Neuroimaging and other neurobiological indices in schizophrenia: relationship to measurement of functional outcome

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Background As understanding of the pathobiology of schizophrenia increases, the challenge is to relate such measures to outcome at a functional level.

Aims To consider our current understanding of how neurobiological variables relate to functional outcome and might constitute outcome measures in their own right.

Method Critical appraisal of recent evidence on structural and functional imaging, neurological evaluation, early neurodevelopmental indices, genomics, proteomics, metabolomics and apoptotic mechanisms in relation to outcome.

Results Studies conducted prospectively from the first episode of schizophrenia are generating more reliable findings but currently lack predictive power. Prediction of transition from ‘high-risk’ status to first episode has proved somewhat more fruitful, but the gain has been modest and circumscribed.

Conclusions Our current level of understanding does not yet allow the generation of predictive models on an individual patient basis. Genomic and metabolomic studies hold particular potential for generating clinically meaningful ‘biomarkers’ but considerable further work is necessary.

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Over recent decades our understanding of the pathobiology of schizophrenia has increased materially. The body of knowledge accumulated gives us some insight into: (a) aetiological factors, in terms of genetic risk variants (Harrison & Weinberger, 2005; Owen et al, 2003; Karayiorgou & Gogos, 2006) and environmental adversities, both biological and psychosocial (van Os et al, 2003; SPAUWen et al, 2006); (b) putative pathophysiological processes, in terms of developmental disruption in critical neuronal networks (Waddington et al, 1999; Waddington & Morgan, 2001; Harrison & Weinberger, 2005; Stephan et al, 2006) and the role of these early events in ‘kick starting’ a lifetime-trajectory model of the disorder (DeLisi, 1999; Waddington et al, 1999, 2007; Baldwin et al, 2004); and (c) the relationship of such pathophysiology to aspects of psychopathology and cognitive deficit (Flashman & Green, 2004).

However, it is important not to underestimate the superficiality of these insights. Studies are, in the main, cross-sectional in nature, often in people with an established illness, and thus fail to inform directly on the relationship of biological variables to subsequent course of illness at any level. A new generation of prospective studies, particularly those from the first psychotic episode (Keshavan et al, 2005; Waddington, 2005), now allows these relationships to be explored systematically, but have focused primarily on the conundrum of whether the biological variables themselves are static or progressive thereafter and how such biology might relate to the longitudinal characteristics of psychopathology and cognitive deficit.

Thus, a fundamental challenge remains: how do we relate cross-sectional and prospective studies of biological measures not just to psychopathology and cognition but also to functional outcome, even on a population basis. More specifically, in the present context the yet greater challenge is to relate specific neurobiological indices to their individual outcomes. The purpose of this article is to outline current understanding of the relationship between neurobiological variables and functional outcome, both on a population basis and in terms of the individual patient, and whether any neurobiological variables have potential for becoming outcome measures in their own right.

STRUCTURAL IMAGING

Magnetic resonance imaging Magnetic resonance imaging (MRI) has established that subtle but widespread abnormalities of cortical and subcortical brain structure are present in schizophrenia on a population basis (Lawrie & Abukmeil, 1998; Wright et al, 2000; Shenton et al, 2001; Honea et al, 2005). A related technique, diffusion tensor imaging (DTI), is a relatively new modality that can examine, through fractional anisotropy, the microstructure of white matter and, through fibre tractography, aspects of neuronal connectivity in the brain. The majority of a limited number of DTI studies to date (Kanaan et al, 2005) have indicated reductions in white matter integrity which supports a broader interpretation of structural brain pathology in schizophrenia to involve cortical disconnectivity (Stephan et al, 2006).

Cross-sectional relationship to outcome Studies have sought to relate structural brain pathology on MRI to aspects of outcome on a cross-sectional basis, usually by subdividing patients retrospectively into ‘good’ v. ‘poor’ outcome groups and comparing them on various MRI measures at a single index assessment. For example, while patients of whatever outcome evidenced smaller thalamic volume relative to controls, those with poor outcome (i.e. hospitalised for more than 50% of the total duration of illness and continuously hospitalised over the past 3 years) evidenced enlargement of the lateral and third ventricles and reduced overall grey matter volume, particularly in the prefrontal cortex, whereas those hospitalised for less than 10% of total duration of illness and not hospitalised over the past year did not (Smaal et al, 2001). Similarly, patients of whatever outcome evidenced an overall reduction in grey matter volume relative to controls, particularly in the frontal and
temporal lobes, but those with poor outcome, ‘Kraepelinian’ schizophrenia (i.e. continuously hospitalised or completely dependent on others for basic needs, unemployed, with severe negative symptoms and severe thought disorder) evidenced reduced grey matter volume in the temporal and occipital but not in the frontal lobes relative to their good-outcome (i.e. non-‘Kraepelinian’) counterparts (Mitelman et al, 2003).

