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Review

Platform for systems medicine research and diagnostic applications in psychotic disorders—The METSY project

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ABSTRACT

Psychotic disorders are associated with metabolic abnormalities including alterations in glucose and lipid metabolism. A major challenge in the treatment of psychosis is to identify patients with vulnerable metabolic profiles who may be at risk of developing cardiometabolic co-morbidities. It is established that both central and peripheral metabolic organs use lipids to control energy balance and regulate peripheral insulin sensitivity. The endocannabinoid system, implicated in the regulation of glucose and lipid metabolism, has been shown to be dysregulated in psychosis. It is currently unclear how these endocannabinoid abnormalities relate to metabolic changes in psychosis. Here we review recent research in the field of metabolic co-morbidities in psychotic disorders as well as the methods to study them and potential links to the endocannabinoid system. We also describe the bioinformatics platforms developed in the EU project METSY for the investigations of the biological etiology in patients at risk of psychosis and in first episode psychosis patients. The METSY project was established with the aim to identify and evaluate multi-modal peripheral and neuroimaging markers that may be able to predict the onset and prognosis of psychiatric and metabolic symptoms in patients at risk of developing psychosis and first episode psychosis patients. Given the intrinsic complexity and widespread role of lipid metabolism, a systems biology approach which combines molecular, structural and functional neuroimaging methods with detailed metabolic characterisation and multi-variate network analysis is essential in order to identify how lipid dysregulation may contribute to psychotic disorders. A decision support system, integrating clinical, neuropsychological and neuroimaging data, was also developed in order to aid clinical decision making in psychosis. Knowledge of common and specific mechanisms may aid the etiopathogenic understanding of psychotic and metabolic disorders, facilitate early disease detection, aid treatment selection and elucidate new targets for pharmacological treatments.

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1. Introduction

Psychosis is a mental illness characterized by impairments in reality testing or reality distortion. Psychotic symptoms can appear in many psychiatric disorders such as schizophrenia or psychotic episodes in affective disorders. Psychotic symptoms are typically observed as delusions, hallucinations, disorganized speech, and bizarre or catatonic behavior. The incidence of psychotic disorders peaks in young adulthood [1], a period of development when significant changes in fatty acid composition occur in the cerebral cortex due to axonal myelination [2]. The increased rates of myelination during adolescence, both in cortical regions and in hubs of the connectome, have been associated with a gene expression profile enriched for schizophrenia-related genes [3]. The lifetime prevalence of these disorders is about 3.5%, the most common being schizophrenia with approximately 1% lifetime prevalence [4]. The cost of psychotic disorders in Europe was estimated at 93.3 billion euros in 2010 [5]. Schizophrenia is associated with a reduced life expectancy of 15–20 years [6,7] due to a high prevalence of cardiovascular disease [8] and metabolic syndrome [9].

In September 2013, the collaborative European project METSY (Neuroimaging platform for characterisation of metabolic co-morbidities in psychotic disorders) was initiated (http://metsy.eu/), with the overall objective to identify and evaluate multi-modal peripheral and neuroimaging markers that can predict and monitor psychotic and metabolic symptoms, aiding the diagnosis and prognosis of both psychiatric and metabolic diseases. The aim of this collaborative project is to investigate how dysregulations in the lipid metabolism might explain psychiatric and metabolic abnormalities by using neuroimaging and bioinformatics methods.

In this paper, we highlight and review the key research questions addressed by the METSY project and describe the bioinformatics platforms that we used in order to investigate the biological etiology in first episode psychosis patients and in subjects at risk of psychosis.

2. Metabolic co-morbidities in psychotic disorders

Unhealthy lifestyles and pharmacological side effects have been suggested to be a major cause of excess mortality rates in patients with psychotic disorders. Schizophrenia patients exhibiting negative symptoms such as anhedonia and social withdrawal are more prone to becoming overweight and developing metabolic syndrome, which may in turn increase the risk of cardiovascular morbidity [10]. Additionally, the use of antipsychotic medication, especially second generation antipsychotics, has been consistently associated with weight gain, insulin resistance and the development of metabolic syndrome [11–14], which seems to be more marked in younger people [15]. After only six months of treatment with specific second-generation antipsychotics, the percentage of previously drug naïve first episode psychosis patients at risk of developing the metabolic syndrome rises from 17% to 40% [16]. This evidence suggests that these psychotropic drugs target brain regions involved in regulating energy balance and metabolism.

