BRITISH JOURNAL OF PSYCHIATRY (2007), 191 (suppl. 51), s123–s127. doi: 10.1192/bjp.191.51.s123

# Duration of prodromal phase and severity of volumetric abnormalities in first-episode psychosis*

JULIA M. LAPPIN, PAOLA DAZZAN, KEVIN MORGAN, CRAIG MORGAN, XAVIER CHITNIS, JOHN SUCKLING, PAUL FEARON, PETER B. JONES, JULIAN LEFF, ROBIN M. MURRAY and PHILIP K. McGUIRE

**Background** First-episode psychosis is typically preceded by a prodrome in which there is deterioration in global and social functioning.

**Aims** To examine whether the duration of the prodromal phase influences grey and white matter volumes at the onset of psychosis.

**Methods** Eighty-two people were scanned using magnetic resonance imaging when they developed a first episode of psychosis. The duration of the prodromal phase was estimated from detailed interviews and medical records. Voxel-based morphometry was used to assess neuroanatomical abnormalities.

**Results** A long prodromal phase was associated with smaller grey matter volumes in the cingulate, frontal and left insular cortex, and with less white matter volume bilaterally in the superior longitudinal and uncinate fasciculi and the cingulum.

**Conclusions** The severity of volumetric abnormalities in first-episode psychosis was greater in those with a long prodrome.

**Declaration of interest** None. Funding detailed in Acknowledgements.

*Preliminary analysis of these data was presented in abstract form at the XIII Biennial Winter Workshop on Schizophrenia, Davos, Switzerland, 2006.

The first episode of psychosis is typically preceded by a prodromal phase during which there is a gradual deterioration in global and social functioning and the emergence of attenuated positive and negative psychotic symptoms (Hafner & Nowotny, 1995; Yung *et al*, 2003). We set out to establish whether the duration of such sub-threshold symptoms, or prodrome, prior to illness onset is related to severity of neuroanatomical changes at the onset of frank psychosis. A large group of people was scanned using magnetic resonance imaging (MRI) at the time of the first episode. We expected that the longer the duration of the prodrome, the smaller the volumes in grey matter regions and white matter tracts implicated in psychotic disorders. Thus, we predicted that a longer prodrome would be associated with relatively smaller grey matter volumes in the prefrontal, cingulate and medial temporal cortex, and smaller white matter volumes in the tracts that interconnect these regions.

## METHOD

### Participants

Participants were recruited as part of a large epidemiological study of first-episode psychosis (Dazzan *et al*, 2004). A total of 281 people met inclusion criteria for a functional psychotic illness (DSM–IV 295–298, psychotic codings; American Psychiatric Association, 1994); 90 declined to participate; of the remaining 191, 115 consented to an MRI scan. These 115 patients were a mean of 6 years younger (mean age 27.9 years, s.d.=8.4 *v.* 33.7, s.d.=12.3, $t$=3.5, $P$=0.001) and had a higher proportion of White British members (36% *v.* 18%, $\chi^2$=6.95, $P$=0.008) but were otherwise comparable to the total sample in terms of gender, years of education, diagnosis and duration of illness. There were no significant group differences in demographic or clinical features between those who did and did not consent to scanning.

Of those who consented to MRI, 10 terminated scanning before image acquisition could be completed and 15 were excluded owing to participant motion ($n$=13) or radiological abnormalities (1 congenital hydrocephalus, 1 subarachnoid cyst). Data from 90 participants were thus available for image analysis.

### Clinical measures

Participants were assessed using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN; World Health Organization, 1994) interview. Diagnostic codes were assigned according to DSM–IV criteria in consensus meetings with senior clinicians. A total symptom score was obtained by summing the individual symptom item scores according to Wing & Sturt's (1978) procedure for the Present State Examination (PSE). Premorbid IQ was assessed using the National Adult Reading Test (NART; Nelson & Willison, 1991) and handedness using the Annett Hand Preference Questionnaire (Annett, 1970).

