Neurobiology of early psychosis*

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Background Neurobiological studies of the early course of psychoses, such as schizophrenia, allow investigation of pathophysiology without the confounds of illness chronicity and treatment.

Aims To review the recent literature on the biology of the early course of psychoses.

Method We carried out a critical appraisal of the recent findings in the neurobiology of early psychoses, using structural, functional and neurochemical imaging techniques.

Results Brain structural alterations are present early in the illness and may predate symptom onset. Some changes, notably those in frontal and temporal lobes, can progress during the early phases of the illness. Functional and neurochemical brain abnormalities can also be seen in the premorbid and the early phases of the illness. Some, although not all, changes can be trait-like whereas some others might progress during the early years.

Conclusions A better understanding of such changes, especially during the critical periods of the prodrome, around the transition to the psychotic phase and during the early phases of the illness is crucial for continued research into preventive intervention strategies.

Declaration of interest None.

*Paper presented at the Third International Early Psychosis Conference, Copenhagen, Denmark, September 2002.

Despite over a century of research, the pathophysiology of schizophrenia and related psychotic disorders remains unclear. Early observations of the neurobiology of schizophrenia and related psychoses largely relied either on post-mortem studies of mostly older patients with chronic schizophrenia or on neuroimaging studies of patients with established schizophrenia, many of whom were treated with medications. These findings, therefore, are limited by the potential confounds of the effects of ageing, illness chronicity and medication.

Studies of individuals in the early phases of schizophrenia avoid such confounds and allow us to elucidate the effects of primary illness processes (Keshavan & Schooler, 1992). First, these studies allow prospective longitudinal evaluation of the course and predictive value of the neurobiological changes. Most neurobiological studies in early psychosis do not consider the heterogeneity of the initial presentation, and this may explain some of the contradictory findings. Early psychosis represents a broad range of possible diagnostic and prognostic categories that include, but are not limited to, the more traditionally studied schizophrenia and schizoaffective disorder. Only about half of patients with early psychosis (Harding *et al*, 1987; Moller & Von Zerssen, 1995) will develop a chronic form of schizophrenia with poor levels of functioning and major impairment in cognition. Second, not everyone who has features of the prodromal phases of the illness goes on to develop the psychotic illness. Studies of the prodromal and early course of psychotic disorders provide an opportunity to elucidate the neurobiological mechanisms responsible for the transition from the prodrome to schizophrenia or other psychotic disorders.

The importance of studying the neurobiology of early psychosis stems from the recent emphasis on early identification and preventive intervention in disorders such as schizophrenia (Wyatt, 1991; Lieberman *et al*, 2001). The onset of psychotic symptoms in schizophrenia is often preceded by a premorbid phase, characterised by subtle neuromotor and cognitive impairments that may date back to birth. The prodromal phase is associated with cognitive impairment, affective symptoms, social withdrawal, and/or sub-threshold (attenuated) positive symptoms. Recent studies suggest that more than a third of patients presenting with prodromal symptoms, if untreated, 'convert' to schizophrenia or a related psychotic disorder (McGorry *et al*, 2002; Yung *et al*, 2003). The duration of the psychotic symptoms prior to treatment typically averages about a year, and the average prodromal duration is about 3 years across studies (McGlashan, 1996). If untreated, the early phases of schizophrenia result in a progressive accrual of morbidity; the longer the period of untreated illness, the worse appears to be the outcome (Lieberman *et al*, 2001; McGorry *et al*, 2001; Keshavan *et al*, 2003*a*). Studies of patients at 'ultra-high risk' of psychosis and in the early phase schizophrenia and related disorders are critical for our prevention and early intervention efforts, since the deteriorative processes of this illness may set in during this critical time window (McGlashan, 1996).

Neurobiological investigations in early psychosis have greatly benefited from recent conceptual models that have suggested a number of testable hypotheses. The traditional (or 'early') neurodevelopmental model posits abnormalities in foetal brain development as mediating the failure of brain functions in early adulthood. An array of data, such as an increased rate of obstetric complications, minor physical abnormalities, neurological soft signs and subtle behavioural abnormalities in children who later developed schizophrenia, support this model for schizophrenia in particular, but most likely also for a range of other neuropsychiatric disorders. However, their prevalence in the non-affected population is substantial and their positive predictive value for the development of schizophrenia is limited (Murray & Lewis, 1987; Weinberger, 1987). The illness onset, typically in adolescence and early adulthood, is suggestive of brain maturational abnormality around or prior to the onset of psychosis. Excessive synaptic/dendritic pruning around the peri-onset phase of illness (Feinberg, 1982, 1990; Keshavan *et al*, 1994) has been postulated as one

https://doi.org/10.1192/bjp.187.48.s8 Published online by Cambridge University Press

potential pathological mechanism underpinning the onset of psychosis in adolescence or early adulthood, but the understanding of the underlying neurobiology of this phase of illness is still limited. The idea that active biological changes could occur during the prodromal phase or the often lengthy period of untreated psychosis has led to the neurodegenerative models (Garver, 1987; McGorry & McConville, 2000; Lieberman *et al*, 2001). Unifying models have also been proposed and include two (Bayer *et al*, 1999) and three hit models (Keshavan & Hogarty, 1999; Velakoulis *et al*, 2000; Pantelis *et al*, 2003*c*) of schizophrenia; environmental factors, such as illicit drug use and psychosocial stress, also may be the potential secondary triggers accompanying the onset and course of schizophrenia (Allin & Murray, 2002; Buhler *et al*, 2002). Neurobiological studies of early psychoses have the potential to examine predictions generated by these seemingly contrasting models.

