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Metabolomics of Psychotic Disorders

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Abstract

Metabolomics, the global study of metabolites, has recently emerged as a promising approach for identification of potential diagnostic and treatment response biomarkers for psychotic disorders. To date, numerous studies have utilised metabolomics to better understand psychotic disorders and findings from these studies have begun to converge. In this review, we briefly describe the metabolomics approach including the different platforms used to analyse metabolites in biological samples from patients. We also summarise promising metabolic and pharmaco-metabolic biomarkers reported in the current psychotic disorder literature, which point to the dysregulation of fatty acid metabolism and the imbalance in oxidants/antioxidants that is present at illness onset. Finally, we conclude with a commentary on the challenges and future contribution of the metabolomics approach within the larger biomarker discovery framework currently being utilised in the field of psychiatry.

Introduction

One of the earliest biomarker approaches in psychiatry [1] employed chromatography to detect a urinary metabolite [3,4-dimethoxyphenylethylamine, later identified as *p*-tyramine [2]] that formed a controversial "pink spot" on paper chromatographs among those with schizophrenia but not controls. Since then, genomic (i.e., global sequence variation) and transcriptomic (i.e., global gene expression) approaches have dominated biomarker discovery efforts in psychotic disorders. However, the global study of metabolites (i.e., metabolomics) has emerged as a promising approach for identification of potential diagnostic and treatment response biomarkers for psychotic disorders. Whilst metabolomic studies of psychotic disorders are in their infancy, convergence in the current evidence is already emerging. In this review we briefly describe the metabolomics approach, summarise promising metabolic and pharmacometabolic biomarkers reported in the current psychotic disorder literature, and conclude with commentary on the challenges and future contribution of the metabolomics approach within the larger biomarker discovery frame work currently being utilised in the field of psychiatry.

The Metabolomics Approach

Detailed descriptions of protocols and platforms used in metabolomic studies have been presented elsewhere [3-5]. Metabolites can be separated from a variety of tissue types and quantified using several platforms. Studies of psychotic disorders have utilised Cerebrospinal Fluid (CSF), plasma/serum, erythrocytes, urine, or post-mortem brain tissue to identify metabolic signatures that differentiate patients from controls. Post-mortem brain and CSF samples are naturally preferred in the study of psychotic disorders but in practice, tissue that is more clinically accessible such as plasma or urine is typically used. The most common platforms used to interrogate the metabolome include Gas Chromatography with Mass Spectroscopy (GC-MS), Liquid Chromatography with Mass Spectroscopy (LC-MS), Liquid Chromatography Electrochemical Array detection (LCECA), and Nuclear Magnetic Resonance spectroscopy (NMRS). Platform selection is highly dependent on the experimental aims of the study. Importantly, none of the metabolomic platforms are capable of characterising all metabolites present in a particular biological sample [6]. In addition, each platform has drawbacks regarding sample processing, time and equipment required, resolution, and robustness. Thus, it has been advocated that a combination of platforms should be used on each sample to provide the most comprehensive metabolomic information [4,7].

Metabolomics of Psychotic Disorders

Metabolic markers of psychotic disorders

Metabolomic studies to date have identified several metabolic abnormalities in patients with psychotic disorders compared to controls (Table 1). The most consistently reported metabolic perturbations are in pathways common to fatty acids and the pro-oxidant/antioxidant balance. Two large studies involving first episode drug naïve patients with schizophrenia showed significant increases in serum fatty acids [8] and the Cerebrospinal Fluid (CSF) metabolic profile(including increased glucose and decreased acetate and lactate) [9]. These changes were at least partially ameliorated with antipsychotic treatment; where treatment with atypical antipsychotics for nine days normalised the CSF metabolic profile of 50%of patients with schizophrenia [9] but not with typical antipsychotics (e.g. fluphenazine, haloperidol or perazine). The authors noted that when compared to patients with acute paranoid schizophrenia,patients who had received antipsychotics during their first psychotic episode were more likely to have a normalisation in metabolic profile than those who did not. Conversely, nine days of treatment with typical antipsychotics normalised fatty acids whilst atypical antipsychotics had no significant effect [8]. A third large study involving patients with schizophrenia who were either first episode antipsychotic naïve or had relapse and been medication free for at least one month, measured metabolites in both serum and urine [10]. The

