich 2014).

Peripheral blood is one of the most valuable samples for biomarker discovery, validation and clinical use because of the ease of collection and biological significance. The use of STRING (search tool for the retrieval of interacting genes/proteins) (Franceschini et al. 2013) to visualise functional protein association networks (http://string-db.org) allows us to depict a cluster of the most consistently differentially expressed proteins in the blood samples of schizophrenia patients (Table 2, Figure 2). Several abnormalities associated with immune and inflammation pathways have been described in first-onset drug-naïve schizophrenia patients, such as interleukins (IL-10, IL-17, IL-ra), ICAM1 and CCL5 (Schwarz et al. 2012b, 2014). Indeed, IL-1ra and IL-10 levels decreased after treatment with atypical antipsychotics and were correlated with symptom improvement (de Witte et al. 2014).

Antineuronal autoantibodies can act as syndrome modulators

The excitatory amino acid glutamate is the most important neurotransmitter in the brain. Glutamate acts on different glutamate receptor subtypes, such as ionotropic receptors, e.g. NMDA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate receptors, and metabotropic glutamate receptors. The glutamate (or NMDA receptor) hypothesis of schizophrenia was first proposed in the early 1980s (Kim et al. 1980). This hypothesis evolved from work showing low glutamate levels in the CSF of schizophrenia patients (Kim et al. 1980) and from the clinical findings that phencyclidine and its congener ketamine, which block NMDA receptors, induce both schizophrenia-like psychosis with positive and negative symptoms and cognitive impairment in healthy subjects (Javitt and Zukin 1991; Krystal et al. 1994; Kornhuber and Weller 1997). The proposed neurophysiological biomarkers (e.g. prepulse inhibition, auditory P50 gating, mismatch negativity, γ oscillations and smooth pursuit eye movements) in schizophrenia (Thibaut et al. 2015) are associated with glutamatergic neurotransmission in the brain (Javitt et al. 2008).

Circulating autoantibodies (ABs) directed against brain epitopes have long been known and mainly associated with classical autoimmune diseases or paraneoplastic syndromes (Sutton and Winer 2002; Diamond et al. 2009; Coutinho et al. 2014). In particular, the recent discovery of ABs against the NMDA

Table 2. Proteomic findings (since 2010) from studies in peripheral blood and post-mortem brain samples from schizophrenia patients compared to controls.

Gene symbol	Protein name	References
Most common proteins found in blood samples		
A2M	Alpha-2-macroglobulin	Domenici et al. (2010); Schwarz et al. (2010, 2012a)
APOA1	Apolipoprotein A1	Domenici et al. (2010); Schwarz et al. (2010, 2012b); Jaros et al. (2012)
BDNF	Brain-derived neurotrophic factor	Domenici et al. (2010); Schwarz et al. (2010, 2012a, 2014)
C4BP	Complement component 4 binding protein	Jaros et al. (2012); Li et al. (2012)
CCL5	Chemokine (C-C motif) ligand 5	Domenici et al. (2010); Schwarz et al. (2012a)
CD5L	CD5 molecule-like	Li et al. (2012); Schwarz et al. (2012b)
CHGA	Chromogranin A (parathyroid secretory protein 1)	Guest et al. (2011); Schwarz et al. (2012b)
CTGF	Connective tissue growth factor	Schwarz et al. (2012a, 2012b)
EGF	Epidermal growth factor	Domenici et al. (2010); Schwarz et al. (2012a)
F7	Coagulation factor VII	Li et al. (2012); Schwarz et al. (2012a)
GOT1	Glutamic-oxaloacetic transaminase 1	Schwarz et al. (2012a, 2012b)
HGF	Hepatocyte growth factor	Schwarz et al. (2012b, 2012c)
ICAM1	Intercellular adhesion molecule 1	Li et al. (2012); Schwarz et al. (2012a)
IGFBP	Insulin-like growth factor binding protein	Jaros et al. (2012); Schwarz et al. (2012a)
IL-10	Interleukin 10	Schwarz et al. (2012a); de Witte et al. (2014)
IL-16	Interleukin 16	Schwarz et al. (2012c, 2014)
IL-17	Interleukin 17	Schwarz et al. (2012a, 2012b)
IL-1RN	Interleukin 1 receptor antagonist	de Witte et al. (2014); Schwarz et al. (2014)
INS	Insulin	Domenici et al. (2010); Guest et al. (2011); Schwarz et al. (2012c, 2014)
ITIH	Inter-alpha-trypsin inhibitor heavy chain	Jaros et al. (2012); Li et al. (2012)
LHB	Luteinizing hormone beta polypeptide	Schwarz et al. (2010; 2012a)
MIF	Macrophage migration inhibitory factor	Schwarz et al. (2012a, 2014)
PROS1	Protein S (alpha)	Li et al. (2012); Schwarz et al. (2012b)
SCF	Stem cell factor	Domenici et al. (2010); Schwarz et al. (2012a)
SERPINA7	Serpin Peptidase Inhibitor, clade A, member 7	Domenici et al. (2010); Schwarz et al. (2012b)
SPP1	Secreted phosphoprotein 1	Schwarz et al. (2012b, 2012c)
Most common proteins found in brain samples		
ACTB	Actin, beta	Martins-de-Souza et al. (2010b, 2010c); Föcking et al. (2011)
DPYSL	Dihydropyrimidine-like	Martins-de-Souza et al. (2010c); Föcking et al. (2011)
GFAP	Glial fibrillary acidic protein	Martins-de-Souza et al. (2010b); Föcking et al. (2011)
GLUL	Glutamate-ammonia ligase	Martins-de-Souza et al. (2010b, 2010c)
HSPA8	Heat shock 70kDa protein 8	Martins-de-Souza et al. (2010b); Föcking et al. (2011)
NEFL	Neurofilament, light polypeptide	Martins-de-Souza et al. (2010c); Föcking et al. (2011); Saia-Cereda et al. (2015)
NEFM	Neurofilament, medium polypeptide	Martins-de-Souza et al. (2010b, 2010c); Saia-Cereda et al. (2015)
PRDX6	Peroxiredoxin 6	Martins-de-Souza et al. (2010c); Wesseling et al. (2013); Saia-Cereda et al. (2015)
TUBB	Tubulin, beta	Martins-de-Souza et al. (2010c); Föcking et al. (2011); Saia-Cereda et al. (2015)

