PROJECT FINAL REPORT

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4.1 Final publishable summary report

Executive summary

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 an open research question how these endocannabinoid abnormalities relate to metabolic changes in psychosis. 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. The project brought together clinicians, researchers and industry partners in the domains of psychiatry, neuroimaging, metabolic research, systems biology and bioinformatics.

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. METSY applied comprehensive metabolomics as well as neuroimaging (MRI and PET) in first-episode (FEP) or clinical high-risk (CHR) for psychosis in studies across the four clinical sites. The project led to several key findings including detailed prospective characterisation of inflammation/metabolism in FEP, predictive signatures of psychosis in CHR patients, identification of FEP patients at highest risk of rapid weight gain by metabolomics, and identification of dysregulation of the endocannabinoid system in the brain of FEP/CHR patients as well as in the periphery. 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. Other expected impacts of the project are (1) new validated multi-modal markers for early disease detection and monitoring, (2) new tools for the identification of subjects who may benefit from specific treatment (3) discovery of new avenues for disease prevention and therapy, and (4) new tools and processes for applying brain imaging in personalised medicine. Over the lifetime of the project, the topic of metabolic co-morbidities in psychotic has gained increasing prominence in the field of psychosis research. For example, most recently, METSY participants organized a special session on this topic at the 6th Biennial Schizophrenia International Research Society Conference in Florence, Italy (April 2018), SIRS 2018.

A summary description of project context and objectives

The METSY **overall objective** was to identify, prioritize and evaluate multi-modal blood and neuroimaging markers with diagnostic potential for prediction and monitoring of psychotic disorders and associated metabolic co-morbidities.

The main objective of *METSY* was met by combinations of clinical research, state-of-the-art technologies and systems biology, divided into six specific objectives:

O1. To apply neuroimaging strategies to characterise structural and metabolic changes in the brain during the first stages of psychosis.
O2. To apply imaging strategies to characterise the endocannabinoid pathways in the brain and relate them to lipid molecular networks.
O3. To characterise genetic and lipid molecular networks as measured in biofluids in early psychosis and identify how these networks associate with patient outcomes.
O4. To develop and demonstrate methodology for combined PET and MRI imaging.
O5. To develop bioinformatics tools to integrate brain image information with clinical and molecular profile data.
O6. To identify, prioritize and evaluate multi-modal circulating and neuroimaging markers with diagnostic potential for prediction and monitoring of psychotic disorders and associated metabolic co-morbidities.

Research comprised of three activity areas, articulated into six S/T work packages (WPs), as shown in Figure 1:

(*1*) human cohort studies (WPs 1-3),
(*2*) methodology developments (WPs 4 and 5), and
(*3*) translational research (WP 6).

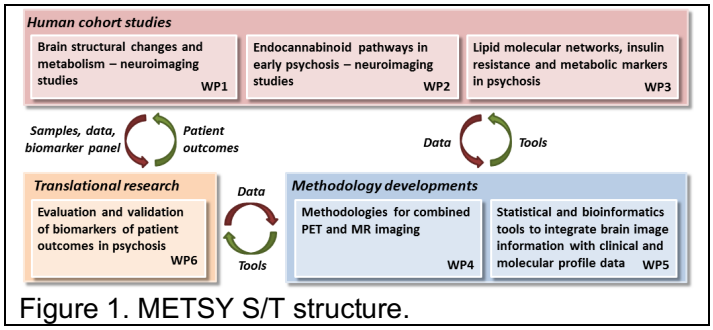

Figure 1. METSY S/T structure.

METSY also included two WPs dedicated to dissemination and management. *The S/T WPs followed the progression of the work plan and reflected the six specific objectives.*

WP 1 pursued detailed neuroimaging and neuropsychology characterisation in longitudinal studies involving patients at-risk or with first episode of psychosis. FEP and CHR subjects and matched healthy controls were followed up simultaneously with analogous methodology in order to extract neuroimaging information useful for characterization of the development of psychosis and associated metabolic outcomes.

WP 2 pursued detailed neuroimaging and metabolic studies of endocannabinoid pathways including synthesis and degradation systems. More accurate methods for direct quantification of CB1 receptors have been recently developed. In collaboration with NIH a CB1 tracer ([18F]FMPEP-d2) was validated and was be used in the project proposal in Turku (P1) and London (P6) with inter-center methodology harmonization process.

WP 3 pursued detailed metabolic characterization, metabolomics as well as studied immune/oxidative stress markers in the cohorts included in WP 1. Data was analysed in collaboration with WP 5.

WP 4 developed methods for combined PET and MR image acquisition and analysis. Consecutive baseline scans, i.e., CB1R and the presynaptic dopamine synthesis tracer [18F]DOPA were performed and the binding outcome interactions (correlation and hub analyses) was a starting point for methodology testing. Early protocols were utilized first in healthy volunteers and then later in early pilot patients. Optimised protocols for the PET/MR hybrid camera (Philips IngenuityTF) were developed and evaluated. Dedicated software packages, specifically adapted to match the

requirements of WP1 and WP2 for combined PET and MRI data visualization and analysis were developed on the Imalytics Research Workstation (Philips Research, Aachen, DE).

WP 5 pursued statistical developments to integrate image data with other phenotypic data, including from ‘omics’ analyses, aiming to extract the signals of potential diagnostic value. Semantic modelling was used to annotate these data with biological and literature-based annotations. Disease State Index was evaluated as a decision-support system in psychosis.

WP 6 validated the multi-modal circulating and neuroimage markers which are sensitive to metabolic disturbances in the brain of at-risk or psychotic patients using an independent prospective sample series from 250 first-episode patients and their healthy controls, which were not included as part of biomarker discovery in WPs 1-3.

A description of the main S&T results/foregrounds

Scientific background

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 (Arango et al., 2011). 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 (Correll et al., 2011; Howes et al., 2004; Jin et al., 2004; Newcomer, 2005), which seems to be more marked in younger people (De Hert et al., 2011). 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% (Fraguas et al., 2008). 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 (Kirkpatrick et al., 2012; Pillinger et al., 2017). 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 (Nuevo et al., 2011). 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%) (Mukherjee et al., 1989). Some recent genetic studies have detected genes that increase the risk of both schizophrenia and type 2 diabetes (T2D) (Hansen et al., 2011); however, there have been negative findings as well (Kajio et al., 2014; Padmanabhan et al., 2016). 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 (Marconi et al., 2016). 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 (Gatta-Cherifi and Cota, 2015; Lu and Mackie, 2016). 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 (Pagotto et al., 2006). The CB1R has been implicated in the etiology of metabolic diseases based on evidence that CB1R agonists dysregulate both glucose and lipid metabolism (Scheen and Paquot, 2009). 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 (Colombo et al., 1998). However, further research is warranted to investigate how endocannabinoid dysregulation in psychosis relates to metabolic abnormalities in psychosis.

Metabolomics studies

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 (He et al., 2012; Kaddurah-Daouk et al., 2007; McEvoy et al., 2013; Oresic et al., 2012; Oresic et al., 2011b; Paredes et al., 2014). However, metabolomics has also played an important role in unravelling putative biomarkers

and underlying pathways in several other diseases of the central nervous system (Quinones and Kaddurah-Daouk, 2009), including major depressive disorder (Ali-Sisto et al., 2016; Kaddurah-Daouk et al., 2012), Autism spectrum disorder (West et al., 2014), Alzheimer's (Han et al., 2011; Kaddurah-Daouk et al., 2011; Oresic et al., 2011a; Trushina et al., 2013) and Parkinsons (Ahmed et al., 2009; Bogdanov et al., 2008; Hatano et al., 2016) 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 (Oresic et al., 2011b). 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. 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 (Suvitaival et al., 2016), where weight gain was associated with increased levels of triglycerides with low carbon number and double bond count at baseline (**Figure 2**). These lipids are known to be associated with increased liver fat (Luukkonen et al., 2016; Oresic et al., 2013). 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 underlying metabolic changes shown in first-episode psychosis. Validation metabolomics studies have been conducted by ORU & UTU in the final stage of the METSY project in FEP (KCL, UTU, SERMAS) and CHR (KCL, EU-GEI cohort) cohorts, aiming to validate lipid signatures associated with weight gain as well as to discover or confirm metabolic signatures associated with FEP and CHR. A total of 866 samples were analysed by lipidomics, incl. 206 in the EU-GEI cohort (CHR individuals). If confirmed, the lipid signatures associated with weight-gain in FEP patients may be clinically useful, as it may help identify the most vulnerable individuals who may benefit from metabolic therapy (anti-obesity/diabetes) in addition to antipsychotic therapy.