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Pathway			**Sample Size**			**Concentration**	
Metabolite	**Platform**	**Tissue**	**N**	**SZ**	**Controls**	**relative to controls**	**Reference**
Fatty acid metabolism							
glycerate	GC-MS	serum	222	112	110	↑	[15]
eicosenoic acid	GC-MS	serum	222	112	110	↑	[15]
beta-hydroxybutyrate	GC-MS, NMR	serum, urine	222	112	110	↑	[15]
palmitic acid	GC-MS	serum	36	18	18	↓	[11]
linoleic acid	GC-MS	serum	36	18	18	↓	[11]
oleic acid	GC-MS	serum	36	18	18	↓	[11]
stearic acid	GC-MS	serum	36	18	18	↓	[11]
unsaturated fatty acids	NMR	plasma	22	11	11	↓*	[12]
Glycerolipid metabolism							
glycerol	GC-MS	serum	36	18	18	↑	[11]
Carbohydrate metabolism							
pyruvate	GC-MS	serum	222	112	110	↑	[15]
acetate	NMR	CSF, serum	152	82	70	↓	[14]
lactate	NMR	CSF, serum	152	82	70	↓	[14]
	NMR	plasma	22	11	11	↑*	[12]
	GC-MS	serum	36	18	18	↑	[11]
Glycolysis							
glucose	GC-MS	serum	36	18	18	↑	[11]
	NMR	CSF, serum	152	82	70	↑	[14]
	NMR	urine	22	11	11	↑*	[12]
	NMR	plasma	22	11	11	↓*	[12]
Amino-acid metabolism							
cystine	GC-MS	serum	222	112	110	↓	[15]
ornithine	FIA-MS	plasma	481	213	216	↑	[21]
arginine	FIA-MS	plasma	481	213	216	↓	[21]
glutamine	FIA-MS	plasma	481	213	216	↓	[21]
histadine	FIA-MS	plasma	481	213	216	↓	[21]
1,3-Bisphosphoglycerate	GC-MS	serum	36	18	18	↓	[11]
valine	NMR	urine	22	11	11	↑*	[12]
trimethylamine-N-oxide	NMR	urine	22	11	11	↓*	[12]
Inositol phosphate metabolism							
myo-inositol	GC-MS	serum	36	18	18	↑	[11]
glucuronic acid	GC-MS	serum	36	18	18	↑	[11]
Alanine, aspartate and glutamate metabolism							
alanine	NMR	plasma	22	11	11	↑*	[12]
N-acetylaspartate	GC-MS	serum	36	18	18	↓	[11]
aspartate	GC-MS	serum	36	18	18	↓	[11]
Glycine, serine and threonine metabolism							
glycine	GC-MS	serum	36	18	18	↓	[11]
	NMR	plasma	22	11	11	↑*	[12]
	NMR	urine	22	11	11	↑*	[12]
Tricarboxylic acid cycle							
citrate	GC-MS	serum	36	18	18	↓	[11]
	NMR	urine	22	11	11	↓*	[12]
α-Ketoglutarate	GC-MS	serum	36	18	18	↓	[11]
	NMR	urine	22	11	11	↓*	[12]
Vitamin E metabolism							
γ-Tocopherol	GC-MS	serum	36	18	18	↓	[11]
Uric acid metabolism							
allantoin	GC-MS	serum	36	18	18	↑	[11]
Purine metabolism							
uric acid	UPLC-MS/MS	plasma	22	11	11	↓*	[12]
Tryptophan metabolism							
tryptophan	GC-MS	serum	36	18	18	↓	[11]
Fatty acid amides							

