Editorial

Third-generation neuroimaging in early schizophrenia: translating research evidence into clinical utility[†]

Stefan Borgwardt and Paolo Fusar-Poli

Summary

Psychiatric imaging needs to move away from simple investigations of the neurobiology underlying the early phases of schizophrenia to translate imaging findings in the clinical field, targeting clinical outcomes including transition, remission and response to preventive interventions.

Stefan Borgwardt (pictured) is a psychiatrist, neuroscientist and professor of neuropsychiatry. He holds posts in both the Department of Psychiatry and the Medical Image Analysis Centre at the University of Basel. He is also affiliated with the Department of Psychosis Studies at the Institute of Psychiatry, London. Paolo Fusar-Poli is an associate clinical professor at the Department of Psychosis Studies, Institute of Psychiatry, King's College London, and consultant psychiatrist at the OASIS Team, South London and Maudsley NHS Foundation Trust.

In this issue of the *Journal*, Bodnar and colleagues report identifying increased activity in the cingulate cortex, specific to semantic processing during memory encoding, in participants with non-remitted first-episode schizophrenia compared with participants who achieved remission.[1] The finding of altered cingulate brain activity measured by functional magnetic resonance imaging (fMRI) during semantic memory encoding/processing may underlie core pathophysiological and clinical issues during the early phases of schizophrenia. We believe that the specific merit of this study is that it brings us closer towards translating psychiatric neuroimaging into clinical practice, suggesting that these alterations may be of potential use for detecting treatment response.

First-generation psychiatric neuroimaging focused on simple structural brain alterations associated with the neurobiology of the illness. These early studies adopted imaging methods including computerised tomography (CT) to investigate brain size abnormalities[2] or positron emission tomography (PET) to assess glucose utilisation in schizophrenia.[3] Second-generation psychiatric neuroimaging studies benefited from more sophisticated techniques that included structural methods (sMRI) coupled with whole-brain automated methods (voxel-based morphometry (VBM)), white-matter methods (diffusion tensor imaging (DTI) and tractography), functional methods (fMRI) and advanced neurochemical imaging (PET techniques addressing receptor bindings and pre-/post-synaptic functions, magnetic resonance spectroscopy (MRS)) and sophisticated meta-analytical imaging methods. Furthermore, when early clinical intervention in schizophrenia became a major objective of mental health services, the imaging research interest shifted from the chronic phases to the early period. Despite this progress, nearly three decades after Johnstone *et al*'s first computerised axial

tomography of the brain of individuals with schizophrenia,[4] no consistent or reliable anatomical or functional alterations have been unequivocally associated with psychosis or schizophrenia and no clinical applications have been developed in psychiatric neuroimaging.

Translating psychiatric imaging into clinical utility

The lack of clinical relevance for psychiatric imaging is particularly concerning in the early phases of schizophrenia, because of the severe clinical, functional, social and economic long-term consequences of the illness. In this sense the finding of Bodnar *et al* that alterations in the cingulate cortex during a first episode of schizophrenia are related to psychopathology and outcomes are of great interest.[1] Structural alterations in the cingulate cortex have been confirmed at a meta-analytical level in participants presenting with a first episode of schizophrenia.[5] However, cingulate function and structure has been reported to be especially sensitive to remedial antipsychotic treatment in schizophrenia[6] and there is evidence indicating that a few weeks of antipsychotic treatment modulate the functional response in this region.[7] As the participants in Bodnar *et al*'s study were receiving antipsychotics, the clinical significance of their findings is questioned. Antipsychotic exposure can play a prominent confounding role in second-generation psychiatric imaging, militating against its clinical application.[8] One possible approach to circumvent this problem would be to selectively analyse participants with a first episode who are drug naive. In a recent meta-analysis including participants with untreated first-episode schizophrenia we confirmed that structural alterations in the cingulate cortex are present before the initiation of antipsychotic treatment.[9]

An alternative option would be to endorse 'close in' clinical high-risk approaches to identify a group of individuals with higher transition rates (18% after 6 months of follow-up, 22% after 1 year, 29% after 2 years and 36% after 3 years[10]) than those observed in the general population. This clinical strategy aims at identifying neural changes occurring prior to the onset of schizophrenia and may improve the ability of neuroimaging to predict clinical outcomes in schizophrenia (for a review of structural and functional findings see Fusar-Poli *et al*[11] and Smieskova *et al*[12]). Overall, these studies have shown that several abnormalities in brain anatomy and neurophysiology that are fundamental to schizophrenia are also present in people at high risk of schizophrenia, and may therefore represent vulnerability

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markers.[11] Interestingly, structural brain abnormalities in the insula and temporal lobe are also found to covary with levels of schizotypy in healthy individuals.[13] A recent meta-analysis of whole brain structural studies comparing 896 participants at high risk with 701 controls confirmed cingulate alterations in the high-risk group when compared with the control group, and additional abnormalities in temporal, prefrontal, parahippocampal/hippocampal regions.[11] Volumetric reductions in cingulate as well as in temporal, insular, prefrontal cortex and in cerebellum have also been associated with longitudinal development of schizophrenia over follow-up.[12] However, because of the paucity of structural imaging studies specifically linking brain changes and clinical outcomes, second-generation imaging studies are not able to definitively ascertain which structural abnormalities are specific to vulnerability as opposed to later transition to schizophrenia.

