Grey matters – Mapping the transition to psychosis

Stefan Borgwardt, Paolo Fusar-Poli, Anita Riecher-Rössler, Philip McGuire

1. INTRODUCTION

Despite a large body of neuroimaging studies in schizophrenia showing multiple subtle brain abnormalities in this disease, we do not know the exact time course of their occurrence. Meta-analytic reviews on studies so far primarily conducted on samples of chronic schizophrenic patients indicate that these patients compared to healthy controls show reduced brain size, enlarged lateral and third ventricles, reduced frontal lobe volume, reduced volumes of temporo-limbic structures and of corpus callosum, and increased volume of basal ganglia (Vita, De Peri, Silenzi, Dieci, 2006).

Neuroimaging studies from first episode schizophrenia subjects find small reductions in brain volumes at initial presentation (Steen, Mull, McClure, Hamer & Lieberman, 2006), and volume loss over time in those patients who have a deteriorating clinical course (Ho, Andreasen, Nopoulos, Arndt, Magnotta & Flaum, 2003). In this situation it seems fundamental for the understanding of the pathogenesis of these brain changes to establish the

timing when they occur, in particular to find out whether they are already present prior to the occurrence of a first psychotic episode. It is also unclear what biological processes underlie the transition from and at-risk mental state to psychosis.

In this paper, we will examine cross-sectional and longitudinal structural neuroimaging studies that aimed to distinguish high-risk subjects who later developed psychosis from those who did not. We have focused on studies using voxel based morphometry (VBM) and thus assessing grey matter volumes by surveying the whole brain (Ashburner & Friston, 2000). We have included two summary tables of cross-sectional (table 1) and longitudinal (table 2) structural neuroimaging studies of subjects with an at-risk mental state (ARMS).

2. GREY MATTER VOLUME ABNORMALITIES IN THE PRODROMAL STAGE OF PSYCHOSIS - FINDINGS FROM CROSS-SECTIONAL STUDIES

Neuroimaging studies clearly indicate that schizophrenia is associated with neuroanatomical abnormalities, with the most replicated findings being ventricular enlargement and reductions in frontal and medial temporal lobe grey matter volume (Shenton, Dickey, Frumin & McCarley, 2001; Wright, Rabe-Hesketh, Woodruff, David, Murray & Bullmore, 2000). However

the extent to which these are related to a vulnerability to schizophrenia, as opposed to the disorder per se, is less certain. Thus qualitatively similar abnormalities are also evident in the first-degree relatives and co-twins of patients with schizophrenia (Baare et al., 2001; Hulshoff Pol et al., 2004; Keshavan et al., 1997; Lawrie et al., 1999; Sharma et al., 1998; Staal, Hulshoff Pol, Schnack, Hoogendoorn, Jellema & Kahn, 2000; Suddath, Christison, Torrey, Casanova & Weinberger, 1990). Twin studies suggest that these structural abnormalities (Baare, et al., 2001; van Haren, et al., 2004), as well as others in dorsolateral prefrontal, and superior temporal cortex, the hippocampus and white matter are at least partially genetically determined (Borgwardt, Picchioni, Ettinger, Toulopoulou, Murray, McGuire, 2010; Cannon et al., 2002; Hulshoff Pol et al., 2004).

It is not clear as yet at what stage of the disorder these brain abnormalities occur. Neurodevelopmental models of schizophrenia propose that brain abnormalities are present before the onset of psychosis, but there is also evidence that at least some of MRI abnormalities progress over the course of the disorder (Pantelis et al., 2005). MRI studies of non-psychotic subjects who are at high risk of psychosis indicate that regional volumetric abnormalities comparable to those seen in schizophrenia are evident in those who are vulnerable to psychosis.

Using a prospective design, the Edinburgh High Risk study identified reductions in the grey matter volume bilaterally in the anterior cingulate and in the left parahippocampal gyrus in the relatives of patients with schizophrenia (Job, Whalley, McConnell, Glabus, Johnstone & Lawrie, 2003). From the same group, Lawrie et al. found that the relatives of patients with schizophrenia had reduced left medial temporal volume, decreased global white and grey matter volumes were found in the non-psychotic co-twins of patients with schizophrenia (Lawrie et al., 1999). In the same group of subjects with a high genetic risk of developing schizophrenia, Job et al. reported no significant differences between high-risk subjects with or without later transition (Lawrie, McIntosh, Hall, Owens & Johnstone, 2008).