oleamide	LC-TOF-MS	serum	129	70	59	↑	[22]
linoleamide	LC-TOF-MS	serum	129	70	59	↑	[22]
hepatodecenoic amide	LC-TOF-MS	serum	129	70	59	↑	[22]
palmitic amide	LC-TOF-MS	serum	129	70	59	↑	[22]
palmitoleic amide	LC-TOF-MS	serum	129	70	59	↑	[22]
myristic amide	LC-TOF-MS	serum	129	70	59	↑	[22]
Antioxidants							
total antioxidant status	spectrophotometric assays	plasma	197	49	102	↓	[17]
glutathione	spectrophotometric assays	erythrocytes	197	49	102	↓	[17]
	spectrophotometry	erythrocytes	68	23	45	↓	[22]
glutathione peroxidase	spectrophotometric assays	erythrocytes	197	49	102	↑	[17]
	spectrophotometry	erythrocytes	68	23	45	↑	[22]
catalase	spectrophotometry	erythrocytes	68	23	45	↓	[22]
taurine	NMR	urine	22	11	11	↓*	[12]
Oxidants							
homocysteine	HPLC	plasma	38	19	19	↑	[14]
protein carbonyl content	ELISA	plasma	38	19	19	↑	[14]
	reaction with dinitrophenylhydrazine	serum	118	61	57	↑	[15]
3-Nitrotyrosine	ELISA	plasma	38	19	19	↑	[14]
thiobarbituric acid reactive substances	spectrophotometry	plasma	38	19	19	↑	[14]
	not clear	serum	118	61	57	↑	[15]
xanthine oxidase	spectrophotometry	cytosol of occipital cortex	24	12	12	↓	[17]
	spectrophotometry	cytosol of thalamus	24	12	12	↓	[17]
Phospholipids							
phosphatidylcholineae C38:6	FIA-MS	plasma	481	265	216	↓	[21]
lysophosphatidylcholine	UPLC-MS/MS	plasma	22	11	11	↑	[12]
phosphatidylcholine	UPLC-MS/MS	plasma	22	11	11	↓*	[12]
Cytokines							
interleukin-6	ELISA	serum	118	61	57	↑	[15]
interleukin-10	ELISA	serum	118	61	57	↑	[15]
Steroid biosynthesis							
cholesterol	GC-MS	serum	36	18	18	↑	[11]
Lipoproteins							
low-density lipoprotein	NMR	plasma	22	11	11	↓*	[12]
very low-density lipoprotein	NMR	plasma	22	11	11	↓*	[12]
very low-density lipoprotein/low density lipid protein	NMR	plasma	22	11	11	↓*	[12]
high density lipid protein	NMR	plasma	22	11	11	↓*	[12]
lipid	NMR	plasma	22	11	11	↓*	[12]
lipoprotein	NMR	plasma	22	11	11	↓*	[12]
Other pathways							
lactobionic acid	GC-MS	serum	36	18	18	↑	[11]
erythrose	GC-MS	serum	36	18	18	↑	[11]
3-indolebutyrate fragments	UPLC-MS/MS	plasma	22	11	11	↑*	[12]
hippurate	UPLC-MS/MS	urine	22	11	11	↓	[12]
	NMR	urine	22	11	11	↓	[12]
creatine	NMR	urine	22	11	11	↓*	[12]
creatinine	NMR	urine	22	11	11	↓*	[12]
	UPLC-MS/MS	urine	22	11	11	↓*	[12]
pregnanediol	UPLC-MS/MS	urine	22	11	11	↑*	[12]
	NMR	urine	22	11	11	↓*	[12]
3-hydroxybutyrate	NMR	plasma	22	11	11	↓*	[12]
acetoacetate	NMR	plasma	22	11	11	↓*	[12]

*did not survive Bonferroni correction. CSF; cerebrospinal fluid, ELISA; enzyme-linked Immunosorbent assay, FIA-MS;Flow Injection Analysis/Thermospray Mass Spectrometry,GC-MS; gas chromatography-mass spectrometry , HPLC; high performace liquid chromatography, LC-TOF-MS; liquid chromatography-time of fight-mass spectrometry,NMR; nuclear magnetic resonance spectroscopy, SZ; schizophrenia, UPLC-MS/MS;ultra-performance liquid chromatography−tandem mass spectrometry

Table 1: Metabolic abnormalities in patients with psychotic disorders.