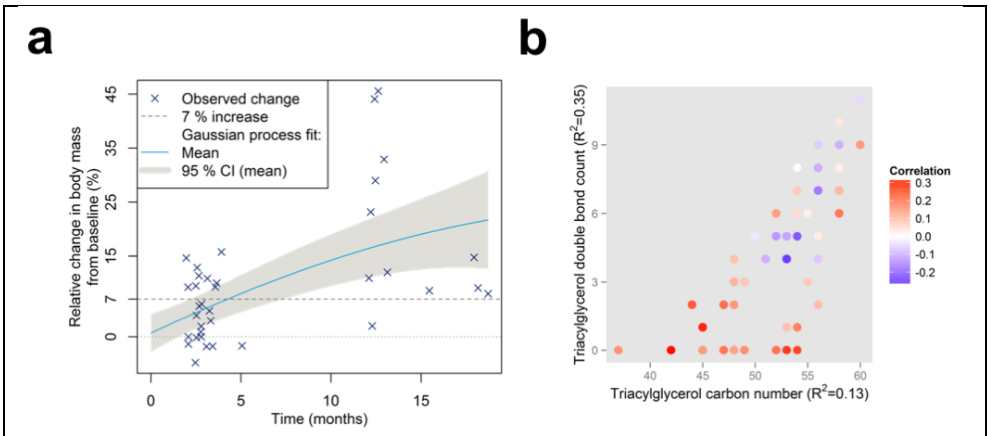

Figure 2. Lipidomic profiles and weight gain in FEP patients (Suvitaival et al., 2016). (**a**) Relative weight gain (blue crosses) from baseline as a function of time in the FEP case group. The median increase in body mass was 3 kg and 11 kg from baseline to the two-month and one-year follow-up points, respectively. Nonlinear Gaussian process regression model was fit on the weight gain data to visually highlight the trend. (**b**) Association between the level of triacylglycerols (TGs) at baseline and the two-month follow-up weight gain (Spearman correlation; color of the points) with respect to the number of carbon atoms (x-axis) and the number of double bonds between carbon atoms (y-axis). The baseline levels of saturated and mono-unsaturated compounds (y=0 and y=1, respectively) are associated with short-term weight gain (red color). The coefficient of determination (R^2) of the linear model for the association as a function of triacylglycerol carbon number and double bond count are shown in the x-axis and y-axis labels, respectively (both $p<0.05$).

Neuroimaging studies

Background

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 (Brugger and Howes, 2017). 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 (Arango et al., 2012; Cahn et al., 2009). These volumetric changes are also shown in antipsychotic- naïve patients and become greater over time (Haijma et al., 2013), and have been correlated with poor clinical outcomes (Arango et al., 2012). Interestingly, volumetric reductions in frontal and temporal grey matter have also been linked to weight gain in healthy subjects (Minichino et al., 2017). These findings suggest that volumetric changes in the structure of the brain are related to the severity of clinical and metabolic changes in psychosis.

In vivo molecular imaging studies have consistently shown that un-medicated patients with schizophrenia exhibit an increase in striatal dopamine synthesis and release (Hietala et al., 1995; Howes and Murray, 2014; Laruelle et al., 1996). 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 (Harkany et al., 2007) , 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 (Yasuno et al., 2008), the use of irreversible tracers and the failure to use arterial blood sampling to quantify the tracer kinetics (Ceccarini et al., 2013; Wong et al., 2010). 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 (Normandin et al., 2015; Terry et al., 2010; Terry et al., 2009; Tsujikawa et al., 2014). 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 (Ranganathan et al., 2016).

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.

Patient recruitment

Final recruitment within METSY reached the following final numbers for neuroimaging (as well as

metabolomics studies): 268 subjects with FEP (goal 250), 29 subjects with clinical high risk for psychosis (CHR) (goal 100) and 231 healthy controls (HC) were recruited. Of them, 207 FEP subjects have an MRI, all of the CHR subjects have an MRI and 210 HC participants have an MRI at baseline. Regarding laboratory data, baseline data are available for 213 FEP subjects, 28 CHR subjects and 193 HC participants. The final effort carried out by all centres allowed an important and significant increase in the numbers of FEP and HC subjects. The final impulse in the recruitment of controls, matched by general socio-demographic characteristics with FEP helped increase the final size sample. However, the final number of CHR subjects is far from the target for different reasons. Different health care systems in different European countries have different ways to assess the CHR. For example, in Finland and in Spain, patients no longer enter the psychiatric health care system at this stage, making it very difficult to recruit subjects at risk. In this regard, from the beginning of the study, only THL, UTU and KCL committed themselves to recruit CHR subjects.

During this period, effort has been directed towards follow-up of the participants in the study. The 1-year follow-up is almost finished, with still a number of patients scheduled for evaluations. Database design has been completed and final minor issues with clinical harmonization have been solved. Baseline clinical data has been sent from clinical sites to Biomax and integrated in the common database. Clinical centres have sent baseline imaging data to SERMAS for storage and analysis and processed data has afterwards been sent to Biomax for inclusion in the database.

Data harmonisation and processing

Amongst all participating centres, the following aspects were harmonized:

- Clinical diagnostic interview: After looking for differences among the clinical and the research versions of the Structured Clinical Interview for DSM-IV (SCID-I), only slight variance was found between them. However, as version used did not affect the aim of the instrument application, that is to establish a clinical diagnosis in Axis I, all participants agreed on continuing using the SCID-I version they had (UTU, THL and KCL use the SCID-I research version and SERMAS the SCID-I clinical version). Only one site (SERMAS) is enrolling minors, and therefore Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) is used for kids´ assessment. Diagnosis will be included in the database.
- Severity of psychotic symptoms: To assess severity of psychotic symptoms, THL is using the Brief Psychiatric Rating Scale (BPRS-Extended) complemented by SANS avolition, anhedonia and alogia, whilst UTU, KCL and SERMAS use the Positive and Negative Syndrome Scale (PANSS). After examining this discordance, all centres agreed on continue using scales as they were doing, as total scores of BPRS and PANSS could be interchangeable without affecting internal validity of both scales (Ventura et al. 1993). PANSS and BPRS will be converted into standard scores for further analysis. All items of PANSS and BPRS will be included in the database (including the modifications used in THL) and afterwards conversion into standard scores will also be included. PANSS interrater reliability was later obtained between evaluators at different sites (see below in interrater reliability).
- Prodromal psychotic symptoms: To assess the presence of prodromal psychotic symptoms, all sites agreed on using the Structured Interview for Prodromal Symptoms (SIPS 5.0). SIPS interrater reliability was later obtained between evaluators at different sites (as described in the 18th month report).
- Global Functioning: All centres agreed on exclusively using the Global Assessment of Functioning scale (GAF) to assess global functioning. They also agreed on deleting the SOFAS scale that some centres were administering. GAF interrater reliability was later obtained between evaluators at different sites (as described in the 18th month report).
- Diet: After looking through the diet questionnaires in each sites, all centres agreed that each one will have their own diet scales due to the diversity of dietary habits in each country. With the DIET scale used by SERMAS, dietary habits can be classified in 3 categories: healthy, need changes, and unhealthy.

- BMI and waist perimeter, cannabis use, smoking, exercise, socioeconomic status (SES), years of education and race were also harmonized. THL exercise assessment will be used by each centre.
- Cannabis: Agreements on cannabis included: Joints per week is not a reliable measure, so instead current/Lifetime use/abuse/dependence and >50 times/days current/lifetime will be used.

Interrater reliability for GAF, PANSS, and SIPS was established (as described in the 18th month report).

Regarding harmonization of neuropsychological data, measures used to assess IQ, attention, processing speed, and working memory have been harmonized. Both direct scores (raw) and standardized scores (T-scores) have been added in the main database. The standardized scores are calculated by each site with the normative data of their own country. Merging data between sites will be made with standardized scores. Variables will be created when at least two sites use the same/compatible test. Each site will provide information regarding which neuropsychological tests have and have not available normative data in their language. Research domains for higher executive functions will be adjusted depending on the different analyses. The use of the following measures has been prioritized: Vocabulary WAIS-III (IQ), TMT-A and CPT (Attention), TMT-B (Executive function) Digit Symbol Coding WAIS-III (Processing Speed), Categories FAS (Verbal Processing Speed), Letter number sequencing-WAIS-III (Working Memory), WMS-III-WAIS-III (Working Memory), HVLT-R (verbal learning) and BVMT (visual learning).

Finally, during this period, clinical sites have sent MRI images and these MRI images have been processed with the same pipeline. The T1-weighted images of all METSY participants have been analysed in FreeSurfer (v5.3) to provide detailed anatomical information customized for each participant. The FreeSurfer analysis stream includes intensity bias field removal, skull stripping, and assigning a neuro-anatomical label (e.g., hippocampus, amygdala, etc.) to each voxel. In addition to the volume-based analysis, FreeSurfer constructs models of the pial and white surface. These surfaces have been used to quantify cortical thickness, surface area, and volume at regional and vertex-wise scales for each METSY participant.

In order to detect and correct artefacts introduced during collection of the Diffusion Tensor Imaging scan, a quality control protocol for METSY subjects have been implemented. First, artefacts related to intensity are detected by computing the normalized correlation between intensity in successive slices across the diffusion volume. Any diffusion volumes containing one or more artefacts are excluded. Next, eddy-current and head motion correction is performed using Fmri Software Library (FSL) tools. Finally, machine-related (i.e., B0 field inhomogeneity) spatial distortions are corrected by warping each participant's T2-b0 image to the anatomical T2-weighted image of the same individual. Anatomically constrained probabilistic diffusion tractography have been carried out using the Tracts Constrained by UnderLying Anatomy (TRACULA) tool within FreeSurfer using default settings (Yendicki et al. 2011). Mean values of fractional anisotropy, mean diffusivity, axial diffusivity and radial diffusivity of major white matter tracts have been calculated for each METSY participant.