receptor subunit NR1 (NMDAR1-ABs) in connection with a condition called anti-NMDA receptor encephalitis (Dalmau et al. 2008) has raised hopes that these ABs may potentially explain an "immunological subgroup" of schizophrenia, thereby also serving as biomarkers for these discrete cases (Steiner et al. 2013, 2014). This hope was originally nurtured by (1) the description of anti-NMDA receptor encephalitis symptoms, which typically include psychosis and cognitive decline (Dalmau et al. 2008), and (2) the functionally similar consequences of AB-induced NMDAR1 internalisation and receptor antagonism by ketamine, MK801, or related drugs; both (1) and (2) support the glutamate hypothesis of schizophrenia (Laruelle 2014). Meanwhile, as explained in the following, this concept has had to be revised, and it is safe to say that NMDAR1-Abs, as well as probably most other serum ABs against brain epitopes, are per se not indicators or biomarkers of schizophrenia or any other neuropsychiatric diseases (Dahm et al. 2014; Hammer et al. 2014a).

In fact, an unexpectedly high seroprevalence of NMDAR1-ABs (which was age dependent up to >20%) was recently reported in both healthy people and patients with a neuropsychiatric disorder (schizophrenia, schizoaffective disorder, unipolar and bipolar depression, personality disorders, Parkinson's disease, stroke and amyotrophic lateral sclerosis) (total $N = 4236$). AB titres and immunoglobulin (Ig) class and functionality were comparable across all groups, no matter whether healthy or ill (Steiner et al. 2013, 2014; Dahm et al. 2014; Hammer et al. 2014a). To test whether similar results would be obtained for 24 other brain antigen-directed ABs previously connected with pathological conditions, the research groups also screened the serum of these 4,236 individuals for ABs against e.g. amphiphysin, ARHGAP26, CASPR2, dopamine receptors D1-D5, MOG, GAD65, Ma2, Yo and Ma1. As for NMDAR1-ABs, comparable seroprevalence, AB titres, and Ig class distribution were noted across all groups, healthy or ill, even though the maximum seroprevalence of these ABs (2%) was much lower than that of NMDAR1-Abs, which showed an age-dependent seroprevalence of up to >20% (Busse et al. 2014; Dahm et al. 2014). Moreover, when considering