metabolites that were significantly dysregulated included those in fatty acid metabolism pathways for both serum and urine, supporting the results from previous studies and demonstrating that antipsychotics are unlikely to be wholly responsible for changes in fatty acids. The amelioration of metabolic changes with antipsychotic treatment is not limited to first episode patients and may be linked with the therapeutic response, where hospitalised patients with an established diagnosis of schizophrenia who responded to risperidone treatment showed a significant improvement in the ratio of unsaturated to saturated fatty acids compared to those who did not respond [11]. What is not clear from these studies is whether the amelioration of changes to fatty acids corresponds with the therapeutic response for all antipsychotics. More comprehensive studies are needed to determine whether there is ongoing dysregulation of fatty acids in patients who did not respond to treatment, as this would show clear delineation of treatment response and may be useful as a biomarker of prognosis.

Pharmacometabolomic markers

The consistent finding of a dysregulation in the metabolic profile of individuals with psychotic disorders suggests metabolism plays an important role in psychosis. However, many of these findings have been called into question in light of the metabolic syndrome associated with the administration of antipsychotic medications (in particular with atypical antipsychotics). It is therefore pertinent to address whether there is evidence to support the idea that antipsychotic medications are responsible for the changes seen in the metabolome. Table 2 summarises recent studies that have examined the effect of antipsychotic medications on metabolic markers.

The systematic assessment of plasma and urine in first episode antipsychotic-naïve patients showed that at baseline, patient's metabolic profiles were altered, with 32 metabolites changed compared to controls. However, after correcting for multiple testing only decreased urinary hippurate and increased plasma lysophosphatidyl choline were significantly different to controls [12]. Compared to baseline, after six weeks treatment with risperidone 28 metabolites had changed but these did not survive correction for multiple testing [12]. These results suggest that a larger cohort and more focussed panel of metabolites should be investigated in future studies.

A study including patients with schizophrenia, schizoaffective disorder or schizophreniform disorder who had been non-compliant with treatment for three weeks prior to admission, investigated the effect of antipsychotics on seven lipid classes [13]. Patients were treated with risperidone, olanzapine or aripriprazole for between two to three weeks as inpatients and plasma was collected at baseline and then following treatment as inpatients as well. The Clinical Global Impressions (CGI) scale was also administered at baseline and after treatment. At baseline, there was a significant decrease in fatty acids from the Phosphatidylethanolamine (PE) lipid class in patients compared to controls. After treatment with olanzapine there were significant increases in PE, Phosphatidylcholine (PC) and Triacylglycerol (TG) and a decrease in free Fatty acids (FA) compared to baseline. Risperidone treatment increased PE, PC and Lysophosphatidylcholine (LY) compared to baseline, whilst aripiprazole treatment only increased PE compared to baseline. Three metabolites from the PE lipid class and one metabolite from the diacylglycerol and LY classes significantly correlated with early clinical response to treatment as measured by changes in the CGI [13]. A similar albeit smaller study in unmedicated Han Chinese patients with schizophrenia, investigated the effect of risperidone on metabolic pathways in order to identify potential biomarkers of schizophrenia and of treatment response [11]. Serum was collected and the Positive and Negative Symptom Scale (PANSS) was administered at baseline and after eight weeks of risperidone treatment. There were 22 metabolites that classified patients with schizophrenia distinctly from controls. Of these, there were four from the fatty acid metabolism pathway, three from the glycolysis pathway, two from the *tricarboxcylic acid cycle*, two from the alanine, aspartate and glutamate metabolism pathways and two from inositol phosphate metabolism [11].

In addition, patients were separated into responders and non-responders after eight weeks. In patients who responded to treatment 13 metabolites were differentially affected compared to eight metabolites in the non-responders. Of these the pathways affected included: glycolysis, purine metabolism, vitamin E metabolism, alanine, aspartate and glutamate metabolism, tryptophan metabolism, fatty acid metabolism, steroid biosynthesis, tyrosine metabolism and carbohydrate metabolism. Four of the metabolites (from the glycolysis, steroid biosynthesis and carbohydrate metabolism pathways) were commonly affected between the responders and non-responders, indicating that the changes in these four metabolites are probably due to a drug effect [11]. Overall, these data confirm a dysregulation in fatty acids in schizophrenia and suggest that antipsychotics may partially correct disturbances in metabolites in schizophrenia and that changes in metabolites are associated with an improvement in symptoms. However, it is currently unclear why there is a disturbance in fatty acids in schizophrenia.