Previously, a reliability study was conducted to assess whether images acquired at the different acquisition centers (Madrid, London, Turku, and Helsinki) could be combined in a mega-analysis. Five healthy volunteers travelled to each site and images were acquired. Images were uploaded to the DICOMSERVER in Madrid and processed using FreeSurfer (for T1-weighted images) and TRACULA (for Diffusion Tensor Images). The results of the reliability study for T1 were already. For DTI, the harmonization process included five volunteers were scanned in all sites (**Figure 3**):

- Fundación Cien (Madrid, Spain)
- AMI – Centre (Espoo, Finland)
- PET – Centre (Turku, Finland)
- King's College Institute of Psychiatry (London, United Kingdom)

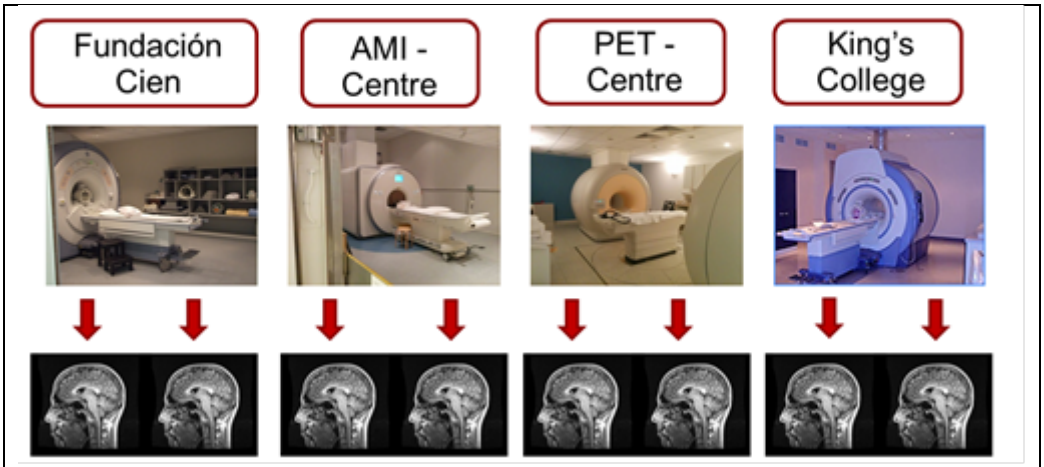

Figure 3. Harmonisation of MRI/DTI data across the four study centres.

CB1R PET analyses

Recruitment targets for patients with FEP and Controls were well achieved (**Table 1**). Recruitment of CHR cases numbers was abandoned based on early decisions to focus on baseline FEPs and controls.

Table 1. WP2: Subjects (n) scanned with CB1R PET with complete data

PET data	UTU	KCL	Total/goal
HC	22	20	42/35
FEP	15	20	35/35
CHR	0	0	0/35
Total	37	40	77

UTU and KCL PET and MRI data pre-processing has been harmonized. Modelling results using 2TCM and MTGA Logan plot are in line with previous [18F]FMPEP-*d2* and [11C]MEPPEP studies. Preliminary findings from the collected samples (**Table 1**) are: *(a)* a lower CB1R availability of FEPs in both sites (**Figure 4**) and *(b)* lower CB1R availability of females in the UTU control sample. Logan plot Parametric images (DVtot) show regional associations between CB1R availability and cognitive capacity in HCs as well as CB1R availability and BPRS psychotic symptoms in male FEPs.'

All available matching serum samples from UTU and KCL have been analysed using the endocannabinoid platform developed by UTU in collaboration with ORU. Preliminary results are: (a) lower circulating levels of OEA and AA in FEPs in the UTU sample. There were no significant differences between patients and controls in the KCL sample; and (b) association of 1+2-AG and OEA to hippocampal CB1R availability in HCs but not FEPs as measured by PET and [18F]FMPEP-d2. Endocannabinoids have also, by the end of the project, been analysed in FEP samples from THL as well as in CHR samples from the EU-GEI cohort.

Together, the preliminary data generated within METSY dies suggest that the endocannabinoid system is dysregulated in gender-specific manner in the brain of FEP patients and that there may be an association between the endocannabinoid systems in the brain and in the periphery. The final studies performed in METSY (EU-GEI) as well as future studies will need to determine if the endocannabinoid system may be a mechanistic underlying link between the metabolic co-morbidities incl. elevated liver fat and early psychosis.

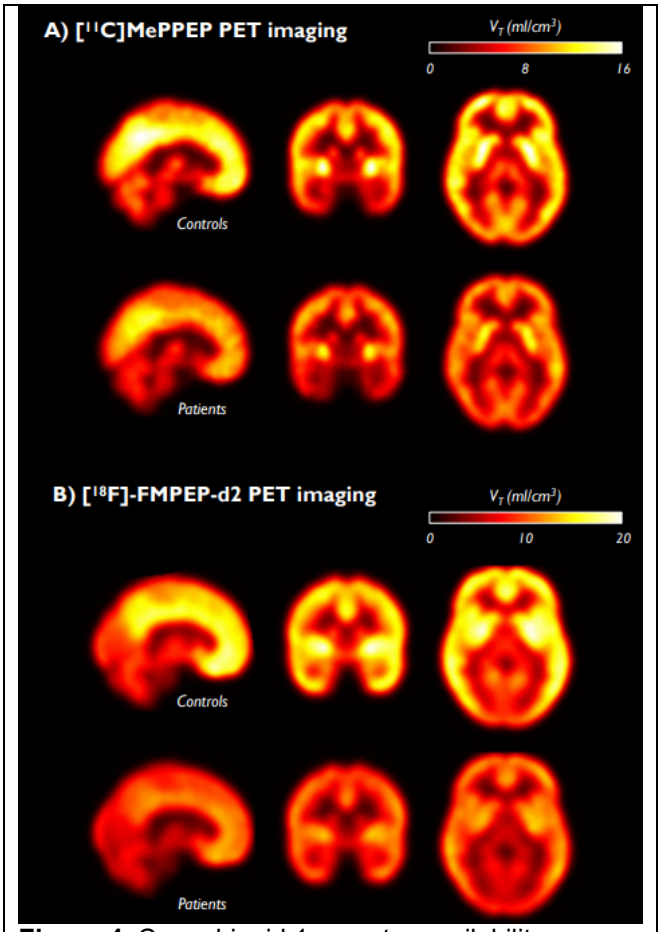

Figure 4. Cannabinoid 1 receptor availability was significantly lower in first episode psychosis patients relative to healthy volunteers as determined by [^{11}C]MePPEP PET quantification (A) and [^{18}F]FMPEP-d_2 PET quantification (B).

Integrative bioinformatics platform

The METSY bioinformatics platform is comprised of three inter-related components (Frank et al., 2018) (**Figure 5**):

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.

Extracting predictive biomarkers from multiple types of information requires the integration and correlation of existing 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 (Barabasi, 2007; Hofree et al., 2013). 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 (Galperin and Fernandez-Suarez, 2012)) 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 (Maier et al., 2011). 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.

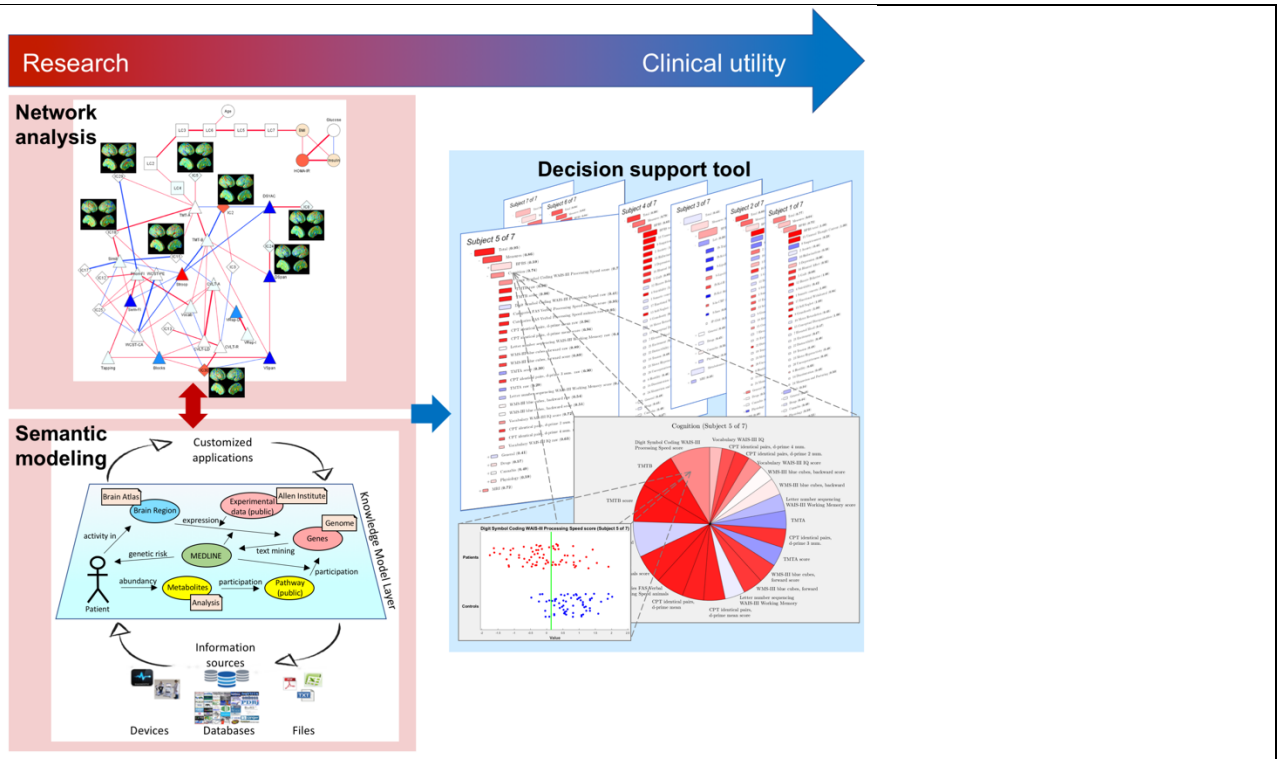

Figure 5. Outline of the METSY bioinformatics platform, bridging the systems medicine research approaches with the applications in the clinic. The platform integrates three components: network analysis, semantic modelling and decision support system. (**A**) Network analysis to integrate heterogeneous data (multi-omics, in vivo molecular neuroimaging, structural neuroimaging, functional neuroimaging and psychosocial) based on partical correlations. (**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.

