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

JOHN L. WADDINGTON

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.

Declaration of interest None. Funding detailed in Acknowledgements.

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*, 2005; Karayiorgou & Gogos, 2006) and environmental adversities, both biological and psychosocial (van Os *et al*, 2005; 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 (Staal *et al*, 2001). Similarly, patients of whatever outcome evidenced an overall reduction in grey matter volume relative to controls, particularly in the frontal and

https://doi.org/10.1192/bjp.191.50.s52 Published online by Cambridge University Press

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; Pariante *et al*, 2005). More extensive studies have indicated exposure to typical

https://doi.org/10.1192/bjp.191.50.s52 Published online by Cambridge University Press

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 *v.* non-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 orbitofrontal 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 gyrus, 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 frontostriatal 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).

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) also accesses functional processes, primarily the concentration of various brain metabolites, to provide more detailed information on regional cellular mechanisms.

Although a variety of cross-sectional MRS findings in schizophrenia have been reported (Keshavan *et al*, 2005), only one study to date has systematically applied this technique prospectively from the first psychotic episode in relation to outcome. Over a prospective period of 1.5 years, a lower *N*-acetylaspartate/creatine ratio, a putative index of neuronal integrity, at the first episode was associated with poorer outcome in terms of global assessment of functioning, social and occupational functioning and number of hospital admissions (Wood *et al*, 2006). As for fMRI, the extension of MRS studies to those at high risk and first-episode patients on a prospective basis, to include assessments beyond transition to psychosis, has the potential to provide important additional information on prediction of long-term outcome. Similarly, as for fMRI, possible confounding effects of antipsychotic drugs on MRS 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 ^{123}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

https://doi.org/10.1192/bjp.191.50.s52 Published online by Cambridge University Press

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 NEURODEVELOPMENTAL 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 dysmorphogenesis

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 hypertelorism 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 dysmorphogenesis

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.

https://doi.org/10.1192/bjp.191.50.s52 Published online by Cambridge University Press

PROTEOMICS, METABOLOMICS AND APOPTOTIC MECHANISMS

Both proteomic and metabolomic studies in schizophrenia are in their infancy, with metabolomics (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-naive or minimally treated patients with first-episode schizophrenia, the glucoregulatory metabolic profile was characteristically 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 subtle, progressive loss of cerebral grey matter, particularly over the early 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 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 contemporary 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 lifetime 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.

ACKNOWLEDGEMENTS

The author's studies are supported by Science Foundation Ireland, the Health Research Board and the Health Service Executive – North Eastern Area.

REFERENCES

Baldwin, P., Hennessy, R. J., Morgan, M. G., *et al* (2004) Controversies in schizophrenia research: the 'continuum' challenge, heterogeneity vs homogeneity, and lifetime developmental-'neuroprogressive' trajectory. In *Search for the Causes of Schizophrenia* (eds W. Gattaz & H. Haffner), pp. 394–409. Steinkopff.

Bombin, I., Arango, C. & Buchanan, R. W. (2005) Significance and meaning of neurological signs in schizophrenia: two decades later. *Schizophrenia Bulletin*, **31**, 962–977.

Bramon, E., Walshe, M., McDonald, C., *et al* (2005) Dermatoglyphics and schizophrenia: a meta-analysis and investigation of the impact of obstetric complications upon a-b ridge count. *Schizophrenia Research*, **75**, 399–404.

Cannon, T. D., Hennah, W., van Erp, T. G. M., *et al* (2005) Association of DISC1/TRAX haplotypes with schizophrenia, reduced prefrontal gray matter, and impaired short- and long-term memory. *Archives of General Psychiatry*, **62**, 1205–1213.

Catts, V. S., Catts, S. V., McGrath, J. J., *et al* (2006) Apoptosis and schizophrenia: a pilot study based on dermal fibroblast cell lines. *Schizophrenia Research*, **84**, 20–28.

Chen, E. Y. H, Hui, L. M. C., Chan, R. C. K., *et al* (2005) A 3-year prospective study of neurological soft signs in first-episode schizophrenia. *Schizophrenia Research*, **75**, 45–54.

Corripio, I., Perez, V., Catafau, A. M., *et al* (2006) Striatal D2 receptor binding as a marker of prognosis and outcome in untreated first-episode psychosis. *NeuroImage*, **29**, 662–666.

Davis, C. E., Jeste, D. V. & Eyler, L. T. (2005) Review of longitudinal functional neuroimaging studies of drug treatments in patients with schizophrenia. *Schizophrenia Research*, **78**, 45–60.