METHOD

We summarise the structural, functional and neurochemical brain changes in the early phase of psychotic disorders and their implications for future research and new innovative treatment approaches. A full review of the extensive literature in this area is beyond the scope of this paper; the main themes are summarised here, and the reader is also referred to larger works (Copolov *et al*, 2000; Keshavan *et al*, 2000; Lieberman *et al*, 2001; Callicott, 2003; Pantelis *et al*, 2003*c*).

RESULTS

Structural neuroimaging studies

Over the past quarter century, computed tomography (CT) (Johnstone *et al*, 1976; Weinberger *et al*, 1979; Pfefferbaum *et al*, 1988) and magnetic resonance imaging (MRI) studies (Lawrie & Abukmeil, 1998; Shenton *et al*, 2001) have aimed to characterise significant abnormalities in brain structure in patients with schizophrenia and to reinforce the view that schizophrenia was indeed a disease of the central nervous system. The observed differences in brain structure include larger ventricular volumes, smaller cerebral grey matter volumes and smaller hippocampal volumes. The key question of more recent interest has been whether these findings reflect a static or an active pathological process (Weinberger & McClure, 2002), a distinction critical to developing a conceptual model to explain the development of schizophrenia.

Earlier cross-sectional CT and MRI studies failed to find a relationship between illness duration and brain findings in chronically ill subjects (Zipursky *et al*, 1988; Marsh *et al*, 1994). In a more recent study Hulshoff Pol *et al* (2002) used MRI to study whole brain grey matter volumes over the adult age range in 159 patients with schizophrenia and 158 healthy comparison subjects. They found a significant group-by-age interaction with grey matter volumes declining at a more rapid rate in patients with schizophrenia. In another study of patients with established schizophrenia that examined brain grey matter using a voxel-based analysis method, Velakoulis *et al* (2000) found that duration of illness was associated with a reduction in grey matter volume in the right medial temporal lobe and medial cerebellum, and the anterior cingulate bilaterally. With this study design, however, it is not possible to know whether this effect can be explained by sampling bias (i.e. the older the patients, the more likely they are to be drawn from poor outcome chronically ill samples) or whether this reflects progressive changes that one might actually see within individuals over time.

It could be the case that being psychotic is in some way toxic to the brain and that by controlling the psychosis with antipsychotic medication, the progression of brain abnormalities might be limited. An MRI study in never-treated chronic schizophrenia patients (ill for over 10 years) in South India (McCreadie *et al*, 2002) found no association between illness duration and ventricular volume. Ho *et al* (2003) studied 156 patients with a first episode of schizophrenia and also failed to detect any significant correlations between duration of untreated psychosis and brain volumetric measures. Alternatively, the progression of brain changes might be self-limiting, with maximal differences achieved in the first years of the illness. Pursuing this possibility requires studying patients early in the course of their illness and carrying out follow-up scans.

Studies of first-episode schizophrenia (Lim *et al*, 1996; Zipursky *et al*, 1998) suggest that patients with first-episode psychosis differ from healthy comparison individuals on structural brain measures, but less so than observed in samples of chronically ill patients with schizophrenia. At first glance, this might seem to support the view that progression of these abnormalities is taking place over the course of the illness. As suggested above, an equally tenable possibility is that a selection effect may be taking place by which subjects with more pronounced brain differences early in their illness might be more likely to find themselves in a poor outcome chronically ill group (Zipursky *et al*, 1998). Longitudinal studies are required in order to distinguish between these two hypotheses.

Longitudinal follow-up studies of patients with first-episode psychosis have yielded conflicting results. Gur and colleagues described changes in MRI measures in 20 patients with first-episode schizophrenia, 20 previously treated patients and 17 controls studied twice over periods ranging from 12 to 68 months (Gur *et al*, 1998); patients with first-episode psychosis had more pronounced left frontal lobe volume reductions than previously treated patients and greater bilateral tissue reductions in the temporal lobes. However, greater reductions in frontal and temporal volumes were highly correlated with greater medication doses in the patients with first-episode psychosis but not in previously treated patients. Wood *et al* (2001) in their longitudinal MRI study of 30 patients with first-episode psychosis, 12 patients with established schizophrenia and 26 control subjects identified significant reductions in whole brain volume that were most apparent in the early phase of the illness and showed a greater loss with greater inter-scan interval over a 4-year period. In a recent more detailed analysis of this cohort, this loss of brain volume was explained by grey matter loss in dorsal prefrontal and parietal cortical regions (Sun *et al*, 2003). Cahn *et al* (2002) have described decreases in total grey matter volume and increases in lateral ventricle volume in 34 patients with first-episode schizophrenia compared with 36 healthy comparison subjects scanned over a 1-year interval. The decrease in global grey matter volume was, however, significantly correlated with higher cumulative doses of antipsychotic medication. That the association between medication dose and duration has not been evident in studies of more chronically ill patients suggests that there may be a ceiling effect such that once the differences are apparent early in treatment, little

https://doi.org/10.1192/bjp.187.48.s8 Published online by Cambridge University Press

further progression takes place (Lieberman *et al*, 2003).