However, pharmacological side effects and unhealthy lifestyles only explain a fraction of the metabolic co-morbidities shown in psychosis. Abnormal glucose homeostasis, hyperinsulinemia and accumulation of visceral fat are already evident in drug-naïve first episode psychosis patients, independently of obesity [17,18]. In the WHO World Health Survey, as compared with the absence of symptoms, having one psychotic symptom was associated with higher odds (OR 1.71; 95% CI, 1.61–1.81) of diabetes mellitus in the general population, with increasing likelihood as the number of psychotic symptoms increased [19]. Furthermore, unaffected first-degree relatives of people with schizophrenia also have higher rates of diabetes mellitus (19–30%) compared to the general population (1.2–6.3%) [20]. Some recent genetic studies have detected genes that increase the risk of both schizophrenia and type 2 diabetes (T2D) [21]; however, there have been negative findings as well [22,23]. Taken together, these observations suggest that metabolic disturbances associated with obesity may contribute to the etiopathogenesis of psychosis.

The role of cannabis use in increasing the relative risk for the development of psychosis is well established [24]. The endocannabinoid system is comprised of lipid-derived endogenous cannabinoid ligands, enzymes involved in the synthesis and degradation of these ligands and the cannabinoid 1 and 2 receptors which have affinity to these endogenous cannabinoid ligands. The cannabinoid 1 receptor has been postulated to be dysregulated in both psychotic and metabolic diseases [25,26]. The CB1R is a G-protein coupled receptor widely distributed centrally throughout the cortex, striatum, hippocampus and cerebellum. However, CB1Rs are also distributed in the periphery throughout the gastrointestinal tract, liver, adipose tissue and adrenal glands [27]. The CB1R has been implicated in the etiology of metabolic diseases based on evidence that CB1R agonists dysregulate both glucose and lipid metabolism [28]. In line with these findings, selective CB1R antagonists have been demonstrated to be effective for weight-loss leading to favorable changes in both lipid and glucose levels [29]. However, further research is warranted to investigate how endocannabinoid dysregulation in psychosis relates to metabolic abnormalities in psychosis.

3. Experimental approaches used to study metabolic co-morbidities in psychoses – METSY platforms

3.1. Metabolomics

Metabolomics is a comprehensive study of small molecules (i.e., metabolites) in cells, tissues and biofluids, including their biochemical transformation and responses to environmental and genetic perturbations. Metabolomics provides new tools to study the etiopathology of psychotic disorders as well as metabolic dysregulation arising following the use of antipsychotics [30–35]. However, metabolomics has also played an important role in unravelling putative biomarkers and underlying pathways in several other diseases of the central nervous system [36], including major depressive disorder [37,38], Autism spectrum disorder [39], Alzheimer's [40–43] and Parkinsons [44–46] diseases. Since the metabolome is sensitive to both genetic and environmental factors, such as drug exposure, metabolomics was chosen as a key 'omics' platform for molecular phenotyping in the METSY project.

Studying the metabolome in a population-based study, Oresic and colleagues found that schizophrenia was associated with elevated serum levels of specific triglycerides, hyperinsulinemia, and the upregulation of the serum amino acid proline [31]. Using a network approach, the metabolic profiles were combined with other clinical and lifestyle data to create a diagnostic model which discriminated schizophrenia from other psychotic illnesses. Recently, as part of the METSY project, metabolomics has also been applied to study the metabolite profiles predicting weight gain and the development of other metabolic abnormalities in patients with first-episode psychosis [47], where weight gain was associated with increased levels of triglycerides with low carbon number and double bond count at baseline. These lipids are known to be associated with increased liver fat [48,49]. These preliminary results suggest that the first-episode psychosis patients who are at the highest risk of rapid weight gain, tend to have increased levels of lipids linked to liver fat prior to becoming obese. However, it is unclear whether there is a common biological mechanism

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underlying metabolic changes shown in first-episode psychosis. Clearly larger prospective studies are needed in order to confirm these findings – which is one of the research activities of the METSY project.

