technique for testing mechanistic hypothesis about (subject-specific) pathophysiological processes is dynamic causal modelling. Cross-sectional studies have already indicated the potential of this modelling in the prediction of the onset of psychosis and also treatment responses[11]. In particular, fronto-parietal connectivity during working memory processing was found to be progressively reduced from healthy controls to high-risk subjects further to first-episode psychosis, whereas this coupling returned to levels indistinguishable from controls in antipsychotic-treated first-episode patients.

Useful clinical predictions have to be made at the single subject level. Although model-based computational approaches are promising, it has yet to be shown whether they allow individual decision-making. Another established tool for this purpose is the application of machine learning approaches. These approaches have been increasingly used to dissect different stages of psychosis using structural and functional imaging data. Using a support vector machine analysis with gray matter volumes, Koutsouleris et al[12] were able to separate psychosis converters from non-converters in two independent samples with an accuracy of 80%.

A recent study has also indicated that the assessment of white matter integrity may predict treatment responses in first-episode psychosis[13]. Along this line, an ongoing multicentre trial named Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE), conducted in antipsychotic naïve patients with a first episode of schizophrenia or schizophreniform disorder, is testing whether MRI measures can be helpful to identify predictors of response to treatment.

In conclusion, neuroimaging studies have improved our understanding of the neurobiological mechanisms underlying psychosis. However, underpowered, cross-sectional study designs without hypothesis-driven strategies have so far impeded the achievement of a neuroimaging-based prediction of psychosis onset. Although many challenges lie ahead, the field is now moving towards conducting large multicentre studies to overcome some of these limitations. Such collaborations, in combination with standardized clinical and analytical approaches, will be required to exploit the entire potential of neuroimaging and to ultimately evaluate its clinical utility for psychosis services.

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Identifying multimodal signatures associated with symptom clusters: the example of the IMAGEMEND project

Mental disorders are amongst the leading causes of disability worldwide. This is in part attributable to ongoing challenges in defining biological markers that can usefully aid in the diagnosis and treatment of individuals with these disorders. In order to move forward we need to address conceptual and experimental challenges that include: a) imprecise determination of the pathophysiological processes involved; b) insufficiently powered patient cohorts; c) uninformative pharmacological probes, given the poor differentiation in mode of action of existing agents; d) the logistic complexity of the multi-site investigations needed to establish generalizability and reproducibility; e) the limited predictive and explanatory power of individual biological markers; f) concerns about the statistical, logistic and financial viability of complex algorithms in routine care.

The Imaging Genetics for Mental Disorders (IMAGEMEND) project provides a platform for addressing these challenges. It brings together 14 institutions from nine countries (Australia, Germany, Iceland, Italy, Norway, Switzerland, The Netherlands, U.K. and U.S.). Workflow is organized in targeted work-packages. The focus is on three disorders – schizophrenia, bipolar disorder and attention-deficit hyperactivity disorder (ADHD) – that show significant genetic, environmental and clinical overlap. Here we outline the conceptual premises and organizational design of the project. Details on the samples, measures and bioinformatics approaches used can be found at http://www.imagemend.eu/.

The first essential element of the project is its transdiagnostic focus. Multiple lines of evidence support the notion that pathophysiological processes relevant to mental disorders may be more directly linked to symptom clusters transcending diagnostic boundaries than to specific syndromes[1]. The goal of the study is to identify multimodal signatures associated with symptom clusters using a data-driven approach that harnesses the power of the collaborative bioresource of the

consortium. However, current clinical diagnoses are both familiar to clinicians and patients and also form the basis of current treatment planning and drug licensing. With this in mind, the study will also test whether DSM and ICD diagnoses of schizophrenia, bipolar disorder and ADHD may be associated with multimodal signatures that can be clinically useful.

A second essential element of the project is the multimodal systems-level approach. Three research modalities, namely neuroimaging, genetics and environmental exposures, have made significant contributions to our current understanding of mental disorders. Neuroimaging has documented that schizophrenia, bipolar disorder and ADHD are brain disorders that involve structural and functional neural networks[1-4]. Alterations in these networks have been shown to have diagnostic relevance in differentiating patients from controls[5] and in predicting outcome[6] and treatment response[7]. Environmental exposures, such as urbanicity[8], and genetic variation[9] known to increase the risk for disease also disrupt the organization of neural networks. IMAGEMEND tests the hypothesis that different combinations of measures from these research modalities (i.e., multimodal signatures) can be defined and used to delineate more homogeneous, biologically informed patient cohorts.

Consortium partners have already contributed data on a total of 12,667 individuals, of whom 1,493 have been diagnosed with schizophrenia, 1,184 with bipolar disorder and 400 with ADHD, while 8,554 are screened healthy controls. The bioresource also includes data from relatives (N=1,036) and from population-derived groups of individuals. The latter group comprises a population sample of 2,000 youth recruited, assessed and followed up for 2 years. The sample has been characterized using several psychopathology scales which allow the characterization of youth along multiple dimensions of risk. The availability of genotypic data enables the estimation of polygenic scores[10] based on available genetic studies on schizophrenia, bipolar disorder and ADHD. Throughout the project, genotyping, neuroimaging and clinical data will be added to create one of the most extensive multimodal resources in psychiatry.

The project will test for phase-specific multimodal signatures relevant to conversion to disease, to differential diagnosis and prognosis and to treatment response and tolerability, as each may be associated with qualitatively different pathophysiology and biological markers. Accordingly, the "presymptomatic marker" work-package seeks to identify multimodal signatures for the prediction of syndromal conversion in high-risk individuals, thus paving the way for preventive interventions. The "diagnostic marker" work-package focuses on multimodal signatures linked to current diagnostic constructs or to diagnosis-independent pathophysiological processes. The "predictive marker" work-package targets biological markers that track response, relapse and side effects in large-scale patient populations for whom longitudinal data (up to 4 years) are already available within the consortium. All participants have received naturalistic treatment, as any clinical tools developed by the study aim to be used in real-world clinical settings.

The project will employ and benchmark a variety of computational methods, including machine learning (e.g., support vector machines and "learning using privileged information"). A primary aim is to examine the effect of increasing the complexity of data input on the performance of predictive algorithms and determine optimal combinations. The best performing algorithms will be then tested for reproducibility and longitudinal stability.

The "translation" work-package will utilize identified diagnostic and predictive multimodal signatures towards development of clinical tests to aid in diagnosis and treatment selection. The most likely format of these products will be a software with a user-friendly interface that will use imaging and other data provided by clinicians in order to yield probability estimates of diagnosis or course of treatment response. Additionally, therapeutic tools will include a clinical real-time functional magnetic resonance imaging software with a novel interface that allows illness-related selection of feedback paradigms and automatic definition of brain regions and networks for individualized neurofeedback training.

To sum up, IMAGEMEND is a large collaborative effort to identify clinically relevant multimodal signatures, based on a systems-level understanding of pathophysiological processes, and to translate this knowledge into tools for the advancement of clinical care for mental disorders.

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