Medications may explain some, but not all, of the structural brain abnormalities reported in schizophrenia. Differences in ventricular volume have been reported in studies prior to the introduction of antipsychotic medications in never-treated patients (McCreadie *et al*, 2002) and in unaffected (and untreated) family members (Cannon *et al*, 1998; Sharma *et al*, 1998). Smaller intracranial volumes have been reported in both affected and unaffected monozygotic twins who are discordant for schizophrenia, suggesting that genetic risk may contribute to the expression of the brain abnormalities reported in schizophrenia (Baare *et al*, 2001).

That brain findings are present at the time of the first episode does not establish that they have been present or stable since birth. Just as schizophrenia may evolve through a prodromal stage in many individuals, it is possible that the brain changes are also evolving during this time and driving the clinical deterioration characteristic of the prodromal period. The recent interest in identifying individuals at ultra-high risk for developing psychosis (Phillips *et al*, 2002) allows imaging of patients prior to and after emergence of the illness and thereby study of the neurobiology of transition to psychosis. Individuals at genetic risk for developing schizophrenia had smaller volumes of the left amygdala–hippocampal complex and thalamic nuclei than controls (Lawrie *et al*, 2001; Keshavan *et al*, 2002*a*). In the Edinburgh High Risk Study, over a 2-year follow-up period, at-risk participants as a group did not show greater regional brain volume changes than healthy controls, although at-risk participants with psychotic symptoms showed greater changes over the follow-up period than those without psychotic symptoms (Miller *et al*, 2002). Pantelis *et al* (2003*a*) carried out a longitudinal study of individuals treated in the PACE clinic in Melbourne, a specialist service for people at ultra-high risk for psychosis (for definition of criteria see Yung *et al*, 1996), which involved baseline and 12-month follow-up scans. Of the 75 participants who had a baseline scan, 23 developed psychosis and 52 did not. At their initial scan, those who later became psychotic had less grey matter in the right medial temporal, lateral temporal and inferior frontal cortex and in the cingulate cortex bilaterally. Ten individuals who were rescanned had developed psychosis in the follow-up period and 11 had not. Grey matter volume reductions were more pronounced in those who became psychotic, suggesting that an active disease process may be taking place in the brain. Some of the patients received antipsychotic medication in the interval between scans, so treatment cannot be ruled out as an explanation for the differential changes found in those who became psychotic. The absence of an age-matched healthy comparison group further limits the interpretation of this study. New techniques, such as diffusion tensor imaging, may provide important opportunities to study brain development longitudinally in individuals in the early stages of schizophrenia (Begre *et al*, 2003).

Cognition, electrophysiology and functional neuroimaging studies

In general, cognitive studies of early psychosis have mirrored the findings in chronic schizophrenia, with a similar pattern of impairments in executive function, attention and memory being identified (Heinrichs & Zakzanis, 1998). However, the magnitude of the impairments found in some of these studies indicates a smaller magnitude of deficits, although this may depend on the particular domain being examined. This has been shown both when tests are organised into sub-batteries by domain (e.g. Hoff *et al*, 1992; Bilder *et al*, 2000) and when individual tests are examined (Mohamed *et al*, 1999). There has, however, been debate about whether the impairment is generalised or whether there is evidence of a difference between cognitive domains (despite the similarity in results). Some studies (e.g. Mohamed *et al*, 1999) suggest that although small differences can be found between different domains, the effect size of the differences between domains is overshadowed by the much larger effect size of the difference between the patients and the controls (in the Mohamed *et al* study the largest effect size for differences between domains was −0.52, but for the difference between patients and controls 25 out of 30 tests had a Cohen's *d* of greater than 0.75). Although this may be partly attributed to poor matching of tests assessing different domains, it also suggests that the difference between domains might not be clinically meaningful. Other authors have suggested that although a generalised deficit is present, there is a differential impairment. This is most often found to be in the area of memory and learning (e.g. Saykin *et al*, 1994; Hutton *et al*, 1998) although the domains of attention and/or executive skills are also the lower scores in the profile (e.g. Albus *et al*, 1996). Saykin *et al* (1994) and Bilder *et al* (2000) utilised standardised residualised scores as a means to overcome the problems associated with poorly matched tasks. They both found that verbal memory and learning scores were lower than predicted on the basis of other scores, providing support for a differential impairment. In contrast, in the study by Weickert *et al* (2000), in which groups of patients were defined according to the extent of a generalised intellectual impairment, consistent deficits on the Wisconsin Card Sorting Test (WCST) were found, providing further evidence for differential impairment in executive function.