### Prodrome

The prodrome was defined as the period in weeks from the time of first definite change in behavioural, psychological or emotional functioning to the onset of the first psychotic episode. The key feature of this criterion was the presence of a fundamental change in function that persisted from its onset until the time of first episode of psychosis (e.g. non-attendance at work/college with no clear explanation for change in behaviour). In line with previous studies (Craig *et al*, 2000), onset of psychosis was defined as the presence for 1 week or more of one of the following psychotic symptoms (as defined in the SCAN): delusions; hallucinations; marked thought disorder; marked psychomotor disorder (other than simple retardation or acceleration); and bizarre, grossly inappropriate and/or disorganised behaviour with a marked deterioration in function. Data relating to date of first behavioural change and date of onset of psychosis were collated from interviews with the participant and a close relative, and clinical notes using the Personal and Psychiatric History Schedule (PPHS; Jablensky *et al*, 1992; World Health Organization, 1994). Interrater reliability was assessed for those involved in rating (C.M. and J.M.L.) by each independently

rating these measures on a random subset of 50 participants from the original sample. Reliability was judged as satisfactory (inter-class correlation $r$=0.903). Duration of untreated psychosis was measured and defined as the period in weeks from the onset of frank psychotic phenomena to first contact with statutory mental health services. Duration of untreated illness was defined as the sum of duration of prodrome plus the duration of untreated psychosis.

### MRI protocol

Magnetic resonance images were acquired with a GE Signa 1.5 T system (GE Medical Systems, Milwaukee, USA) at the Maudsley Hospital (London, UK). Contiguous, high-resolution 3-mm thick, interleaved dual-echo images were acquired in the coronal plane, providing coverage of the entire brain. Proton density- and T2-weighted image acquisition was almost simultaneous: time to echo (TE1) 20 ms, (TE2) 85 ms; time to resolution (TR) 4000 ms; 8-echo train length; matrix size 256 x 192; field of view 22 cm × 16.5 cm).

Images were processed using SBAMM voxel-based semi-automated methods (Bullmore *et al*, 1999; Suckling *et al*, 1999). In brief, extracerebral tissues were removed using an automated algorithm and manual editing. Intracerebral tissue voxels were categorised into grey matter, white matter, cerebrospinal fluid (CSF), or dura/vasculature using a modified fuzzy clustering algorithm (Suckling *et al*, 1999). A template image was constructed in standard space from proton-density images of six healthy controls using the AFNI program (Dazzan *et al*, 2004). Each participant's proton-density weighted image was then registered onto the template with a nine-parameter affine registration, minimising between-level difference between images. The derived mapping was applied to the corresponding tissue maps.

Length of prodrome was regressed onto estimated grey matter and white matter volumes at each voxel in standard space. The test statistic calculated was the regression coefficient divided by its standard deviation to generate an effect map. Permutation testing was used to assess statistical significance, and regional relationships were tested at the level of voxel clusters (Bullmore *et al*, 1999; Sigmundsson *et al*, 2001). The statistical threshold for cluster significance was set such that the expected number of false-positive clusters ($P$ value times number of tests) was less than one.

## RESULTS

### Sample

Socio-demographic and clinical characteristics of the sample are shown in Table 1.

### Prodrome

The distribution of prodrome length expressed in weeks was non-Gaussian. A small number of participants ($n$=8) had an extremely long prodrome (>169 weeks), which was grossly outwith the distribution for the sample as a whole. Logarithmic transformation was not sufficient to convert the data to normal distribution, and therefore these participants were excluded as statistical outliers.

Eighty-two participants remained for subsequent analyses; these were a mean of 5 years younger (mean age 27.1, s.d.=8.0 *v.* 32.7, s.d.=11.1 years, $t$=3.8, $P$=0.002) and had a higher proportion of White British members (38% *v.* 21%, $\chi^2$= 6.24, $P$=0.01), but were otherwise comparable to the total sample in terms of gender, years of education, diagnosis and duration of illness.

