

Predicting first episode psychosis in those at high risk for genetic or cognitive reasons

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Structural and functional magnetic resonance imaging (MRI) of patients with psychosis has advanced to the point where there are clear abnormalities at a group level between patients and groups of healthy controls, and suggestions of different patterns of abnormalities between groups of patients. A major area of research endeavour is being able to translate these group differences into clinically relevant predictions at an individual patient level. Here, we briefly summarize our main findings in cohorts at high risk of psychosis because they come from families in which several members have schizophrenia or bipolar disorder, or have educational impairments. We highlight consistent predictors of psychosis in those at high risk of schizophrenia for genetic or cognitive reasons, as compared with quite distinct profiles between those at genetic high risk of schizophrenia *v.* bipolar disorder on functional MRI during an executive language task. We also consider future research directions and ethical issues in the early diagnostic testing of people at high risk of psychosis.

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Introduction

One of the greatest problems facing contemporary psychiatry is the lack of objective diagnostic tests. Brain imaging offers arguably the greatest potential in this regard, giving direct access as it does to the brain/mind *in vivo*. Magnetic resonance imaging (MRI) has particular advantages of wide availability and a lack of exposure to ionizing radiation. There have now been hundreds of structural and functional MRI studies of patients with schizophrenia and bipolar disorder as compared with controls which demonstrate consistent abnormalities in groups of the two patient populations (Lawrie & Abukmeil, 1998, Wright *et al.* 2000). Direct and indirect comparisons demonstrate not only some overlap between the patient populations but also some possible distinctions. Patients with schizophrenia have reduced whole brain volumes, with greater reductions in prefrontal cortex and parts of the temporal lobe including the hippocampus and the amygdala; whereas patients with bipolar disorder tend to have similar abnormalities of a lesser degree, with possible sparing of some cortical regions and of the amygdala (Arnone *et al.* 2009). Here, we discuss whether these changes are evident in populations of high risk for schizophrenia or bipolar disorder, and the extent to which any such changes could be used to predict diagnosis at an earlier stage and perhaps in a more objective way than using standard clinical criteria.

The Edinburgh high risk study (EHRS) of Schizophrenia

The EHRS is a longitudinal prospective cohort study of people at high genetic risk of developing schizophrenia over subsequent years as they have at least two first and/or second degree relatives affected. Participants were aged 16–25 years at the beginning of the study (initial mean age 21 years) and recruited from all over Scotland. In total 162 such people gave some clinical, behavioural, cognitive and/or brain imaging data, of whom 21 went on to develop schizophrenia (Johnstone *et al.* 2005). An additional 60 of the high risk subjects had psychotic symptoms, as elicited on a structured interview with the Present State Examination, which appeared to wax and wane in severity in association with cannabis use and life events, but did not translate into schizophrenia. Despite detailed cognitive testing the best performing neuropsychological test as a predictor of schizophrenia was actually a negative predictor, relatively good memory on the Rey-Auditory Verbal Learning Test being associated with the background level of risk for schizophrenia (~13%) in this population (Whyte *et al.* 2006). By far the highest positive predictive values (PPV) and negative predictive values (NPV) from non-imaging variables were two measures of schizotypy, the very detailed structured interview for Schizotypy (PPV 29%, NPV 98%), and the very quick self-completed Rust Inventory of Schizotypal Cognitions (PPV 50%, NPV 94%). Structural MRI scans at baseline in 147 of the high-risk subjects showed that they had reduced volumes of the amygdala-hippocampal complex and thalamus compared with healthy controls (Lawrie *et al.* 1999), but these were relatively weak

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predictors of psychosis (Johnstone *et al.* 2005). Far more promising as a potential predictor with clinical utility was a measure of right pre-frontal cortex gyral folding – the ‘gyrification index’ (GI) – which was increased in those subjects with high genetic risk who went on to develop schizophrenia compared with those who did not (PPV 64%, NPV 58%; Harris *et al.* 2007).

All the assessments were repeated at approximately 18–24 months and reductions in the left (para-) hippocampal uncus and fusiform gyrus characterized those with psychotic symptoms who went on to get schizophrenia – with similar predictive powers as above (Job *et al.* 2006). Adapting the GI software we developed (Moorhead *et al.* 2006) allowed us to automatically extract whole brain, prefrontal and temporal lobe volume across the entire 434 scans conducted over almost 10 years in the EHRS, despite the fact that we had to change the scanner approximately half way through. This technique showed reductions across all these brain regions of approximately 1–2% per year until the time of diagnosis, on average 2.5 years later (McIntosh *et al.* 2011). Moreover, the extent of these reductions, particularly in the prefrontal lobe, was strongly and highly statistically significantly correlated with increasing severity of the symptoms that characterize psychosis, i.e. delusions, hallucinations and thought disorder.

Overall, in the EHRS, we have demonstrated that both changes over time in key brain regions, and even one base line structural MRI scan, appropriately analysed, can be used to predict schizophrenia years in advance on a single subject basis. We continue work to refine our image analysis protocols to increase the predictive power of our analyses.

