Implementing MR Imaging into Clinical Routine Screening in Patients with Psychosis?

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INTRODUCTION

Engendered by the first modern MR imaging study great enthusiasm and hope emerged that neuroimaging would help identifying the specific neurobiological pathology of psychosis. In contrast to the agnostic nature of the symptom-based clinical classification system about the underlying disease mechanisms, neuroimaging is particularly promising because it is able to non-invasively capture pathophysiological abnormalities at its core, the brain. In particular, psychoradiology, an emerging subspecialty in the field of neuroradiology, mainly taking the advantage of MR imaging multimodal nature, is showing promise in its clinical application to the psychiatric illnesses. The promise of MR imaging for the management of psychosis is to better understand the pathophysiology of psychotic symptoms at the very beginning of their development in order to apply early pathology tailored interventions. Interventions need directly target the pathophysiological processes causing psychosis in a manner that enduringly modifies its progression. Discernible brain pathology associated with psychosis includes reductions in global and regional gray matter volume, ventricular enlargement, cerebral atrophy, and cavum septi pellucidi. MR imaging provides a means of identifying such organic causes and could be used in the initial assessment of patients at early stages of psychosis.

Besides identifying radiological abnormalities, MR imaging has emerged as a very powerful tool to map direct neurobiological processes associated with emerging psychosis.
MR imaging studies have demonstrated that transition to full-blown psychosis is associated with structural and functional abnormalities in many different brain regions.\textsuperscript{12–15} These findings gave rise to hope that routine MR imaging scanning could be used to stratify psychotic patients according to clinical outcome and subgroups of patients could then be offered different forms of treatment.\textsuperscript{16–18}

As yet, however, MR imaging still has only a minor role in the clinical assessment of patients at early stages of psychosis and whether it should be implemented as routine screening instrument in psychotic patients has continued to generate debate.\textsuperscript{19–21} In this article, we first outline evidence regarding the clinical utility of MR imaging to (1) detect neurological abnormalities and (2) predict clinical outcomes in patients at early stages of psychosis. It is then concluded whether it is reasonable to implement MR imaging as an initial clinical screening instrument now and present potential next developments.

MR IMAGING TO IDENTIFY RADIOLOGICAL ABNORMALITIES IN EARLY PSYCHOSIS

Although it is considered good practice to include a neuroimaging assessment in the initial clinical assessment of patients with psychosis,\textsuperscript{22} this is not routinely carried out in all patients. Even though the proportion of patients with organic psychosis is small,\textsuperscript{23} it is crucial to identify such radiological abnormalities as early as possible, as urgent treatment of the primary disease may be required.\textsuperscript{24} Although it is widely acknowledged that MR imaging is suitable to identify organic causes of psychosis, it has been argued that scanning people with psychosis is too logistically difficult to be clinically worthwhile and might induce anxiety-related reactions.\textsuperscript{25} From an economical point of view, a previous cost-effectiveness analysis found that MR imaging (and computed tomography) as part of the standard screening procedure is justifiable only if the prevalence rate for organic causes amenable to treatment is 1% and the time between presentation and assessment is less than 3 months.\textsuperscript{19}

Radiological studies on the utility of MR imaging as clinical screening instrument provide inconsistent recommendations. A previous study reported radiological brain abnormalities in 22.2% of patients with first-episode psychosis (FEP) and in 50% of patients with chronic psychosis.\textsuperscript{9} Seven percent and 19%, respectively, of patients in the 2 patient groups required routine referral based on this finding, whereas 2.0% and 1.1%, respectively, even required urgent referral. Given that MR imaging as part of the standard screening procedure is only justifiable if the prevalence rate for organic causes amenable to treatment is 1%,\textsuperscript{19} this study\textsuperscript{8} showed that even if only a small proportion of patients benefited directly from MR imaging scanning, it is economically worthwhile. In a more recent study, 11% of clinically relevant radiological abnormalities have been reported in patients with psychosis.\textsuperscript{24} However, in contrast to Lubman and colleagues,\textsuperscript{8} in this sample of 656 patients, none of the neuropathological findings observed have been interpreted as a possible substrate for organic psychosis. The investigators therefore concluded that radiological assessments of MR imaging scans should not be considered a necessary component of routine screening in psychotic patients, because the minimum economical rate of 1% is not met,\textsuperscript{19} that is, at least 6 patients should have met criteria for organic psychosis in this sample.