**Table 1** Socio-demographic and clinical characteristics of 82 participants

| Characteristic | |
|---|---|
| Length of prodrome,weeks | |
| Mean (s.d.) | 21 (36) |
| Median (IQR) | 5 (1–27) |
| Duration of untreated psychosis, weeks | |
| Mean (s.d.) | 26 (52) |
| Median (IQR) | 6 (2–22) |
| Duration of untreated illness, weeks | |
| Mean (s.d.) | 46 (65) |
| Median (IQR) | 22 (7–53) |
| Male gender, *n* (%) | 51 (62) |
| Right handedness, *n* (%)[1] | 71 (90) |
| Diagnosis, *n* (%) | |
| Schizophrenia | 46 (56) |
| Affective psychoses | 26 (31) |
| Other psychoses | 10 (12) |
| Age, years: mean (s.d.) | 27.2 (8) |
| Education, years: mean (s.d.) | 12.8 (2) |
| Premorbid IQ: mean (s.d.)[2] | 95.9 (16) |
| Typical antipsychotics, *n* (%) | 38 (46) |
| Atypical antipsychotics, *n* (%)[3] | 33 (40) |
| Drug-free, *n* (%) | 12 (15) |
| Days on treatment: mean (s.d.) | |
| Typical antipsychotics | 62.6 (59) |
| Atypical antipsychotics | 63 (59) |
| Current dose | |
| Typical antipsychotics, mg in chlorpromazine equivalents: mean (s.d.) | 283.5 (233) |
| Atypical antipsychotics, mg olanzapine: mean (s.d.) | 13.4 (5) |
| Total symptom score (SCAN) | 30.2 (16) |
| Total grey matter volume, $cm^3$: mean (s.d.) | 576.2 (60) |
| Total white matter volume, $cm^3$: mean (s.d.) | 469.0 (51) |
| Total CSF volume, $cm^3$: mean (s.d.) | 154.2 (30) |

IQR, interquartile range; SCAN, Schedule for Clinical Assessment in Neuropsychiatry; CSF, cerebrospinal fluid.
1. Data missing for 4 participants.
2. Data missing for 11 participants.
3. Number of participants taking antipsychotic treatment throughout the 3 weeks prior to scanning.
4. Calculated for those on olanzapine (70 % of those on atypicals).



https://doi.org/10.1192/bjp.191.51.s123 Published online by Cambridge University Press

The mean length of prodrome was 21 weeks (s.d.=36, range 1–157, IQR 1=27). The mean duration of untreated psychosis was 26 weeks (s.d.=52, range 1–313, IQR=2–22). The mean duration of untreated illness was 46 weeks (s.d.=64, range 1–344, IQR=7–52). Seventy participants (85%) had received antipsychotic treatment at the time of the MRI scan. The mean duration of antipsychotic treatment was 9 weeks.

Length of prodrome did not vary significantly with gender, age, type of psychotic disorder (schizophrenia, affective psychosis, other), total duration of antipsychotic exposure, illness severity (as indexed by total symptom score on the SCAN) or premorbid IQ (NART; Table 2).

**Table 2** Relationship of socio-demographic and clinical variables to prodrome length

| Characteristic | Prodrome length Mean (s.d.) |
|---|---|
| Diagnosis | |
| Schizophrenia (*n*=46) | 22.5 (38) |
| Affective psychosis (*n*=26) | 16.5 (39) |
| Other (*n*=10) | 22.8 (18) |
| Gender | |
| Male (*n*=51) | 16.9 (32) |
| Female (*n*=31) | 26.8 (43) |
| Marital Status | |
| Married or steady relationship (*n*=20) | 20.1 (28) |
| Single, separated or divorced (*n*=59) | 18.6 (37) |
| Occupational status | |
| Employed (*n*=35) | 21.9 (42) |
| Unemployed (*n*=44) | 17.9 (28) |
| Antipsychotic treatment | |
| Typicals (*n*=24) | 21.6 (46) |
| Atypicals (*n*=19) | 12.4 (21) |
| Mixed (*n*=14) | 32.9 (46) |
| None (*n*=25) | 19.1 (30) |

### Global brain volumes

Length of prodrome was not significantly correlated with the total volume of any of the grey matter, the white matter or the CSF (Table 2).