However, such studies illustrate how the indirect nature and inconsistency of the relationship between MRI measures and retrospective, dichotomous indices of outcome, on a population basis, precludes the generation of a predictive model in relation to the individual patient. Such models can only be generated in longitudinal studies.

**Longitudinal relationship to outcome over chronic illness**

The putative utility of MRI measures as indices of outcome is associated with the enduring debate on the extent to which structural brain pathology in schizophrenia does or does not progress. The weight of evidence from longitudinal studies beginning at various stages of illness (Pantelis et al, 2005), together with incisive, pseudo-longitudinal analyses of cross-sectional studies (Woods et al, 2005), now suggests a small but significant acceleration in the loss of cortical grey matter volume with associated enlargement of cerebrospinal fluid (CSF) spaces in the long term. To the extent that one can generalise from very early-onset schizophrenia in children to the more typical presentation in young adulthood, there is initial evidence for dynamic tissue loss that progresses to frontal, but less so to cingulate and temporal cortex, in ‘waves’ along the anterior–posterior and dorsal–ventral axes (Vidal et al, 2006).

Studies have related such longitudinal changes to aspects of outcome, usually in terms of MRI measures and assessments of clinical course made on two occasions at the beginning and end of a given period of follow-up. For example, over a mean interval of 3.6 years (range 0.6–7.5), patients who had been ill for a mean of 15.3 years (range 2.2–26.5) evidenced greater decline in cortical grey matter and greater increase in both frontal and temporal cortical sulcal and ventricular CSF volumes relative to controls. The rate of expansion in frontal sulci was associated with higher overall positive symptom scores and a longer percentage of time spent in hospital over follow-up; the rate of decrease in grey matter and of sulcal expansion in prefrontal cortex was associated with higher overall negative symptom scores and longer percentage of time spent in hospital; and the rate of decrease in grey matter and of sulcal expansion in temporal cortex was associated with higher overall negative symptom scores (Mathalon et al, 2001).

However, although such studies support the presence of some subtle but poorly understood neuroprogressive process in schizophrenia, they involve people with differing durations of chronic illness at the start of variable periods of longitudinal assessment who are assessed using a limited range of outcome measures, on a population basis. Thus, they are unable to generate a predictive model in relation to individual patients. Such models can only be generated in prospective studies from the first psychotic episode.

**Prospective relationship to outcome from the first episode**

It is now clear that some aspects of structural brain pathology evident on MRI in chronic schizophrenia, particularly reduction in whole brain and hippocampal volumes, together with enlargement of the third and lateral ventricles, are present at the time of the first psychotic episode and therefore pre-date onset of diagnostic symptoms (Steen et al, 2006; Vita et al, 2006). Diffusion tensor imaging also indicates lower fractional anisotropy, consistent with white matter abnormalities at the first episode (Szeszko et al, 2005). Thereafter, as considered above in the context of chronic illness, there is a small but significant acceleration in loss of cortical grey matter volume with associated enlargement of CSF spaces (Pantelis et al, 2005; Whitford et al, 2006). The ‘anchor’ event of the first psychotic episode provides a frame of reference from which any relationships between MRI parameters and long-term outcome can be explored prospectively.

Studies have related such longitudinal change to prospective evaluation of outcome, usually in terms of MRI measures and assessments of clinical course made on two occasions: at the first episode and at variable periods of follow-up. For example, in a prospective study over 3 years, extent of ventricular enlargement during this period was associated with poor outcome as dichotomised in terms of remission of positive symptoms; extent of reduction in frontal lobe white matter volume and of increase in frontal lobe sulcal CSF volume were associated with greater negative symptom severity; extent of reduction in frontal lobe grey matter volume was associated with poorer executive functioning over follow-up (Ho et al, 2003).