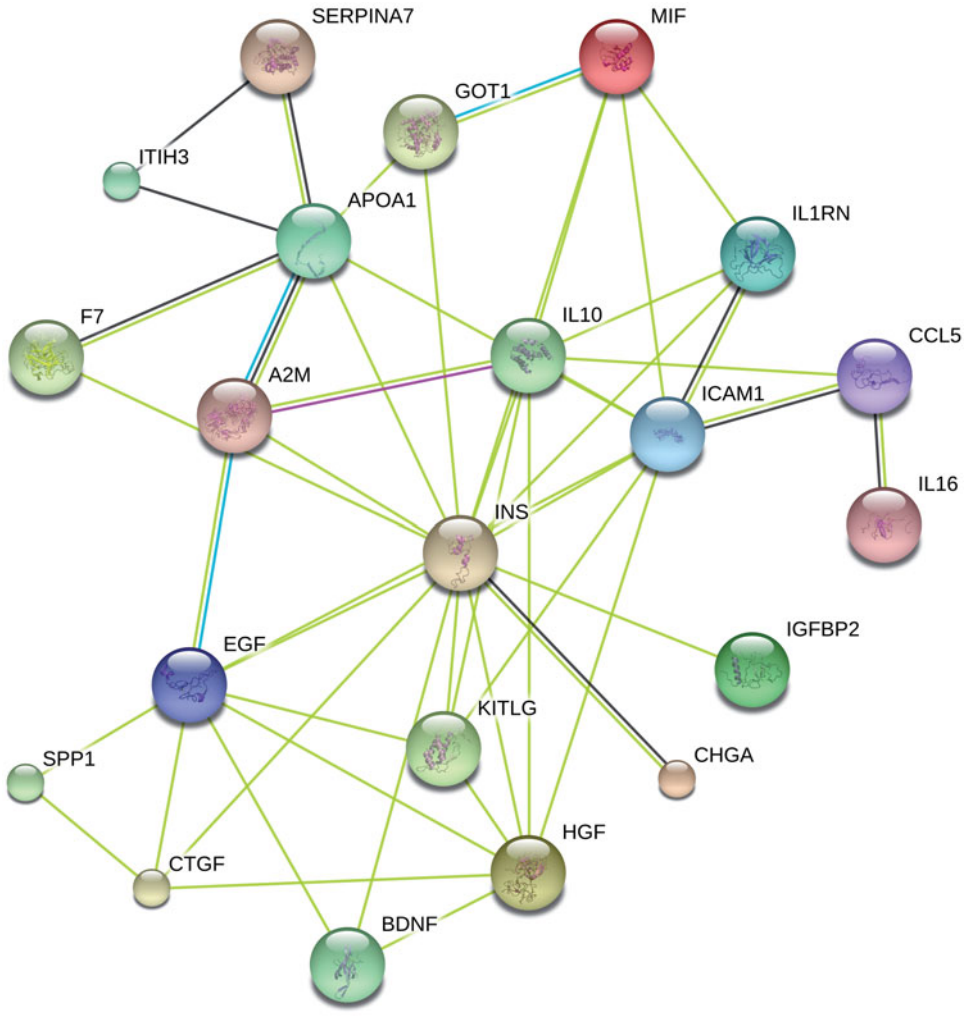

Figure 2. Network visualisation of proteins commonly found to be differentially expressed in the peripheral blood of schizophrenia patients compared to controls. The network was analysed by STRING (search tool for the retrieval of interacting genes/proteins: http://string-db.org).

both the cellular location of the selected 24 antigens and the Ig class of the circulating ABs, Dahm et al. (2014) made the surprising observation that the predominant Ig class depended on antigen location, with intracellular antigens predisposing to IgG (chi square $=218.91$, $P = 2.8 \times 10^{-48}$). The fact that NMDAR1-AB titres and Ig class and functionalty, as tested by an in vitro NMDAR1 internalisation assay (Hammer et al. 2014a, 2014b), were comparable among disease groups and healthy individuals raised the fundamental question of why healthy AB carriers are healthy and why, e.g. AB-positive schizophrenia patients do not show any deterioration of their symptoms (Hammer et al. 2014a). This led to the hypothesis that in the presence of an intact blood–brain barrier (BBB) ABs would not enter the brain in amounts sufficient to exert any appreciable effects.

This hypothesis was supported by a series of experiments and by retrospective analyses for consequences of serum ABs in conditions of BBB breakdown: (1) *ApoE* KO mice with well-established BBB leakage (Fullerton et al. 2001; Saher et al. 2012), injected intravenously with extracted serum Ig from human NMDAR1-AB carriers, showed alterations in spontaneous open-field activity and in the response to MK-801 (Hammer et al. 2014a); (2) seropositive individuals with a history of neurotrauma or birth complications had more neurological abnormalities than seronegative patients (Hammer et al. 2014a); and (3) the interaction of A*POE4* carrier status, causing leakage of the BBB that increases with age (Halliday et al. 2013), and NMDAR1-AB seropositivity, was associated with schizoaffective disorder ($P = .001$, odds ratio $= 6.109$) (Hammer et al. 2014b). As regards potential predisposing factors for NMDAR1-AB formation, besides ovarian teratoma (as described in the original paper on anti-NMDAR1 encephalitis; Dalmau et al. 2008), a GWAS on AB carriers versus non-carriers identified a

genome-wide significant hit for a common genetic variant (rs524991) (Hammer et al. 2014a). In addition, individuals with ABs against influenza A or B were found more likely to be NMDAR1-AB seropositive, suggesting molecular mimicry as a potential inducer of NMDAR1-AB formation. Other common neurotropic infections, including those with members of the herpes virus family, or HLA alleles did not reveal any association (Hammer et al. 2014a).

In a subsequent hypothesis-driven study on patients with acute ischaemic stroke in the middle cerebral artery territory, pre-existing serum NMDAR1-ABs were protective in individuals with a hitherto intact BBB, leading to reduced evolution of lesion size from days 1 to 7 (Zerche et al. 2015). Probably because of AB consumption after stroke, NMDAR1-AB titres dropped on day 2, but had risen to previous levels again by day 7. The effects of NMDAR1-ABs were comparable among Ig classes also in this study (Zerche et al. 2015).

