European Neuropsychopharmacology (2009) **19**, 835–840

www.elsevier.com/locate/euroneuro

Brain structural changes associated with chronicity and antipsychotic treatment in schizophrenia

Luisa Tomelleri[a,b,c], Jigar Jogia[c], Cinzia Perlini[a,b], Marcella Bellani[a,b], Adele Ferro[a,b], Gianluca Rambaldelli[a,b], Michele Tansella[a,b], Sophia Frangou[c], Paolo Brambilla[b,d,*]

The Neuroimaging Network of the ECNP networks initiative

[a] *Section of Psychiatry and Clinical Psychology, Department of Medicine and Public Health, University of Verona, Italy*
[b] *Inter-University Center for Behavioural Neurosciences (ICBN), University of Verona and DPMSC, Section of Psychiatry, University of Udine, Italy*
[c] *Section of Neurobiology of Psychosis, Institute of Psychiatry, King's College London, London, UK*
[d] *Scientific Institute 'E. Medea', Udine, Italy*

Received 24 June 2009; accepted 22 July 2009

KEYWORDS
MRI;
Imaging;
Frontal lobes;
Temporal lobes

Abstract

Accumulating evidence suggest a life-long impact of disease related mechanisms on brain structure in schizophrenia which may be modified by antipsychotic treatment. The aim of the present study was to investigate in a large sample of patients with schizophrenia the effect of illness duration and antipsychotic treatment on brain structure. Seventy-one schizophrenic patients and 79 age and gender matched healthy participants underwent brain magnetic resonance imaging (MRI). All images were processed with voxel based morphometry, using SPM5. Compared to healthy participants, patients showed decrements in gray matter volume in the left medial and left inferior frontal gyrus. In addition, duration of illness was negatively associated with gray matter volume in prefrontal regions bilaterally, in the temporal pole on the left and the caudal superior temporal gyrus on the right. Cumulative exposure to antipsychotics correlated positively with gray matter volumes in the cingulate gyrus for typical agents and in the thalamus for atypical drugs. These findings (a) indicate that structural abnormalities in prefrontal and temporal cortices in schizophrenia are progressive and, (b) suggest that antipsychotic medication has a significant impact on brain morphology.

1. Background

It is now generally recognized that schizophrenia is associated with brain structural abnormalities. However, at the present time, the effects of illness duration as well as medication on these morphological changes are still under

* Corresponding author. Dipartimento di Patologia e Medicina Clinica e Sperimentale, Cattedra di Psichiatria, Policlinico Universitario, Via Colugna 50, 33100 Udine, Italy. Tel.: +39 0432 55 9494; fax: +39 0432 54 5526.
E-mail address: paolo.brambilla@uniud.it (P. Brambilla).

0924-977X/$ - see front matter © 2009 Elsevier B.V. and ECNP. All rights reserved.
doi:10.1016/j.euroneuro.2009.07.007

debate. Longitudinal neuroimaging studies have reported reduction in gray matter volume, particularly within the frontal lobes, in patients with chronic (Gur et al., 1998a; van Haren et al., 2007) and first-episode schizophrenia (Gur et al., 1998a; Lieberman et al., 2005; Hulshoff Pol and Kahn, 2008) over periods of 1–5 years. In addition, studies based on cross-sectional brain imaging data that examined patients with longer periods of illness (up to 40 years), have also found a negative correlation between chronicity and cortical volumes, particularly in the prefrontal cortex (Molina et al., 2004; Premkumar et al., 2006).

Emerging data suggest that antipsychotic medication may interact with disease mechanisms to delay, prevent or reverse the cortical volume loss (Lieberman et al., 2005; Dazzan et al., 2005; McCormick et al., 2005; Kopelman et al., 2005; Scherk and Falkai, 2006, Adams and Jayaram, 2007). This effect is thought to be more pronounced with atypical agents, which appear to preserve cortical gray matter volumes (Lieberman et al., 2005; van Haren et al., 2007), and not with typical antipsychotics (Scherk and Falkai, 2006). In order to disentangle the contribution of duration of illness and antipsychotic exposure we obtained structural Magnetic Resonance Imaging (MRI) data from a sample of 71 patients with schizophrenia recruited from the geographically defined catchment area of South Verona. Patients had variable illness duration and antipsychotic exposure. A group of 79 healthy volunteers were also included as comparison subjects. Our initial prediction was that (a) after controlling for antipsychotic exposure, illness duration will show an inverse correlation with frontal and temporal gray matter and (b) after controlling for illness duration, cumulative exposure to atypical antipsychotics would show a positive correlation with gray matter volume in the same regions.