A recently published article further contributed to this debate by first pointing out that the great majority of patients with psychosis were able to tolerate the scanning procedure very well, suggesting that an MR imaging assessment is practicable and logistically feasible in most patients with FEP, including patients in whom scanning is being done for clinical purposes.\textsuperscript{20} Secondly, in accordance with other reports,\textsuperscript{8,24,26,27} this study further observed that radiological abnormalities were relatively common in patients with FEP (6% of the research sample and 15% of the clinical sample), although they were also evident in healthy controls. None of the findings in patients with FEP entailed a change in clinical management. These results are comparable to a previous study in 37 people at clinical high risk for psychosis showing that radiological abnormalities are already present before the onset of the disorder.\textsuperscript{9} Notably, the prevalence rates in high-risk subjects (35%) was similar to those in patients with FEP (40%).\textsuperscript{9} They are unlikely to be related to antipsychotic medication, as most individuals at high risk and with FEP had never or only very briefly had been treated with antipsychotics.

Taken together, Falkenberg and colleagues\textsuperscript{20} provide the most recent evidence for the clinical utility of MR imaging to detect gross brain abnormalities in patients with psychosis. The investigators concluded that MR imaging as part of the initial clinical assessment is feasible in most patients with FEP, even though most of them do not require a change in clinical management.\textsuperscript{20} Nevertheless, aside from economic considerations,\textsuperscript{19} the investigators\textsuperscript{20} also emphasize that the consequences of failing to exclude such disorders in a young adult may be so grave that it is
worth assessing everyone and suggest including MR imaging scans in the clinical assessment of all patients presenting with emerging psychosis.

MR IMAGING TO PREDICT CLINICAL OUTCOMES IN EARLY PSYCHOSIS

In addition to identifying organic psychosis, MR imaging is an indispensable tool to elucidate the neurobiological substrates that might underlie primary (or idiopathic) psychotic illness and in particular the transition to full-blown psychosis. Numerous imaging studies have demonstrated structural, functional, and chemical brain abnormalities in clinical high-risk patients. Up to now, most studies used structural MR imaging to investigate alterations in regional gray matter volume in psychosis, whereas some of them might predate the transition to psychosis. Although such findings have significantly improved our understanding of the pathophysiological mechanisms underlying emerging psychosis, these group-level abnormalities do not capture individual deviations and therefore limit the prognostic accuracy of the data. Useful clinical predictions have to be made at the single-subject level. An established method for this purpose is the application of pattern recognition techniques, such as machine learning. These methods may promote an objective way to increase prognostic certainty to levels required for individualized prevention. Applying machine-learning approaches to neuroimaging data has the potential to revolutionize psychiatry by delivering prediction of individual patient outcome. There has been an increase in the use and development of machine-learning techniques in clinical neuroscience and in particular in the field of individualized early psychosis prediction. Robust prediction models that are able to inform clinical outcomes in early phases of psychosis might be tremendously useful to stratify individual intervention scenarios. Using whole-brain gray matter volume, previous machine-learning studies demonstrated a more than 80% accuracy in predicting psychosis onset in clinical high-risk subjects. Furthermore, it has been shown that the pattern of gray matter volume can predict social functioning impairments in high-risk subjects with more than 75% accuracy. Notably, prognostic performance in the latter case could be significantly improved by combining information from clinical and MR imaging models. Another study investigated whether cortical surface alterations analyzed by means of multivariate pattern recognition methods could enable the single-subject identification of functional outcomes in clinical high-risk individuals.

Given that gray matter reductions seen in patients occur before the transition to psychosis, during the transition, or in the immediate postonset phase, morphometric methods such as the measurement of surface area or gyration are perhaps more sensitive to detect the pathophysiology in the prodromal phase. Cortical surface-based pattern classification predicted good versus poor outcome status in clinical high-risk individuals with an accuracy of 82% as determined by nested leave-one-out-validation. These results are of high clinical relevance given that functioning may become worse even without transition to psychosis.

More recent MR imaging studies revealed that brain abnormalities in psychosis are not solely attributable to changes in local regions and connections but rather emerge from changes in the topology of the network as a whole, the connectome of the brain. Such network studies capture an important aspect of developmental maturation crucial for understanding the pathophysiology of psychotic disorders. Previous studies reported reduced small-worldness of structural brain networks in patients with schizophrenia, clinical high-risk subjects, people at increased familial risk for schizophrenia, and individuals with subclinical psychotic experiences, characterized by increased segregation and reduced integration of anatomical covariance (see Refs. for reviews of network analyses in psychosis). A recent study investigated whether transition to psychosis is associated with topological alterations in gyration networks and whether this network information improves individual prediction of psychosis onset. Gyration is a compelling marker of early neurodevelopment and may be sensitive to detect the pathophysiology in the prodromal phase. The findings of this cross-sectional MR imaging study showed that patients who develop psychosis reveal abnormalities in the gyration-connectome and that topological measures of the gyration-connectome predict the future outcome of transition with more than 80% accuracy. This result highlights the potential of applying machine-learning techniques to detect the clinical outcomes for psychosis in clinical high-risk individuals.

IMPLEMENTING MR IMAGING AS ROUTINE SCREENING IN THE CLINIC: ARE WE THERE YET?