Beside NMDAR1-ABs, more than 10 antigenic targets causing psychosis are known (Pollak et al. 2016) and we expect many more targets for autoimmunity to be identified. Together, these findings challenge an unambiguous causal relationship of brain antigen-directed serum ABs with brain disease. Rather, they suggest that (1) ABs directed against brain antigens contribute to shaping our brain functions in disease states associated with BBB breakdown, e.g. in inflammatory conditions; and (2) a thus far underexplored extensive "physiological autoimmunity" may account for a novel category of epigenetic modulation.

Cytokine networks and immune-neurotransmitter interplay

Inflammation has long been associated with psychiatric illnesses. The most widely investigated molecules involved in neuroinflammation are cytokines, i.e. pleiotropic glycoproteins produced by both peripheral immunocompetent cells and glial cells in the CNS. Cytokines usually have a role in mediating immune signals and inflammatory processes in the peripheral system; however, in the CNS they are also involved in various neural interactions such as neurogenesis and synaptic plasticity. This may be the most prominent characteristic distinguishing "neuroinflammation" from systematic inflammation. Pro-inflammatory cytokines such as IL-1β, IL-6, and tumour necrosis factor alpha (TNF-α) primarily mediate and facilitate neural activity as well as inflammatory processes. Particularly during the early period of development, activated pro-inflammatory cytokines may exert detrimental effects on the brain. There is mounting evidence that prenatal exposure to pro-inflammatory cytokines induces impaired spatial memory, neuronal loss, and gliosis in the hippocampus (Samuelsson et al. 2006). These neurodevelopmental injuries due to excessive pro-inflammatory cytokines can also raise susceptibility to schizophrenia (Brown & Derkits 2010; Na et al. 2014) (Figure 3). First-episode schizophrenia patients have been investigated during 12 months follow-up and a severe pro-/anti-inflammatory dysregulation has been detected. Especially cyclooxgygenase-2 expression, nuclear transcription factor κB, inducible nictric oxide synthase, nitrites and PGE2 are increased as proinflammatory biomarkers in schizophrenia, while anti-inflammatory biomarkers are decreased at first episode, e.g. inhibitory protein (IκBα), prostaglandin 15d-PGJ2, peroxisome proliferator activated receptor gamma (Garcia-Bueno et al. 2014a). An imbalance hypothesis of schizophrenia has been proposed with increase in intracellular components of an inflammatory pathway along with a decreased expression in the anti-inflammatory pathways that act as potential protection factors (Garcia-Bueno et al. 2014b; Leza et al. 2015). This leads to the development of new treatment strategies such as anti-inflammatory or anti-oxidant drugs as add-ons to antipsychotics in schizophrenia (Leza et al. 2015).

The activities of pro-inflammatory cytokines are mainly regulated by microglia. Microglia cells are resident within the CNS and have immune functions similar to macrophages, which exhibit phagocytic activity as scavengers. Microglia cells account for approximately 15% of the total cells in the brain; they are involved in various neural activities and also have immunological functions. Under normal physiological conditions, microglia cells remain in the resting phenotype and exert neurotrophic activities such as promotion of synaptogenesis and neurogenesis and the activation of neurotrophic factors via stimulation of pro-inflammatory cytokines (Domenici et al. 2010). However, when the brain is injured and the homeostasis of the microenvironment is disturbed, microglia become active and produce large amounts of pro-inflammatory cytokines, chemokines and reactive oxidants (Lehnardt 2010). These increased pro-inflammatory mediators do not necessarily damage normal tissues; rather, the primary aim of this inflammatory surge is to defend and restore the neural integrity of the CNS. However, uncontrolled and sustained inflammatory alterations have detrimental effects and further exacerbate neuronal injury. With regard to chronic inflammation, the imbalance between pro- and anti-inflammatory activities determines the consequent

detrimental results, rather than the absolute amount of pro-inflammatory cytokines. Uncontrolled chronic inflammation in the CNS leads to excessive oxidative reaction and impaired neurogenesis. All these processes have been thought to contribute to vulnerability to severe mental illnesses such as schizophrenia. For example, pro-inflammatory cytokines and inflammation contribute to working memory deficits, one of the principal cognitive symptoms of schizophrenia (Holden et al. 2008).