2. Methods

2.1. Subjects

2.1.1. Patients

Seventy-one patients fulfilling Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association, 1994) for schizophrenia were recruited from the South Verona Psychiatric Case Register (Amaddeo et al., 1997; Tansella and Burti, 2003). The register includes information about patients residing in the epidemiologically defined catchment area of South Verona (with a population of approximately 100,000 inhabitants) and treated by the South Verona Community-based Mental Health Service (CMHS) and related clinics.

2.1.2. Healthy individuals

Seventy-nine individuals without any personal lifetime history of DMS-IV Axis I disorders were also recruited from the same catchment area. Exclusion criteria for all participants were (a) alcohol or substance abuse, within the preceding 6 months, as defined by the DSM-IV (b) any current major medical or neurological illness, (c) history of traumatic head injury with loss of consciousness, (d) DSM-IV axis I comorbidity. Additional exclusion criteria for comparison subjects were (a) any self-reported history of psychiatric disorders in first-degree relatives and (b) any prescribed medication.

2.2. Clinical assessment

Diagnostic evaluation was based on the Item Group Checklist of the Schedule for Clinical Assessment in Neuropsychiatry (IGC-SCAN) (World Health Organization, 1992). These assessments were conducted blind to diagnosis by trained clinical psychologists with extensive experience in using the SCAN. The Italian version of the SCAN was edited by our group (World Health Organization, 1996) and our investigators attended specific courses held by official trainers on how to administer this scale. The inter- and intra-rater reliability of the IGC-SCAN assessments was monitored by regular quality control meetings. Diagnostic validity was further confirmed by clinical consensus of two qualified psychiatrists.

Patients' psychopathology was rated with the Brief Psychiatric Rating Scale (BPRS 24-item version) (Ventura et al., 2000). Information about age of onset, duration of illness, and number of hospital admissions was obtained during interview and from medical records. Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). Duration of illness was calculated as the age of the patient minus the age of onset of the disorder. Age of onset was defined as the first time the patient had contact with psychiatric services for psychosis. Interview and case history reviews were conducted at the time of MRI acquisition, which included information on type, dose and lifetime exposure to antipsychotic medication. Four patients reported lifetime substance or alcohol abuse but none in the 6 months preceding their MRI examination.

Patients were divided into three groups based on their treatment at the time of the MRI scan, the unmedicated group, the group on atypical and the group on typical antipsychotics. Patients taking both typical and atypical agents were included in the typical group.

The study was approved by the Ethics Committee of the Azienda Ospedaliera of Verona. All participants provided signed informed consent, after having understood the nature and purpose of the study.

2.3. Neuroimaging image acquisition

MRI scans were acquired using a 1.5 T Siemens Magnetom Symphony Maestro Class, Syngo MR 2002B. All participants were provided with earplugs to reduce acoustic noise and their head was comfortably placed in a head holder and held stable in order to minimize movement artefact. Initially, exploratory T1-weighted images (TR = 450 ms, TE = 14 ms, flip angle = 90°, FOV = 230 × 230, slice thickness = 5 mm, matrix size = 384 × 512) were obtained to verify the subject's head position and the quality of the image. A sequence of DP/T2-weighted images were then obtained. (TR = 2500 ms, TE = 24/121 ms, flip angle = 180°, FOV = 230 × 230, slice thickness = 5 mm, matrix size = 410 × 512) according to an axial plane parallel to the anterior–posterior commissures (AC–PC), in order to exclude focal lesions. Subsequently, a coronal 3D MPR sequence was acquired (TR = 2060 ms, TE = 3.9 ms, flip angle = 15°, FOV = 176 × 235, slice thickness = 1.25 mm, matrix size = 270 × 512, TI = 1100) to obtain 144 images covering the entire brain.

2.4. Image analysis

Each subject's MRI dataset was normalised and segmented into gray matter (GM), white matter (WM) and cerebrovascular fluid (CSF) using unified segmentation (Ashburner and Friston, 2005) in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Segmented images were modulated so that the intensity of each voxel represented a volume measure. Images were then smoothed using a Gaussian kernel of 12 mm full width half maximum and global tissue volumes were calculated by summing voxel values over each segmented image. Fractional tissue measures were then calculated by dividing gray, white matter and CSF volumes by the Total Intracranial Volume (TIV).