Relatively little is known about the nature of the abnormalities in the 'at-risk mental state' (for summary, see table 1). Using a region of interest approach, (Phillips et al., 2002) reported that hippocampal volume in ARMS individuals was smaller than that in controls but not than in patients with first episode psychosis. However, the prodromal group, those who later developed psychosis had a larger left hippocampal volume than those who did not. More recently, using a voxel-based approach in subjects from the same centre in Melbourne, (Pantelis et al., 2003) found that subjects with 'prodromal' symptoms who later became psychotic had smaller inferior frontal and cingulate gyrus volumes than than those who

did not. In another longitudinal study, using a region of interest approach, (Velakoulis et al., 2006) reported that patients at high risk of psychosis had normal baseline hippocampal and amygdala grey matter volumes whether or not they subsequently developed psychosis.

In a cross-sectional study from Basel, MRI data from an ARMS sample (n=35) (independent of subsequent clinical outcome) were compared with healthy controls and first-episode patients. Compared with healthy controls, both first-episode patients and ARMS subjects showed significantly less gray matter volume in the posterior part of the left superior temporal gyrus and the adjacent part of the left insula, and in a second region involving the posterior cingulate gyrus and precuneus (Borgwardt et al., 2008; Borgwardt et al., 2007b). However, the ARMS group was heterogenous including both, patients who later developed psychosis and those who did not. Within the ARMS group, those subjects who developed psychosis (ARMS-T; n=12) had less grey matter than subjects who did not (ARMS-NT; n=23) in the right insula, inferior frontal and superior frontal gyrus (Borgwardt et al., 2007b). These volumetric differences within the ARMS group were associated with the subsequent development of psychosis and could be related to a process which underlies a progression from a high risk state towards a psychotic illness.

The subgroup of these ARMS subjects who subsequently became psychotic were found to have regional gray matter reductions relative to healthy controls in the posterior cingulate gyrus, precuneus, and paracentral lobule bilaterally which extended into the left superior parietal lobule before transition to psychosis (Borgwardt et al., 2007a), but more gray matter volume in some areas of the left parietal/posterior temporal region. This was consistent with previous reports of relatively increased hippocampal volume (Phillips et al., 2002) in subjects with an ARMS who later develop psychosis. We discussed that these differences might be related to an active pathological process that underlies the transition to psychosis. These results suggested that the at-risk mental state was associated with reductions in grey matter volume in areas that are also reduced in schizophrenia, suggesting that these abnormalities do not only occur with transition to psychosis, but are a correlate of an increased vulnerability to psychosis.

3. GREY MATTER CHANGES DURING THE TRANSITION TO PSYCHOSIS – FINDINGS FROM LONGITUDINAL STUDIES

Relatively little is known about the nature of the brain abnormalities in this high-risk group close to the actual process of transition to psychosis (Wood, Pantelis, Velakoulis, Yucel, Fornito & McGorry, 2008) (for summary table 2). The transition from prodromal phase into frank

psychosis (Job, Whalley, Johnstone & Lawrie, 2005; Pantelis et al., 2003) and the first two years of the first-episode (Farrow, Whitford, Williams, Gomes & Harris, 2005) has been associated with frontal and temporal decreases in gray matter. Using a similar voxel-based approach in subjects with an ARMS, (Pantelis et al., 2003)found that subjects with 'prodromal' symptoms who developed psychosis showed a longitudinal reduction in gray matter volume in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyri. In this first longitudinal MRI study in ARMS, it was found that the subset who developed psychosis showed a longitudinal reduction in gray matter volume in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyri. In another longitudinal study with largely the same subjects (Sun et al., 2008), greater brain contraction was found in the right prefrontal region in people with transition to psychosis compared with ARMS subjects who did not develop psychosis. Another voxel-based morphometry study in patients at genetic risk of psychosis reported that the onset of psychosis in these individuals was associated with reduced gray matter in the temporal lobes, the right frontal lobe and right parietal lobe (Job, Whalley, Johnstone & Lawrie, 2005). These findings are consistent with prospective studies in patients with established schizophrenia, which indicate that longitudinal reductions in regional gray matter volume also occur in chronic patients (Cahn et al., 2002; Ho et al.,

2003; Kasai et al., 2003; Kubicki et al., 2002; Mathalon, Sullivan, Lim & Pfefferbaum, 2001; Sporn et al., 2003).