The potential of MR imaging for the detection of radiological abnormalities is undeniable and it
has been shown that MR imaging as part of the clinical assessment is feasible in most patients with psychosis.20 High-resolution MR imaging can now be acquired in a relatively short scanning time, which is particularly useful in patients who may be acutely unwell. Although abnormalities that could account for a psychosis are rare, the impact of missing them is so tremendous that it is well justified to assess everyone with current acquisition protocols. However, identification of actionable brain pathology is so insufficient that it is not a good allocation of health care resources in a resource limited environment. Implementing MR imaging as a standard screening tool would also help to collect more data and thereby enhance the possibility to identify radiological abnormalities other than the already familiar ones. Diagnoses of organic psychosis might be further improved with the development of new diagnostic assessments. For instance, T2 or fluid-attenuated inversion recovery hyperintensities may help to detect psychotic patients with anti-NMDAR encephalitis.70 Furthermore, although radiological examinations are still based on visual inspection, the development of quantitative analytical approaches (such as machine learning) might help to make objective diagnoses of organic psychosis in the near future.

High-resolution MR imaging combined with sophisticated quantitative analyses may not only improve the detection of organic causes but also the prediction of clinical outcomes (eg, transition, functioning) in high-risk subjects. Although previous results from machine-learning studies designed to predict clinical outcomes in high-risk subjects are promising,40–43,68 major hurdles lie ahead before MR imaging is ready to be implemented in the clinic for prognostic assessments. The first issue is that most studies are currently underpowered. To exploit the entire potential of MR imaging and to ultimately evaluate its prognostic utility for psychiatric services, we need quantitative results from large patient samples using predefined research protocols. Currently ongoing multicenter studies, such as PRONIA (Personalized Prognostic Tools for Early Psychosis Management), PSYSCAN (Translating Neuroimaging Findings From Research Into Clinical Practice), and NAPLS (North American Prodrome Longitudinal Study), will be able to address this issue by delivering large samples. Once outcomes are defined using well-established and clinically meaningful criteria, outcome-specific predictors need to be selected71 by considering, for instance, evidence from systematic reviews or meta-analysis.72 Given that psychosis is best understood in terms of brain network dysfunction rather than by abnormalities in isolated brain regions,47–53 brain network markers might be particularly promising to determine staging of psychosis.13,73,74 A prognostic model also can consist of predictors from the same imaging modality (eg, volume, surface, or gyrification data) or across different modalities (eg, structural and functional MR imaging data). In any case, it is critical to consider the incidence of the outcome, that is, that the event per variable ratio is at least 10.75 Integrating MR imaging data with nonimaging measures that have independently been linked with altered outcomes in psychosis (eg, polygenic risk score, inflammatory markers) may also enhance predictive power, although it has yet to be tested.16 Similarly, it is also possible to combine MR imaging data with clinical data, as recently demonstrated,43 given that biological assays such as MR imaging will unlikely replace clinical assessments but might help to supplement them.76 The simplest approach for data fusion is to concatenate all data into the same model.69 It is also possible to combine the prognostic performance across separate models (eg, clinical and MR imaging model) by using ensemble learning strategies77 or a multistage sequential testing approach.11,78 After feature selection and data preparation (including proper handling of missing data),75 prognostic models can be developed.72 A critical step during model development is to estimate the model’s performance using internal validation methods to adjust for optimism.72 Internal validation is performed on the development data set by fitting the model in a training data set and then assessing performance in a test data set of unseen cases from the same population.75 Frequent internal validation methods are k-fold cross-validation and bootstrapping.75 To address heterogeneity across patients is then essential to test the generalizability of the developed model on individuals outside the development set.79 The less the validation differs from the development sample, the stronger the test of generalizability of the model.80 To our knowledge, no prognostic MR imaging model in psychotic patients has been externally validated up to now. Once these models have been validated on external (new) data sets in prospective patient studies, which is most challenging, these technologies need to be implemented into real-world clinical routine. Model impact studies with a comparative design are needed to test whether prediction models change individuals’ or health care professionals’ behavior or clinical decision making.81,82 Easy-to-use Web-based interfaces that can automatically give predictions for individual patients can certainly improve implementation processes.83 Such online calculators using clinical
implementing the early detection and intervention services. 

imaging for clinical decision making in early stages of the disorder. Recent developments in data acquisition and quantitative analyses might further lead to objective diagnosis of organic psychosis. Although first evidence is promising, we further show that MR imaging-based prognostic models for individuals at early stages of psychosis are not yet ready to be implemented as clinical baseline assessment. Further progress requires the collection of large samples, selection of standardized outcome-specific predictors, a methodologically sound development of prognostic models, and their validation in large independent samples. The field is armed to tackle these challenges and to exploit the entire potential of MR imaging for clinical decision making in early detection and intervention services.

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