Such data, supporting a differential rather than generalised impairment, are also consistent with the findings from brain structural (described above) and functional imaging studies implicating regions of the prefrontal cortex and their connections with other areas, particularly subcortical and limbic regions (Liddle *et al*, 2000; Pantelis *et al*, 2002). The most consistent finding in schizophrenia has been of hypofrontality, which is most apparent when patients are tested while undertaking neuropsychological tasks relevant to the prefrontal cortex (Velakoulis & Pantelis, 1996; Davidson & Heinrichs, 2003), although this notion has been challenged (Manoach *et al*, 1999; Callicott *et al*, 2000). In their meta-analysis of 155 structural (MRI) and functional (positron emission tomography and single photon emission tomography) imaging studies of frontal and temporal lobe regions, Davidson & Heinrichs (2003) found that hypofrontality during cognitive activation showed the strongest effect and distinguished approximately half of schizophrenia patients from healthy controls (Cohen's $d=-0.81$; for resting studies, $d=-0.65$), whereas temporal lobe function did not discriminate the groups. In contrast, for structural imaging, the largest effect sizes were found for left superior temporal gyrus and left and right hippocampal volumes ($d=-0.55$, -0.55, -0.58, respectively). A preliminary meta-analysis of 14 functional MRI studies found that resting scans, regardless of cognitive task use, differed between patients with

https://doi.org/10.1192/bjp.187.48.s8 Published online by Cambridge University Press

schizophrenia and control individuals, whereas patients displayed less robust activation to cognitive challenge (Kindermann *et al*, 1997). Although such meta-analyses are informative, available studies have not been able to address some key questions, including: (a) other brain regions in which abnormal function has been identified (e.g. Carter *et al*, 1997; Haznedar *et al*, 1997; Yucel *et al*, 2002); (b) the interaction between different regions that is currently relevant to the notion of disturbed connectivity (e.g. Fletcher *et al*, 1999); and (c) the relationship between structural and functional imaging measures (e.g. Weinberger *et al*, 1992; Bertolino *et al*, 2000; Bilder *et al*, 2000; Callicott *et al*, 2000). Further, meta-analyses have not addressed the importance of controlling for behavioural performance on tasks used during activation studies. For example, in the studies by Manoach *et al* (1999) and by Callicott *et al* (2000) patients showing only a slight impairment in performance on graded tasks of executive function had greater rather than less activation in dorsal prefrontal cortex.

The current functional imaging literature is also limited in addressing issues such as illness stage and medication-related effects, as there are relatively few studies in the earliest stages of psychosis, especially in neuroleptic-naïve or unmedicated patients and even fewer in high-risk populations. In the resting study of 70 unmedicated patients with schizophrenia, who had at least 4 weeks off medication, Siegel and colleagues (Miller *et al*, 2002), found reduced activity in medial rather than dorsal prefrontal cortex and in associated regions of striatum and thalamus. Similarly, Stevens *et al* (1998) found that inferior and ventral regions were hypofunctioning. However, such studies do not take account of the long-term effects of medication and illness duration. In contrast, Barch *et al* (2001), in their well-designed functional MRI study examined neuroleptic-naïve first episode patients with schizophrenia using a context-dependent working memory task and found that dorsolateral prefrontal cortex, rather than other prefrontal regions, was specifically implicated from the outset of illness. These results are consistent with the findings of impaired working memory deficits in first-episode psychosis (Hutton *et al*, 1998; Proffitt *et al*, 2000; Wood *et al*, 2002). Two other studies in neuroleptic-naïve patients confirmed hypofrontality at illness onset (Parellada *et al*, 1998; Riehemann *et al*, 2001). The only available functional imaging study in a high-risk prepsychotic sample is consistent with the findings at illness onset (Keshavan *et al*, 2002*b*), which is also consistent with deficits in working memory in a similar population (Wood *et al*, 2003).

In parallel with the debate about whether brain structural abnormalities are static or progressive, various studies have assessed the stability of cognitive deficits over time and a few recent studies have examined change in brain function longitudinally. While the comparison of first episode with chronic patients suggests some decline in function, longitudinal studies have found little change over the years following the first episode (Censits *et al*, 1997; Gold *et al*, 1999; Hoff *et al*, 1999). In addition, a meta-analytical study of memory (Aleman *et al*, 1999) found little difference in effect size between studies with chronic compared with first-episode populations. Relationships have been identified between change in clinical symptoms and change in neuropsychological scores. For example, some studies (Censits *et al*, 1997; Gold *et al*, 1999; Brewer *et al*, 2001; Schuepbach *et al*, 2002) have found that change in negative symptoms is associated with change in neuropsychological scores, whereas another (Hoff *et al*, 1999) found a similar relationship with change in positive symptoms. These studies need to be interpreted with caution, particularly as few have distinguished between primary and secondary negative symptoms (Kirkpatrick *et al*, 2001). Overall, the longitudinal and some cross-sectional studies (e.g. meta-analyses that compare the effect size associated with first-episode and chronic schizophrenia) support the view that fairly extensive cognitive deficits are present by the first episode of psychosis and that they are likely to be a stable, ongoing, trait-like feature of the person's illness. This impairment appears to be relatively unaffected by the person's level of clinical symptoms.