In order to provide systematic and structured information suitable for algorithmic analysis, METSY structured the current knowledge (i.e. scientific literature, implicit expert knowledge, databases) into concepts, which can be mapped to the experimental and clinical data (**Figure 6**). 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 (Losko and Heumann, 2009; Maier et al., 2011), 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 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 (Rosse and Mejino, 2003) and the FreeSurfer neuroanatomy atlas (Desikan et al., 2006); while “metabolites” might be derived from the Human Metabolome Database (Wishart et al., 2013) 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).

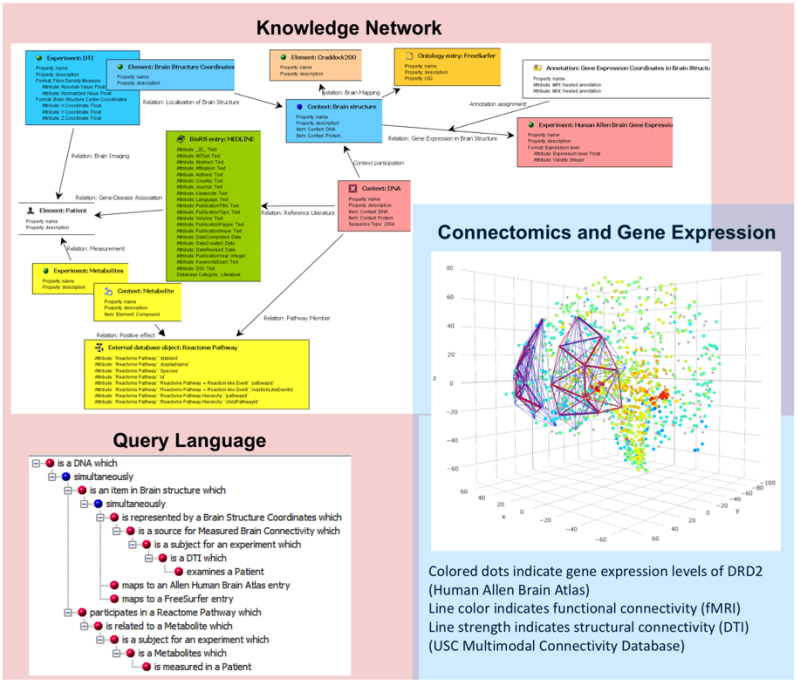

Figure 6. Example of integrative analysis of connectome and gene expression data by using the semantic approach. Coloured dots indicate gene expression values for FKBP5 (taken from Human Allen Brain Atlas). Red colours indicate high expression values whereas blue colours indicate low values. In addition, 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.

Within METSY, this approach allowed us to integrate structural brain connectivity data from the USC Multimodal Connectivity Database (UMCD) (Brown et al., 2012) with functional brain area information from the Brede database (Nielsen, 2014) and brain gene expression data from the Allen Brain atlas (Hawrylycz et al., 2012). 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 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.

Decision support system

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 (Mattila et al., 2011), 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 (Mattila et al., 2012) 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) (Mattila et al., 2012) 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 (**Figure 5**). 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.

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The potential impact (including the socio-economic impact and the wider societal implications of the project so far) and the main dissemination activities and exploitation of results

METSY optimized the use of existing MRI and PET technologies for the study of psychotic disorders, with specific focus on their metabolic co-morbidities. Additionally, the project developed the tools (procedures, software) for combined MRI and PET neuroimaging, as well as statistical and bioinformatics tools to integrate this information with other phenotypic data including metabolic characterisation as obtained from metabolomics of biofluids. Specifically, *METSY developed and validated multiple innovative multi-modal biomarkers* based on neuroimaging and metabolic profiling to the stage where they can be considered for developments towards the implementation in healthcare setting. For clinical biomarker development it is needless to say that the further the biomarker is developed, more value it carries. *Discovery studies* were carried out in WPs 1-3, while the *validation studies* were done in WP 6.

Notably, all these activities were highly integrated and include a strong component of computational systems biology (WP 5) and neuroimaging technology development (WP 4). In metabolomics studies, the discovery and validation steps are usually performed by using “global platforms”, covering a broad range of analytes. Once the biomarker analytes are known, a robust and rugged method needs to be developed and validated which may be applicable in clinical setting. As anticipated ion the to the very end of the assay development stage, *e.g.* as a diagnostic kit ready for use in healthcare setting. However, they were developed far enough that commercial exploitation and pilot studies in healthcare setting can be considered. The commercial exploitation of such biomarkers and related assays will be considered case-by-case according to *METSY* management procedures, and may involve further in house developments, launching spin-outs, licensing, or industrial partnerships.

For broad acceptance of the biomarker in healthcare setting, biomarker needs to be further confirmed in independent replication studies and its utility needs to be demonstrated in multiple studies, with some leading to publications in notable medical journals. Although these additional studies were not considered within *METSY*, once the assays and multi-modal panels are developed in WP 6, *METSY* will consider offering them for applications in other on-going or future studies or projects. The conditions of involvement will be considered on case-by-case basis according to *METSY* management procedures. In addition to participating SME and industrial partner, also other *METSY* partners have a strong track record in commercial exploitation of scientific findings, including in launching multiple spinout companies, licensing deals, or industry partnerships across a broad range of business areas.

Encouragement of SME participation and fostering innovation in Europe in line with the Europe2020 agenda.
METSY included one SME in the domain of bioinformatics. In line with Europe 2020 Smart Growth priorities and strongly facilitating the integration with a large European industry partner,
METSY had strong impact on creating new products/services that generated growth and jobs and helped address social challenges with the help of innovative combination of neuroimaging and metabolic research *via* the use of state-of-the-art methods of bioinformatics and statistics.

METSY supported the goals of the European Pact for Mental Health.
Affective and non-affective psychoses are relatively prevalent mental illnesses. It has been estimated that the lifetime prevalence of all psychotic disorders is about 3.5 %. Psychotic bipolar disorder and psychotic depression are common affective psychoses whereas schizophrenia is the most common as well as the most severe one among the non-affective psychoses in terms of functional outcome. Schizophrenia is clinically characterised with a typical onset in adolescence or early adulthood with disturbances of perception, thinking, behaviour and emotional life. Schizophrenia and other psychotic disorders are also a major public health problem because of their burden and prevalence. Brain disorders cost Europe almost 800 billion € a year. Among all brain

disorders psychotic disorders come second, only after mood disorders, in terms of cost to Europe. In a recent report it has been estimated that in Europe there are over 5 million people with psychotic disorders and that the cost to Europe is 93.6 billion € a year. *METSY* provided better predictive diagnostic tools to detect and monitor psychosis which is directly relevant to two priority areas of the European Pact on Mental Health and Well-being: (II) Mental health in youth and education, and (III) Mental health in workplace settings.

Dissemination and/or exploitation of project results, and management of IP

Dissemination of new knowledge within the scientific community is an intrinsic interest of research, and aims at strengthening and reinforcing the European research activities by multiplication and initiation of networking and collaborations beyond the consortium. Dissemination of results and new knowledge obtained in *METSY* is of high priority, emphasized by the dedication of a work package to dissemination issues. Within *METSY* WP 7 was dedicated on result exploitation:

1. To attain a high level of public awareness of *METSY* activities and discoveries and of the relevance to systems medicine

2. To maximize exploitation of *METSY* discoveries in healthcare and personalised medicine settings

3. To protect *METSY* intellectual property.

Dissemination of knowledge took place at different levels:

1. Within the *METSY* consortium (internal meetings and reports);
2. To the scientific community (publication in international peer reviewed journals, presentations at national and international conferences);
3. To patients as well as healthcare professionals and decision makers *via* patient organizations;
4. To the broad public.

The project manager was responsible to oversee all dissemination activities, which were also defined in the Consortium Agreement.

Means to disseminate new knowledge within the scientific community were:

1. Publications in high-impact, peer-reviewed international journals
2. Presentations at international conferences
3. *METSY* Workshops
4. Filing of patent applications
5. Multiplication by recruitment and training of scientists at the PhD and postdoctoral level
6. Open workshops
7. Presentation of *METSY*, its objective, aims and potentials on a public domain web page.

Means to disseminate to patients as well as healthcare professionals and decision makers were:

1. Organization of special workshops for patients and/or healthcare professionals related to specific *METSY* S/T activities and outcomes,
2. Active participation in international conferences, such as organization of *METSY* sessions at these meetings. As an already existing example of such activities, M. Orešič (P1) organized a symposium at 14th International Congress on Schizophrenia Research (April 2013; Orlando/FL/USA) on the topic of molecular biomarkers in schizophrenia.