### Regional brain volumes

#### *Grey matter*

There were two regions where there was an inverse relationship between length of prodrome and grey matter volume ($P$=0.002, <1 false-positive; Table 3; Fig. DS1 in the data supplement to the online version of this paper). The first cluster included the anterior and posterior cingulate gyri bilaterally, and extended locally into the medial frontal gyri bilaterally (Fig. DS1). A second cluster was focused on the left insula, extending into the left inferior frontal gyrus.

#### *White matter*

Length of prodrome was inversely correlated with white matter volume in two similar regions in each hemisphere ($P$=0.003, <1 false-positive; Table 3; Fig. DS2 in the data supplement to the online version). Both clusters had their focus in the superior longitudinal fasciculus at the level of the genu of the corpus callosum, and also included white matter in the cingulum, corpus callosum and internal capsule.

There were also three much less extensive clusters where prodrome duration was positively correlated with white matter volume ($P$=0.003, <1 false positive; Table 3; Fig. DS2). One was centred in the right inferior longitudinal fasciculus (ILF), with involvement of the right uncinate fasciculus. The second involved the white matter subjacent to the right orbital gyrus, with extension into the right fusiform gyrus; and the final cluster was centred in the left acoustic radiation with involvement of the left ILF at the level of the mid-thalamus, and extended anteriorly in the uncinate fasciculus.

## DISCUSSION

### Grey and white matter abnormalities

This study provides the first data to indicate that the length of time spent in prodromal illness directly correlates with the degree of brain structural abnormalities present at the onset of psychosis. Moreover, this relationship was evident in grey and white matter areas that are typically affected in psychotic disorders, and the polarity of the relationship in these areas (smaller volume with longer prodrome) corresponds to the reduction that is evident in psychotic disorders. Reduced prefrontal, insular and cingulate volume have consistently been reported in neuroimaging studies of schizophrenia (Wright *et al*, 2000; Sigmundsson *et al*, 2001; Job *et al*, 2002) and, to a lesser extent, bipolar illness (Drevets *et al*, 1997; McDonald *et al*, 2004). Similarly, reduced white matter volume in the superior longitudinal and uncinate fasciculi, and in the cingulum has been described in volumetric MRI studies of schizophrenia (Sigmundsson *et al*, 2001) and bipolar disorder (Haznedar *et al*, 2005). Diffusion tensor imaging studies indicate that these tracts are also sites of reduced fractional anisotropy in schizophrenia (interpreted as reflecting reduced white matter integrity), but this technique has been less frequently employed in bipolar disorder (Lim *et al*, 1999; Kubicki *et al*, 2002). Our white matter findings are of particular interest because the superior longitudinal fasciculi and the cingulum carry connections to and from the prefrontal, cingulate and temporal regions (Catani *et al*, 2002; Wakana *et al*, 2004), where we found grey matter reductions correlated with longer prodrome.

### Comparison with high-risk studies

A correlation between the duration of the prodromal phase and the severity of MRI abnormalities at the first episode is consistent with data from prospective MRI studies of individuals at high risk of psychosis during the prodromal period. To date, only two previous studies have examined changes in brain structure at several time points in small numbers of people at high risk for psychosis. Pantelis *et al* (2003) scanned people in the prodromal phase and again after they developed psychosis and found that there was a progressive



https://doi.org/10.1192/bjp.191.51.s123 Published online by Cambridge University Press

**Table 3** Regional differences in grey and white matter associated with length of prodrome

| Anatomical area | Cluster size voxel number | Location of cluster centre, *x*, *y*, *z* |
|---|---|---|
| Gray matter reductions: | | |
| R cingulate gyrus, extending to L cingulate gyrus, and R and L medial frontal gyri | 641 | 0.2, 4.3, 38.8 |
| L insula, extending to L inferior frontal gyrus | 362 | −35.5, 1.9, 2.2 |
| White matter reductions | | |
| L superior longitudinal fasciculus, with extension to L cingulum, L corpus callosal and L internal capsule fibres | 2133 | −24.4, −6.7, 26.2 |
| R superior longitudinal fasciculus, with extension to R cingulum, R corpus callosal and R internal capsule fibres | 2729 | 24.7, 3.1, 24.9 |
| White matter excesses | | |
| L acoustic radiation, with involvement of L inferior longitudinal fasciculus and L uncinate fasciculus | 182 | −34.7, −30.4, 8.9 |
| R inferior longitudinal fasciciulus, extending to R uncinate fasciculus | 408 | 42.5, −26.8, −8.7 |
| R orbital gyral white matter, extending to fusiform white matter | 384 | 32.2, −68.0, −21.6 |