Although this study addressed relationships between longitudinal changes in MRI parameters and outcome measures, a critical question is whether any cross-sectional MRI measure made at the first episode is predictive of subsequent outcome as assessed prospectively. In a prospective study over 2 years, total brain volume and volumes of cortical grey and white matter, third and lateral ventricles and cerebellum at the first or second episode failed to predict outcome in terms of positive or negative symptoms, social disability and need for care (van Haren et al, 2003). Similarly, in a prospective study over 5 years, smaller temporal lobe grey matter volume at the first episode was associated with persistence of hallucinations; however, initial temporal and frontal lobe tissue and sulcal and ventricular CSF volumes were unrelated to negative symptoms, extent of hospitalisation or psychosocial outcome (quality of relationships, sexual activity, recreation and work performance) over follow-up (Milev et al, 2003). In a further prospective study over 2 years, decreasing volume of the dorsolateral prefrontal cortex at the first episode was associated with poorer functional outcome, in terms of social and employment indices, at 1 but not at 2 years (Prasad et al, 2005).

However, although such studies further elaborate the presence of some subtle but poorly understood neuroprogressive process in schizophrenia, they indicate that MRI measures made at and following the first psychotic episode have only limited capacity to predict outcome on a patient population basis. Thus, they are unable to generate a predictive model in relation to individual patients. One potential confound in all such studies is an effect of long-term antipsychotic treatment on brain tissue volumes. Magnetic resonance imaging studies have indicated that volumes of the basal ganglia and pituitary are increased following exposure to typical but not atypical antipsychotics (Lieberman et al, 2005; Pariente et al, 2005). More extensive studies have indicated exposure to typical
antipsychotics to be associated with some reduction in cortical grey matter volume, whereas atypical agents can be associated with some increase in this volume (Dazzan et al., 2005; Garver et al., 2005; Lieberman et al., 2005). Given the practical difficulties in conducting MRI studies during the first episode in a person with no antipsychotic treatment, especially in a clinical setting, these effects could clearly confound the search for relationships between MRI measures and outcome.

**PROSPECTIVE RELATIONSHIP TO TRANSITION FROM HIGH-RISK/PRODROME TO FIRST EPISODE**

Over the past several years there has emerged a yet earlier domain of outcome: that of transition from high-risk status (defined usually in terms of affected family member(s), attenuated or transient psychotic symptoms and functional decline) to first-episode psychosis.

In a novel and important MRI study over a prospective period of at least 1 year (Pantelis et al., 2003), those high-risk participants who developed first-episode psychosis were characterised by a reduction in parahippocampal, fusiform and orbito-frontal cortex, and in cingulate gyri; for those who did not develop a first psychotic episode, no such longitudinal changes were evident. On addressing the critical question of whether any cross-sectional MRI measure made in the high-risk state is predictive of outcome as assessed prospectively, transition to a first psychotic episode was associated with reduced grey matter volume in the medial and lateral temporal, inferior frontal and cingulate cortex.

In a related study over a prospective period of 5 years, those high-risk participants who received two MRI scans at an interval of 2 years and subsequently received a diagnosis of schizophrenia were distinguished from those who did not receive this diagnosis by reduction in grey matter density in temporal gyri, uncus and cerebellum between those two scans; cross-sectional MRI measures made in the high-risk state did not differ between those who did and did not go on to receive a diagnosis of schizophrenia (Job et al., 2005). However, transition to psychosis, not just to schizophrenia but also particularly to psychotic depression, is associated with larger pituitary volume in the high-risk state, suggesting stress-related activation of the hypothalamic–pituitary–adrenal axis (Garner et al., 2005). However, it is far from clear whether such findings, made on a patient population basis, allow generation of a predictive model in relation to individual patients.

**FUNCTIONAL IMAGING**

**Functional magnetic resonance imaging**

Functional magnetic resonance imaging (fMRI) accesses regional neuronal activation in terms of change in blood oxygenation. Although a variety of cross-sectional fMRI findings in schizophrenia have been reported (Tost et al., 2005), systematic, prospective studies from the high-risk state or the first psychotic episode in relation to outcome are in their infancy.

A recent cross-sectional study has examined frontal and cingulate cortex, thalamic and basal ganglia activation during executive processing in those at high risk and in both early-phase and patients with chronic illness in comparison with controls (Morey et al., 2005). The findings indicate that prefrontal function begins to decline before the emergence of diagnostic symptoms and impairment in frontostral trend function is evident thereafter. Recently, a prospective study over a period of 5 years has examined activation during a sentence completion task (Whalley et al., 2006). Cross-sectional fMRI measures made in the high-risk state indicated that those who went on to receive a diagnosis of schizophrenia were distinguished from those who did not by decreased activation of the anterior cingulate, increased activation of the parietal lobe and smaller increases in activation with increasing task difficulty. However, only four high-risk participants evidenced transition to schizophrenia over the follow-up period (Whalley et al., 2006). The elaboration of such fMRI studies in those at high risk and first-episode patients on a prospective basis has the potential to provide important additional information on the prediction of long-term outcome. However, possible confounding effects of antipsychotic drugs on fMRI measures remain a cause for concern (Davis et al., 2005).