3.2. Neuroimaging methods

An extensive body of literature over the last 40 years has documented subtle but widespread structural and functional changes in the brains of patients with non-affective and affective psychotic disorders. These changes are usually most prominent in fronto-temporal regions but it is now evident that these changes are more widespread, extending to posterior brain regions [50]. The progression of structural brain changes, particularly grey matter volume loss, has been found in the early onset schizophrenia, including both adult and adolescent-onset cases [51,52]. These volumetric changes are also shown in antipsychotic- naïve patients and become greater over time [53], and have been correlated with poor clinical outcomes [51]. Interestingly, volumetric reductions in frontal and temporal grey matter have also been linked to weight gain in healthy subjects [54]. These findings suggest that volumetric changes in the structure of the brain are related to the severity of clinical and metabolic changes in psychosis.

Psychoses and most notably schizophrenia are widely characterized as disorders of brain disconnectivity. The term 'connectome' coined by Sporns and colleagues emphasizes the importance of appreciating network-level connectivity in order to understand brain function and dysfunction [55]. The 'connectomics' imaging – literature postulates that there are two overlapping types of disconnectivity in psychosis: context-independent functional connectivity deficits and context-dependent alterations with transient hypo- and hyperactivity patterns [56]. However, further research is warranted to investigate how network-level connectivity can be modulated by molecular alterations.

In vivo molecular imaging studies have consistently shown that un-medicated patients with schizophrenia exhibit an increase in striatal dopamine synthesis and release [57–59]. However, it is clear that dopamine dysregulation in psychosis is part of a larger problem in the connectome involving also other neurotransmitter pathways, in particular the glutamate and GABA systems. The endocannabinoid receptor CB1R, located on pre-synaptic nerve terminals of glutamatergic and GABAergic nerve terminals, plays a fundamental neuro-modulatory role in the brain due to its ability to inhibit the release of both excitatory and inhibitory neurotransmitters. CB1R begin modulating the fine tuning of excitatory/inhibitory neurotransmitter release during periods of pre- and postnatal brain development [60], thought to be central in the etiology of schizophrenia-spectrum disorders. Previous attempts to quantify the CB1R *in vivo* in schizophrenia have been largely unsuccessful due to high levels of tracer lipophilicity [61], the use of irreversible tracers and the failure to use arterial blood sampling to quantify the tracer kinetics [62,63]. However, it is now possible to elucidate the role of CB1R in patients with psychosis due to the development of specific positron emission tomography (PET) radiotracers, such as [11C]OMAR, [^{11}C]MEPPEP and [^{18}F]FMPEP-*d2*. These tracers bind reversibly with high specificity to CB1R in healthy volunteers and have appropriate kinetic properties for compartmental modeling of receptor availability as well as good test-retest reliability [64–67]. A recent study using arterial blood sampling and appropriate quantification techniques found that medication naïve schizophrenia patients abstaining from cannabis use showed a down-regulation of the CB1R in the hypothalamus, hippocampus, amygdala, caudate and insula [68]. In line with these findings, non-medicated with schizophrenia also show greater central levels of anandamide, an endogenous cannabinoid agonist compared to healthy volunteers [69]. However, further work is needed to elucidate how central and peripheral endocannabinoid dysregulation is linked to metabolic dysregulation in schizophrenia.

PET and MRI are established neuroimaging tools, but generally used independently. Recently, a hybrid PET/MR system, which allows for acquisition of such complementary information consecutively in the same study session without repositioning of the subject has been established. This system provides truly simultaneous, complementary information on different aspects of brain function (e.g., CBR1 availability, white matter integrity) by the different modalities without the temporal limitations of conducting separate PET and MRI scans. MRI-based data on brain morphology and white matter tract integrity have been used to quantify structural connectivity patterns of the brain of the cannabinoid systems as measured with PET and network connectivity, such as the default mode network (DMN) in the brain. The DMN is activated when the brain is at wakeful rest and not focusing on the outer world but rather engaged with internal tasks (e.g. daydreaming, spontaneous thoughts, memories). DMN is usually regarded as a predominantly context-independent phenomenon. Despite the fact that resting state functional magnetic resonance imaging (R-fMRI) has become a powerful tool to explore the dysconnectivity of brain networks in psychotic disorders, very little is known about the role of specific neurotransmitters involved in emergence and maintaining DMN activity.