Increased levels of pro-inflammatory cytokines are the most consistent immunological finding in schizophrenia (Kim et al. 2004; Miller et al. 2011). There is a controversial discussion whether these changes are linked with the pathophysiology of the disease or whether these elevated cytokine levels may reflect an unspecific phenomenon, e.g. due to increased levels of chronic stress perception. One important confounder is medication, especially antipsychotic treatment, because some of the antipsychotic drugs have immune-modulating properties. However, there is evidence for the heredity of elevated cytokine levels in schizophrenia patients: their non-affected relatives show elevated levels, too (Gaughran et al. 2002; Martinez-Gras et al. 2012). Moreover, distinct cytokines, including IL-1β, IL-6, and transforming growth factor β (TGF-β), appear to be state markers, while others like IL-12, interferon gamma, and TNF-α seem to be trait markers (Kirkpatrick & Miller 2013). In addition, higher plasma levels of IL-2 appear to be a promising and specific biomarker for schizophrenia (Drexhage et al. 2010), which may reflect the clinical symptoms as well as cognitive function (Asevedo et al. 2014) particularly since the levels decrease following treatment with antipsychotic drugs (Kim et al. 2001; Zhang et al. 2004). In first-episode schizophrenia patients, associations between the anti-inflammatory prostaglandin 15d-PGJ2 and sustained attention and cyclooxygenase-2 (COX-2) expression and executive function have been detected (Cabrera et al. 2016), pointing to clinical relevant effects of inflammatory biomarkers in schizophrenia. Further evidence for the relevance of an active immune process in schizophrenia comes from clinical trials that demonstrated the therapeutic effect of anti-inflammatory drugs – especially inhibitors of COX-2 (an enzyme that promotes inflammatory processes) (Muller et al. 2002, 2013). Because pro-inflammatory cytokines are strong inducers of COX-2 enzyme activity (Rummel et al. 2006), the therapeutic effect of COX-2 inhibitors may be linked to cytokine levels. Elevated pro-inflammatory cytokines and chronic neuroinflammation are also findings common to various neuropsychiatric diseases, such as Alzheimer's disease (Shaftel et al. 2008), Parkinson's disease (Tansey & Goldberg 2010), and major depressive disorders (Kim et al. 2007; Song & Wang 2011). Although the exact mechanisms remain unclear, current evidence suggests that neuroinflammation may involve neurotransmitter pathways. Currently, one of the most widely investigated functional links between the immune and neurotransmitter systems is the kynurenine pathway of tryptophan metabolism, which is crucially modulated

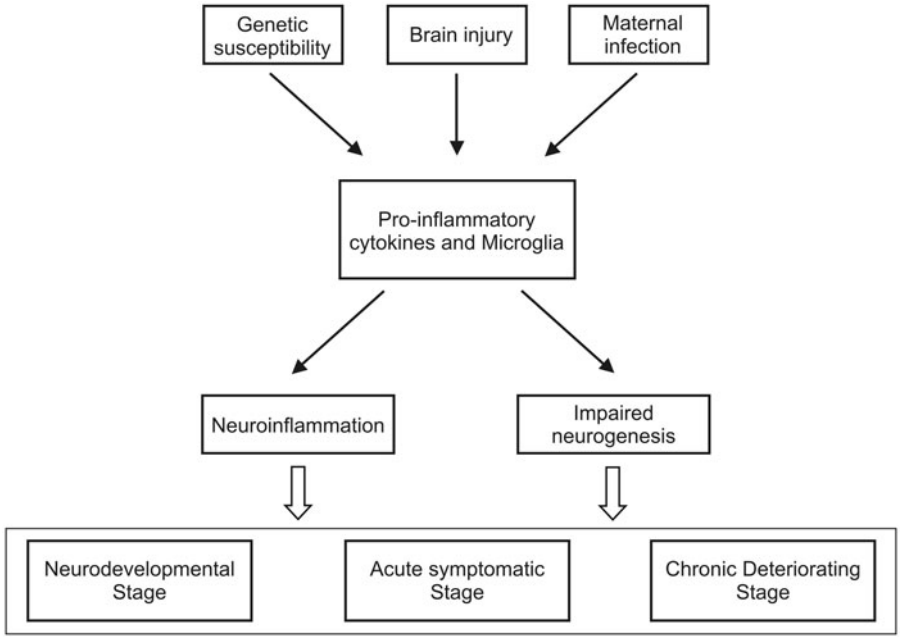

Figure 3. The possible role of cytokines in neuroinflammation and neurogenesis in schizophrenia.

by cytokines (Campbell et al. 2014). It would be beyond the scope of this article to go into details, but because of its neuroactive effects kynurenic acid seems to play a key role in the pathophysiology of schizophrenia (Schwarcz et al. 2012). Excessive kynurenic acid levels have been consistently reported to be associated with schizophrenia, especially in relation to cognitive deficits (for review see Muller et al. 2011). Interestingly, COX-2 inhibitors reduce kynurenic acid levels, whereas COX-1 inhibitors enhance them (Schwieler et al. 2005). This effect of COX-2 inhibitors on kynurenic acid levels could explain the therapeutic effect in clinical trials. On the other hand, COX-1 inhibitors could theoretically exacerbate the severity of schizophrenia symptoms. Several studies have reported that indomethacin, a drug with strong COX-1 inhibitory activity, is associated with psychosis (Tharumaratnam et al. 2000), supporting this theory. Altogether, there is evidence that anti-inflammatory treatment can ameliorate the psychopathology of schizophrenia by reducing pro-inflammatory cytokines, COX-2 activity, and kynurenic acid (Myint & Kim 2014). Moreover, induced by inflammatory stimuli in schizophrenia and bipolar disorder, microglia are known to activate the kynurenic acid pathway leading to blockade of the NMDA receptor and subsequent symptoms of psychosis (Sellgren et al. 2015). More comprehensive and in-depth studies are needed to figure out the complex network of kynurenine pathway alterations and the functional link of this pathway to cytokine changes in schizophrenia. There is a possibility that even similar cytokine profiles with increased pro-inflammatory cytokines could lead to depression or schizophrenia, depending on genetic and environmental susceptibilities. In summary, neuroinflammation appears to play an important role in the development of schizophrenia in the presence of genetic and prenatal vulnerabilities. Since the immune process is highly dynamic and changes are often transient, more research into the longitudinal patterns of immune profiles (the majority of studies have focussed on cross-sectional group differences) will be helpful to determine whether markers of this system are good candidates for indicating treatment response (Lai et al. 2016).