In this context, it is worth noting the unreliability of the term 'first episode' and the potential implications this has for defining the onset of the cognitive deficits in psychosis. The term 'first episode' has been used to cover a relatively long period of time. For example, in the Bilder *et al* (2000) study, 21% of participants were tested more than a year after the onset of treatment, while the mean illness duration in the Saykin *et al* (1994) study was 2 years. This is further confused by the fact that the term 'illness duration' could be used to cover the duration of untreated psychosis before contact with the psychiatric service. Caution in accurately defining the term first episode is needed to ensure that active changes are occurring in the earliest phase of illness. For example, in a recent study of the cognitive abilities of patients with first-episode psychosis who were within 6 months of psychosis onset, in comparison with a group of patients with chronic schizophrenia and normal control participants (Wood *et al*, 2002), the patients with first-episode psychosis had no impairment on a visual associative memory task, whereas patients with chronic schizophrenia were significantly impaired. In contrast, the impairments of both patient groups on a spatial working memory task were very similar. This suggests that there may be some differential impairment in cognitive function over the illness course, with some present at or prior to the onset of the disorder, whereas others arise with prolonged psychosis. Clearly, longitudinal studies are needed from the earliest phase of psychotic disorders to elucidate whether deficits develop as the illness progresses. The limited available longitudinal functional imaging studies have focused on the effects of medication, and have demonstrated differences between typical and atypical antipsychotics (Honey *et al*, 1999; Liddle *et al*, 2000; Miller *et al*, 2001), suggesting some consistency with the neuropsychological studies that have identified improvement in neuropsychological function with atypical neuroleptics (Meltzer & McGurk, 1999; Bilder *et al*, 2002).

Another approach that is helpful in addressing the issue of whether neuropsychological and functional impairments are stable trait features of schizophrenia and psychosis is to examine neuropsychological and brain activity in prepsychotic, high-risk, individuals. Neuropsychological investigations have been performed as part of investigations, including the long-term high-risk studies that followed children into adulthood, such as the New York, Stony Brook, Copenhagen and Israeli High-Risk Studies, whereas more recent strategies, exemplified by the Edinburgh High Risk, and Melbourne Ultra High-Risk Studies, have used alternative approaches in order to increase the yield and reduce the period of follow-up required. Various groups have adopted the ultra-high risk strategy and

https://doi.org/10.1192/bjp.187.48.s8 Published online by Cambridge University Press

results on neuropsychological functioning from these studies are beginning to emerge (Cornblatt, 2002; Hambrecht *et al*, 2002; Brewer *et al*, 2003; Wood *et al*, 2003). The early high-risk studies are summarised elsewhere in special issues of *Schizophrenia Bulletin* in 1985 (vol. 11, issue 1) and 1987 (vol. 13, issue 3). Briefly, with respect to neuropsychology these earlier studies focused on attention, with more limited information available with respect to other cognitive domains (Weintraub, 1987; Mirsky *et al*, 1995; Wolf & Cornblatt, 1996). The New York High-Risk Study has been most informative in this respect, with the demonstration that childhood deficits in attention, motor skills and short-term memory, measured at 7–12 years of age, identified 58%, 75% and 83% (respectively) of those who later developed a schizophrenia-related psychosis (Erlenmeyer-Kimling *et al*, 2000). However, other groups have only partly replicated these findings. The Edinburgh High Risk Study found that verbal memory and executive function did distinguish between young relatives with and without psychotic symptoms during follow-up; other cognitive measures showed few clear differences (Cosway *et al*, 2002). This lack of replication may depend on the domains assessed and the timing of the assessment (Andersen, 2003; Pantelis *et al*, 2003*c*; Wood *et al*, 2003).

The more recent studies have comprehensively assessed neuropsychological function, although not all data have been published as yet. In the studies by the Edinburgh group, slightly lower levels of global cognitive function were identified in a high-risk cohort than in a group of matched controls (Byrne *et al*, 1999). When this difference was controlled for, the high-risk group was significantly impaired only on a global memory test and on a sentence completion test that implicates executive functions. However, none of the participants in that study had become acutely psychotic at the time of publication, which highlights one of the problems of research in high-risk populations, namely, that it will remain unclear to what extent neuropsychological deficits identified premorbidly are predictive of the later onset of schizophrenia until there has been an adequate follow-up period to determine who will develop psychosis, such as in the New York High-Risk Study discussed above. Another approach has been to identify cases from long-term population-based follow-up studies, as in the Dunedin Multidisciplinary Health and Development Study (Poulton *et al*, 2000), which identified reduced intelligence and receptive language skills in children between the ages of 3 and 9 years who later fulfilled criteria for schizophreniform disorder (Cannon *et al*, 2002). Although difficult to set up and undertake, such an approach is particularly informative as it does not focus only on the offspring of patients with schizophrenia. Although these studies provide evidence that early neuropsychological deficits may be markers of impending illness later in life, the question of specificity of these findings to schizophrenia remains unclear.