**EMISSION TOMOGRAPHY**

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are related techniques that access functional processes such as receptor availability, drug–receptor occupancies, transmitter biosynthesis/catabolism and cerebral metabolic activity. Although a variety of cross-sectional PET/SPECT findings in schizophrenia have been reported, only a few studies have systematically applied these techniques prospectively from the high-risk state or the first psychotic episode in relation to outcome. These relate primarily to contemporary versions of the long-standing dopamine hyperactivity model of psychosis, as recently elaborated (Kapur et al., 2005; Seeman et al., 2006).

Over a prospective period of 2 years, higher SPECT binding of $^{125}$I-iodobenzamide to striatal $D_2$ dopamine receptors at the first psychotic episode was associated with poorer social and occupational outcome among those who attained a follow-up diagnosis of schizophrenia but not among those who retained a diagnosis of schizophreniform disorder (Corripio et al., 2006). Recently, a PET study of striatal $^{18}$F-DOPA uptake has indicated dopamine overactivity in people in the high-risk state. These people are being followed prospectively to determine whether those who go
on to evidence a first psychotic episode have raised $^{18}$F-DOPA uptake compared with those who do not (Howes et al, 2006). Elaboration of such prospective PET/SPECT studies of those at high risk to include assessment of outcome beyond transition to psychosis has the potential to provide important additional information on prediction of long-term outcome. As for fMRI and MRS, possible confounding effects of antipsychotic drugs on PET/SPECT measures remain a cause for concern (Davis et al, 2005).

**NEUROLOGICAL EVALUATION**

**Electroencephalography**

Although electroencephalography (EEG) has a history in biological psychiatry that long pre-dates the emergence of MRI, fMRI, MRS and PET/SPECT techniques, it has failed to match their impact. The recent introduction of techniques such as gamma synchrony has contributed to a new wave of incisive studies.

For example, a cross-sectional study in first-episode schizophrenia has reported decreased magnitude and delayed latency for frontal gamma 1 but not gamma 2 synchrony time-locked to target auditory stimuli, indicating disturbance in connectivity of neural activity in early sensory response to task-relevant stimuli, in a manner that may be modulated by antipsychotic drugs (Symond et al, 2005). The extension of such EEG studies to those at high risk and first-episode patients on a prospective basis has the potential to provide important additional information on prediction of long-term outcome.

**Neurological soft signs**

Neurological soft signs are non-localising abnormalities that cannot be related to impairment in a specific brain region and are not part of a well-defined neurological syndrome. They constitute evidence for otherwise unspecified brain dysfunction and have been shown consistently to occur to excess in schizophrenia (Bombin et al, 2005).

Studies have indicated that the extent of neurological soft signs at the first episode has little relationship to long-term outcome, for example global or occupational functioning (Bombin et al, 2005). Recently, in a study over a prospective period of 4 years from the first episode, improvement in neurological soft signs score was associated with better overall outcome over the same period (Whitty et al, 2006). However, in a study over a prospective period of 1 year, extent of neurological soft signs at the first episode failed to predict outcome in terms of psychopathology or rate of relapse, defined as hospitalisation or unscheduled visit due to exacerbation, but did predict emergence of tardive dyskinesia (Emsley et al, 2005). Similarly, in a study over a prospective period of 3 years, extent of neurological soft signs at the first episode failed to predict outcome in terms of relapse or occupational functioning (Chen et al, 2005). Thus, the findings to date do not indicate that neurological soft signs exert material prediction of long-term outcome.

**EARLY NEURO-DEVELOPMENTAL INDICES**

Minor physical anomalies are slight anatomical malformations of body regions that share the ectodermal origins of the brain. Their presence indicates adverse events acting over the first or second trimester (Waddington et al, 1999). Thus, although found reliably to be overrepresented in schizophrenia (McNeil et al, 2000), minor physical anomalies occur to excess in most disorders of early neurodevelopmental origin and therefore likely constitute a non-specific, qualitative indicator of early biological adversity that bears little specific relationship to outcome in schizophrenia.

**Anthropometrics of craniofacial dysmorphism**

Aspects of dysmorphogenesis, particularly of craniofacial regions that bear the most intimate embryological relationship with early brain development, can be measured using classic anthropometric techniques (Lane et al, 1997). However, in a recent prospective study over a period of 5 years, cross-sectional measurement of hyperelorism made in the high-risk state did not distinguish those who went on to receive a diagnosis of schizophrenia from those who did not (Johnstone et al, 2005).