Hypotheses related to current metabolomics findings

There are several hypotheses for the dysregulation of fatty acids and/or the pro-oxidant/antioxidant imbalance commonly reported in schizophrenia. One hypothesis postulates that there may be interplay between increased lipid peroxidation resulting from oxidative stress and lack of antioxidants, which may account for the dysregulation of fatty acid pathways. Some studies have reported an elevation of lipid peroxidation in patients with schizophrenia and this has been attributed to an elevation in homocysteine [14,15].

The first study [14] investigated lipid peroxidation as measured by Thiobarbituric Acid Reactive Substances (TBARS), as well as 3-nitrotyrosine-containing proteins (3-NCP), homocysteine and protein carbonyl content (PCC; a measure of oxidative damage to proteins) in patients with schizophrenia. All measures were significantly elevated in patients compared to controls, and there was a strong positive correlation between levels of homocysteine and TBARS, 3-NCP and PCC in schizophrenia. Given that oxidation is thought to increase with age and therefore be a potential confound in studies of factors investigating oxidative stress, it is important to note that patients in this study were less than 40 years of age. In the second study [15], markers of oxidative stress were measured among patients in the early (<10 years since illness onset) and late (≥ 10 years since illness onset) stages of schizophrenia and compared to controls. They showed that interleukin-6, TBARS and PCC were significantly higher in both patient groups compared to controls. In addition, interleukin-10 was significantly decreased in patients in the early and late stages compared to controls, albeit only among the late stage patients was the decrease statistically significant [15].

Another hypothesis that explains the dysregulation of fatty acids in schizophrenia postulates that because the glucose demand is higher in the brains of patients with schizophrenia ketones are substituted, which are derived from fatty acid metabolism, driving an increase in fatty acid synthesis [10]. Currently, it is unclear why glucose demand