Smoothed gray matter segmented images were analysed using voxel based morphometry in SPM5. An analysis of covariance with TIV as a covariate and gender as additional factor was used to examine the effect of diagnosis (patients vs healthy participants) with a threshold of $p < 0.05$ family wise error (FWE). The relationship

of cumulative exposure to typical or atypical medication, BPRS scores and duration of illness with brain structure was examined using multiple regressions at voxel level; contrasts were constructed to examine correlations with increasing and decreasing gray matter volume with medication exposure, BPRS score and duration of illness. Gender and TIV were included as nuisance variables. Statistical parametric maps were produced for $p<0.05$ FEW. Coordinates from significant voxels were converted from Montreal Neurological Institute (MNI) space to Talairach and Tournoux coordinates (Talairach and Tournoux, 1988) as described by Brett (1999).

2.5. Statistical analysis of demographic and clinical data

We used *t*-tests and chi-square analyses as appropriate implemented in SPSS for Windows software, version 13 (SPSS Inc., Chicago) to compare demographic details between patients with schizophrenia and comparison subjects, and the 2-tailed statistical significance level was set at $p<0.05$.

3. Results

Demographic and clinical details of the 70 patients and 79 healthy individuals are shown in Table 1. Data from one patient were not analysed, because of significant movement artefacts, noted on visual inspection. There were no significant differences between patients only exposed to atypicals compared to those on primarily prescribed typical antipsychotics on age of onset, number of hospital admissions and BPRS score (all $p>0.52$). Patients who had been prescribed mostly typical antipsychotics had marginally longer illness duration (16.70 years ± 11.48) compared to those on mostly on atypical (11.96 years ± 9.6) but this did not reach significance ($p=0.08$).

3.1. Effect of diagnosis

There were significant decrements in gray matter volume in the left middle and inferior frontal gyri (BA 8, *x y z* = −34 38 44, cluster size = 108, *z* score = 5.57 BA 47, *x y z* = −44 13 −4, cluster size = 85, *z* score = 5.00) in patients with schizophrenia compared to normal controls (Fig. 1). Correlations with BPRS scores did not yield any suprathresold clusters.

3.2. Effect of illness duration

We found negative correlations between duration of illness and gray matter volume, mostly in prefrontal and temporal regions.

Table 1 Demographic and clinical characteristics of the sample.

	Schizophrenia patients (*N*=70)	Healthy participants (*N*=79)	Statistics	*p*
Age in years	39.73 ± 10.94	40.29 ± 11.91	$t=0.29$, $df=140$	0.76
Gender (female: male)	25 :45	38: 41	$\chi^2=2.33$, $df=1$	0.13
Handedness (RH: LH)	67:3	76:3		
Age of onset in years (range)	26.25 ± 9.24 (15–58)			
Duration of illness in years mean ± S.D. (range)	14.13 ± 10.731 (0.2–43)			
Number of hospital admissions mean ± S.D. (range)	(*N*=69) 4.33 ± 8.19 (0–50)			
BPRS total score mean ± S.D. (range)	43.85 ± 16.36 (24–100.17)			
Positive symptoms	11.03 ± 5.8			
Negative symptoms	11.55 ± 4.25			
TIV mean ± S.D	1.49 ± 0.19	1.47 ± 0.16	$t=-0.82$, $df=147$	0.41
Medication use [a]				
No. of subjects on antipsychotics (%)	68 (97.1)			
No. of subjects on atypical antipsychotic (%)	45 (64.2)			
– Olanzapine	25(36.7)			
– Clozapine	9(13.2)			
– Risperidone	9(13.2)			
– Quetiapine	2(2.9)			
No. of subjects on typical antipsychotic (%)	25 (35.7)			
– Haloperidol	16 (23.5)			
– Chlorpromazine	3(4.4)			
– Fluphenazine	2(2.9)			
– Clotiapine	2(2.9)			
– Zuclopenthixol	1(1.4)			
– Thioridazine	1(1.4)			
No. of unmedicated subjects (%)	2 (1.4%)			
CPZ equivalents				
Atypicals mean ± S.D	193.6 ± 92.7		$t=0.372$,	0.71
Typicals mean ± S.D	206.2 ± 186.4		$df=66$	

N = number of subjects, S.D. = standard deviation, GAF = DSM-IV Axis V: Global Assessment of functioning scale, BPRS = Brief Psychiatric Rating Scale, CPZ = chlorpromazine, TIV = total intracranial volume, RH = right hand, LH = left hand.