Linking imaging findings to clinical status

In this sense, Bodnar et al's study linking imaging findings with remission status points to a crucial gap in the high-risk literature.[1] In fact, a recent systematic review showed a literature bias in that nearly half of the high-risk studies provided no characteristics of those participants who did not develop schizophrenia.[14] The largest study published to date showed the non-converting high-risk group demonstrated significant improvement in attenuated positive symptoms, negative symptoms, and social and role functioning with more than 50% of this non-converting sample no longer presenting with any high-risk symptoms.[15] However, this group remained on average at a lower level of functioning than non-psychiatric comparison participants, suggesting that initial high-risk categorisation is associated with persistent disability for a significant proportion.[15] In line with Bodnar and colleagues' approach it would be very useful to address brain changes associated with remission status within the high-risk cohort to identify protective neurobiological markers of later development of illness. In terms of predicting clinical outcome and strengthening clinical applications for psychiatric imaging, there is evidence from functional and neurochemical high-risk studies that the extent of abnormality at baseline is predictive of subsequent conversion to psychosis.[12] These neurofunctional abnormalities were not only related to different duration of high risk but also to grey matter reductions.[16] Furthermore, structural abnormalities were positively correlated with clinical outcomes such as global functioning, negative symptomatology and hallucinations. Additional MRS studies in high-risk individuals have linked abnormal neuronal density and membrane turnover in cingulate as well as in frontal and insular lobes with later development of psychosis.[17] Positron emission tomography studies addressing dopaminergic neurotransmission before and after the onset of psychosis found an increased striatal presynaptic dopamine synthesis capacity that predicts the onset of illness,[18] in line with consistent evidence pointing to early striatal presynaptic dopaminergic alterations in schizophrenia.[19] Overall, second-generation imaging research into the high-risk state for psychosis has exponentially progressed, sustaining preventive interventions in clinical psychiatry.[20] However, despite the potential, the validity of high-risk criteria is still greatly debated and the problem of the high number of false positives severely undermines the benefits of preventive interventions.

Third-generation psychiatric imaging

There is, therefore, an urgent need for psychiatric imaging to move towards third-generation paradigms in line with Bodnar et al's study. Studies need to move away from simple investigations of the neurobiology underlying the early phases of schizophrenia, towards imaging that translates into clinically useful information, targeting longitudinal outcomes including transition, remission and response to preventive interventions. Third-generation psychiatric imaging in early psychosis will benefit from utilising even more complex techniques including multimodal approaches,[21] multicenter analyses[22] or automated diagnostic methods (support vector machines (SVMs)).[23] In particular, multivariate pattern recognition methods such as SVM are able to predict progression through different disease stages and categorise individual brain scans by separation of images from different groups, taking into account the interregional dependencies of different pathologies. Support vector machines use information from all voxels to reflect differences between groups in order to create models that allow predictions of clinical outcomes in individual patients (i.e. prediction of subsequent conversion to psychosis) with an accuracy of 82%.[24]

Future third-generation imaging studies in early schizophrenia will also benefit from the incorporation of new sources of neurobiological information such as whole genome sequencing, proteomic, lipidomic and expression profiles and cellular models derived from recent research on induced pluripotent stem cells.[25] For psychiatric imaging to be something more than basic neuroscience more studies such as the one by Bodnar et al are urgently required in the high-risk and early schizophrenia literature, to selectively link basic research and clinical outcomes.[26] These new third-generation neuroimaging approaches will sustain a research enterprise that it is hoped will improve and create therapeutic options for early schizophrenia and ultimately help in the treatment of our patients.

Stefan Borgwardt, MD, Department of Psychiatry and Medical Image Analysis Centre, University of Basel, Switzerland, and King's College London, Institute of Psychiatry, Department of Psychosis Studies, London, UK; **Paolo Fusar-Poli**, MD, PhD, King's College London, Institute of Psychiatry, Department of Psychosis Studies, London, UK

Correspondence: Stefan J. Borgwardt, Department of Psychiatry, University of Basel, c/o University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland. Email: sborgwardt@uhbs.ch

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