Pathway			**Sample Size**						
Metabolite	**Platform**	**Tissue**	**N**	**SZ**	**Controls**	**Antipsychotic**	**Length of treatment**	**Concentration relative to pre-treatment**	**Reference**
Lipid class									
free fatty acids	HPLC	plasma	43	27	16	olanzapine	2-3 weeks	↓	[13]
phosphatidylcholine	HPLC	plasma	43	27	16	olanzapine	2-3 weeks	↑	[13]
	HPLC	plasma	43	27	16	risperidone	2-3 weeks	↑	[13]
phosphatidylethanolamine	HPLC	plasma	43	27	16	olanzapine	2-3 weeks	↑	[13]
	HPLC	plasma	43	27	16	risperidone	2-3 weeks	↑	[13]
	HPLC	plasma	43	27	16	aripriprazole	2-3 weeks	↑	[13]
	HPLC	plasma	43	27	16	olanzapine	2-3 weeks	↑	[13]
lysophosphatidylcholine	UPLC-MS/MS	plasma	22	11	11	risperidone	6 weeks	↑*	[12]
phosphatidylcholine	UPLC-MS/MS	plasma	22	11	11	risperidone	6 weeks	↓*	[12]
Glycolysis									
glucose	GC-MS	serum	36	18	18	risperidone	8 weeks	↑	[11]
	NMR	urine	22	11	11	risperidone	6 weeks	↑*	[12]
	NMR	plasma	22	11	11	risperidone	6 weeks	↑*	[12]
lactate	GC-MS	serum	36	18	18	risperidone	8 weeks	↑	[11]
	NMR	plasma	22	11	11	risperidone	6 weeks	↑*	[12]
Purine metabolism									
uric acid	GC-MS	serum	36	18	18	risperidone	8 weeks	↑	[11]
	UPLC-MS/MS	plasma	22	11	11	risperidone	6 weeks	↓*	[12]
	UPLC-MS/MS	urine	22	11	11	risperidone	6 weeks	↑*	[12]
Vitamin E metabolism									
γ-Tocopherol	GC-MS	serum	36	18	18	risperidone	8 weeks	↑	[11]
Alanine, aspartate and glutamate metabolism									
aspartate	GC-MS	serum	36	18	18	risperidone	8 weeks	↓	[11]
Tryptophan metabolism									
tryptophan	GC-MS	serum	36	18	18	risperidone	8 weeks	↑	[11]
Fatty acid metabolism									
linoleic acid	GC-MS	serum	36	18	18	risperidone	8 weeks	↑	[11]
oleic acid	GC-MS	serum	36	18	18	risperidone	8 weeks	↑	[11]
stearic acid	GC-MS	serum	36	18	18	risperidone	8 weeks	↓	[11]
Steroid biosynthesis									
cholesterol	GC-MS	serum	36	18	18	risperidone	8 weeks	↑	[11]
Tyrosine metabolism									
tyrosine	GC-MS	serum	36	18	18	risperidone	8 weeks	↑	[11]
phenylalanine	GC-MS	serum	36	18	18	risperidone	8 weeks	↑	[11]
Carbohydate metabolism									
erythrose	GC-MS	serum	36	18	18	risperidone	8 weeks	↓	[11]
Glycine, serine and threonine metabolism									
glycine	NMR	plasma	22	11	11	risperidone	6 weeks	↑*	[12]
Lipoproteins									
lipoprotein	NMR	plasma	22	11	11	risperidone	6 weeks	↑*	[12]
low-density lipoprotein	NMR	plasma	22	11	11	risperidone	6 weeks	↑*	[12]
very low-density lipoprotein	NMR	plasma	22	11	11	risperidone	6 weeks	↑*	[12]
very low-density lipoprotein/low density lipid protein	NMR	plasma	22	11	11	risperidone	6 weeks	↑*	[12]
high density lipid protein	NMR	plasma	22	11	11	risperidone	6 weeks	↑*	[12]
lipid	NMR	plasma	22	11	11	risperidone	6 weeks	↓*	[12]
unsaturated fatty acids	NMR	plasma	22	11	11	risperidone	6 weeks	↑*	[12]
Antioxidants									
taurine	NMR	urine	22	11	11	risperidone	6 weeks	↓*	[12]
Amino-acid metabolism									
trimethylamine-N-oxide	NMR	urine	22	11	11	risperidone	6 weeks	↓*	[12]
Other pathways									
3-indolebutyrate fragments	UPLC-MS/MS	plasma	22	11	11	risperidone	6 weeks	↑*	[12]
creatine	NMR	urine	22	11	11	risperidone	6 weeks	↓*	[12]
creatinine	UPLC-MS/MS	urine	22	11	11	risperidone	6 weeks	↓*	[12]
	NMR	urine	22	11	11	risperidone	6 weeks	↓*	[12]
pregnanediol	UPLC-MS/MS	urine	22	11	11	risperidone	6 weeks	↑*	[12]
3-hydroxybutyrate	NMR	plasma	22	11	11	risperidone	6 weeks	↓*	[12]
acetoacetate	NMR	plasma	22	11	11	risperidone	6 weeks	↓*	[12]

*did not survive Bonferroni correction. GC-MS; gas chromatography-mass spectrometry , HPLC; high performace liquid chromatography, NMR; nuclear magnetic resonance spectroscopy, SZ; schizophrenia, UPLC-MS/MS; ultra-performance liquid chromatography−tandem mass spectrometry

Table 2: Effect of antipsychotic medications on metabolic markers.

is higher in the brains of people with schizophrenia. Thus, until we understand the underlying mechanisms, efforts to address this demand will remain out of reach.