In another longitudinal MRI study (Borgwardt et al., 2008b), ARMS subjects were scanned when they first presented with 'prodromal' symptoms and were then followed clinically for 3 years. Those who developed psychosis during this period were scanned again after its onset. The other subjects were scanned at the end of the 3-year follow up period. On the basis of previous longitudinal MRI studies of the ARMS and of other groups at high risk of psychosis (i.e. genetic risk), we tested the hypothesis that transition to psychosis would be associated with longitudinal reductions in gray matter volume in the frontal, cingulate and temporal cortex. In this longitudinal voxel-based morphometry study regional gray matter volumes were analysed in 10 subjects with an ARMS before and after transition to psychosis (converters) and in 10 comparable control ARMS subjects without transition to psychosis (non-converters). The main findings of this study were a decrease of cortical volumes in converters in the orbitofrontal cortex that included the right orbital and left rectal gyrus as well as in the right inferior temporal, superior frontal, and superior parietal lobule, the left precuneus, and the right hemisphere of the cerebellum. These findings suggest that at least some of the cortical gray matter abnormalities known in schizophrenia patients occur during the acute process of transition to psychosis.

A recent meta-analysis (Smieskova et al., 2010) of structural MRI studies of individuals at high-risk of psychosis showed small to medium effect sizes of decreased prefrontal, cingulate, insular and cerebellar gray matter volume in subjects with later transition to psychosis (HR-T) compared to those without transition (HR-NT). This meta-analysis also revealed relatively larger whole brain volumes in HR-T compared to HR-NT subjects (mean Cohen's d 0.36, 95% CI 0.27 – 0. 46). Despite methodological differences between studies, structural abnormalities in prefrontal, anterior cingulate, medial temporal and cerebellar cortex might be predictive for development of psychosis within HR subjects.

Overall, the few longitudinal studies of grey matter volume changes in subjects with an ARMS confirm previous reports on emerging psychosis and suggests that there may be subtle alterations in brain structure associated with vulnerability to psychosis, but other brain structural changes found in schizophrenia may emerge as psychosis develops.

4. CONCLUSIONS

People with an at-risk mental state show qualitatively similar volumetric abnormalities to patients with schizophrenia, although they are generally less severe. There is also evidence that some of these MRI abnormalities are specifically linked to the later onset of psychosis, as opposed to an increased vulnerability to psychosis. However, the studies which produced

these findings involved relatively small samples, and larger studies are needed to clarify which abnormalities are illness-specific.

Table 1. Grey matter volumes in the At Risk Mental State (ARMS) – Findings from cross-sectional studies

	N	MRI method	MRI findings	
			ARMS vs. controls	Converters vs. non-converters
(Phillips et al 2002)	60 ARMS (20 ARMS-T vs. 40 ARMS-NT); 139 controls	Region of Interest (ROI) analysis of hippocampal and whole brain volume	Smaller left and right hippocampi in ARMS compared to controls	Larger left hippocampus in converters compared to non-converters
(Pantelis et al 2003)	75 ARMS (23 ARMS-T vs. 52 ARMS-NT)	Voxel-based morphometry (VBM) analysis	-[No control group]	Converters had smaller grey matter volume in the right medial temporal, lateral temporal.

				And inferior frontal cortex, and in the cingulate bilaterally
(Garner et al 2005)	31 ARMS-T vs. 63 ARMS-NT	ROI analysis of pituitary volume	-[No control group]	Converters had a significantly larger (12%) pituitary volume.
(Velakoulis et al 2006)	135 ARMS (39 ARMS-T vs. 96 ARMS-NT); 87 controls	ROI analysis of hippocampal, amygdala, whole brain and intracranial volumes	No differences.	No differences.
(Borgwardt et al	35 ARMS (23 ARMS-T, 12 ARMS-NT), 25	Voxel-based morphometry (VBM) analysis	Reduced GM volume in the posterior	Subjects who later developed

2007a, b)	FE, 22 controls		cingulate gyrus and precuneus	psychosis had less grey matter than subjects who did not in the right insula, inferior frontal and superior temporal gyrus