The role of phospholipase A2 and membrane metabolism in schizophrenia

Phospholipase A_2 (PLA_2) comprises a super-family of enzymes that have a major role in membrane phospholipid homeostasis. These enzymes catalyse the hydrolysis of the *sn-2* position of membrane phospholipids, yielding free fatty acid and lysophospholipids. The activity of PLA_2 generates intracellular signalling molecules and downstream products such as AA and choline (Schaloske & Dennis 2006; Burke & Dennis 2009). AA, a polyunsaturated omega-6 fatty acid, can be converted into pro-inflammatory lipid mediators, such as prostaglandins, leucotrienes and related compounds (Fenton et al. 2000; Kudo & Murakami 2002; Rao et al. 2013a). AA and its eicosanoid metabolites have been shown to regulate neural function through modulation of ion channels, second messenger systems, gene expression, and neurotransmitter uptake and release (Lautens et al. 1998).

PLA_2 enzymes are classified into three major groups on the basis of their structure, cellular localisation, requirement for Ca^{2+} and substrate specificity. The major groups of brain PLA_2 include secretory PLA_2 ($sPLA_2$), cystosolic PLA_2 ($cPLA_2$) and calcium-independent PLA_2 ($iPLA_2$). Expression, allelic analyses studies and genetic polymorphism associates PLA_2 with schizophrenia (Junqueira et al. 2004; Nadalin et al. 2008; Meng et al. 2010). PLA_2 subtypes are involved in distinct biological functions and processes. The subtypes $iPLA_2$ and $cPLA_2$ are related to neuronal degeneration and death, and both $cPLA_2$ and $sPLA_2$ are related to inflammatory processes (Lambeau and Gelb 2008; Schaeffer et al. 2011).

Evidence has been accumulating that schizophrenia involves abnormalities in the metabolism and composition of brain membrane phospholipids (du Bois et al. 2005). Increased PLA_2 activity was detected in serum, plasma and platelets of drug-free schizophrenia patients (Gattaz et al. 1987, 1990, 1995; Tavares et al. 2003), and this finding was replicated in blood and post-mortem brain tissue (Noponen et al. 1993; Ross et al. 1997, 1999; Smesny et al. 2005). Moreover, treatment with antipsychotic drugs was found to reduce PLA_2 activity significantly, restoring the enzyme activity in schizophrenia patients to levels similar to those observed in controls (Gattaz et al. 1987; Schmitt et al. 2001; Tavares et al. 2003).

Studies with ^{31}P-magnetic spectroscopy suggest an acceleration of phospholipid metabolism in the frontal lobe of schizophrenia patients. In these studies, researchers investigated the resonances of phosphomonoester (PME) and phosphodiester (PDE), the precursors and metabolites, respectively, of phospholipids in the brain. Schizophrenia patients showed a decrease of PME and an increase of PDE in the frontal lobe (Williamson et al. 1991; Fujimoto et al. 1992; Keshavan et al. 1993; Pettegrew et al. 1993; Deicken et al. 1994, 1995; Fukuzako et al. 1994; Hinsberger et al. 1997). An acceleration of phospholipids metabolism was also

found in the post-mortem frontal lobe of people diagnosed with schizophrenia (Horrobin et al. 1991). These brain findings support the results of earlier studies that showed a decreased phospholipids and AA concentration in the erythrocytes of schizophrenia patients (Rotrosen & Wolkin 1987; Glen et al. 1994; Peet et al. 1994) and an increased concentration of lysophosphatidylcholine metabolites in their platelet membranes (Pangerl et al. 1991; Schmitt et al. 2001).

Berger and collaborators proposed an increase of PLA_2 activity at the time of the first episode as a possible indicator of increased effort to maintain structural and functional integrity, potentially as a compensatory process after a developmental deficit or neurotoxic effects of acute psychosis (Berger et al. 2006).

A study of PLA_2 activity in the hippocampus of patients with epilepsy and psychosis also described an increase of this enzyme. Given the clinical similarities, it is conceivable that psychosis in epilepsy may share some common biological substrate with schizophrenia (Gattaz et al. 2011).

The alterations in membrane phospholipids seen in schizophrenia brains influence the stability, fluidity and permeability of neuronal membranes. Indeed, several studies have described an increased membrane fluidity in post-mortem brains from schizophrenia patients. Of interest is that the infusion of PLA_2 inhibitor into rat brain decreased the membrane fluidity in post-mortem brain tissue (Farooqui et al. 2000; Schaeffer et al. 2005; Eckert et al. 2011).