The final hypothesis is that the oxidant/antioxidant balance is disturbed in schizophrenia and that this may lead to the grey matter loss seen in first episode patients. This hypothesis was recently investigated by measuring grey matter volume in patients with first episode psychosis at baseline and then again at two years follows up [16]. In addition, glutathione, an antioxidant, was measured in erythrocytes collected at baseline. At follow up, all patients showed a significant loss of total grey matter volume in the frontal and parietal cortices of the left hemisphere only. When analysed according to diagnosis, patients with schizophrenia showed the same pattern of grey matter loss. In patients diagnosed with 'other psychotic disorders' only the parietal region was significantly changed and patients with bipolar disorder showed no significant changes. Interestingly, glutathione was significantly decreased in the patients with schizophrenia only compared to controls and there was a relationship between glutathione levels and left temporal grey matter volume [16]. The same group investigated the balance between markers of oxidative stress and antioxidants in patients with first episode psychosis [17]. Diagnoses were confirmed as schizophrenia spectrum disorders (SCH) (48.04%), (which includes schizophrenia, schizophreniform and schizoaffective disorders); Psychotic disorders: Not Otherwise Specified (PNOS) (24.51%); Bipolar disorder with Psychosis (BIP) (17.65%); and Depressive disorder with Psychotic symptoms (DEP) (9.80%). Oxidative stress was measured by analysing erythrocyte glutathione peroxidase, catalase and superoxide dismutase activities. Plasma was analysed for lipid peroxidation using lipid hydroperoxides, total antioxidants and glutathione. Total antioxidant status was significantly decreased in all diagnostic groups except for DEP and there was a between-groups effect where SCH and BIP were lower than other groups. Compared to controls, glutathione was significantly decreased in SCH only and lipid hydroperoxides were significantly lower in BIP only. Glutathione peroxide activity was significantly increased in SCH and BIP compared to controls. There was no significant difference in the oxidative stress molecules or lipid hydroperoxides between patients taking antipsychotics and patients not taking antipsychotics. There was a positive association between global assessment of functioning and total antioxidant status. This supports the notion that the balance between oxidative stress and antioxidants is disrupted in psychotic disorders in favour of oxidants and is unlikely to be mediated by antipsychotics. The relationship between global functioning and total antioxidant status is an indication of the importance the oxidant/antioxidant balance has on the quality of life of patients. This may reflect a future therapeutic target, however, the effect of modulating the oxidant/antioxidant balance in improving patient functioning needs to be explored further.

Challenges and Future Contribution of Metabolomics

We have previously described the major challenges in the search for biomarkers to aid in diagnosis, treatment and prognosis of psychotic disorders [18,19]. Common to all biomarker discovery research are challenges associated with diagnostic heterogeneity, low cross-platform comparability, immature analytic algorithms, and difficulty in verification/replication. Challenges particularly germane to the current state of metabolomics research, albeit not exclusive, include small sample sizes, population stratification, and characterisation of confounds such as diet, exercise, and comorbid disease states (e.g. cardiovascular disease). Although it is acknowledged that the perfect biomarker discovery study is likely unattainable, techniques for reducing diagnostic and population heterogeneity, technological advancements, improved statistical methods, accelerated collaborative efforts between investigators, and integration of multiple 'omics' approaches will enhance our ability to discover and apply biomarkers to psychotic disorders. The specific contribution of metabolomics in this effort will likely be substantial, given increasing evidence pointing to metabolites as the final product of interactions between genotypic variation, expression, translation, molecular networks, and the cellular environment. Thus, we suspect a relatively steep incline in metabolomics research over the next decade that will most definitely aid in our ability to identify, understand, and treat psychotic disorders in the future.

Conclusion

Metabolomics whilst in its infancy has so far suggested a dysregulation of fatty acids in psychotic disorders that may be associated with an imbalance of oxidants and antioxidants. This dysregulation is present at illness onset and therefore is likely not mediated by antipsychotic medication. What is unclear is whether this dysregulation is present before illness onset and could be useful as a biomarker of those at risk of developing a psychotic episode. It is also unclear whether the changes in fatty acids have any effect on the symptoms of psychotic disorders such as schizophrenia. Albeit a recent trial [20] suggested long-chain omega-3 fatty acids may reduce positive (e.g. delusions, hallucinations) and negative (eg. flat affect, apathy) symptoms as well as reduce the risk of progressing to psychosis among youth with sub threshold states. Although there is some evidence that antipsychotics may ameliorate the changes in fatty acids and that this may be associated with treatment response, these effects need to be investigated more thoroughly while addressing other methodological challenges previously mentioned.

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