Note: ARMS-T = subjects with an ARMS who made transition to psychosis, ARMS-NT = subjects with an ARMS who did not made transition to psychosis, FE = patients with first-episode psychosis, ROI = Region of Interest, VBM = Voxel-based morphometry

Table 2. Grey matter volumes in the At Risk Mental State (ARMS) – Findings from longitudinal studies

Center	Study group	Follow up period	MRI method	MRI findings Progressive changes
Edinburgh High Risk Study[4]	Lawrie et al. 2002 19 genetic high risk subjects with subthreshold psychotic symptoms (12 at first scan)	2 years	ROI[1] analyses	Reductions in temporal lobes (relative change: 2.3-2.5 %), caudate (0.7-1.1 %), and prefrontal cortex (0.3-0.4 %) bilaterally
	Job et al. 2005 a) 18 genetic high risk subjects with subthreshold psychotic symptoms b) 8 genetic high risk subjects who have developed schizophrenia	2 years	VBM analysis of GM[3] density	a) Reductions in the right cerebellum and amygdala as well as in the, left fusiform gyrus, uncus, superior and inferior temporal gyrus, and in the

				parahippocampal gyrus bilaterally. b) Reductions in the left inferior temporal gyrus, left uncus and the right cerebellum
Ultrahigh-Risk (UHR) Studies from Melbourne[4]	Pantelis et al. 2003 a) 10 ARMS converters b) 11 ARMS non-converters	1 year	VBM[2] analysis of GM[3] volume	a) Converters had gray matter volume reductions in the left parahippocampal, fusiform, orbitofrontal and cerebellar cortices, and the cingulate gyri. b) In non-converters, GM reductions were restricted to the cerebellum

	Sun et al. 2008 12 ARMS converters vs. 23 ARMS non-converters	1 year	Cortical surface motion analysis	Compared to non-converters, converters had greater brain surface contraction in the right prefrontal region, and with a non-significant trend in the left prefrontal region and bilateral occipital poles
Basel FEPSY study	Borgwardt et al 2008 20 ARMS: 10 converters and 10 non-converters	3-4 years	VBM[2] analysis of GM[3] volume	In subjects who developed psychosis there were longitudinal volume reductions in the orbitofrontal, superior frontal, inferior temporal, medial and superior parietal cortex, and in the cerebellum.

				There were no longitudinal changes in subjects who did not develop psychosis

[1] ROI = Region-of-Interest

[2] VBM = Voxel-based morphometry

[3] GM = Gray matter

[4] Samples from the same center are largely overlapping.

REFERENCES

Ashburner, J. & Friston, K. J. (2000) Voxel-based morphometry--the methods. *Neuroimage*, 11, 805-821.

Baare, W. F., van Oel, C. J., Hulshoff Pol, H. E., Schnack, H. G., Durston, S., Sitskoorn, M. M. & Kahn, R. S. (2001) Volumes of brain structures in twins discordant for schizophrenia. *Arch Gen Psychiatry*, 58, 33-40.

Borgwardt, S. J., McGuire, P. K., Aston, J., Berger, G., Dazzan, P., Gschwandtner, U., Pfluger, M., D'Souza, M., Radue, E. W. & Riecher-Rossler, A. (2007a) Structural brain abnormalities in individuals with an at-risk mental state who later develop psychosis. *Br J Psychiatry Suppl*, 51, s69-75.

Borgwardt, S. J., McGuire, P. K., Aston, J., Gschwandtner, U., Pfluger, M. O., Stieglitz, R. D., Radue, E. W. & Riecher-Rossler, A. (2008b) Reductions in frontal, temporal and parietal volume associated with the onset of psychosis. *Schizophr Res*. 106(2-3):108-14.

Borgwardt, S.J., Picchioni, M.M., Ettinger, U., Toulopoulou, T., Murray, R., McGuire, P.K. (2010) Regional gray matter volume in

monozygotic twins concordant and discordant for schizophrenia. Biol Psychiatry 67(10):956-64.