Means to disseminate to the public were:
1. Press releases in national newspapers, initiated by the information offices at the participating

organizations;
2. Open door events in the participating organizations;
3. Science and Society events;
4. Presentation of *METSY*, its objective, aims and potentials on a public domain web page.

METSY had specific initiatives to strengthen its dissemination potential:

1. *METSY web page.* One important means to integrate all dissemination activities was the web page of *METSY*, where knowledge was made available to the scientific community and the public. A private domain was established to make internal knowledge easily accessible for all partners. The private domain includes internal interim reports, pre-views of scientific publications and internal news. The web page was regularly updated and designed to meet the needs of the consortium.
2. *Preparation of joint papers and position statements.* The Steering Committee actively pursued opportunities for *METSY* to publish joint papers and position statements in the name of *METSY*. The *METSY* joint papers attract more attention to other means of dissemination such as the *METSY* web page, and therefore had a multiplication value.

Exploitation of *METSY* results and management of Intellectual Property – industry participants

Biomax

The BioXM™ Knowledge Management Environment is developed by Biomax Informatics AG and is available as a commercial product in life science research and clinical application environments. Generation of a psychotic disease and metabolic co-morbidities knowledgebase and integration with newly developed clinical decision support systems (WP 5) broadened the clinical applicability of the system to psychotic disease (earlier it was focused on pulmonary care).

The experience and research results gained during the project, regarding structuring, mapping and mining results of brain imaging technologies in the context of diagnostics allowed Biomax to further extend its established commercial footprint in the field of clinical knowledge management in research and application. While there is strong competition from large non-European companies (*e.g.* Microsoft Almaga Life Sciences) regarding general clinical data management infrastructure the added value provided by targeted content and knowledge representation, developed in projects such as METSY, allowed Biomax to provide added value and expand its position in the life science knowledge management and bioinformatics market with a total volume in 2010 of about $ 3.5 billion and a focus on content in purchase decisions (Frost&Sullivan Market report 2010, RNCOS Market Outlook 2010, Global Industry Analysts report 2011).

Philips

The Imalytics Research Workstation is developed by Philips Research and is available as a commercial product. It serves as a platform for new applications to be used in preclinical and clinical research environments. Project results of WP 4 became new modules on the Imalytics platform, and thereby have the potential for direct commercialisation.
Insights and first prototypes generated in this project were transferred to various business units within Philips Healthcare at a later stage. Developed modules may also be made available on the clinical workstation IntelliSpace Portal (requiring regulatory approval, which is out of scope for this project).

Furthermore, the demonstration of the clinical benefits of hybrid PET/MR neuroimaging that were pursued in this project substantiated the need for this innovative hybrid imaging technology for early prediction and monitoring of psychotic disorders, thus fostering sales to academic hospitals and specialized neuroimaging centres.

Overview of Intellectual Property (IP) opportunity
The effective management and exploitation of Intellectual Property (IP) was a critical component of *METSY*. It is essential that the outcomes of the research are adequately protected in such a way that they are attractive for commercial exploitation. Consideration must be given to the categories of IP that are likely products of the Work Packages. For example:
1. ***Diagnostic biomarkers applicable in healthcare setting.*** Activities in WPs 1-3 and 6 led to novel biomarkers for the specific clinical outcomes of relevance to healthcare and personalized medicine. The IP may include specific analytical assays for the biomarkers or more broadly the multi-modal biomarker signatures together with the method to predict the relevant outcomes using these analyte(s) as well as potentially other information.
2. ***Technology solutions for neuroimaging.*** The technology/software developments in WPs 2, 4, and 5 have a potential to lead to new or improved existing products by the industrial participants, as well as to novel product ideas, e.g., software tools for diagnostics and patient monitoring in psychiatric disorders (WPs 4, 5).

Management of IP
As recommended in the FP7 guidelines and according to standard practice, IP was considered in the following categories:
1. Background (pre-existing IP);
2. Foreground (knowledge generated from the Collaborative Project whether or not it may be patentable).
Foreground may be owned by the single party that generated the Foreground or jointly owned by several parties that have contributed to the Foreground. The ownership and rights of use of Foreground generated through the performance of this collaborative project were defined in the consortium agreement which will combine standard practice with several innovative features to enhance the effectiveness through which Foreground can be exploited and/or commercialized. A summary of the key considerations is provided here:

1. Identification. Academic research scientists will often not recognize valuable foreground that could form the basis of a patent. This is not surprising since such training is not routinely provided or available to researchers. The current program addressed this by two actions:
1. it provided training in knowledge protection and transfer, and IP. This action took advantage of the existing technology transfer organizations within *METSY*. The partner organizations have well developed and professional technology transfer offices. In addition, the program included two SMEs, for which the effective management of IP is an essential part of their activities. *METSY* offered a workshop taught by experts from the technology transfer organizations and with representatives from SMEs to provide the industry perspective. The workshop focused on how to identify a foreground opportunity that should be protected and on the best strategy for its protection.

2. ***Technology scouts.*** This is, relative to academic practice, a highly innovative feature of the *METSY* program that has been inspired by current industry practice. Industry employs technology scouts who are trained in the identification of valuable IP and technology partnering opportunities and who attend meetings and conferences or visit biotechnology or academic clusters in order to identify what may be of interest to their company. *METSY* collected volunteers within the programme (preferably at the Postdoctoral level) who have an interest in the exploitation of foreground and commercialization of research results. These were briefed, mentored and trained by the technology transfer specialists to act as technology scouts within *METSY*. Their task will be to identify opportunities arising from the research that should be protected and/or exploited. This activity also served to provide a first training to the postdoctoral fellows in industry-relevant actions and may be particularly attractive to those researchers considering a career in industry.

2. Protection. The breadth of claims and positioning of the claims are essential elements in establishing the value of a patent. Consequently, it is important to consider the full possible breath of claims that could be made regarding a particular asset of foreground. This was achieved within the current proposal by implementation of a Foreground Evaluation Committee (FEC), which

included a blend of expertise that added value to patents by identifying enlarged scope or wider positioning of claims. The FEC was composed of clinical researchers, academic researchers, representatives of the technology transfer offices and a patent attorney. The FEC reviewed each opportunity presented by the technology scouts (or directly by research scientists whenever they should take such initiative) with a view to maximize its value and to recommend an effective patent filing strategy or other form of protection strategy. The FEC also assisted in determining the assignment of ownership of jointly-owned Foreground.

3. Rights of Use. All Foreground generated within *METSY* is made available to the consortium for non-commercial research, training and educational purposes. Whenever possible this philosophy is also applied on a Europe-wide scope to any Foreground that has potential for creation of value in the European research base such that the Foreground is made available non-exclusively for non-commercial research, training and education to the research community. Pending confirmation of this and other stipulation by the negotiated consortium agreement, it is anticipated that any party generating individually Foreground that is the subject of a patented invention has the right to use and licence such invention at their sole discretion. Rights of use of patented inventions developed with contributions of more than one partner within *METSY* is determined by agreement between the concerned partners on an exploitation and licensing plan. This plan may stipulate that one contributing partner licenses exclusively their share of the joint invention to another contributing partner for commercialization. Alternatively, each party sharing the ownership of Foreground may be entitled to issue non-exclusive licenses at their sole discretion but without the right to sublicense. Please note that patented Background that is required for the performance of *METSY* will be provided by each party as a royalty-free non-exclusive license.

The address of the project public website, if applicable as well as relevant contact details.

www.metsy.eu

Project logo

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4.2 Use and dissemination of foreground

Section A

Template A1: List of all scientific (peer reviewed) publications relating to the foreground of the project.

TEMPLATE A1: LIST OF SCIENTIFIC (PEER REVIEWED) PUBLICATIONS, STARTING WITH THE MOST IMPORTANT ONES

NO.	Title	Main author	Title of the periodical or the series	Number, date or frequency	Publisher	Place of publication	Year of publication	Relevant pages	Permanent identifiers[1] (if available)	Is/Will open access[2] provided to this publication?
1	*Aberrant cortical integration in first-episode psychosis during natural audiovisual processing.*	Teemu Mäntylä	*Biological Psychiatry*	*in press*	*Elsevier*		*2018*	*in press*		no
2	Theory of mind in a first-episode psychosis population using the Hinting Task	Maija Lindgren	Psychiatry Research	263	Elsevier		2018	185-192	doi: 10.1016/j.psychres.2018.03.014.	no
3	Connectivity of the precuneus-posterior cingulate cortex with the anterior cingulate cortex-medial prefrontal cortex differs consistently between control subjects and first-episode psychosis patients during a movie stimulus.	Eva Rikandi	Schizophrenia Research	in press	Elsevier		2018	in press	doi: 10.1016/j.schres.2018.03.018.	no
4	Childhood adversities and clinical symptomatology in first-episode psychosis	Maija Lindgren	Psychiatry Research	258	Elsevier		2017	374-381	doi: 10.1016/j.psychres.2017.08.070.	no
5	Precuneus functioning differentiates first-episode psychosis patients during the fantasy movie Alice in Wonderland	Eva Rikandi	Psychological Medicine	47	Cambridge University Press		2017	495-506	doi: 10.1017/S0033291716002609.	no
6	Serum metabolite profile associates with the development of metabolic co-morbidities in first-episode psychosis.	Tommi Suvitaival	Translational Psychiatry	6	Nature Publishing group		2016	e951	doi: 10.1038/tp.2016.222.	yes
7	Platform for systems medicine research and diagnostic applications in psychotic disorders-The METSY project.	Elisabeth Frank	European Psychiatry	50	Elsevier		2018	40-46	doi: 10.1016/j.eurpsy.2017.12.001.	no
8	Applying Systems Medicine in the clinic.	Maier D.	*Current Opinion in Systems Biology*	3			2017	77-87	10.1016/j.coisb.2017.04.014	no
9	The complex association between the antioxidant defense system and clinical status in early psychosis	García A	*PLOS one*	April 26	PLOS One		2018		10.1371/journal.pone.0194685	yes
10	Platform for systems medicine research and diagnostic applications in psychotic disorders-The METSY project.	Frank E.	European psychiatry : the journal of the Association of European Psychiatrists (in press)	Apr;50	Elsevier		2018	40-46	29361398;10.1016/j.eurpsy.2017.12.001	no
11	Towards understanding and acting on risk factors for developmental psychopathology	Moreno E.	Eur Child Adolesc Psychiatry	1	Springer Science+Business Media		2018	1-3	10.1007/s00787-018-1117-0	yes