4. Platform for modeling multi-modal data in the studies of psychotic disorders

The METSY bioinformatics platform is comprised of three interrelated components (Fig. 1):

1. Network analysis to integrate heterogeneous data (multi-omics, in vivo molecular neuroimaging, structural neuroimaging, functional neuroimaging and psychosocial);
2. Semantic modelling to annotate heterogeneous data with biological and literature-based annotations;
3. Development of a decision support system to facilitate decision-making in the clinic based on multi-modal diagnostic information.

4.1. Integrative approaches to identify the biomarkers of psychotic disorders

Network analysis and metabolomics can be powerful tools for dissecting complex disease-related metabolic pathways and for identifying candidate diagnostic and prognostic markers in psychiatric research [31]. The integration of this kind of analysis with imaging and genetic data may facilitate the identification of early risk biomarkers associated with the comorbid cardiometabolic complications in psychosis.

Network analyses combining metabolomics and genetics data have previously been used to identify metabolic profiles associated with the specific schizophrenia risk genes in the first-episode patients [33]. This study showed that aberrations in biosynthetic pathways linked to glutamine and arginine metabolism might contribute to etiopathogenesis of schizophrenia. Orešič et al. studied plasma lipidomic profiles in twin pairs discordant for schizophrenia and found that patients were more likely to be insulin resistant and have high triglyceride levels, compared to their co-twins [32]. Furthermore, integrative analysis of neuroimaging and lipidomics data revealed that volumetric reductions in grey matter were associated with elevated triglyceride levels.

Extracting predictive biomarkers from multiple types of information requires the integration and correlation of existing

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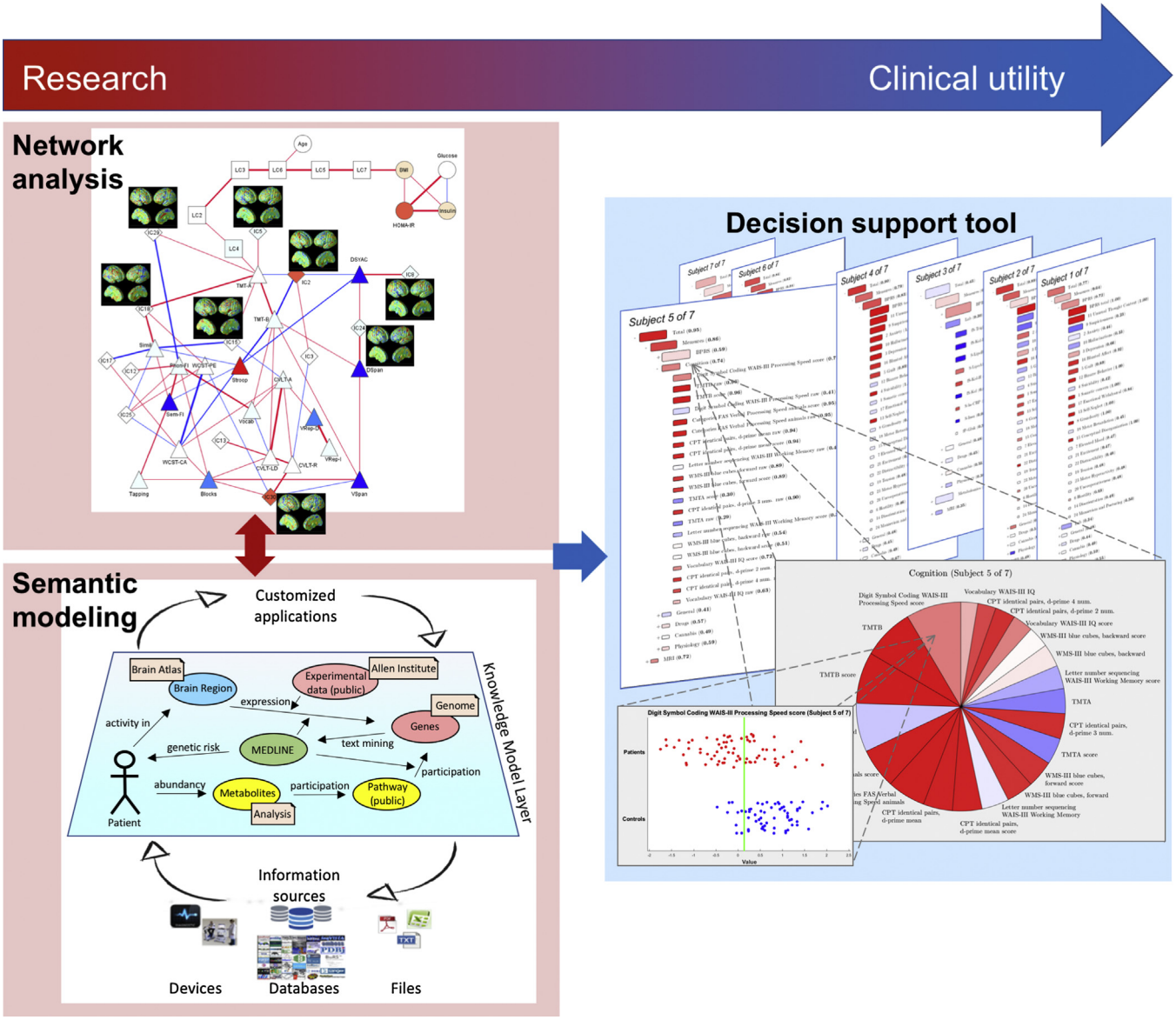