Borgwardt, S. J., Riecher-Rossler, A., Dazzan, P., Chitnis, X., Aston, J., Drewe, M., Gschwandtner, U., Haller, S., Pfluger, M., Rechsteiner, E., D'Souza, M., Stieglitz, R. D., Radu, E. W. & McGuire, P. K. (2007b) Regional gray matter volume abnormalities in the at risk mental state. *Biol Psychiatry*, 61, 1148-1156.

Cahn, W., Hulshoff Pol, H. E., Lems, E. B., van Haren, N. E., Schnack, H. G., van der Linden, J. A., Schothorst, P. F., van Engeland, H. & Kahn, R. S. (2002) Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. *Arch Gen Psychiatry*, 59, 1002-1010.

Cannon, T. D., Thompson, P. M., van Erp, T. G., Toga, A. W., Poutanen, V. P., Huttunen, M., Lonnqvist, J., Standerskjold-Nordenstam, C. G., Narr, K. L., Khaledy, M., Zoumalan, C. I., Dail, R. & Kaprio, J. (2002) Cortex mapping reveals regionally specific patterns of genetic and disease-specific gray-matter deficits in twins discordant for schizophrenia. *Proc Natl Acad Sci U S A*, 99, 3228-3233.

Farrow, T. F., Whitford, T. J., Williams, L. M., Gomes, L. & Harris, A. W. (2005) Diagnosis-related regional gray matter loss over two years in first episode schizophrenia and bipolar disorder. *Biol Psychiatry*, 58, 713-723.

Ho, B. C., Andreasen, N. C., Nopoulos, P., Arndt, S., Magnotta, V. & Flaum, M. (2003) Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Arch Gen Psychiatry*, 60, 585-594.

Hulshoff Pol, H. E., Brans, R. G., van Haren, N. E., Schnack, H. G., Langen, M., Baare, W. F., van Oel, C. J. & Kahn, R. S. (2004) Gray and white matter volume abnormalities in monozygotic and same-gender dizygotic twins discordant for schizophrenia. *Biol Psychiatry*, 55, 126-130.

Job, D. E., Whalley, H. C., Johnstone, E. C. & Lawrie, S. M. (2005) Grey matter changes over time in high risk subjects developing schizophrenia. *Neuroimage*, 25, 1023-1030.

Job, D. E., Whalley, H. C., McConnell, S., Glabus, M., Johnstone, E. C. & Lawrie, S. M. (2003) Voxel-based morphometry of grey matter

densities in subjects at high risk of schizophrenia. *Schizophr Res*, 64, 1-13.

Kasai, K., Shenton, M. E., Salisbury, D. F., Hirayasu, Y., Lee, C. U., Ciszewski, A. A., Yurgelun-Todd, D., Kikinis, R., Jolesz, F. A. & McCarley, R. W. (2003) Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. *Am J Psychiatry*, 160, 156-164.

Keshavan, M. S., Montrose, D. M., Pierri, J. N., Dick, E. L., Rosenberg, D., Talagala, L. & Sweeney, J. A. (1997) Magnetic resonance imaging and spectroscopy in offspring at risk for schizophrenia: preliminary studies. *Prog Neuropsychopharmacol Biol Psychiatry*, 21, 1285-1295.

Kubicki, M., Shenton, M. E., Salisbury, D. F., Hirayasu, Y., Kasai, K., Kikinis, R., Jolesz, F. A. & McCarley, R. W. (2002) Voxel-based morphometric analysis of gray matter in first episode schizophrenia. *Neuroimage*, 17, 1711-1719.

Lawrie, S. M., McIntosh, A. M., Hall, J., Owens, D. G. & Johnstone, E. C. (2008) Brain structure and function changes during the

development of schizophrenia: the evidence from studies of subjects at increased genetic risk. *Schizophr Bull*, 34, 330-340.

Lawrie, S. M., Whalley, H., Kestelman, J. N., Abukmeil, S. S., Byrne, M., Hodges, A., Rimmington, J. E., Best, J. J., Owens, D. G. & Johnstone, E. C. (1999) Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. *Lancet*, 353, 30-33.

Mathalon, D. H., Sullivan, E. V., Lim, K. O. & Pfefferbaum, A. (2001) Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry*, 58, 148-157.