R, right; L, left.

reduction in grey matter volume in the cingulate, prefrontal and medial temporal cortex. Job *et al* (2005) also reported a longitudinal reduction in medial temporal and cerebellar volume during the prodrome, and that these changes occurred within the prodromal phase well in advance of the first episode. Our study provides complementary findings: we have established that there is a correlation between length of prodromal symptoms and severity of neuroanatomical abnormalities. This is important because if these occur secondary to progressive changes caused by subthreshold prodromal symptoms, it is clear that the length of prodromal illness is important in pathogenesis, rather than there being some 'toxic' threshold being reached with the onset of frank psychotic symptoms.

However, although our findings are consistent with this hypothesis, we cannot conclude from our cross-sectional study that the brain abnormalities identified represent progressive changes. Indeed, the differences in regional volumes within our participants with first-episode psychosis may already have been present before the prodromal phase, perhaps reflecting factors that vary between patients and differentially affect both brain structure and the form of onset of the disorder. For example, this explanation might apply if those who developed schizophrenia had both a longer prodrome and more extensive MRI abnormalities than those with an affective psychosis, or if people who were highly symptomatic at the first episode had a longer prodrome than those who presented with less florid symptoms. In the present study the length of prodrome was similar for people with schizophrenia, affective or other psychoses, and it was also unrelated to the overall severity of symptoms. Similarly, prodrome duration was unrelated to age, gender, IQ, nature of antipsychotic treatment and duration of treatment prior to scanning. Thus, although an effect of factors other than a progressive process cannot be excluded, we found no evidence to support this. None the less, it is important to acknowledge the possibility that any changes occurring in brain structure need not follow a purely linear course throughout the entire prodrome. Indeed it seems likely that, after a given time, rate of change must diminish or brain volume would decrease to zero. Our interpretation of the findings as representing a linear change over time is both scientifically plausible and parsimonious.

## Definition of prodrome

Estimates of prodrome duration in the present study were made retrospectively, which might have limited their accuracy. We sought to minimise inaccuracy by using information from the participants' relatives and friends, as well as from the participants themselves, and by systematically examining all available clinical records. Moreover, in practice a truly prospective measure of prodrome duration is difficult to obtain. Even people who are ascertained before the first episode will have been experiencing prodromal symptoms for some time (Yung *et al*, 2003), such that their date of illness onset still has to be estimated retrospectively. In any event, in the present study it is the relative length of the prodrome in different participants rather than its absolute duration that is relevant, making the precision of the absolute estimate less critical. The average length of prodrome in our sample was shorter than reported in previous studies (Pantelis *et al*, 2003), and this might reflect differences in the respective samples examined. Our participants were people with first-episode psychosis ascertained in an epidemiological study, whereas previous estimates have been derived from people with prodromal symptoms referred to specialist clinics (Pantelis *et al*, 2003).

## Voxel-based methodology

We used voxel-based morphometry for the evaluation of brain structure, measuring relative intensities of grey or white matter values at a given voxel. Thus, observed differences between groups might represent differences in factors affecting tissue intensity such as hydration status, or vascular or metabolic changes. Also, it is always possible that some of the grey and white matter abnormalities that we have demonstrated could be a result of an artefact of the warping of the images into standard (Talairach) space.