[a] This refers to the medication patients were prescribed on the day of their MRI scan and not to their cumulative lifetime exposure.

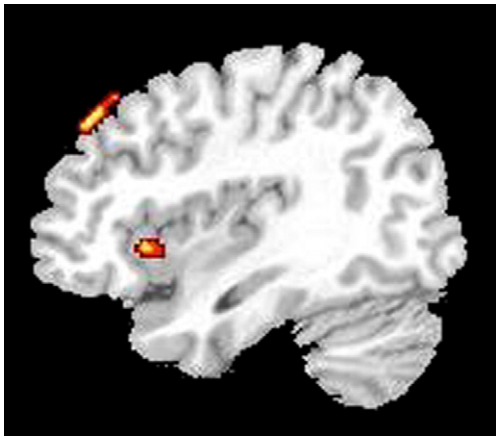

Figure 1 Decrements in gray matter volume in patients compared to normal controls.

Specifically, these association were found with (a) a ventrolateral prefrontal region on the right side (BA 47, *x y z*=57 31 −5, cluster size=106, *z* score=5.14), (b) a large frontopolar cluster bilaterally (BA 10/11, *x y z*=2 61 −13, cluster size=1329, *z* score=5.07; *x y z*=−16 69 13, cluster size=1329, *z* score=5.07; *x y z*=−16,67 −13, cluster size 1329, *z* score=4.85; *x y z*=14 65 23, cluster size=65 *z* score=5.07), (c) an extensive left temporal region (BA 38, *x y z*=−20 10 −26, cluster size=1039, *z* score=4.95; and BA22, *x y z*=−63 −2 6, cluster size=1039, *z* score=4.86) expanding caudally to the postcentral gyrus (BA 43, *x y z*=−69 −19 16, cluster size=1039, *z* score=4.88), (d) a right temporal region (BA 22, *x y z*=48 12 −2, cluster size=474, *z* score=4.86; and BA 20, *x y z*=61 −44 −18, cluster size=507, *z* score=4.71). Additional negative correlations were found within the cerebellum bilaterally (*x y z*=−22 −89 −29, cluster size=211, *z* score=5.08; *x y z*=53 −54 −23, cluster size=507, *z* score=4.96) and the superior parietal cortex on the left side (BA 7, *x y z*=−16 −73 52, cluster level=63, *z* score=4.86) (Fig. 2).

3.3. Effect of cumulative antipsychotic exposure

No significant correlations with antipsychotic exposure were noted at the predefined threshold of $p<0.05$ FWE. Using a height threshold of $p<0.01$ (uncorrected) and a minimum cluster size of 50 voxels, positive correlations between gray matter volume and cumulative exposure to antipsychotics were found (a) in the posterior cingulate gyrus bilaterally (BA29, right: *x y z*=6 −36 17, *z* score=2.88; left *x y z*=−4 −36 17, *z* score=2.81; total cluster size 149) and in the left anterior cingulate (BA24, *x y z*=−4,2,26, *z* score=2.82, cluster size 78) for typical agents and (b) in the right thalamus for atypical antipsychotics (ventral posterior lateral nucleus, *x y z*=18 −17 5, *z* score=2.91, cluster size 56) (Fig. 3).

4. Discussion

This study found decrements in grey matter volume in the left prefrontal cortex in patients suffering from schizophrenia compared to healthy participants, consistent with previous reports (Honea et al., 2005). Moreover, we found widespread negative correlations between duration of illness and gray matter volume in prefrontal, temporal and parietal cortical regions as well as in the cerebellum. In contrast, cumulative exposure to antipsychotics correlated positively with gray matter volumes in the cingulate gyrus for typical antipsychotics and in the thalamus for atypical agents.