Pantelis, C., Velakoulis, D., McGorry, P. D., Wood, S. J., Suckling, J., Phillips, L. J., Yung, A. R., Bullmore, E. T., Brewer, W., Soulsby, B., Desmond, P. & McGuire, P. K. (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., Velakoulis, D., Sun, D., Berger, G., Stuart, G. W., Yung, A., Phillips, L. & McGorry, P. D. (2005) Structural brain imaging evidence for multiple pathological

processes at different stages of brain development in schizophrenia. *Schizophr Bull*, 31, 672-696.

Phillips, L. J., Velakoulis, D., Pantelis, C., Wood, S., Yuen, H. P., Yung, A. R., Desmond, P., Brewer, W. & McGorry, P. D. (2002) Non-reduction in hippocampal volume is associated with higher risk of psychosis. *Schizophr Res*, 58, 145-158.

Sharma, T., Lancaster, E., Lee, D., Lewis, S., Sigmundsson, T., Takei, N., Gurling, H., Barta, P., Pearlson, G. & Murray, R. (1998) Brain changes in schizophrenia. Volumetric MRI study of families multiply affected with schizophrenia--the Maudsley Family Study 5. *Br J Psychiatry*, 173, 132-138.

Shenton, M. E., Dickey, C. C., Frumin, M. & McCarley, R. W. (2001) A review of MRI findings in schizophrenia. *Schizophr Res*, 49, 1-52.

Smieskova, R., Fusar-Poli, P., Allen, P., Bendfeldt, K., Stieglitz, R. D., Drewe, J., Radue, E. W., McGuire, P. K., Riecher-Rossler, A. & Borgwardt, S. J. (2010) Neuroimaging predictors of transition to psychosis--a systematic review and meta-analysis. *Neurosci Biobehav Rev*, 34, 1207-1222.

Sporn, A. L., Greenstein, D. K., Gogtay, N., Jeffries, N. O., Lenane, M., Gochman, P., Clasen, L. S., Blumenthal, J., Giedd, J. N. & Rapoport, J. L. (2003) Progressive brain volume loss during adolescence in childhood-onset schizophrenia. *Am J Psychiatry*, 160, 2181-2189.

Staal, W. G., Hulshoff Pol, H. E., Schnack, H. G., Hoogendoorn, M. L., Jellema, K. & Kahn, R. S. (2000) Structural brain abnormalities in patients with schizophrenia and their healthy siblings. *Am J Psychiatry*, 157, 416-421.

Steen, R.G., Mull, C., McClure, R., Hamer, R.M., & Lieberman, J.A. (2006) Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry 188:510-8.

Suddath, R. L., Christison, G. W., Torrey, E. F., Casanova, M. F. & Weinberger, D. R. (1990) Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *N Engl J Med*, 322, 789-794.

Sun, D., Phillips, L., Velakoulis, D., Yung, A., McGorry, P. D., Wood, S. J., van Erp, T. G., Thompson, P. M., Toga, A. W., Cannon, T. D. & Pantelis, C. (2008) Progressive brain structural changes mapped as psychosis develops in 'at risk' individuals. *Schizophr Res*. 108(1-3):85-92.

van Haren, N. E., Picchioni, M. M., McDonald, C., Marshall, N., Davis, N., Ribchester, T., Hulshoff Pol, H. E., Sharma, T., Sham, P., Kahn, R. S. & Murray, R. (2004) A controlled study of brain structure in monozygotic twins concordant and discordant for schizophrenia. *Biol Psychiatry*, 56, 454-461.

Velakoulis, D., Wood, S. J., Wong, M. T., McGorry, P. D., Yung, A., Phillips, L., Smith, D., Brewer, W., Proffitt, T., Desmond, P. & Pantelis, C. (2006) Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. *Arch Gen Psychiatry*, 63, 139-149.

Vita, A., De Peri, L., Silenzi, C., & Dieci, M. (2006) Brain morphology in first-episode schizophrenia: a meta-analysis of quantitative magnetic resonance imaging studies. *Schizophr Res.* 82(1):75-88.

Wood, S. J., Pantelis, C., Velakoulis, D., Yucel, M., Fornito, A. & McGorry, P. D. (2008) Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. *Schizophr Bull*, 34, 322-329.

Wright, I. C., Rabe-Hesketh, S., Woodruff, P. W., David, A. S., Murray, R. M. & Bullmore, E. T. (2000) Meta-analysis of regional brain volumes in schizophrenia. *Am J Psychiatry*, 157, 16-25.