The Edinburgh study of comorbidity (ESC)

The ESC has a very similar design to the EHRS, with the main differences being that we studied people at high risk of schizophrenia because they were educationally impaired (mean IQ=70), and analysed the groups *a priori* as to whether they had in addition notable schizotypal features of a similar level to that in the EHRS which were predictive of schizophrenia. We hypothesized those at high risk because they had both low IQ and high schizotypy would exhibit what can be called ‘an extended psychosis phenotype’ that would put them at particularly high risk of developing psychotic symptoms and psychosis itself (Johnstone *et al.* 2007). This has indeed turned out to be the case. Low IQ subjects with schizotypy have very much increased prevalence of hallucinations and delusions (30–40%), impaired memory and increased prefrontal cortical folding on the GI compared with those without

(Johnstone *et al.* 2007, Stanfield *et al.* 2008). Moreover, they also show a complementary pattern of reductions over time in grey matter in the left medial temporal lobe which relates to increasing psychotic symptoms (Moorhead *et al.* 2009). Early indications from ongoing analyses are that these changes over time are focused on the hippocampus, and are greater in those with psychotic symptoms including the small number who have gone on to develop schizophrenia *per se*.

In other words, it appears that participants in these two cohorts at high risk of schizophrenia for quite distinct reasons may have a common set of behavioural, cognitive and imaging predictors of schizophrenia (schizotypy, memory impairment and increased prefrontal gyral folding), which are particularly likely to translate into psychosis with grey matter loss over time in the medial temporal lobe.

The Bipolar family study (BFS)

A third prospective cohort study we have conducted in Edinburgh in recent years concerns those at high genetic risk of bipolar disorder because they have at least two close relatives who are affected with that condition. In total 112 high-risk subjects have participated, with an initial mean age again of 21 years at intake. We have only recently started to analyse and publish findings on this cohort, but our early findings suggest that they are manifestly different to those at high risk of schizophrenia for either genetic or cognitive reasons. Strikingly, during functional MRI while the subjects complete an executive language task (the Hayling Sentence Completion Test) there are quite distinct patterns of activation differences between the two genetic high-risk groups and healthy controls. In particular, during a parametric contrast in which increases or decreases in activation are mapped across varying levels of sentence constraint, thus controlling for non-specific activation in for example reading sentences and pressing buttons, subjects at high genetic risk of bipolar disorder show relative increases in amygdala activation compared with their group of matched healthy controls (Whalley *et al.* 2011). This is quite distinct from the pattern evident on studying those at a high genetic risk of schizophrenia, with exactly the same paradigm and contrast. Those people show a tendency to underactivate medial prefrontal cortex, thalamus and cerebellum (Whalley *et al.* 2004). Thus, it appears that functional MRI has at least the potential to distinguish populations at high genetic risk of different psychoses.

Functional MRI also appears to have the capability of differentially predicting depression and psychosis in both these populations. Of the subjects at high genetic risk for schizophrenia, those with psychotic symptoms showed a tendency to overactivate the parietal

lobe during the Hayling Sentence Completion Task (Whalley *et al.* 2004) and this was a relatively strong predictor of schizophrenia when considered in combination with lingual gyrus activation in a *post hoc* analysis (Whalley *et al.* 2006). In 12 of those subjects who subsequently became depressed, to a clinically significant degree, reductions in dorso-lateral prefrontal cortex (right middle/superior frontal gyrus) as well as increased left superior temporal gyrus activation were evident, and these results survived controlling for the presence of positive psychotic symptoms at the time of the scan (Whalley *et al.* 2008). In marked contrast, those at high genetic risk of bipolar disorder who went on to develop a major depressive disorder, some of whom are likely to go on to develop bipolar disorder, have abnormalities in other regions that predict subsequent depression (Whalley *et al.* submitted).

Ethical and practical considerations

We describe here a set of findings in those at high genetic risk of schizophrenia that replicate in a cohort of those at high cognitive risk of schizophrenia and appear quite different in those at high genetic risk of bipolar disorder. There are also several indications that these results at least have the potential to be used in clinical practice to make early diagnoses of schizophrenia, and possibly also of depression in the context of psychosis. There are, however, some notable limitations of our own work and that from similar research groups that need to be acknowledged and several additional considerations before this work could be implemented into clinical practice.

Representativeness

One consideration is the extent to which our findings could generalize to those who are going on to develop schizophrenia or bipolar disorder in routine clinical practice. While it is true that the majority of patients are not at obviously high genetic or cognitive risk, because of a known family history or cognitive impairment, it is equally true that (apart from rare exceptions of individual genes of major effect) multiple genes contribute to the risk for schizophrenia and bipolar disorder and these are distributed throughout the population. Furthermore, there is at least as yet no indication that the biology of schizophrenia and bipolar disorder differs in those at high genetic or cognitive risk *v.* those who come from different backgrounds. In the only directly comparable data we are aware of, structural and functional MRI studies in populations at high risk of schizophrenia because they have psychotic symptoms show a very similar pattern of

abnormalities in both those at high risk and in those who are going to make the transition to schizophrenia (i.e. are prodromal). Remarkably, reduced medial temporal lobe volume and increased prefrontal cortex volume are evident in those at high risk for clinical reasons, who go on to develop schizophrenia (Smieskova *et al.* 2010; Fusar-Poli *et al.* 2011).

