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EDITORIAL

The Contribution of Neuroimaging to Understanding Schizophrenia; Past, Present, and Future

Iris E. Sommer*[,1] and René S. Kahn[1]

[1]Brain Center Rudolf Magnus, Department of Psychiatry, University Medical Centre Utrecht, Utrecht, the Netherlands

*To whom correspondence should be addressed; Brain Center Rudolf Magnus, Department of Psychiatry, UMC Utrecht, A01.126, Heidelberglaan 100, Utrecht 3584CX, the Netherlands; tel: 31887556365, fax: 31887556543, e-mail: i.sommer@umcutrecht.nl

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This issue of *Schizophrenia Bulletin* presents a selection of imaging papers to clear the backlog. We would like to take the opportunity to indicate where this field should be going and define topics and methods of future imaging studies most needed in schizophrenia research.

Neuroimaging has been an extremely productive and instructive modality in schizophrenia research. The field has grown exponentially—particularly studies employing magnetic resonance imaging (MRI)—and their results have expanded our knowledge of schizophrenia extensively. In cross-sectional studies, thousands of patients have been investigated in hundreds of studies, providing a wealth of data on brain abnormalities in schizophrenia.[1] What's more, since the study of brain development is paramount in understanding schizophrenia, MRI studies exploring schizophrenia have provided, almost as an aside, extensive understanding of the brain as such. To be sure, understanding normal brain development is almost as important in unraveling schizophrenia as it is to study schizophrenia patients proper. Similarly, it is equally relevant to study subjects at (genetic) risk to develop schizophrenia. Indeed, some of these studies, in twins, siblings, and subjects at risk mental state (ARMS) have identified structural,[2,3] functional,[4] and molecular[5] risk factors in the brain underlying the development and outcome of schizophrenia.

Since the seminal computed tomography study by Johnstone et al[6] almost 4 decades ago we now understand much more of the brain anatomy—and function—of schizophrenia patients. First, we found that brain volumes are one of the most highly heritable characteristics in man with a heritability of almost 90%. This is relevant for studying genetic influences on brain development in general[7,8] and in schizophrenia. Second, brain changes, especially those in white matter[9] and their connections,[10] are related to the risk of developing schizophrenia. In contrast, volume changes, especially in the frontal and temporal areas, are related to the illness itself and to the progression of the illness.[11] Third, brain changes, expressed as thinning of the cortex, are predominantly present in frontal and temporal areas and progress as the illness worseness[12] and are related to outcome, number of hospitalizations and possibly, in part, medication use (although it is almost impossible to disentangle the latter effect from severity of illness). Finally, the brain changes precede the onset of the first psychosis and are expressed in white matter abnormalities; as the illness progresses further, brain matter abnormalities are found in cortex and subcortical structures.[13]

However, as all good science should, these studies have raised more questions than they answered. Possibly, the most important of these is the clinical relevance of the studies so far. Can we use them to assist diagnosis, predict risk and illness development, treatment response and outcome? Pattern recognition methods may prove useful in diagnosis at least vs bipolar disorder[14] conversion to illness[15] and treatment response,[16] but studies so far have been relatively small, although some large EU-funded studies, such as Psyscan and Pronia are now ongoing. Such studies also need to include other variables such as social and cognitive performance, presence and severity of signs and symptoms[17] and possibly—if relevant—blood markers. These prediction indexes need to be compared with clinical judgment and the added value of MRI needs to be demonstrated. While the field has so far concentrated on predicting transition to schizophrenia in individuals at increased risk, such as those at high genetic risk (GHR), or those meeting criteria for risk mental state (ARMS) or ultra high risk (UHR), predictive measures in the earlier premorbid phase are needed to enable interventions to prevent cognitive decline, which is thought to occur already during puberty[18] and in some 25% of

subjects even earlier.[19] Given the association between interneuron functioning, neural synchrony, and cognitive performance, electroencephalography and magnetoencephalography may be suitable candidate techniques for sensitive detection of early cognitive dysfunction.[20]

Schizophrenia is a broadly defined disorder, harboring patients with a range of clinical symptoms. It will be the task of future studies to try to understand the significance of this overlap and identify subgroups, be it on the basis of genetics, blood markers, clinical course, symptoms, or brain measures. In almost all neuroimaging studies, the overlap between the healthy control group and the patients has been extensive. The onus on future neuroimaging studies will be to demonstrate that it has the potential to identify clinically relevant subgroups. In this case, positron emission tomography (PET)[21] and magnetic resonance spectography (MRS)[22] may be particularly promising when linked to treatment outcome. PET may also be useful in identifying patients[23] who benefit from the use of anti-inflammatory agents to restore balance of the brain's immune system. As is may prove a valuable augmentation strategy for a subpopulation of patients.[24] Reflections of increased free water as seen with diffusion MRI may provide a valid and less invasive alternative.[25]

For many symptoms in schizophrenia we only partly understand the underlying brain alterations, which hampers the development of new, rational interventions. For example, what goes awry in the language system to cause disordered speech? Insufficient inhibition of non-dominant language areas has been suggested,[26] but replication in larger samples is needed. What happens in the brain during catatonia? Fluordeoxyglucose PET or arterial spin labeling (ASL) MRI could shed light into this dark symptom.[27] Is the mirror-neuron system the underlying basis of social dysfunction?[28] Exactly which mechanisms underlie negative symptoms and cognitive symptoms? Can decreased rich club connectivity in schizophrenia be translated to cognitive dysfunction?[29]

In future studies it will be key to disentangle the various aspects of the disorder that all affect brain structure and function (eg, genetic liability, medication use, cognitive functioning, pre/comorbid substance abuse, life style, etc.). Comparison of patients with schizophrenia to those with other disorders with partly overlapping symptoms or to individuals with isolated symptoms may be elucidating. As heterogeneity undermines hypothesis testing with risk of false negatives, imaging needs to clarify relevant subgroups in which specific hypotheses can be tested. Imaging-derived subgroups may prove a useful tool for profiling to test new treatments in more homogeneous subgroups, a first step toward personalized medicine in schizophrenia. Starting now, we need to move from descriptive studies to studies with clinical application, and we need to move away from imaging with a heterogeneous clinical syndrome as the independent variable to relating imaging to specific pathology.

Finally, the time of studies with modest samples is over. The field seems to have picked up on this. Large collaborative neuroimaging projects are now *de rigueur*, in UHR subjects (NAPLS), first episode schizophrenia (OPTiMiSE), and linking (abnormal) brain structure to genetics (ENIGMA).[30] These efforts have tackled the issue of intercenter variability—at least where it concerns structural MRI (sMRI) studies. Clearly, the same development is needed for functional MRI (fMRI) studies before they can contribute to addressing the questions raised above. This is confounded by the problem that most groups have developed their own fMRI task, or, when using resting state scans, use their personally preferred set of regions of interests (ROIs).

Over the last few decades neuroimaging has moved the field of schizophrenia research considerably forward. It has provided important insight into the causes of the illness and of factors determining its outcome. Possibly even more far-reaching, it has succeeded in creating large and fruitful collaborations that will hopefully—as has been the case in genetics—make the coming decades even more instructive than the past has been.

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