Previous cross-sectional MRI studies in schizophrenia have also reported an inverse relationship between duration of illness and gray matter volume (Molina et al., 2004; Prekumar et al., 2006) but the results were mostly confined to prefrontal regions. This is most likely due to use of region of interest analysis focusing on the prefrontal cortex and the smaller sample size. The widespread impact of chronicity observed here on prefrontal, parietal and temporal cortices is in line with longitudinal studies demonstrating progressive decrease in gray matter volume in these regions (Gur et al., 1998a; Lieberman et al., 2001; van Haren et al., 2007). In particular, our results resonate with reports from early-onset schizophrenia subjects of an accelerated loss of gray matter initially in the parietal and temporal lobes and, at a later stage, in the dorsolateral prefrontal cortex and superior temporal gyri (Thompson et al., 2001). The cross-sectional nature of our dataset allowed us to examine the effect of duration of illness from few months to 43 years but lacks the power of longitudinal studies that can examine within subject changes over time. However, our findings add to the evidence suggesting progressive gray matter loss in patients with schizophrenia. This may be more pronounced at the early stages of the illness (Gur et al., 1998a) but seems to continue throughout the life span (van Haren et al., 2007).

Given that disease related mechanisms may operate throughout life to increase brain morphological deviance in schizophrenia it is essential to examine the effect of antipsychotics on brain structure. It has been suggested

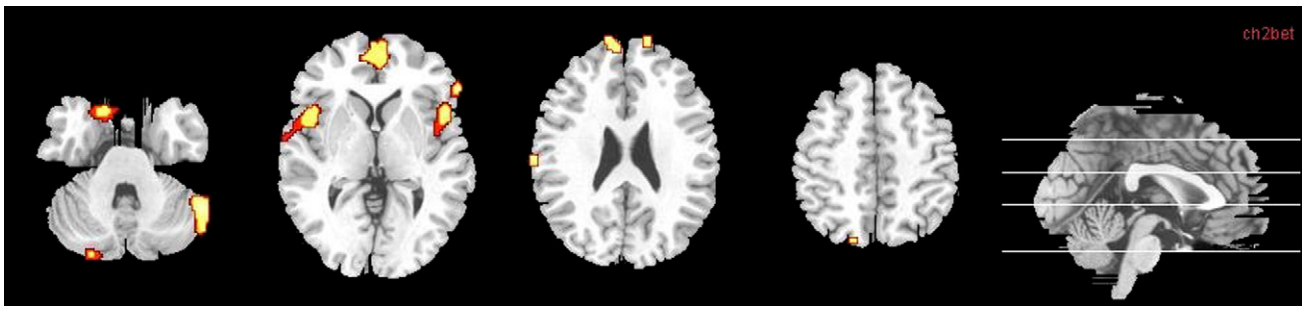

Figure 2 Negative correlation between gray matter volume and duration of illness in schizophrenia.

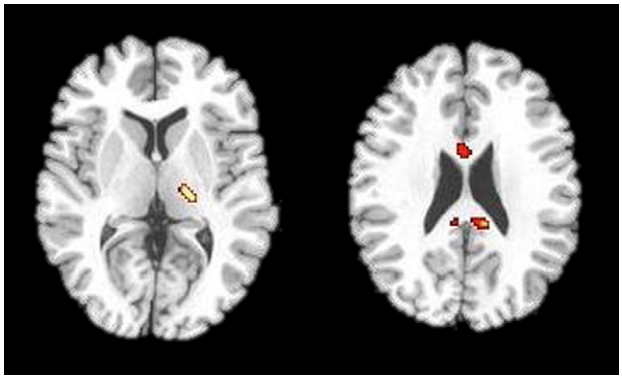

Figure 3 Positive correlation between gray matter volume and atypicals (left side), and typicals.

that antipsychotics mitigate gray matter loss in multiple cortical and subcortical regions in schizophrenia and this effect may be more pronounced for atypical than typical compounds (Scherk and Falkai, 2006; Andreone et al., 2007; van Haren et al., 2007). In this study, cumulative exposure to atypicals was associated with larger thalamic volumes, which is in accordance to prior reports in first-episode (Gur et al., 1998b; Dazzan et al., 2005) as well as in chronic schizophrenia patients (Gur et al., 1998b). The thalamus plays a major role in fronto-temporal communication and participates in modulating emotion and cognition, being impaired in schizophrenia at a structural and at a cytoarchitecture level (Seidman, 1983; Agarwal et al., 2008). Moreover, cumulative exposure to typical agents was associated with larger cingulate gyrus, a key structure for the pathophysiology of schizophrenia (Choi et al., 2005; Baiano et al., 2007). McCormick et al. (2005) also found anterior cingulate gyrus enlargement in treatment-naïve schizophrenia subjects following treatment with typical antipsychotics over a 3-year period. Therefore, the potential effects of antipsychotic medication reported in this study may target two crucial brain regions for schizophrenia. It should also be noted, however, that recent longitudinal studies in patients with first-episode (Lieberman et al., 2005) and chronic schizophrenia (van Haren, et al., 2007) showed decrements in gray matter volumes, mostly in prefrontal regions, associated with typical antipsychotic treatment.

