Is neuroimaging clinically useful in subjects at high risk for psychosis?

Although the massive amount of cross-sectional neuroimaging findings has improved our understanding of the pathophysiological processes underlying emerging psychosis, the clinical implications of these findings have remained scarce. To adequately examine the clinical utility of neuroimaging for the prediction of psychosis onset, a longitudinal analysis of brain changes over time with standardized measures is required. However, such study designs demand high efforts from both participants and investigators.

The few studies tracing gray matter volume over time found reductions in frontal, temporal, parietal and cerebellar cortex in high-risk subjects who developed psychosis[1]. Comparing the longitudinal course of converters with non-converters, some studies found reduced gray matter volumes in frontal, temporal and insular brain regions in the former[2], while other studies reported no differences[3]. Considering white matter alterations, a longitudinal study found a progressive reduction in fractional anisotropy in the left frontal cortex of high-risk subjects who developed psychosis that was not evident in subjects who did not make the transition[4]. There is also a positron emission tomography (PET) study exploring presynaptic striatal dopaminergic function within subjects as they progressed from a prodromal phase to the first episode of psychosis, which found a progressive increase in striatal dopamine synthesis capacity as patients developed psychosis[5].

Some limitations, however, prevent translation of these findings into clinical applications at the moment. The first issue is that most studies are clearly underpowered. The largest published study so far, from the North American Prodrome Longitudinal Study (NAPLS) project, has recently found a steeper rate of gray matter loss in frontal brain regions of 35 high-risk individuals who converted to psychosis compared to 239 subjects without transition[6], but the low transition rate (14.6%) challenges whether these subjects were really at risk.

Another point of contention is the clinical heterogeneity of high-risk samples. This is due to the different high-risk criteria used across centres. Thus, an important next step is to develop standardized clinical instruments for the definition of the high-risk state and a consensus on what we are trying to predict. A further major point is the focus on univariate analyses at the group level. This strategy compares each voxel separately across groups and is thus not taking into account alterations of distributed brain patterns, which is critical given that psychosis is most probably characterized by abnormal (network) connectivity.

Fortunately, the field has been taking huge endeavours to address the above-mentioned limitations. Currently ongoing multicentre studies – such as PRONIA (Personalised Prognostic Tools for Early Psychosis Management), PSYSCAN (Translating Neuroimaging Findings From Research Into Clinical Practice) and NAPLS – will be able to overcome the hurdle of underpowered studies by collecting large high-risk data samples. These data sets should then be analyzed in the light of previously established evidence, leading to hypothesis-driven strategies rather than trying to find the needle in the haystack.

A first and probably the most straightforward strategy is to systematically follow-up replicated evidence from previous cross-sectional studies in chronic psychosis. A nice example of this strategy has been provided in a sample of 243 high-risk subjects obtained from the NAPLS project. This resting state functional magnetic resonance imaging (fMRI) study focused on thalamo-cortical connectivity, because this pathway has been previously implicated in established psychosis[7]. In particular, it explored whether thalamo-cortical connectivity differed between high-risk subjects and healthy controls and whether dysconnectivity was more severe in high-risk subjects with a later transition. The findings revealed hypo-connectivity between the thalamus and prefrontal and cerebellar areas, as well as hyper-connectivity between the thalamus and sensorymotor regions. Both patterns were more prominent in high-risk subjects who converted to psychosis and significantly correlated with prodromal symptom severity. This finding has now to be tested in longitudinal studies to probe whether thalamic connectivity does have prognostic implications for risk of conversion to full-blown psychosis. Furthermore, having in mind that the Human Connectome Project[8] suggests that psychiatric disorders share overlapping patterns of dysconnectivity, it is important to compare longitudinal thalamo-cortical connectivity in high-risk converters with that of other psychiatric illnesses, to validate its specificity.

Another approach is to translate findings from animal research. A concrete example is provided by the methylazoxymethanol acetate (MAM) rodent model, which suggests that augmented hippocampal function (secondary to a loss of interneuron function) underlies elevated striatal dopamine levels associated with psychosis[9]. Although caution is required when translating findings from animals to humans, a recent review showed that neuroimaging findings in high-risk subjects are broadly consistent with the MAM model[10]. Guided by this model, recent cross-sectional investigations in high-risk samples are trying to relate functional with chemical measures within the hippocampal-midbrain-striatal network, which hopefully will provide a scaffold for longitudinal investigations.

However, to address alterations at the brain network level, as for example within the hippocampal-midbrain-striatal circuitry, more sophisticated connectivity approaches are required. Biophysically informed computational modeling allows unifying different aspects of information from the molecular to the system level, thereby helping to formulate more comprehensive pathophysiological hypotheses. One suitable computational

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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A. Schmidt is supported by the Swiss National Science Foundation (grant no. P2ZHP3_155184).

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DOI:10.1002/wps.20333

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