We also considered the possibility that brain changes might occur secondary to antipsychotic treatment in our subjects. There was no difference in length of prodrome between participants considered according to their treatment status (typical antipsychotics, atypicals, mixed, or drug-free; Table 2), so medication status is unlikely to explain our findings.



https://doi.org/10.1192/bjp.191.51.s123 Published online by Cambridge University Press

### Relationship with duration of untreated psychosis

The duration of untreated psychosis has been regarded as another period when a neurotoxic process may be active (Wyatt, 1995). Some studies have reported that the severity of volumetric abnormalities in schizophrenia varies with its duration (Keshavan *et al*, 1998), but others have not (Hoff *et al*, 2000; Ho *et al*, 2003). We have previously examined the volumetric correlates of duration of untreated psychosis in this same sample, and found that a long duration was associated with more extensive reductions in grey matter volume that were limited to a single region (temporal cortex) distinct from those identified in the present study (Lappin *et al*, 2006). Taken together, these data invoke the question of whether there are dynamic changes occurring across integrated brain networks in a temporal sequence. Thus, changes occurring in the prodromal phase predominate in the frontal regions and white matter, whereas later changes related to the transition from prodrome to psychosis (when the duration of untreated psychosis begins) involve other areas such as the temporal cortex. Studies of longitudinal design with scans at several time points are necessary to investigate this possibility.

### Clinical implications

Conventionally, clinical intervention in psychotic disorders begins after the first episode. However, there is increasing interest in the potential benefits of introducing treatment in the prodromal phase (McGorry *et al*, 2002). Although our findings are consistent with the operation of a progressive process during this period, this requires confirmation through further longitudinal MRI studies of people within the prodrome.

## ACKNOWLEDGEMENTS

We wish to thank the ÆSOP researchers who helped with data collection, and Dr Marco Catani for his help and advice. The ÆSOP study was funded by the Medical Research Council (UK) and the Stanley Medical Research Institute. P.D. is funded by a NARSAD Young Investigator Award.

## REFERENCES

**American Psychiatric Association (1994)** *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM–IV). APA.

**Annett, M. (1970)** A classification of hand preference by association analysis. *British Journal of Psychology*, **61**, 303–321.

**Bullmore, E. T., Suckling, J., Overmeyer, S., *et al* (1999)** Global, voxel, and cluster tests, by theory and permutation, for a difference between two groups of structural MR images of the brain. *IEEE Transactions on Medical Imaging*, **18**, 32–42.

**Catani, M., Howard, R. J., Pajevic, S., *et al* (2002)** Virtual in vivo interactive dissection of white matter fasciculi in the human brain. *NeuroImage*, **17**, 77–94.

**Craig, T. J., Bromet, E. J., Fennig, S., *et al* (2000)** Is there an association between duration of untreated psychosis and 24-month clinical outcome in a first-admission series? *American Journal of Psychiatry*, **157**, 60–66.

**Dazzan, P., Morgan, K. D., Orr, K. G., *et al* (2004)** The structural brain correlates of neurological soft signs in AESOP first-episode psychoses study. *Brain*, **127**, 143–153.

**Drevets, W. C., Price, J. L., Simpson, J. R., Jr., *et al* (1997)** Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*, **386**, 824–827.

**Hafner, H. & Nowotny, B. (1995)** Epidemiology of early-onset schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, **245**, 80–92.

**Haznedar, M. M., Roversi, F., Pallanti, S., *et al* (2005)** Fronto-thalamo-striatal grey and white matter volumes and anisotropy of their connections in bipolar spectrum illnesses. *Biological Psychiatry*, **57**, 733–742.

**Ho, B. C., Alicata, D., Ward, J., *et al* (2003)** Untreated initial psychosis: relation to cognitive deficits and brain morphology in first-episode schizophrenia. *American Journal of Psychiatry*, **160**, 142–148.

**Hoff, A. L., Sakuma, M., Razi, K., *et al* (2000)** Lack of association between duration of untreated illness and severity of cognitive and structural brain deficits at the first episode of schizophrenia. *American Journal of Psychiatry*, **157**, 1824–1828.

**Jablensky A., Sartorius N., Ernberg G., *et al* (1992)** Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychological Medicine Monograph Supplement*, **20**, 1–97.