12	Cognitive, and Neuroimaging Evidence of a Neurodevelopmental Continuum in Offspring of Probands With Schizophrenia and Bipolar Disorder	Sugranyes G.	Schizophr Bull.	Oct 21; 43(6)	Oxford Academic		2017	1208-1219	10.1093/schbul/sbx002	No
13	A developmental approach to dimensional expression of psychopathology in child and adolescent offspring of parents with bipolar disorder	Moron-Nozaleda G.	Eur Child Adolesc Psychiatry	Oct;26(10)	Springer Science+Business Media		2017	1165-1175	10.1007/s00787-017-0965-3.	No
14	Prevention in child and adolescent psychiatry: are we there yet?	Moreno C	Eur Child Adolesc Psychiatry	26	Springer Science+Business Media		2017	267	10.1007/s00787-017-0960-8	No
15	Involvement of NRN1 gene in schizophrenia-spectrum and bipolar disorders and its impact on age at onset and cognitive functioning.	Fatjó-Vilas M	World J Biol Psychiatry	Mar; 17(2	World Federation of Societies of Biological Psychiatry		2016	129-39	26700405.	No
16	Age at first-episode modulates diagnosis-related structural brain abnormalities in psychosis	Pina-Camacho L	Schizophrenia Bulletin	42(2)	Oxford University Press		2016	344-57	10.1093/schbul/sbv128	Yes
17	Neurological side-effects of antipsychotics in children and adolescents	Garcia-Amador M	Journal of Clinical Psychopharmacology	35(6)	Lippincott Williams & Wilkins		2015	686-93	10.1097/JCP.00000000000004 19.	No
18	Psychoeducational Group Intervention for Adolescents With Psychosis and Their Families: A Two-Year Follow-Up	Calvo A.	J Am Acad Child Adolesc Psychiatry	Dec;54(12)	Elsevier		2015	984-90	PMID: 26598473	No
	Gender effects on brain changes in early-onset psychosis	Rapado-Castro M	Eur Child Adolesc Psychiatry	24(10)	Springer Science+Business Media		2015	1193-20	F.I.: 3.336	No
19	Unmet needs in paediatric psychopharmacology: Present scenario and future perspectives	Persico AM	European Child and Adolescent Clinical Psychopharmacology	Oct;25(10)	Elsevier		2015	1513-31	1513-31	No
20	Predictors of Placebo Response in Pharmacological Clinical Trials of Negative Symptoms in Schizophrenia: A Meta-regression Analysis	Fraguas D	Schizophr Bull.	Jan 19	Oxford University Press		2018		10.1093/schbul/sbx192	No
21	Negative Symptoms in Early-Onset Psychosis and Their Association With Antipsychotic Treatment Failure.	Downs J.	Schizophr Bull.	Jan 24	Oxfor University Press		2018		10.1093/schbul/sbx197	

[1] A permanent identifier should be a persistent link to the published version full text if open access or abstract if article is pay per view) or to the final manuscript accepted for publication (link to article in repository).

[2] Open Access is defined as free of charge access for anyone via Internet. Please answer "yes" if the open access to the publication is already established and also if the embargo period for open access is not yet over but you intend to establish open access afterwards.

22	Duration of untreated psychosis and neurocognitive functioning in first-episode psychosis: a systematic review and meta-analysis	Allott K	Psychol Med	Nov 27	Cambridge University Press		2017	1-18	10.1017/S0033291717003002	No
23	The association between gene variants and longitudinal structural brain changes in psychosis: a systematic review of longitudinal neuroimaging genetics studies	Harari JH	NPJ Schizophr	Nov 1	Springer Nature		2017	40	10.1038/s41537-017-0036-2	Yes
24	Oxidative Stress and Inflammation in Early Onset First Episode Psychosis: A Systematic Review and Meta-Analysis	Fraguas D	Int J Neuropsychopharmacol	Jun 1;20(6)	Oxford University Press		2017	435-444	10.1093/ijnp/pyx015	Yes
25	Mental disorders of known aetiology and precision medicine in psychiatry: a promising but neglected alliance	Fraguas D.	Psychol Med	Jan;47(2)	Cambridge University Press		2017	193-197	10.1017/S0033291716001355	Yes
26	Gene-environment interaction as a predictor of early adjustment in first episode psychosis	Fraguas D.	Schizophr Res	Nov;189	Elsevier		2017	196-203	10.1016/j.schres.2017.02.021	Np
27	Functional deterioration from the premorbid period to 2 years after the first episode of psychosis in early-onset psychosis	Del Rey-Mejías Á	Eur Child Adolesc Psychiatry	Dec;24(12)	Springer Science+Business Media		2017	1447-59	10.1007/s00787-015-0693-5	No
28	Progressive brain changes in children and adolescents with early-onset psychosis: A meta-analysis of longitudinal MRI studies	Fraguas D.	Schizophr Res	Jun;173(3)	Elsevier		2016	132-139	10.1016/j	No
29	Predictors of outcome in early-onset psychosis: a systematic review	Diaz-Caneja CM	NPJ Schizophr	Mar 4;1	Springer Nature		2015	14005	10.1038/npjschz	Yes

Template A2: List of all dissemination activities (publications, conferences, workshops, web sites/applications, press releases, flyers, articles published in the popular press, videos, media briefings, presentations, exhibitions, thesis, interviews, films, TV clips, posters).

TEMPLATE A2: LIST OF DISSEMINATION ACTIVITIES								
NO.	Type of activities	Main leader	Title	Date/Period	Place	Type of audience	Size of audience	Countries addressed
1	Conference	M Bravo-Sánchez; L Pina-Camacho; CM Díaz-Caneja; M Álvarez-Blázquez; B Arias; J Bobes; I Corripio; R Rodríguez-Jiménez; D Fraguas; C Arango	ECNP Workshop for Young Scientists	3/2014	Niza, France	Scientific community		global
2	Conference	L Pina-Camacho; CM Díaz-Caneja; J García-Prieto; M Parellada; J Castro-Fornieles; A González-Pinto; I Bombín; M Graell; S Otero; M Rapado-Castro; J Janssen; I Baeza; F Del Pozo; M Desco; C Arango.	22nd Congress of the European Psychiatry Association	3/2014	Munich, Germany	Scientific community		global
3	Kick-off consortium meeting	Phillips	WP4	16 Sep 2013		Project members		
4	Annual consortium meeting	Phillips	WP4	25 Sep 2014	Madrid	Project members		

5	Workshop	Dieter Maier	Dieter Maier presented the talk „Knowledge Management in Biomedical Research", Master de Recerca Clínica (MRC), Barcelona	17.01.14	Barcelona, Spain	Scientific Community	60	Spain
6	Workshop	Dieter Maier	CaSyM Workshop System Medicine and Industry, Dieter Maier presented the talk „Knowledge Management for System Medicine“	01.04.14	Lyon, France	Scientific Community, Clinical Researchers, Governement, Industry	60	France
	Seminar	Jarmo Hietala	Brain Association	7.5.2014	Turku, Finland		100	EU
7	Conference	Dieter Maier	Translating Systems Medicine into Practice, Dieter Maier presented the talk „Systems Medicine and translation into practice“	05.09.14	Munich, Germany	Scientific Community, Clinical Researchers, Governement, Industry	80	English spoken EU
8	Conference	E Rodríguez-Toscano; D Fraguas; CM Díaz-Caneja; J Castro-Fornieles; A González-Pinto; I Baeza; C Arango; M Parellada.	27th ECNP Congress	10/2014	Berlín, Germany	Scientific community		global
9	Workshop	Veronica v. St. Paul	SMODIA 2014 Statistical Methods for Omics Data Integration and Analysis, Veronica v. St. Paul presented the talk Knowledge Management for Systems Biology	10.-12.11.14	Crete, Greece	Scientific Community	40	English spoken EU
10	Conference	CM Díaz-Caneja; D Fraguas; L Pina-Camacho; A González-Pinto; J	15th International Congress on Schizophrenia Research	4/2015	Colorado Springs,	Scientific community		global