**Three-dimensional surface imaging of craniofacial dysmorphism**

It is now possible to apply three-dimensional surface imaging technology and geometric morphometrics to the quantitative measurement of facial dysmorphology (Hennessy et al, 2005). Such techniques, which have been shown recently to distinguish people with schizophrenia from controls (Hennessy et al, 2007), might have greater potential for addressing any relationship between dysmorphogenesis and long-term outcome in schizophrenia.

**Dermatoglyphics**

Another index of dysmorphogenesis is dermatoglyphics; for example, a-b ridge count, a quantitative dermatoglyphic measure of the palm, is reduced in schizophrenia (Bramon et al, 2005). However, in a recent prospective study over a period of 5 years, cross-sectional measurement of dermatoglyphics made in the high-risk state did not distinguish those who went on to receive a diagnosis of schizophrenia from those who did not (Johnstone et al, 2005).

**Postnatal MRI**

Although brain MRI in the immediate postnatal period may have some utility in predicting neurodevelopmental outcome at 2 years (Woodward et al, 2006), any ability to predict schizophrenia as an outcome in young adulthood remains unexplored.

**GENOMICS**

Evidence accumulated over recent years indicates that schizophrenia is an oligogenic rather than a single-gene disorder, with several risk genes of small effect having been identified (Harrison & Weinberger, 2005; Owen et al, 2005; Karayiorgou & Gogos, 2006).

Studies of association between particular genetic risk variants and aspects of structural brain pathology on MRI in adult schizophrenia are now available (e.g. Cannon et al, 2005; Gurling et al, 2006; Ho et al, 2006). However, only recently are predictive studies emerging. For example, in a prospective study over a period of 5 years, neuregulin 1 and catechol-O-methyltransferase (COMT) genotypic variants assessed in the high-risk state each increased risk for developing psychotic symptoms of schizophrenia in association with abnormalities of brain structure and function on MRI and fMRI (Hall et al, 2006; McIntosh et al, 2006). Such studies may be of considerable heuristic value in relation to prediction of outcome.
Both proteomic and metabolomic studies in schizophrenia are in their infancy, with metatobolomics (i.e. the study of the repertoire of biochemicals present in cells, tissue and body fluids as encoded by the genome and modified by environmental factors; Kaddurah-Daouk, 2006) now being explored in the search for biomarkers for several aspects of schizophrenia.

In an initial study using nuclear magnetic resonance (NMR) spectra of CSF samples from antipsychotic-naïve or minimally treated patients with first-episode schizophrenia, the glucose regulatory metabolic profile was characteristic altered relative to controls and showed some association with ‘normalisation’ with effective antipsychotic treatment (Holmes et al, 2006). As for genomics, such studies of metabolomics may be of considerable heuristic value in relation to prediction of outcome.

Apoptosis, a form of programmed cell death, is regulated by a complex cascade of pro- and anti-apoptotic proteins that may be altered in schizophrenia and might mediate subtile, progressive loss of cerebral grey matter, particularly over the course, in the absence of evidence for any neurodegenerative process as currently conceptualised (Waddington et al, 1999, 2007; Glantz et al, 2006). Although a recent study noted apoptotic mechanisms in dermal fibroblasts to be anomalous in schizo-fibroblasts to be anomalous in schizophrenia (Catts et al, 2006), any ability to predict outcome remains unexplored. However, such indices join genomics and metabolomics in being of considerable heuristic value in relation to prediction of outcome.

CONCLUSIONS

On a population basis, neuroimaging and other neurobiological studies conducted prospectively from the first episode of schizophrenia have advanced rapidly. They hold out the prospect of more reliable findings with further experimental refinement, but currently lack predictive power.

Prediction of transition from ‘high-risk’ status to first episode has proved somewhat more fruitful, perhaps because of contemporaneous concentration of resources on this critical phase of illness and associated advances in the context of the potential of early intervention to ameliorate such transition, but the gain has been small. The greatest challenge is to relate specific neuroimaging and other neurobiological indices to outcome on an individual patient basis.

At this stage in our understanding of the biology of schizophrenia over its life-time trajectory, the inconsistency and extent of variability in essentially all such measures still precludes generation of predictive models that are utilitarian for individual patients. Recent fMRI, MRS, genomic and metabolomic studies hold the greatest potential for identifying clinically meaningful ‘biomarkers’, but considerable further work is necessary.

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