Our results need to be interpreted with caution because of the non-random allocation of treatment, the cross-sectional design of the study, and the small magnitude of the effect of treatment which was only apparent at a low threshold of statistical significance. In addition, we do not have information about rate of medication changes, and patients' medication adherence, which is likely to have been variable over the course of their illness. Lastly, we did not control for the duration of untreated psychosis which may impact on brain structures in schizophrenia, particularly the left temporal cortex according to some (Keshavan et al., 1998; Lappin et al., 2006; Takahashi et al., 2007), but not all studies (Hoff et al., 2000; Ho et al., 2003, 2005). Therefore, it is best to interpret these findings as contributing to arguments for more detailed longitudinal studies on the effect of antipsychotic medication on brain structure and on the functional and clinical significance of medication-related changes. Such considerations might be particularly useful to explore when considering early intervention in schizophrenia (Killackey et al., 2007).

In conclusion, we provided evidence that chronicity and antipsychotic medication impact on brain morphology in schizophrenia and have opposite effects on gray matter volumes.

Role of the funding source

This work was partly supported by grants from the American Psychiatric Institute for Research and Education (APIRE Young Minds in Psychiatry Award); the Italian Ministry for University and Research (PRIN n. 2005068874), the StartCup Veneto 2007; the Italian Ministry of Health (IRCCS "E. Medea") to Dr. Brambilla and by a grant from the Veneto Region, Italy, (159/03, DGRV n. 4087).

None of these funding agencies had any further role in study design; in the collection, analysis and interpretation of data; in the writing of the report, and in the decision to submit the paper for publication.

Contributors

Luisa Tomelleri managed the literature searches and wrote the manuscript draft.

Cinzia Perlini, Marcella Bellani, Adele Ferro, coordinated patient and control recruitment and scale administration.

Gianluca Rambaldelli, Luisa Tomelleri Jigar Jogia managed MRI data post-processing.

Sophia Frangou supervised the VBM analyses and along with Luisa Tomelleri undertook the statistical analyses.

Michele Tansella supervised subject recruitment.

Paolo Brambilla designed the study and wrote the protocol and along with Sophia Frangou and Luisa Tomelleri wrote the final version of the manuscript.

All authors contributed to and have approved the final manuscript.

Conflict of interest

No authors of this manuscript has fees and grants from, employment by, consultancy for, shared ownership in, or any close relationship with, an organization whose interests, financial or otherwise, may be affected by the publication of the paper.

Acknowledgements

This work was partly supported by grants from the American Psychiatric Institute for Research and Education (APIRE Young Minds in Psychiatry Award); the Italian Ministry for University and Research (PRIN n. 2005068874), the StartCup Veneto 2007; the Italian Ministry of Health (IRCCS "E. Medea") to Dr. Brambilla and by a grant from the Veneto Region, Italy, (159/03, DGRV n. 4087). This study was made possible through collaboration between the Institute of Psychiatry, UK and the Inter-University Center for Behavioural Neurosciences (ICBN), University of Verona and DPMSC, Section of Psychiatry, University of Udine, Italy as part of the Neuroimaging Network of the ECNP Networks initiative which consists of the following centres (principal investigators): Institute of Psychiatry, Kings College London, England (S Frangou), INSERM, Service Hospitalier Frederic Joliot, France (JL Martinot), Saint Anne Hospital, France (P Boyer), Salpétrière Hospital, France (P Fossati), ICBN, University of Udine and University of Verona, Italy (P Brambilla), University of Gottingen, Germany (P Falkai),

University of Munich, Germany (E Meisenthal), University of Edinburgh, Scotland (S Lawrie, A McIntosh).