		Castro-Fornieles; M Graell; C Moreno; JC Leza; M Parellada; C Arango			United States of America			
11	Conference	CM Díaz-Caneja; L Pina-Camacho; A Rodríguez-Quiroga; D Fraguas; M Parellada; C Arango.	16th European Society for Child and Adolescent Psychiatry (ESCAP) Congress	6/2015	Madrid, Spain	Scientific community		global
12	Conference poster	MJ Penzol; CM Díaz-Caneja; E Rodríguez-Toscano; B Arias; A Lobo; A González-Pinto; R Rodríguez-Jiménez; M Parellada.	XVIII Congreso Nacional de Psiquiatría	9/2015	Santiago de Compostela, Spain	Scientific community		Global
13	Annual consortium meeting	Phillips	WP4	10 Sep 2015	Munich	Project members		
14	Workshop	Elisabeth Frank	Healthcare 3.0 in psychatric research	12/2015	Munich, Germany	Scientific Community	15	Germany
15	Workshop	Elisabeth Frank	Healthcare 3.0 in psychatric research	2/2016	Sydney, Australia	Scientific Community, Health care providers	30	Australia
16	Conference	Arango C; Díaz-Caneja CM; Pina-Camacho L; Fraguas D.	55th Annual Meeting of the American College of Neuropsychopharmacology	2/2016	Hollywood, Florida, USA	Scientific community		global

17	Workshop	Angela Bauch	Knowledge generation for Healtcare 3.0	3/2016	London, UK	Industry	30	UK, Japan
18	STFC/NERC Multiscale modelling in Ecotox workshop	Dieter Maier	Knowledge management and semantic modelling for Environmental Research	3/2016	Liverpool, UK	Scientific Community, Industry	40	EU, USA, Canada
19	Conference	De la Serna E; Baeza I; Sugranyes G; Díaz-Caneja CM; Merchán-Naranjo J; Arango C; Castro-Fornieles	5th Biennial Schizophrenia International Research Society Conference	4/2016	Florence, Italy	Scientific community		global
	Schizophrenia network	Jarno Hietala		29.4.2016	Rovaniemi, Finland	Network of professionals	200	EU
20	Conference	Díaz-Caneja CM	60 Congreso de la Asociación Española de Psiquiatría del Niño y el Adolescente	6/2016	San Sebastián, Spain	Scientific community		global
21	Annual consortium meeting	Phillips	METSY WP4 Update	03 Oct 2016	London	Project members		
22	Newsletter	Elisabeth Frank	METSY Complex brain knowledge models for research in psychosis	10/2016		Scientific Community, Industry	2500	Global English spoken
23	Industry exhibition, Poster	Dieter Maier	First conference of the European Association of Systems Medicine (EASyM); Can existing knowledge help us PREPARE in case of an	10/2016	Berlin, Germany	Scientific Community, Health Care, Industry	200	EU

			epidemic crisis? Emergency exercise on Zika virus					
24	Lecture	Jarmo Hietala	Studia Generalia	15.12.2016	Turku,Finland	General population	70	EU
25	Conference	Díaz-Caneja CM	29th European College of Neuropsychopharmacology Congress	12/2016	Vienna, Austria	Scientific community		gobal
26	Conference	Díaz-Caneja CM; Janssen J; Pina-Camacho I; Sugranyes G; Castro-Fornieles J; Arango C.	61º Congreso Nacional de la Asociación Española de Psiquiatría del Niño y el Adolescente	6/2017	Castellón, Spain	Scientific community		global
27	Conference	Oresic M; Hietala J; Frank E.	Workshop on Schizophrenia and other mental disorders	15.-16.6.2017	Pisa, Italy	Scientific Community		global
28	Conference	Díaz-Caneja CM	17th Congress of the European Society for Child and Adolescent Psychiatry	07/2017	Geneve, Switzerland	Scientific community		global
29	Seminar	Oresic M.	METSY closing symposium	21.-22.8.2017	Turku, Finland	Project members	22	Finland, Sweden, Germany, Sain, UK
30	lecture	Jarmo Hietala	Schizophrenia coalition	5.2.2018	Turku, Finland		150	EU
31	Conference Poster	Markus Butz-Ostendorf	Risk Management in First Episode Psychosis Patients	3/2018	Heidelberg, Germany	Scientific Community, Health Care		Germany

32	Symposium lecture	Jarmo Hietala	SIRS	4/2018	Florence, Italy	Scinetific community		Global
33		Markus Butz-Ostendorf	NeuroXM, a knowledge management system for brain science	7/2018	Berlin, Germany	Industry, Health care providers, Policy makers, Media	400	Global English spoken

Section B

Part B1

The applications for patents, trademarks, registered designs, etc. shall be listed according to the template B1 provided hereafter.

The list should, specify at least one unique identifier e.g. European Patent application reference. For patent applications, only if applicable, contributions to standards should be specified. This table is cumulative, which means that it should always show all applications from the beginning until after the end of the project.

TEMPLATE B1: LIST OF APPLICATIONS FOR PATENTS, TRADEMARKS, REGISTERED DESIGNS, ETC.					
Type of IP Rights:	Confidential Click on YES/NO	Foreseen embargo date dd/mm/yyyy	Application reference(s) (e.g. EP123456)	Subject or title of application	Applicant (s) (as on the application)
Patent Application (National UKIPO)	**YES** (until 8/2018)	30/08/2018	1702600.6	NEUROLOGICAL DATA PROCESSING	Dr. Markus Butz-Ostendorf, Dr. Sascha Losko, Dr. Wenzel Kalus
Patent Application (PCT, EPO)	**YES** (until 8/2018)	30/08/2018	PCT/EP2018/053813	NEUROLOGICAL DATA PROCESSING	Dr. Markus Butz-Ostendorf, Dr. Sascha Losko, Dr. Wenzel Kalus

Part B2
Please complete the table hereafter:

Type of Exploitable Foreground	Description of exploitable foreground	Confidential Click on YES/NO	Foreseen embargo date dd/mm/yyyy	Exploitable product(s) or measure(s)	Sector(s) of application	Timetable, commercial or any other use	Patents or other IPR exploitation (licences)	Owner & Other Beneficiary(s) involved
Biomarkers	*Serum lipid signature that predicts rapid weight gain in FEP (and potentially CHR) patients*	*NO*		*Diagnostic tool*	*Healthcare, diagnostic*	*2018-*	*Diagnostic kit patent planned*	*UTU & THL, KCL, ORU*

As one of the key outcomes of METSY, a lipid signature was identified which may be predictive of detoriating metabolic profile of FEP patients (UTU, THL, Steno). Of interest, the lipid profile suggests that patients who rapidly gain weight during the follow-up has increased markers of non-alcoholic fatty liver disease (NAFLD) at baseline, independent of obesity.

By the end of METSY project, samples for validation studies were analysed (UTU, ORU, SERMAS, KCL, UTU), including in EU-GEI cohort (CHR patients, with KCL). Depending on these validation results, the aim is to develop a diagnostic application which could be utilized in the healthcare setting. Such a tool would be important, as it would facilitate treatment recommendation to the most vulnerable patients, e.g. by also recommending anti-obesity/diabetes medications.

4.3 Report on societal implications

Replies to the following questions will assist the Commission to obtain statistics and indicators on societal and socio-economic issues addressed by projects. The questions are arranged in a number of key themes. As well as producing certain statistics, the replies will also help identify those projects that have shown a real engagement with wider societal issues, and thereby identify interesting approaches to these issues and best practices. The replies for individual projects will not be made public.

A General Information *(completed automatically when **Grant Agreement number** is entered.*	
Grant Agreement Number:	602478
Title of Project:	Neuroimaging platform for characterisation of metabolic co-morbidities in psychotic disorders
Name and Title of Coordinator:	Dr. Matej Oresic

B Ethics	
1. Did your project undergo an Ethics Review (and/or Screening)? • If Yes: have you described the progress of compliance with the relevant Ethics Review/Screening Requirements in the frame of the periodic/final project reports? Special Reminder: the progress of compliance with the Ethics Review/Screening Requirements should be described in the Period/Final Project Reports under the Section 3.2.2 *'Work Progress and Achievements'*	***No***
2. Please indicate whether your project involved any of the following issues (tick box) :	
RESEARCH ON HUMANS	
• Did the project involve children?	N
• Did the project involve patients?	Y
• Did the project involve persons not able to give consent?	N
• Did the project involve adult healthy volunteers?	Y
• Did the project involve Human genetic material?	N
• Did the project involve Human biological samples?	Y
• Did the project involve Human data collection?	Y
RESEARCH ON HUMAN EMBRYO/FOETUS	
• Did the project involve Human Embryos?	N
• Did the project involve Human Foetal Tissue / Cells?	N
• Did the project involve Human Embryonic Stem Cells (hESCs)?	N
• Did the project on human Embryonic Stem Cells involve cells in culture?	N
• Did the project on human Embryonic Stem Cells involve the derivation of cells from Embryos?	N
PRIVACY	
• Did the project involve processing of genetic information or personal data (eg. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?	Y

• Did the project involve tracking the location or observation of people?	N
RESEARCH ON ANIMALS	
• Did the project involve research on animals?	N
• Were those animals transgenic small laboratory animals?	N
• Were those animals transgenic farm animals?	N
• Were those animals cloned farm animals?	N
• Were those animals non-human primates?	N
RESEARCH INVOLVING DEVELOPING COUNTRIES	
• Did the project involve the use of local resources (genetic, animal, plant etc)?	**N**
• Was the project of benefit to local community (capacity building, access to healthcare, education etc)?	**N**
DUAL USE	
• Research having direct military use	No
• Research having the potential for terrorist abuse	No

C Workforce Statistics

3. Workforce statistics for the project: Please indicate in the table below the number of people who worked on the project (on a headcount basis).