Fig. 1. Outline of the METSY bioinformatics platform, bridging the systems medicine research approaches with the applications in the clinic. The platform integrates three components: network analysis, semantic modelling and decision support system. (**A**) Network analysis to integrate heterogeneous data (multi-omics, in vivo molecular neuroimaging, structural neuroimaging, functional neuroimaging and psychosocial) based on partical correlations (example from an earlier study [32]). (**B**) Semantic modelling to annotate heterogeneous data with biological and literature-based annotations, representing knowledge as network which integrates associations otherwise separated in individual data sources. Integration is based on mapping of equivalentmeaning and objects across all information types relevant in a life science project. (**C**) Development of a decision support system to facilitate decision-making in the clinic based on multi-modal diagnostic information.

knowledge and data from diverse sources and formats. Network construction and analysis is a promising approach facilitating data integration that is increasingly used in disease related research [70,71]. In this approach, networks are constructed from associations between variables and are integrated with prior knowledge that is also represented in a network form. Currently, most prior knowledge is not readily accessible for analysis since it exists in different repositories for structured (comprising about 1400 public databases on molecular biology related information [72]) and unstructured data such as high-content imaging, physiological, biochemical and clinical data. Bioinformatics methods, developed to bridge multiple sources and scales of knowledge into semantic networks, have recently been extended to imaging data and computational models [73]. Another challenge that can be approached by networks is the representation of gained knowledge, e.g. how do changes of a specific receptor detected by PET imaging influence our prior knowledge about the overall phenomenon. Current neuroimaging methods are focused on correlation of voxel pattern to outcomes, largely neglecting existing mechanistic and structural information during the analysis. In order to provide systematic and structured information suitable for algorithmic analysis, METSY aims to structure the current knowledge (i.e. scientific literature, implicit expert knowledge, databases) into concepts, which can be mapped to the experimental and clinical data (Fig. 2). Using this approach, concepts relevant to a specific research area can be retrieved from the literature or defined by expert consensus and implemented as software concepts. In psychosis research, relevant concepts are for example “brain area”, “symptom” or “metabolite” and associations such as “causes” or “is consumed by”. Within the METSY project, we will apply the BioXM Knowledge Management Environment [73,74], which will allow us to adapt existing concepts throughout the course of the project using a graphical editor. Semantic mapping approaches can also be used to identify defined concepts