Clinical impact

A greater concern is the extent to which the information we can derive with these measures can actually improve the clinical outcome for these people and do so in a cost effective way. It has to be acknowledged here that the best available evidence of the impact of reducing the duration of untreated psychosis is at best limited as to whether or not this improves subsequent outcome, whether by delaying the onset of schizophrenia or improving its subsequent prognosis (Marshall & Rathbone, 2011). While some practitioners of early intervention are very enthusiastic (Bird *et al.* 2010), and such services may be cost effective (Knapp *et al.* 2011), it remains debatable whether any benefits accrue in routine clinical practice and in particular whether any additional benefits would be realized by introducing routine brain imaging in early psychosis. It is questionable whether a couple of hundred pounds for a structural MRI scan or several hundred pounds for a functional MRI scan would be cost effective in practice. On the other hand, the issues in schizophrenia and bipolar disorder are very similar to those in dementia, where structural or functional brain imaging has been recommended on a routine basis for several years. Initially, this was to exclude possible intracranial pathology (Foster *et al.* 1999), but in the past 10 years it has become clear that structural and functional brain imaging could have a role in early diagnosis and differential diagnosis of dementia. Indeed, the recent introduction of qualitative and/or quantitative changes into diagnostic criteria for minimal cognitive impairment and dementia, to facilitate clinical research, has recently been applauded (McKhann *et al.* 2011). An analogous situation would potentially ensue if we started employing brain imaging routinely in evaluation of first episode psychosis. The increasing realization that up to 10% of patients with psychosis have detectable auto immune encephalitis, which sometimes can be detected with MRI, provides further justification for such an approach.

Practicalities

We have shown in the EHRS that brain imaging measures are more powerful predictors of schizophrenia than clinical, behavioural and cognitive

variables. Others have shown the same to be true in prodromal populations (see e.g. Koutsouleris *et al.* 2010, 2012). Structural and functional MRI also perform better than the best (and indeed only) genetic predictor in EHRS—the COMT val/met polymorphism (McIntosh *et al.* 2007). The most powerful prediction is however likely to come from a selective combination of a number of factors in these domains, as with most risk or outcome prediction models in medicine. This then raises issues about the anonymous storage and secure access to data of different types in a usable format. One can envisage a heavily populated database, preferably with data from several centres, to provide relevant reliable markers of what amounts to typical variation within control and psychiatric populations. In practice, it may be good enough to have varying ways of using imaging and other data across different centres depending on the amount of data that can be collected, much as in the recently proposed dementia criteria.

Ethical issues

Before any of these developments there is however a major need to address a number of ethical questions concerning the early diagnosis of psychosis. Very little work has thus far been done to address this. The availability of different treatments and knowledge of their effectiveness is likely to influence people's attitudes to early diagnostic testing and treatment. Indeed, acceptable rates of false positive and false negative diagnoses in different clinical scenarios would alter cut-offs, PPV and NPV for different decisions. The PPV and NPV quoted above in the EHRS are balanced for sensitivity and specificity because we have little information about which treatments would be acceptable. Qualitative studies and large population based questionnaire surveys are therefore required in various high risk populations to see at what level of risk of psychosis they might be prepared to take psychotherapeutic, behavioural or pharmacological interventions with known beneficial and adverse effects. It is for example possible that someone with relatively mild symptoms might be more prepared to accept screening than someone who might be at higher risk and with a greater potential to benefit from earlier treatment. In the rest of medicine, the uptake rate of cervical and breast cancer screening is encouraging, but that is for often fatal diseases for which there are increasingly effective treatments. As regards neuropsychiatric disorders, the uptake of Huntington's Chorea (HC) screening is much less successful, but there is of course no effective treatment for HC. Perhaps the most useful comparisons can again be made with reference to screening programmes for dementia, but that will be

no substitute for work in those at elevated genetic, cognitive and clinical risk for psychosis.

Conclusions

We have briefly discussed here how it is possible to predict schizophrenia in those at elevated genetic risk and that it is possible to do so with high predictive power, particularly with brain imaging measures. The EHRS and ESC shows that a relatively small number of potent predictors identify an extended psychosis phenotype which might be of particular value in prediction. The Bipolar Family Study, in contrast, demonstrates quite a different pattern of abnormalities in those at high genetic risk of bipolar disorder as compared with the first two populations, in keeping with an ever increasing number of studies showing that schizophrenia and bipolar disorder can be distinguished with a number of brain imaging approaches. These may yet prove to be able to predict differential response to the types of treatment used in the two disorders, but this work remains to be done. There also remains a programme of work to translate what essentially remains as group profiles into individual risk scores, to find the optimal combination of imaging and other variables to enhance prediction power, to test the acceptability of these approaches in relevant populations, and then go on to demonstrate their practicality and cost effectiveness. This is a rather daunting agenda but brings with it the promise of impacting upon the outcome of psychosis as well as providing objective diagnostic and therapeutic markers in psychiatry.

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