In order to address the long follow-up period required and the low number of individuals developing psychosis in the high-risk and population-based studies described, the Melbourne group have utilised an ultra-high-risk strategy to identify young people at imminent risk of developing a psychotic illness. Using this approach about 40% of individuals make the transition to psychosis within 12 months of presentation (Yung *et al*, 1998). Initial findings (including neuroimaging findings described earlier) at baseline, prior to illness transition, have identified deficits in spatial working memory ability in those who subsequently developed psychosis (Wood *et al*, 2003), which were similar to those observed in patients with schizophreniform psychosis and established schizophrenia (Wood *et al*, 2002). Deficits in olfactory function are also found specifically in those developing schizophrenia (Brewer *et al*, 2003). In contrast, preliminary findings indicate that some other aspects of memory are not impaired (Pantelis *et al*, 2003*b*). These data, taken together with findings in patients with first-episode and chronic psychosis using the same tasks, provide further evidence that particular domains of function are differentially impaired, and raise the possibility that other domains may only become apparent as the illness develops a more chronic course.

A complementary approach to examining brain function uses event-related brain potentials (ERPs), which can track changes in brain functioning over a short period of time, thereby providing dynamic information about the progression of brain activity during cognitive tasks. Although a number of ERP components have been studied in schizophrenia, most work in early psychosis has focused on mismatch negativity and P300 (for review see Salisbury *et al*, 2003). The mismatch negativity is a negative auditory ERP, occurring 150–250 ms after presentation of 'deviant' stimuli, which are elicited by interspersing infrequent sounds (differing in pitch, duration, intensity or spatial location) in a sequence of repetitive sounds. The mismatch negativity is evoked automatically, is preconscious, is thought to have generators in auditory cortices but may also have a prefrontal generator (Salisbury *et al*, 2003), and may reflect activity of *N*-methyl-D-aspartate (NMDA) receptors (Umbricht *et al*, 2000, 2003). Mismatch negativity is reduced in patients with established schizophrenia (Catts *et al*, 1995; Javitt *et al*, 2000*b*), has been shown to be specific to schizophrenia (Catts *et al*, 1995; Umbricht *et al*, 2003), and these deficits (considered to reflect transient memory traces) have been related to impaired performance on an attentional task (Javitt *et al*, 2000*b*). In contrast, patients with first-episode psychosis early in their course of illness are unimpaired (Salisbury *et al*, 2002), whereas patients within the first 3 years of illness show a mild deficit (Javitt *et al*, 2000*a*). Preliminary longitudinal findings of a small sample of patients over the first 2 years of illness have been presented by Salisbury *et al* (2001), and these authors consider that the mismatch negativity may index progressive neurodegeneration in schizophrenia, involving superior temporal gyrus (Salisbury *et al*, 2003), which may be mediated by NMDA (Olney *et al*, 1999). However, a genetic contribution has also been suggested by recent evidence that patients with schizophrenia and their first-degree relatives show deficits in mismatch negativity (Michie *et al*, 2002), but Jessen *et al* (2001) found that relatives were impaired but patients did not differ from controls. Further, in a study of children at high risk for schizophrenia, mismatch negativity showed some reduction (Schreiber *et al*, 1992). These findings indicate that further studies from the earliest phase of psychosis, in prepsychotic individuals, and studies of unaffected family members are required to assess the evolution and characteristics of this marker of pre-attentive processing. If mismatch negativity does provide an index of progressive changes in schizophrenia, and if they are found to be related to the structural imaging findings described above, this index may provide information

https://doi.org/10.1192/bjp.187.48.s8 Published online by Cambridge University Press

about the mechanisms underlying such changes.

In contrast to the mismatch negativity which is pre-attentive, the P300 occurs to a stimulus that is actively detected and processed and is elicited by the 'oddball' paradigm (for review see Salisbury *et al*, 2003). Because subjects actively attend to detect the rare occurrence of an infrequent target, deficits of or disruption to selective attention processes will disrupt the P300. Typically, patients with chronic schizophrenia show a robust reduction in P300 amplitude, which is trait-like (Jeon & Polich, 2001; Salisbury *et al*, 2003), and these deficits are considered to reflect impairments in sustained attention and higher level cognitive abilities, including working memory (Kimble *et al*, 2000). Symptom remission and atypical neuroleptics have been associated with some increase in P300 (Ford *et al*, 1994; Umbricht *et al*, 1998), although the impairment does not normalise (Salisbury *et al*, 2003). Further, Mathalon *et al* (2000) have shown that while auditory and visual P300s track symptom changes over time, only auditory P300s remained abnormal when patients were least symptomatic, suggesting that the latter was a trait marker. Examination of neuroleptic-naïve patients with first-episode psychosis indicates that the P300 abnormality is present prior to medication (Radwan *et al*, 1991; Hirayasu *et al*, 1998). The early studies of individuals at genetic high risk for developing schizophrenia are reviewed elsewhere (Friedman & Squires-Wheeler, 1994). These studies have found that P300 latencies are prolonged in these individuals (Schreiber *et al*, 1992; Friedman & Squires-Wheeler, 1994), although there are no reports comparing those who subsequently developed psychosis with those who did not. These studies are also consistent with P300 abnormalities identified in unaffected relatives of patients with schizophrenia (Blackwood *et al*, 1991; Frangou *et al*, 1997; Turetsky *et al*, 2000), which have also been related to neuropsychological deficits observed in patients and their relatives (Roxborough *et al*, 1993).