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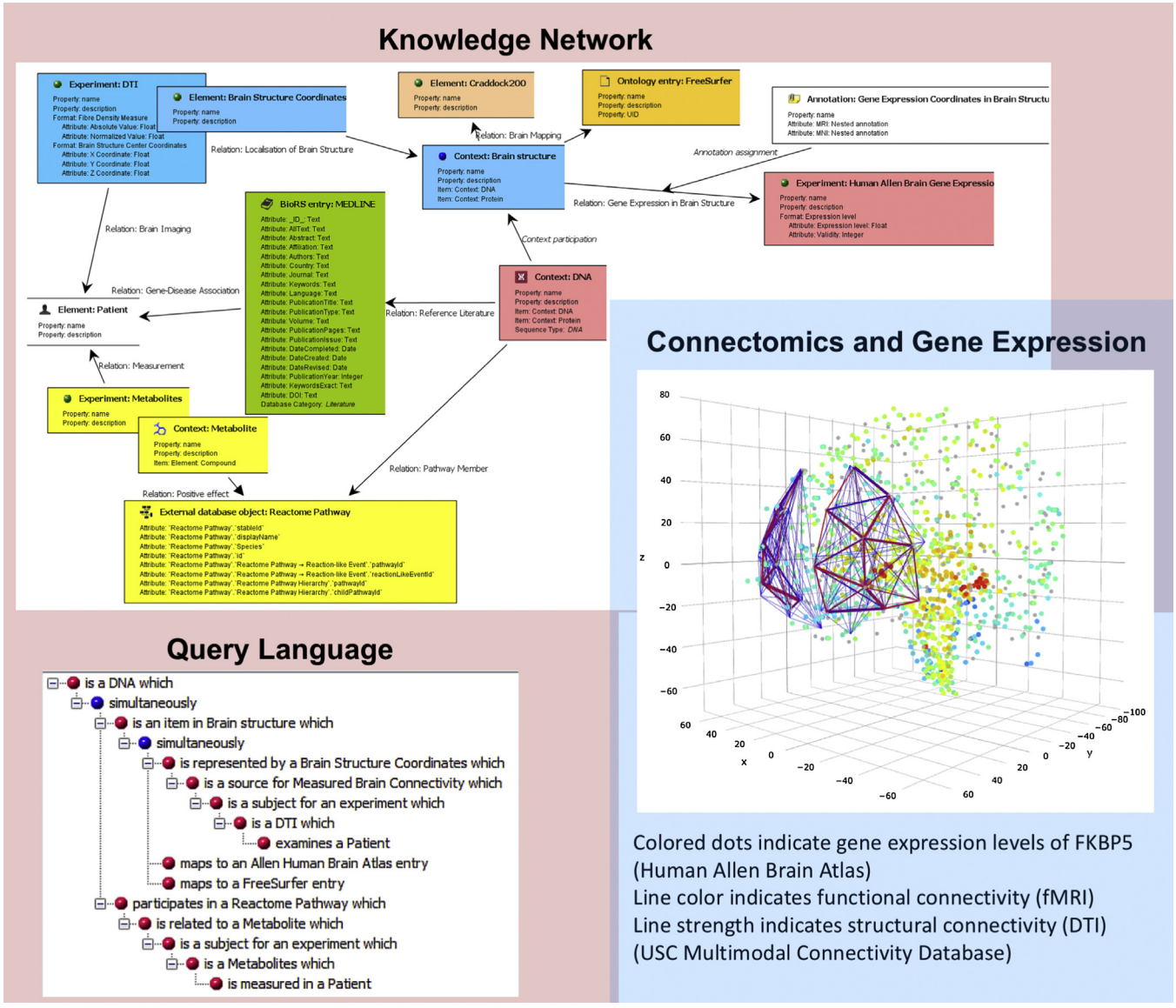

Fig. 2. Example of integrative analysis of connectome and gene expression data by using the semantic approach. Coloured dots indicate gene expression values for FKBP5 (taken from Human Allen Brain Atlas). Red colours indicate high expression values whereas blue colours indicate low values. In addition, we selected prefrontal cortex circuitry and display structural and functional connection strengths measured by DTI and fMRI, respectively. Structural connectivity is depicted by line thickness. Red line colouring indicates strong functional connectivity while blue indicates anti-correlated activity between the connected brain areas. Connection strengths are taken from the NKI_AVRG dataset – the average connectivity of all connectomes of the NKI Rockland study from the Human Connectome Project. Datasets available through the USC Multimodal Connectivity Database. All brain coordinates were transformed to a unified coordinate frame specified by the MNI-152 standard brain. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