References

Agarwal, N., Rambaldelli, G., Perlini, C., Dusi, N., Kitis, O., Bellani, M., Cerini, R., Isola, M., Versace, A., Balestrieri, M., Gasparini, A., Pozzi Mucelli, R., Tansella, M., Brambilla, P., 2008. Microstructural thalamic changes in schizophrenia: a combined anatomical and diffusion weighted MRI study. Journal of Psychiatry and Neurosciences 33, 440–448.

Adams, C.E., Jayaram, M., 2007. Do findings from new trials for schizophrenia fit with existing evidence: not duped…just beguiled? Epidemiologia e Psichiatria Sociale 16, 199–202.

Amaddeo, F., Beecham, J., Bonizzato, P., Fenyo, A., Knapp, M., Tansella, M., 1997. The use of a case register to evaluate the costs of psychiatric care. Acta Psychiatr Scand 95, 189–198.

Andreone, N., Tansella, M., Cerini, R., Rambaldelli, G., Versace, A., Marrella, G., Perlini, C., Dusi, N., Pelizza, L., Balestrieri, M., Barbui, C., Nosè, M., Anna Gasparini, A., Brambilla, P., 2007. Cerebral atrophy and white matter disruption in chronic schizophrenia. Eur Arch Psychiatry Clin Neurosci 25, 3–11.

Ashburner, J., Friston, K.J., 2005. Unified segmentation. Neuroimage 26, 839–851.

Baiano, M., David, A., Versace, A., Churchill, R., Balestrieri, M., Brambilla, P., 2007. Anterior cingulate volumes in schizophrenia: A systematic review and a meta-analysis of MRI studies. Schizophr. Res. 93, 1–12.

Brett, M., 1999. The MNI Brain and the Talairach Atlas. MRC Cognition and Brain Sciences Unit. http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml.

Choi, J.C., Kang, D.H., Kim, J.J., Ha, T.H., Roh, K.S., Youn, T., Kwon, J.S., 2005. Decreased caudal anterior cingulate gyrus volume and positive symptoms in schizophrenia. Psychiatry Research: Neuroimaging 139, 239–247.

Dazzan, P., Morgan, K.D., Orr, K., Hutchinson, G., Chitnis, X., Suckling, J., Fearon, P., McGuire, P., Mallett, R.M., Jones, P.B., Leff, J., Murray, Robin, 2005. Different effects of typical and typical antipsychotics on grey matter in first episode psychosis: the AESOP study. Neuropsychofarmacology 30, 765–774.

Gur, R.E., Cowell, P., Turetsky, B.I., Gallacher, F., Cannon, T., Bilker, W., Gur, R.C., 1998a. A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. Arch Gen Psychiatry 55, 145–152.

Gur, R.E., Maany, V., Mozley, P.D., Swanson, C., Bilker, W., Gur, R.C., 1998b. Subcortical MRI volumes in neuroleptic-naive and treated patients with schizophrenia. Am J Psychiatry 155, 1711–1717.

Ho, B.C., Alicata, D., Ward, J., Moser, D.J., O'Leary, D.S., Arndt, S., Andreasen, N.C., 2003. Untreated initial psychosis: relation to cognitive deficits and brain morphology in first-episode schizophrenia. Am J Psychiatry 160, 142–148.

Ho, B.C., Alicata, D., Mola, C., Andreasen, N.C., 2005. Hippocampus volume and treatment delays in first-episode schizophrenia. Am J Psychiatry 162, 1527–1529.

Hoff, A.L., Sakuma, M., Razi, K., Heydebrand, G., Csernansky, J.G., DeLisi, L.E., 2000. Lack of association between duration of untreated illness and severity of cognitive and structural brain deficits at the first episode of schizophrenia. Am J Psychiatry 157, 1824–1828.

Honea, R., Crow, T.J., Passingham, D., Mackay, C.E., 2005. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry 162, 2233–2245.

Hulshoff Pol, H.E., Kahn, R.S., 2008. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. Schizophrenia Bulletin 34, 354–366 2008.

Keshavan, M.S., Haas, G.L., Kahn, C.E., Aguilar, E., Dick, E.L., Schooler, N.R., Sweeney, J.A., Pettegrew, J.W., 1998. Superior temporal gyrus and the course of early schizophrenia: progressive, static, or reversible? J. Psychiatr Res. 32, 161–167.