Dazzan, P., Morgan, K. D., Orr, K., *et al* (2005) Different effects of typical and atypical antipsychotics on grey matter in first episode psychosis: the AESOP Study. *Neuropsychopharmacology*, **30**, 765–774.

DeLisi, L. E. (1999) Regional brain volume change over the life-time course of schizophrenia. *Journal of Psychiatric Research*, **33**, 535–541.

Emsley, R., Turner, H. J., Oosthuizen, P. P., *et al* (2005) Neurological abnormalities in first-episode schizophrenia: temporal stability and clinical and outcome correlates. *Schizophrenia Research*, **75**, 35–44.

Flashman, L. A. & Green, M. F. (2004) Review of cognition and brain structure in schizophrenia: profiles, longitudinal course, and effects of treatment. *Psychiatric Clinics of North America*, **27**, 1–18.

Garner, B., Pariante, C. M., Wood, S. J. *et al* (2005) Pituitary volume predicts future transition to psychosis in individuals at ultra-high risk of developing psychosis. *Biological Psychiatry*, **58**, 417–423.

Garver, D., Holcomb, J. A. & Christensen, J. D. (2005) Cerebral cortical gray expansion associated with two second-generation antipsychotics. *Biological Psychiatry*, **58**, 62–66.

Glantz, L. A., Gilmore, J. H., Lieberman, J. A., *et al* (2006) Apoptotic mechanisms and the synaptic pathology of schizophrenia. *Schizophrenia Research*, **81**, 47–63.

Gurling, H., Critchley, H., Datta, S. R., *et al* (2006) Genetic association and brain morphology studies and the chromosome 8p22 pericentriolar material 1 (*PCM1*) gene in susceptibility to schizophrenia. *Archives of General Psychiatry*, **63**, 844–854.

Hall, J., Whalley, H. C., Job, D. E., *et al* (2006) A neuregulin 1 variant associated with abnormal cortical function and psychotic symptoms. *Nature Neuroscience*, **9**, 1477–1478.

Harrison, P. J. & Weinberger, D. R. (2005) Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Molecular Psychiatry*, **10**, 40–68.

Hennessy, R. J., McLearie, S., Kinsella, A., *et al* (2005) Facial surface analysis by 3D laser scanning and geometric morphometrics in relation to sexual dimorphism in cerebral-craniofacial morphogenesis and cognitive function. *Journal of Anatomy*, **207**, 283–296.

Hennessy, R. J., Baldwin, P. A., Browne, D. J., *et al* (2007) Three-dimensional laser surface imaging and geometric morphometrics resolve frontonasal dysmorphology in schizophrenia. *Biological Psychiatry*, **61**, 1187–1194.

Ho, B.-C., Andreasen, N. C., Nopoulos, P., *et al* (2003) Progressive structural brain abnormalities and their relationship to clinical outcome. *Archives of General Psychiatry*, **60**, 585–594.

Ho, B.-C., Milev, P., O'Leary, D. S., *et al* (2006) Cognitive and magnetic resonance imaging brain morphometric correlates of brain-derived neurotrophic factor Val66Met gene polymorphism in patients with schizophrenia and healthy volunteers. *Archives of General Psychiatry*, **63**, 731–740.

Holmes, E., Tsang, T. M., Huang, J. T.-J., *et al* (2006) Metabolic profiling of CSF: evidence that early intervention may impact on disease progression and outcome in schizophrenia. *PLoS Medicine*, **3**, e327.

Honea, R., Crow, T. J., Passingham, D., *et al* (2005) Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *American Journal of Psychiatry*, **162**, 2233–2245.

Howes, O. D., Montgomery, A. J., Asselin, M. C., *et al* (2006) The pre-synaptic dopaminergic system in subjects with at risk mental states: initial results from an ongoing [18F]-dopa PET study. *Journal of Psychopharmacology*, **20** (suppl. 5), A69.

https://doi.org/10.1192/bjp.191.50.s52 Published online by Cambridge University Press

Job, D. E., Whalley, H. C., Johnstone, E. C., *et al* (2005) Grey matter changes over time in high risk subjects developing schizophrenia. *NeuroImage*, **25**, 1023–1030.

Johnstone, E. C., Ebmeier, K. P., Miller, P., *et al* (2005) Predicting schizophrenia: findings from the Edinburgh High-Risk Study. *British Journal of Psychiatry*, **186**, 18–25.

Kaddurah-Daouk, R. (2006) Metabolic profiling of patients with schizophrenia. *PLoS Medicine*, **3**, e363.

Kanaan, R. A. A., Kim, J. S., Kaufmann, W. E., *et al* (2005) Diffusion tensor imaging in schizophrenia. *Biological Psychiatry*, **58**, 921–929.