from structured resources such as ontologies, neuroanatomical or functional atlases, databases or literature-mining. For example "brain area" might be populated from the Human anatomy atlas [75] and the FreeSurfer neuroanatomy atlas [76]; while "metabolites" might be derived from the Human Metabolome Database [77] and different symptoms associated to psychosis might be retrieved by automatic literature-mining. In this process, information from different sources can be mapped to the same concepts based on their meaning (semantics) and thereby integrated. This process can be automated for data extraction from various sources based on descriptions of the contained data and its format (metadata); however, some data extraction requires manual selection in cases where the source relates to specific areas of expertise (i.e. identifying the similarity of different neuroanatomical atlases). Within METSY, this approach allowed us to integrate structural brain connectivity data from the USC Multimodal Connectivity Database (UMCD) [78] with functional brain area information from the Brede database [79] and brain gene expression data from the Allen Brain atlas [80]. To this end, an experienced neuroanatomist manually mapped the areas of the Craddock200 atlas used by UMCD to the Brede WOROI ontology (Brede) and Human Allen Brain Atlas (Allen Brain) using MNI coordinates as common denominator. For example, *left hippocampus* (Craddock200) was mapped to *107 Left hippocampus* (Brede WOROI) and *4249001 hippocampal formation, left* (Human Allen Brain Atlas). Individual level data from the three sources was subsequently uploaded into the METSY knowledge portal which may be searched and visualized based on any of the mapped atlases. As an example, a DTI tract might state "in schizophrenic patient A, *left hippocampus* is connected with *mammillary body* by strength 91 while a functional association might be '*left hippocampus* and *mammillary body* are correlated with

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connectivity 0.008 during resting state in healthy volunteers' and finally post-mortem expression data may indicate certain genes expressed in *left hippocampus* and *mammillary body*. Such mappings enable us to directly compute potential functional and molecular consequences of differences shown between schizophrenia patients and healthy volunteers, which are relevant to clinical decision making.

4.2. Decision support system for psychotic disorders

Using integrated data from the METSY knowledge base, a novel clinical decision support and data visualization framework was adapted and applied to tackle heterogeneous patient information. The main focus of the framework was to provide a comprehensive overview of the patient's disease state [81], which denotes a patient's degree of similarity to a previously diagnosed disease population. This was archived by implementing the disease state index (DSI) method and disease state fingerprint (DSF) visualizations [82] for the data contained within the METSY knowledge base. The DSF visualization clearly discloses how different components of the patient data contribute to the DSI, facilitating rapid interpretation of the information. The same methods were previously applied to examine Alzheimers disease and dementias in EU projects PredictAD, PredictND and VPH-DARE@IT.

DSI is a supervised machine learning algorithm, which quantifies the disease state of the patient. The method computes the statistical distributions for each measurement and uses them to quantify the disease state of the patient. The method produces a single variable for the patient, ranging between zero and one. An index value close to zero denotes that the patient has values similar to healthy subjects. By contrast, if the index is close to one, the measurements are more similar to diagnosed patients. The DSI can quantify a score, even if not all measures are available. The DSI classifier is accompanied by a disease state fingerprint (DSF) [82] visualization. The DSF has a tree structure, which represents the structure of the DSI classifier, highlighting which measures have the strongest prognostic value.

Within METSY, the DSI was used to combine volumetric data from MRI, psychiatric measures, clinical measures and selected metabolomics data (Fig. 1). The DSI was trained and tested with volumetric MRI, psychiatric and clinical measures selected based on earlier knowledge from the psychotic disorders. The metabolomics measures were selected based on the machine learning methods with dependency detection.

5. Conclusions

There is an urgent need to identify biomarkers that will facilitate the early detection of the pathophysiological processes leading to metabolic co-morbidities in psychotic patients. Given the complexity of the etiopathogenesis of psychotic disorders and their co-morbidities, biomarkers need to reflect relevant genetic, phenotypic, environmental and psychosocial factors. In METSY, we are adopting a network approach utilizing machine learning as well as semantic modeling strategies, in order to identify the key biomarkers of potential prognostic and diagnostic value. METSY has also developed a decision support tool aiming to improve the diagnosis and prognosis of both psychiatric and metabolic diseases. METSY therefore offers a platform, whereby scientific advancements in medical research can inform and improve clinical practice.

Conflict of interest

E.F., D.M. and M.B.-O. are employed by Biomax Informatics AG and therefore will be affected by any commercial implications caused by this manuscript. The other authors declare no conflict of interest.

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