In the meta-analysis by Jeon & Polich (2001), smaller P300 amplitude was confirmed in patients with schizophrenia compared with control subjects and differed in its effect size topography across the midline and temporal electrode sites. These findings are consistent with evidence that the P300 is reduced over the midline and that there is a left temporal abnormality, which has been associated with reduced volume of the left posterior superior temporal gyrus (McCarley *et al*, 1993). Further, in patients with first-episode schizophrenia a smaller left temporal P300 was also associated with left posterior superior temporal gyrus and planum temporale volumes, whereas patients with affective psychosis did not show these impairments or associations (McCarley *et al*, 2002). Left superior temporal gyrus volumes have been associated with formal thought disorder (Shenton *et al*, 2001). This left temporal abnormality has been described in patients who ceased medication (Faux *et al*, 1993). A left-lateralised P300 deficit has also been described in schizotypal personality disorder (Niznikiewicz *et al*, 2000).

These studies of ERPs and their neurobiological correlates need to be examined in the recent high-risk or ultra-high-risk studies, and may provide trait/state indices, whereas longitudinal studies may provide insights about disease progression.

In vivo neurochemistry

Magnetic resonance spectroscopy (MRS) provides us with a non-invasive tool to investigate metabolites in the living human brain. This technique overcomes one major limitation of post-mortem analysis: the investigation of *in vivo* brain metabolites during the peri-onset and early phases of the illness and the investigation of medication effects on these metabolites. Much MRS work has focused on investigating phosphorus-containing (^{31}P MRS) and proton-containing metabolites (^{1}H MRS) (for reviews see Keshavan *et al*, 2000; Stanley *et al*, 2000).

^{31}P-MRS investigations in drug-naïve patients with first-episode psychosis suggest increased membrane breakdown at the onset of psychosis (Pettegrew *et al*, 1991; Stanley *et al*, 1995; Fukuzako *et al*, 1999) and in most studies there appears to be reduced membrane generation in early and chronic schizophrenia. Cell membrane changes occur prominently during cell generation and synaptogenesis, but also with degenerative processes, such as apoptotic elimination of dendrites and axons (pruning) and cell death. Cell membrane alterations of patients with schizophrenia are also well documented in peripheral and post-mortem brain tissue at different stages of the disorder (for review see Berger *et al*, 2002). Such findings may reflect either a reduction in glia-, synapto- and neurogenesis associated with chronic schizophrenia and/or accelerated programmed cell loss (apoptosis) and/or dendritic and axonal pruning at the onset of the disorder. Studies of adolescent offspring at increased genetic risk for schizophrenia show membrane alterations similar to those observed in patients with early schizophrenia (Klemm *et al*, 2001; Keshavan *et al*, 2003*b*); these changes are more pronounced in the at-risk adolescents who have already begun to manifest psychopathology (Keshavan *et al*, 2003*b*). Interestingly, patients with manic psychosis appear to have an increase in membrane precursors (Kato *et al*, 1993), which may reflect a compensatory increase in cell generation and/or synaptogenesis during manic exacerbation of psychotic disorders. Investigations using high-field ^{31}P MRS (e.g. at 4 T) in early psychosis are just emerging (Theberge *et al*, 2002).

Proton MRS provides us with a tool for measuring *in vivo* brain metabolites, including *N*-acetylaspartate (NAA), creatine, choline, myo-inositol, glutamine, glutamate, glutathione and γ-amino butyric acid (GABA). *N*-acetylaspartate is mainly synthesised in neurons and is therefore regarded as a putative marker for neuronal loss or dysfunction (Urenjak *et al*, 1993; Rudkin & Arnold, 1999). However, NAA levels also depend on the capacity of glial cells which are involved in the uptake and degradation of this metabolite (Passani *et al*, 1998; Baslow, 2000; Bhakoo *et al*, 2001). *N*-acetylaspartate is also a major acetyl-donor for the elongation of long-chain fatty acids and is important for generation of membrane phospholipids, the basic molecules of all cell membranes. Furthermore, NAA is important for mitochondrial metabolism and excitatory neurotransmission (Tsai & Coyle, 1995; Lim *et al*, 1996).