Kapur, S., Mizrahi, R. & Li, M. (2005) From dopamine to salience to psychosis – linking biology, pharmacology and phenomenology of psychosis. *Schizophrenia Research*, **79**, 59–68.

Karayiorgou, M. & Gogos, J. A. (2006) Schizophrenia genetics: uncovering positional candidate genes. *European Journal of Human Genetics*, **14**, 512–519.

Keshavan, M. S., Berger, G., Zipursky, R. B., *et al* (2005) Neurobiology of early psychosis. *British Journal of Psychiatry*, **187** (suppl. 48), s8–s18.

Lane, A., Kinsella, A., Murphy, P., *et al* (1997) The anthropometric assessment of dysmorphic features in schizophrenia as an index of its developmental origins. *Psychological Medicine*, **27**, 1155–1164.

Lawrie, S. M. & Abukmeil, S. S. (1998) Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. *British Journal of Psychiatry*, **172**, 110–120.

Lieberman, J. A., Toffefson, G. D., Charles, C., *et al* (2005) Antipsychotic drug effects on brain morphology in first-episode psychosis. *Archives of General Psychiatry*, **62**, 361–370.

Mathalon, D. H., Sullivan, E. V., Lim, K. O., *et al* (2001) Progressive brain volume changes and the clinical course of schizophrenia in men. *Archives of General Psychiatry*, **58**, 148–157.

McIntosh, A. M., Baig, B. J., Hall, J., *et al* (2006) Relationship of catechol-O-methyltransferase variants to brain structure and function in a population at high risk of psychosis. *Biological Psychiatry*, Epub ahead of print.

McNeil, T. F., Cantor-Graae, E. & Ismail, B. (2000) Obstetric complications and congenital malformation in schizophrenia. *Brain Research Reviews*, **31**, 166–178.

Milev, P., Ho, B.-C., Arndt, S., *et al* (2003) Initial magnetic resonance imaging volumetric brain measurements and outcome in schizophrenia: a prospective longitudinal study with 5-year follow-up. *Biological Psychiatry*, **54**, 608–615.

Mitelman, S. A., Shihabuddin, L., Brickman, A. M., *et al* (2003) MRI assessment of gray and white matter distribution in Brodmann's areas of the cortex in patients with schizophrenia with good and poor outcomes. *American Journal of Psychiatry*, **160**, 2154–2168.

Morey, R. A., Inan, S., Mitchell, T. V., *et al* (2005) Imaging frontostriatal function in ultra-high risk, early, and chronic schizophrenia during executive processing. *Archives of General Psychiatry*, **62**, 254–262.

Owen, M. J, Craddock, N. & O'Donovan, M. C. (2005) Schizophrenia: genes at last? *Trends in Genetics*, **21**, 518–525.

JOHN L. WADDINGTON, PhD, DSc, Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, St Stephen's Green, Dublin 2, and St Davnet's Hospital, Cavan-Monaghan Mental Health Service, Monaghan, Ireland. Email: jwadding@rcsi.ie

Pantelis, C., Velakoulis, D., McGorry, P. D., *et al* (2003) Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet*, **361**, 281–288.

Pantelis, C., Yucel, M., Wood, S. J., *et al* (2005) Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophrenia Bulletin*, **31**, 672–696.

Pariante, C. M., Dazzan, P., Danese, A., *et al* (2005) Increased pituitary volume in antipsychotic-free and antipsychotic-treated patients of the Æsop first-onset psychosis study. *Neuropsychophamacology*, **30**, 1923–1931.

Prasad, K. M., Sahni, S. D., Rohm, B. R., *et al* (2005) Dorsolateral prefrontal cortex morphology and short-term outcome in first-episode schizophrenia. *Psychiatry Research*, **140**, 147–155.

Staal, W. G., Hulshoff, H. E., Schnack, H. G., *et al* (2001) Structural brain abnormalities in chronic schizophrenia at the extremes of the outcome spectrum. *American Journal of Psychiatry*, **158**, 1140–1142.

Seeman, P., Schwarz, J., Chen, J-F., *et al* (2006) Psychosis pathways converge via $D2^{High}$ dopamine receptors. *Synapse*, **60**, 319–346.

Shenton, M. E., Dickey, C. C., Frumin, M., *et al* (2001) A review of MRI findings in schizophrenia. *Schizophrenia Research*, **49**, 1–52.

Spauwen, J., Krabbendam, L., Lieb, R., *et al* (2006) Impact of psychological trauma on the development of psychotic symptoms: relationship with psychosis proneness. *British Journal of Psychiatry*, **188**, 527–533.