Structural changes in grey and white matter are related to vulnerability to schizophrenia, and molecular modification of cell membranes and myelin sheaths are a common factor underlying such vulnerability. This involves dynamic modelling, which includes both synthesis and break-down of phospholipid bilayers. A study by Smesny et al. (2010) was one of the first to provide a link between morphometric abnormalities in schizophrenia and a putative biochemical marker, a finding that gives potential insight into the pathology underlying brain structural changes in schizophrenia. These findings support the hypothesis that PLA_2 activity is associated with (and thus possibly modulates) certain regional brain structural changes in schizophrenia (Smesny et al. 2010).

Inflammatory lipids

As much as 50% of the dry mass of the brain is composed of lipids, making it an important reservoir for several lipid classes. The major brain lipid classes include fatty acyls and alcohols, complex glycerolipids, sphingolipids and sterols. Glycerolipids include neutral glycerides, phosphoglycerides (which contain phosphate, phosphocholine, phosphoethanolamine, phosphoinositol and phosphoserine headgroups) and glycosyl glycerides, while the group of sphingolipids consist of ceramides, sphingomyelin, cerebrosides, sulfatides and ganglosides (Sastry 1985). For a long time, the main function of brain lipids was assumed to be to insulate delicate neurons. However, it is now recognised that lipids not only provide a protective barrier but also are involved in several processes such as neuroinflammation, synaptogenesis, neurogenesis and modification of ion channels and receptor functions (Adibhatla and Hatcher 2007; Veloso et al. 2011) (Figure 4). Figure 4, point 1, highlights how the substrates (lipidomics) and enzymes (proteomics) interplay to generate known and plausible inflammatory lipid biomarkers of schizophrenia.

Genetics, environmental factors, and changes in immune conditions and neurotransmission can influence lipid metabolism. Under normal conditions, homeostasis in lipid metabolism and signalling of neurotransmitter and inflammatory cytokines is maintained. Under pathological conditions, however, there is dysfunction in the normal interaction between inflammatory lipid pathways and neurotransmitters or inflammatory cytokine signalling (Horrobin 1999; Condray and Yao 2011) (Figure 4, point 3).

Neuronal membrane compositions can be altered by lipolysis or by auto-oxidation of omega-6 and omega-3 polyunsaturated fatty acids (PUFAs) (Figure 4, point 2). AA (20:4n-6), the major omega-6 PUFA released by PLA_2 isoforms, is enzymatically modified by prostaglandin synthase 1/2 (PTGS) – also known as cyclooxygenases (COX 1/2) – to form an unstable intermediate, prostaglandin H_2 (PGH_2). Terminal synthases convert PGH_2 to prostaglandins (PGD_2, PGE_2, PGI_2) and thromboxanes (TXA_2 and TXB_2). Another group of enzymes, the lipoxygenases form hydroperoxyeicosatetraenoic acids, which are subsequently converted to leukotrienes (LTB_4, LTC_4/D_4/E_4). Prostaglandins, leukotrienes and cytochrome P450 products of AA are collectively known as eicosanoids. Eicosanoids and their fatty acid precursor play important roles in the pathophysiology of schizophrenia (Schmidt et al. 2013). Metabolism of phospholipids, fatty acids, and prostaglandins are altered in schizophrenia (Horrobin & Huang 1983; Ross 2003; Maida et al. 2006; Martinez-Gras et al. 2011) and thus represent potential biomarkers. Several other unsaturated fatty acids are modified by similar enzyme pathways to form oxylipins (Gabbs et al. 2015). Some oxylipins have inflammatory effects, while others are anti-inflammatory. Thus, interactions between

oxylipins and homeostatic deficits may contribute to schizophrenia.

The other PLA_2 product, lysophosphatidycholine, is acetylated to form another powerful inflammatory lipid known as platelet-activating factor (PAF). Although PAF is involved in neuronal function and brain plasticity, no genetic association was found between PAF metabolism and schizophrenia (Bell et al. 1997; Ohtsuki et al. 2002).

In addition to the above enzyme-catalysed pathways, auto-oxidation of PUFAs generates isoprostanes and neuroprostanes (Figure 4, point 5). These oxidised brain lipids are important in schizophrenia (Strassnig et al. 2005; Young et al. 2007; Dietrich-Muszalska & Olas 2009; Adibhatla & Hatcher 2010). Prostaglandins, leukotrienes and PAF act on specific receptors to mediate their inflammatory effects. Expression of these receptors has not been critically examined in schizophrenia. However, levels of the anti-inflammatory prostaglandin 15-deoxy-PGJ_2 and its nuclear receptor, the peroxisome proliferator-activated receptor, have been shown to be reduced in schizophrenia (Martinez-Gras et al. 2011) (Figure 4, point 5).