Type of Position	Number of Women	Number of Men
Scientific Coordinator		1
Work package leaders	3	4
Experienced researchers (i.e. PhD holders)	9	12
PhD Students	1	2
Other	3	2

4. How many additional researchers (in companies and universities) were recruited specifically for this project?	**7**
Of which, indicate the number of men:	3

D Gender Aspects

5. Did you carry out specific Gender Equality Actions under the project?

- [x] Yes
- [ ] No

6. Which of the following actions did you carry out and how effective were they?

	Not at all effective				Very effective
☑ Design and implement an equal opportunity policy	○	○	○	●	○
☑ Set targets to achieve a gender balance in the workforce	○	○	●	○	○
☐ Organise conferences and workshops on gender	○	○	○	○	○
☐ Actions to improve work-life balance	○	○	○	○	○

○ Other:

7. Was there a gender dimension associated with the research content – i.e. wherever people were the focus of the research as, for example, consumers, users, patients or in trials, was the issue of gender considered and addressed?

- [x] Yes- please specify Some of the research findings show gender-specificity of the outcomes, does demanding designing current and future investigations to account for this unexpected effect.
- [ ] No

E Synergies with Science Education

8. Did your project involve working with students and/or school pupils (e.g. open days, participation in science festivals and events, prizes/competitions or joint projects)?

- [ ] Yes- please specify
- [x] No

9. Did the project generate any science education material (e.g. kits, websites, explanatory booklets, DVDs)?

- [ ] Yes- please specify
- [x] No

F Interdisciplinarity

10. Which disciplines (see list below) are involved in your project?

- [ ] Main discipline[3]: 3.2
- [ ] Associated discipline[3]: 3.1
- [ ] Associated discipline[3]: 1.5

G Engaging with Civil society and policy makers

11a Did your project engage with societal actors beyond the research community? *(if 'No', go to Question 14)*

- [x] Yes
- [ ] No

11b If yes, did you engage with citizens (citizens' panels / juries) or organised civil society (NGOs, patients' groups etc.)?

- [ ] No
- [ ] Yes- in determining what research should be performed

○ Yes - in implementing the research ● Yes, in communicating /disseminating / using the results of the project	
11c In doing so, did your project involve actors whose role is mainly to organise the dialogue with citizens and organised civil society (e.g. professional mediator; communication company, science museums)?	○ Yes ● No
12. Did you engage with government / public bodies or policy makers (including international organisations)	
○ No ● Yes- in framing the research agenda ○ Yes - in implementing the research agenda ● Yes, in communicating /disseminating / using the results of the project	
13a Will the project generate outputs (expertise or scientific advice) which could be used by policy makers? ○ Yes – as a **primary** objective (please indicate areas below- multiple answers possible) ● Yes – as a **secondary** objective (please indicate areas below - multiple answer possible) ○ No	

13b If Yes, in which fields?

Agriculture		Energy		Human rights	
Audiovisual and Media		Enlargement		Information Society	
Budget		Enterprise		Institutional affairs	
Competition		Environment		Internal Market	
Consumers		External Relations		Justice, freedom and security	
Culture		External Trade		Public Health	
Customs		Fisheries and Maritime Affairs		Regional Policy	
Development Economic and Monetary Affairs		Food Safety		Research and Innovation	
Education, Training, Youth		Foreign and Security Policy		Space	
Employment and Social Affairs		Fraud		Taxation	
		Humanitarian aid		Transport	

[3] Insert number from list below (Frascati Manual).

13c If Yes, at which level?

- ○ Local / regional levels
- ○ National level
- ○ European level
- ○ International level

H Use and dissemination

14. How many Articles were published/accepted for publication in peer-reviewed journals?	**29**
To how many of these is open access[4] provided?	
How many of these are published in open access journals?	
How many of these are published in open repositories?	
To how many of these is open access not provided?	
Please check all applicable reasons for not providing open access:	
❑ publisher's licensing agreement would not permit publishing in a repository ❑ no suitable repository available ❑ no suitable open access journal available ❑ no funds available to publish in an open access journal ❑ lack of time and resources ❑ lack of information on open access ❑ other[5]: ……	

15. How many new patent applications ('priority filings') have been made? *("Technologically unique": multiple applications for the same invention in different jurisdictions should be counted as just one application of grant).*		**2**
16. Indicate how many of the following Intellectual Property Rights were applied for (give number in each box).	Trademark	
	Registered design	
	Other	**2**
17. How many spin-off companies were created / are planned as a direct result of the project?		**0**
Indicate the approximate number of additional jobs in these companies:		

18. Please indicate whether your project has a potential impact on employment, in comparison with the situation before your project:

- ❑ Increase in employment, or
- ❑ Safeguard employment, or
- ❑ Decrease in employment,
- ❑ Difficult to estimate / not possible to quantify

- ❑ In small & medium-sized enterprises
- ❑ In large companies
- ❑ None of the above / not relevant to the project

[4] Open Access is defined as free of charge access for anyone via Internet.
[5] For instance: classification for security project.

19. For your project partnership please estimate the employment effect resulting directly from your participation in Full Time Equivalent (*FTE = one person working fulltime for a year*) jobs:	*Indicate figure:*
Difficult to estimate / not possible to quantify	❑

I Media and Communication to the general public

20. As part of the project, were any of the beneficiaries professionals in communication or media relations?

○ Yes ○ No

21. As part of the project, have any beneficiaries received professional media / communication training / advice to improve communication with the general public?

○ Yes ○ No

22 Which of the following have been used to communicate information about your project to the general public, or have resulted from your project?

❑ Press Release	❑ Coverage in specialist press
❑ Media briefing	❑ Coverage in general (non-specialist) press
❑ TV coverage / report	❑ Coverage in national press
❑ Radio coverage / report	❑ Coverage in international press
❑ Brochures /posters / flyers	❑ Website for the general public / internet
❑ DVD /Film /Multimedia	❑ Event targeting general public (festival, conference, exhibition, science café)

23 In which languages are the information products for the general public produced?

❑ Language of the coordinator	❑ English
❑ Other language(s)	

***Question F-10*:** Classification of Scientific Disciplines according to the Frascati Manual 2002 (Proposed Standard Practice for Surveys on Research and Experimental Development, OECD 2002):

FIELDS OF SCIENCE AND TECHNOLOGY

1. NATURAL SCIENCES
1.1 Mathematics and computer sciences [mathematics and other allied fields: computer sciences and other allied subjects (software development only; hardware development should be classified in the engineering fields)]
1.2 Physical sciences (astronomy and space sciences, physics and other allied subjects)
1.3 Chemical sciences (chemistry, other allied subjects)
1.4 Earth and related environmental sciences (geology, geophysics, mineralogy, physical geography and other geosciences, meteorology and other atmospheric sciences including climatic research, oceanography, vulcanology, palaeoecology, other allied sciences)
1.5 Biological sciences (biology, botany, bacteriology, microbiology, zoology, entomology, genetics, biochemistry, biophysics, other allied sciences, excluding clinical and veterinary sciences)

2 ENGINEERING AND TECHNOLOGY

2.1 Civil engineering (architecture engineering, building science and engineering, construction engineering, municipal and structural engineering and other allied subjects)
2.2 Electrical engineering, electronics [electrical engineering, electronics, communication engineering and systems, computer engineering (hardware only) and other allied subjects]
2.3. Other engineering sciences (such as chemical, aeronautical and space, mechanical, metallurgical and materials engineering, and their specialised subdivisions; forest products; applied sciences such as geodesy, industrial chemistry, etc.; the science and technology of food production; specialised technologies of interdisciplinary fields, e.g. systems analysis, metallurgy, mining, textile technology and other applied subjects)

3. MEDICAL SCIENCES
3.1 Basic medicine (anatomy, cytology, physiology, genetics, pharmacy, pharmacology, toxicology, immunology and immunohaematology, clinical chemistry, clinical microbiology, pathology)
3.2 Clinical medicine (anaesthesiology, paediatrics, obstetrics and gynaecology, internal medicine, surgery, dentistry, neurology, psychiatry, radiology, therapeutics, otorhinolaryngology, ophthalmology)
3.3 Health sciences (public health services, social medicine, hygiene, nursing, epidemiology)

4. AGRICULTURAL SCIENCES
4.1 Agriculture, forestry, fisheries and allied sciences (agronomy, animal husbandry, fisheries, forestry, horticulture, other allied subjects)
4.2 Veterinary medicine

5. SOCIAL SCIENCES
5.1 Psychology
5.2 Economics
5.3 Educational sciences (education and training and other allied subjects)
5.4 Other social sciences [anthropology (social and cultural) and ethnology, demography, geography (human, economic and social), town and country planning, management, law, linguistics, political sciences, sociology, organisation and methods, miscellaneous social sciences and interdisciplinary , methodological and historical S1T activities relating to subjects in this group. Physical anthropology, physical geography and psychophysiology should normally be classified with the natural sciences].

6. HUMANITIES
6.1 History (history, prehistory and history, together with auxiliary historical disciplines such as archaeology, numismatics, palaeography, genealogy, etc.)
6.2 Languages and literature (ancient and modern)
6.3 Other humanities [philosophy (including the history of science and technology) arts, history of art, art criticism, painting, sculpture, musicology, dramatic art excluding artistic "research" of any kind, religion, theology, other fields and subjects pertaining to the humanities, methodological, historical and other S1T activities relating to the subjects in this group]