Staal, W. G., Hulshoff, H. E., Schnack, H. G., *et al* (2001) Structural brain abnormalities in chronic schizophrenia at the extremes of the outcome spectrum. *American Journal of Psychiatry*, **158**, 1140–1142.

Steen, R. G., Mull, C., McClure, R., *et al* (2006) Brain volume in first-episode schizophrenia. Systematic review and meta-analysis of magnetic resonance imaging studies. *British Journal of Psychiatry*, **188**, 510–518.

Stephan, K. E., Baldeweg, T. & Friston, K. J. (2006) Synaptic plasticity and dysconnection in schizophrenia. *Biological Psychiatry*, **59**, 929–939.

Symond, M. B., Harris, A. W. F., Gordon, E., *et al* (2005) "Gamma Synchrony" in first-episode schizophrenia: a disorder of temporal connectivity? *American Journal of Psychiatry*, **162**, 459–465.

Szeszko, P. R., Ardekani, B. A., Ashtari, M., *et al* (2005) White matter abnormalities in first-episode schizophrenia or schizoaffective disorder: a diffusion tensor imaging study. *American Journal of Psychiatry*, **162**, 602–605.

Tost, H., Ende, G., Ruf, M., *et al* (2005) Functional imaging research in schizophrenia. *International Review of Neurobiology*, **67**, 95–118.

van Haren, N. E. M., Chan, W., Pol, H. E. H., *et al* (2003) Brain volumes as predictor of outcome in recent-onset schizophrenia: a multi-center MRI study. *Schizophrenia Research*, **64**, 41–52.

van Os, J., Krabbendam, L., Myin-Germeys, I., *et al* (2005) The schizophrenia envirome. *Current Opinion in Psychiatry*, **18**, 141–145.

Vidal, C. N., Rapoport, J. L., Hayashi, K. M., *et al* (2006) Dynamically spreading frontal and cingulate deficits mapped in adolescents with schizophrenia. *Archives of General Psychiatry*, **63**, 25–35.

Vita, A., De Peri, L., Silenzi, C., *et al* (2006) Brain morphology in first-episode schizophrenia: a meta-analysis of quantitative magnetic resonance imaging studies. *Schizophrenia Research*, **82**, 75–88.

Waddington, J. L. (2005) What have we learned from the new generation of prospective studies on first episode psychosis? *Schizophrenia Bulletin*, **31**, 623.

Waddington, J. L. & Morgan, M. G. (2001) Pathobiology of schizophrenia. In *Comprehensive Care of Schizophrenia* (eds J. A. Lieberman & R. M. Murray), pp. 28–35. Martin Dunitz.

Waddington, J. L., Lane, A., Larkin, C., *et al* (1999) The neurodevelopmental basis of schizophrenia: clinical clues from cerebro-craniofacial dysmorphogenesis, and the roots of a lifetime trajectory of disease. *Biological Psychiatry*, **46**, 31–39.

Waddington, J. L., Kingston, T. & O'Tuathaigh, C. M. P. (2007) Longitudinal studies on course of illness in schizophrenia: a lifetime trajectory perspective. In *The Year in Schizophrenia* (Vol. 1) (eds W. T. Carpenter & G. Thaker). Clinical Publishing (in press).

Whalley, H. C., Simonotto, E., Moorhead, W., *et al* (2006) Functional imaging as a predictor of schizophrenia. *Biological Psychiatry*, **60**, 454–462.

Whitford, T. J., Grieve, S. M., Farrow, T. F. D., *et al* (2006) Progressive grey matter atrophy over the first 2–3 years of illness in first-episode schizophrenia: a tensor-based morphometry study. *NeuroImage*, **32**, 511–519.

Whitty, P., Clarke, M., McTigue, O., *et al* (2006) Diagnostic specificity and predictors of neurological soft signs in schizophrenia, bipolar disorder and other psychoses over the first 4 years of illness. *Schizophrenia Research*, **86**, 110–117.

Wood, S. J., Berger, G, E., Lambert, M., *et al* (2006) Prediction of functional outcome 18 months after a first psychotic episode. *Archives of General Psychiatry*, **63**, 969–976.

Woods, B. T., Ward, K. E. & Johnson, E. H. (2005) Meta-analysis of the time-course of brain volume reduction in schizophrenia: implications for pathogenesis and early treatment. *Schizophrenia Research*, **73**, 221–228.

Woodward, L. J., Anderson, P. J., Austin, N. C., *et al* (2006) Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *New England Journal of Medicine*, **355**, 685–694.

Wright, I. C., Rabe-Hesketh, S., Woodruff, P. W., *et al* (2000) Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry*, **157**, 16–25.

https://doi.org/10.1192/bjp.191.50.s52 Published online by Cambridge University Press