**Job, D. E., Whalley, H. C., McConnell, S., *et al* (2002)** Structural grey matter differences between first-episode schizophrenics and normal controls using voxel-based morphometry. *NeuroImage*, **17**, 880–889.

**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.

**Keshavan, M. S., Haas, G. L., Kahn, C. E., *et al* (1998)** Superior temporal gyrus and the course of early schizophrenia: progressive, static, or reversible? *Journal of Psychiatric Research*, **32**, 161–167.

**Kubicki, M., Westin, C. F., Maier, S. E., *et al* (2002)** Uncinate fasciculus findings in schizophrenia: a magnetic resonance diffusion tensor imaging study. *American Journal of Psychiatry*, **159**, 813–820.

**Lappin, J. M., Morgan, K., Morgan, C., *et al* (2006)** Grey matter abnormalities associated with duration of untreated psychosis. *Schizophrenia Research*, **83**, 145–153.

**Lim, K. O., Hedehus, M., Moseley, M., *et al* (1999)** Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. *Archives of General Psychiatry*, **56**, 367–374.

**McDonald, C., Bullmore, E. T., Sham, P. C., *et al* (2004)** Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. *Archives of General Psychiatry*, **61**, 974–984.

**McGorry, P. D., Yung, A. R., Phillips, L. J., *et al* (2002)** Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Archives of General Psychiatry*, **59**, 921–928.

**Nelson, H. E. & Willison, J. R. (1991)** *National Adult Reading Test (part II): Test Manual* (2nd edn.). nferNelson.

**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.

**Sigmundsson, T., Suckling, J., Maier, M., *et al* (2001)** Structural abnormalities in frontal, temporal, and limbic regions and interconnecting white matter tracts in schizophrenic patients with prominent negative symptoms. *American Journal of Psychiatry*, **158**, 234–243.

**Suckling, J., Sigmundsson, T., Greenwood, K., *et al* (1999)** A modified fuzzy clustering algorithm for operator independent brain tissue classification of dual echo MR images. *Magnetic Resonance Imaging*, **17**, 1065–1076.

**Wakana, S., Jiang, H., Nagae-Poetscher, L. M., *et al* (2004)** Fiber tract-based atlas of human white matter anatomy. *Radiology*, **230**, 77–87.

**World Health Organization (1994)** *Schedules for Clinical Assessment in Neuropsychiatry (SCAN) – Version 2.0*. WHO.

**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.

**Wyatt, R. J. (1995)** Early intervention for schizophrenia: can the course of the illness be altered? *Biological Psychiatry*, **38**, 1–3.

**Yung, A. R., Phillips, L. J., Yuen, H. P., *et al* (2003)** Psychosis prediction: 12-month follow up of a high-risk (prodromal) group. *Schizophrenia Research*, **60**, 21–32.

JULIA LAPPIN, MBChB, MSc, MRCPsych, PAOLA DAZZAN, MBChB, MSc, MRCPsych, King's College London, Institute of Psychiatry, London; KEVIN MORGAN, PhD, Brain Mapping Unit, University of Cambridge; CRAIG MORGAN, PhD, XAVIER CHITNIS, MSc, King's College London, Institute of Psychiatry, London; JOHN SUCKLING, PhD, Department of Psychiatry, University of Cambridge; PAUL FEARON, MBChB, MSc, MRCPsych, King's College London, Institute of Psychiatry, London; PETER B. JONES, MBChB, PhD, MRCPsych, Department of Psychiatry, University of Cambridge; JULIAN LEFF, MBChB, PhD, FRCPsych, ROBIN M. MURRAY, MBChB, MPhil, FRCPsych, PHILIP K. McGUIRE, MBChB, MD, PhD, MRCPsych, King's College London, Institute of Psychiatry, London, UK

Correspondence: Dr Paola Dazzan, PO Box 63, Division of Psychological Medicine, Institute of Psychiatry, De Crespigny Park, London SE5 8AF. Email: Paola.Dazzan@iop.kcl.ac.uk



https://doi.org/10.1192/bjp.191.51.s123 Published online by Cambridge University Press