Killackey, E., Yung, A., McGorry, P.D., 2007. Early Psychosis: Where we've been, where we still have to go. Epidemiologia e Psichiatria Sociale, 16, 102–108.

Kopelman, A., Andreasen, N., Nopoulos, P., 2005. Morphology of the anterior cingulate gyrus in patients with schizophrenia: relationship to typical neuroleptic exposure. Am J Psychiatry 162, 1872–1878.

Lappin, J.M., Morgan, K., Morgan, C., Hutchison, G., Chitnis, X., Suckling, J., Fearon, P., McGuire, P.K., Jones, P.B., Leff, J., Murray, R.M., Dazzan, P., 2006. Gray matter abnormalities associated with duration of untreated psychosis. Schizophr Res, 83, 145–153.

Lieberman, J.A., Chakos, M., Wu, H., Alvir, J., Hoffman, E., Robinson, D., Bilder, R., 2001. Longitudinal study of brain morphology in first episode schizophrenia. Biol psychiatry 49, 487–499.

Lieberman, J.A., Tollefson, G.D., Charles, C., Charles, C., Zipursky, R., Sharma, T., Kahn, R.S., Keefe, R.S., Green, A.I., Gur, R.E., McEvoy, J., Perkins, D., Hamer, R.M., Gu, H., Tohen, M., HGDH Study Group, 2005. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 62, 361–370.

McCormick, L., Decker, L., Nopoulos, P., Ho, B.H., Andreasen, N., 2005. Effects of atypical and typical neroleptics on anterior cingulate volume in schizophrenia. Schizophrenia Research 80, 73–84.

Molina, V., Sanz, J., Sarramea, F., Benito, C., Palomo, T., 2004. Lower prefrontal gray matter volume in schizophrenia in chronic but not in first episode schizophrenia patients. Schizophrenia Research 131, 61–71.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.

Premkumar, P., Kumari, V., Corr, P.J.J., Sharma, T., 2006. Frontal lobe volumes in schizophrenia: effects of stage and duration of illness. Journal of Psychiatric Research 40, 627–637.

Scherk, H., Falkai, P., 2006. Effects of antipsychotics on brain structure. Curr Pin Psychiatry 19, 145–150.

Seidman, L.J., 1983. Schizophrenia and brain dysfunctions: an integration of recent neurodiagnostic findings. Psychol Bull 9, 195–238.

Talairach, J., Tournoux, P., 1988. Co-planar Stereotaxic Atlas of the Human Brain. Thieme, New York.

Takahashi, T., Suzuki, M., Tanino, R., Zhou, S.Y., Hagino, H., Niu, L., Kawasaki, Y., Seto, H., Kurachi, M., 2007. Volume reduction of the left planum temporale gray matter associated with long duration of untreated psychosis in schizophrenia: a preliminary report. Psychiatry Res: Neuroimaging 154, 209–219.

Tansella, M., Burti, L., 2003. Integrating evaluative research and community-based mental health care in Verona, Italy. Br J Psychiatr 183, 167–169.

Thompson, P.M., Vidal, C., Giedd, J.N., Gochman, P., Blumenthal, J., Nicolson, R., Toga, A.W., Rapaport, J.L., 2001. Mapping adolescent brain change reveals dynamic wave of accelerate gray matter loss in very early-onset schizophrenia. Proceedings of the National Academy of Science USA 98, 11650–11655.

van Haren, N.E., Hulshoff Pol, H.E., Schnack, H.G., Cahn, W., Mandl, R.C., Collins, D.L., Evans, A.C., Kahn, R.S., 2007. Focal gray matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. Neuropsychopharmacology 32, 2057–2066.

Ventura, J., Nuechterlein, K.H., Subotnik, L., Gutkind, D., Gilbert, E.A., 2000. Symptom dimensions in recent-onset schizophrenia and mania: a principal component analysis of the 24-item Brief Psychiatric Rating Scale. Psychiatry Res. 97, 129–135.

World Health Organisation, 1992. Schedules for Clinical Assessment in Neuropsychiatry. WHO, Geneva.

World Health Organisation (1996). Schede di valutazione clinica in neuropsichiatria. SCAN 2.1. In: Tansella, Nardini, M., Series editors. Il Pensiero Scientifico Editore, Roma.