Reductions in NAA peaks were found in most studies of patients with chronic schizophrenia encompassing several different brain regions (hippocampus, thalamus and frontal cortex), were variably present in first-degree relatives, and were associated with cortical atrophy and negative symptoms (for discussion and references see Keshavan *et al*, 2000; Vance *et al*, 2000). *N*-acetylaspartate reductions in the prefrontal cortex have been found to be associated with reduced physiological capacity for working memory as well as with exaggerated responses of dopamine

https://doi.org/10.1192/bjp.187.48.s8 Published online by Cambridge University Press

neurons to amphetamine, a surrogate biological measure of positive symptoms (Weinberger *et al*, 2001). However, proton MRS studies in drug-naïve patients with first-episode psychosis have been less conclusive (Keshavan *et al*, 2000), and the data suggest that neuronal integrity in early phases of illness may still be intact and neuronal circuits only functionally impaired (Bartha *et al*, 1997, 1999). *N*-acetylaspartate reductions have been found to be correlated with increased illness duration (Ende *et al*, 2000) supporting the possibility of a progressive impairment of neuronal integrity as the illness unfolds. *N*-acetylaspartate changes may also represent dynamic measures of neuropathological change as a function of illness and/or change (Bertolino *et al*, 2001). Future longitudinal MRS studies before and after transition to psychosis may contribute to a better understanding of the relevance of NAA findings in the early phase of schizophrenia and related disorders.

DISCUSSION

Structural imaging studies point to increases in cerebrospinal fluid volumes and widespread grey matter reductions in varying degrees across samples of patients with schizophrenia. These differences are more prominent in patients with chronic psychosis as compared with patients with first-episode psychosis and are also present, to a smaller degree, in unaffected relatives, unaffected co-twins and individuals at ultra-high risk for developing schizophrenia and related disorders. These differences appear to deviate to some degree from normal with time but it is unclear whether this is a direct effect of some antipsychotic medications or due to the illness process itself. Consistent with structural findings, ^{1}H MRS studies suggest that impairments in neuronal integrity are more prominent in chronic as compared with first-episode patients, and can also be found to some degree in unaffected first-degree relatives. ^{31}P MRS studies suggest alterations in membrane phospholipid metabolism early in the course of the illness; these changes are correlated with cognitive impairments and negative symptoms, although their possible disease-related progress remains to be documented by longitudinal data. Studies of cognitive and electrophysiological processes in schizophrenia have suggested general as well as selective neuropsychological impairments, with some deficits being present early in a trait-like manner and some others showing progression. Functional imaging studies have allowed characterisation of the functional neuroanatomical circuitry involved early in the illness; again, the course of these functional changes and the illness versus treatment effects over time remain unclear. Overall, the pathophysiological significance of the neurobiological observations in early psychoses remains vague, although tantalising clues are beginning to appear.

Several lines of future research are of promise in this burgeoning field. First, advances in neuroimaging technology now allow us to examine the neurobiology of psychosis in finer detail. High-field magnets ($\sim$3 T or higher) allow better spatial resolution for structural imaging studies; better neurochemical resolution for MRS may help investigation of key metabolites, such as glutamate and GABA. Multimodal imaging studies combining functional MRI and ERP techniques will increase temporal resolution and allow close examination of disordered cognitive processes. Second, observations that the early course of schizophrenia is associated with progressive changes in brain structure and function highlight the importance of longitudinal studies of individuals at ultra-high risk for developing psychosis who are not receiving antipsychotic medication to track the underlying biology of transition to the psychotic illnesses, as well as studies of patients with first-episode psychosis to determine the biology of disease progression following illness onset. Recognising these biological processes can eventually help to develop phase-specific treatments that may be able to protect the vulnerable individual from the emergence and/or progression of the illness. Third, the observations of similar, albeit less severe, neurobiological changes in relatives of patients with schizophrenia and other psychotic disorders suggest that these studies may help us to better define the endophenotype of these illnesses, and eventually elucidate the susceptibility genes for illness onset, treatment response or outcome. Finally, neurobiological research in early psychosis, to be successful, requires service structures that can access adequate numbers of early psychosis patients. The recent emergence of specialised early recognition and intervention services for early psychotic disorders throughout the world (Edwards & McGorry, 2002) will make neurobiological research in early psychoses both timely and feasible.

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CLINICIAL IMPLICATIONS

- It is important to understand the neurobiological changes during the premorbid phase of psychoses to identify persons at increased risk and for prevention efforts.
- Clarification of the biology of transition to psychosis in prodromal patients is critical for our efforts to identify early and potentially prevent the emergence of psychotic illness.
- A better knowledge of the biological changes during the early phases can help to develop strategies for minimising long-term morbidity and disability.

LIMITATIONS

- Although several neurobiological changes have been consistently found in early schizophrenia, none is specific to be of diagnostic value at this time.
- The implications of the neurobiological alterations for treatment are still unclear.
- Neurobiological research in the early phases of schizophrenia is often hampered by the lack of specialised health service settings that can adequately access adequate numbers of such people.

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https://doi.org/10.1192/bjp.187.48.s8 Published online by Cambridge University Press

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