Omega-3 fatty acids (docosahexaenoic acid, DHA, 22:6n-3, and eicosapentaenoic acid, EPA, 20:5n-3) have recently been shown to form anti-inflammatory/immuno-resolving signalling lipids that counterbalance the activity of inflammatory signalling lipids (Serhan 2014; Serhan et al. 2015). Not surprisingly, omega-3 PUFAs have been shown to be beneficial in the management of schizophrenia (Peet 2006; Das 2013; Marano et al. 2013; Emsley et al. 2014). Thus, the ratio of omega-6 to -3 is a potential marker of schizophrenia.

It is evident that lipid inflammatory pathways are important in the pathology of schizophrenia. However, a complete understanding of these metabolic pathways is required to reveal better treatment modalities for this disabling condition. Approaches that use modern mass spectrometry (Fonteh et al. 2006) (which has been successfully applied to other brain diseases; Fonteh et al. 2013, 2014), HPTLC, molecular imaging and magnetic resonance spectroscopy (Bluml et al. 2003; Schmitt et al. 2004; Matsumoto et al. 2011) to define lipid changes and proteomics (Fonteh et al. 2006; Huhmer et al. 2006) to define enzyme expression will pinpoint useful biomarkers for the diagnosis of schizophrenia or the monitoring of the efficacy of new schizophrenia treatments. With the range of metabolic pathways involved, dietary intervention combined with

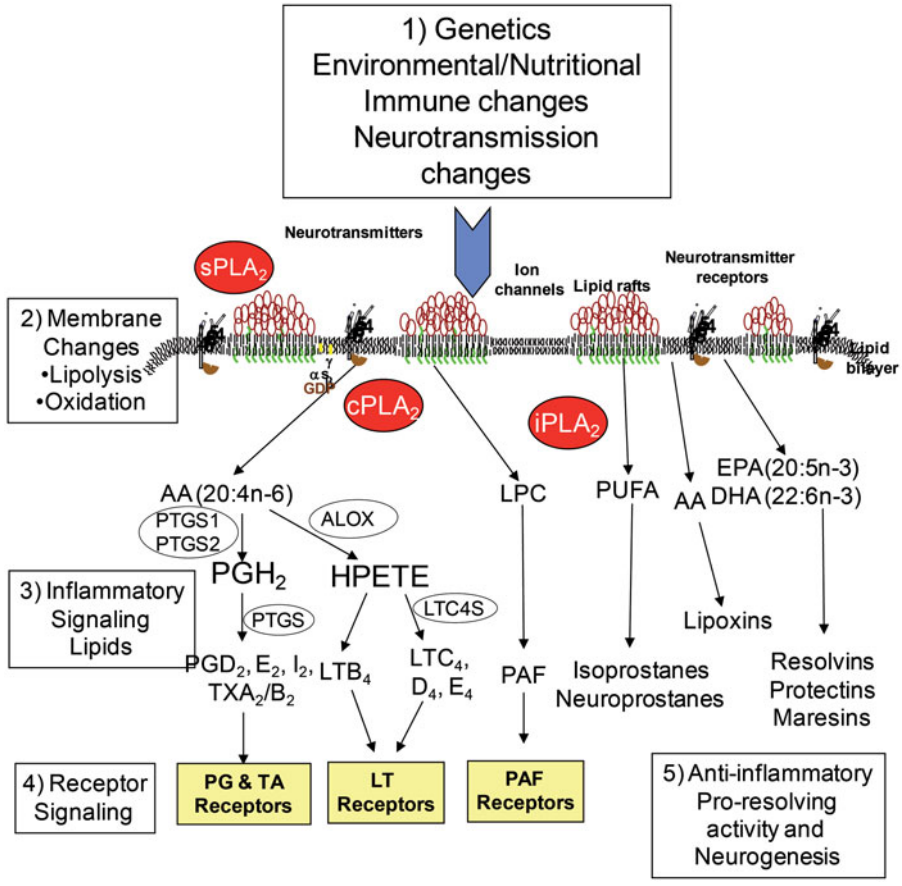

Figure 4. Changes in lipid mediator pathways in schizophrenia. For abbreviations see Table 2.

specific enzyme modulators to control the formation of inflammatory lipid mediators may become useful strategies for treating schizophrenia.

Conclusion

Given the complex and polygenic nature of schizophrenia, it seems likely that sample sizes for biomarker discovery and validation need to be potentially expanded up to numbers similar to the case-control GWAS performed by the PGC, with cohort sizes of several tens of thousands of participants (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). The most interesting avenue from the perspective of clinical management, however, would be the study of predictive biomarkers for treatment response and prognosis. Towards this goal, large longitudinal cohorts are essential in which a thorough phenotypic and clinical evaluation is paired for example with gene expression and proteome or phospholipid analysis in blood at multiple time points. This might allow biomarkers to be retrospectively identified, with hopefully predictive potential. A German consortium (http://www.kfo241.de, http://www.psycourse.de) has initiated such an attempt and implemented a bioinformatics framework to handle sensitive phenotypic data and biomaterial that may allow progress to be made towards the future discovery of schizophrenia biomarkers (Demiroglu et al. 2012).

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