Eur Arch Psychiatry Clin Neurosci (2009) 259:505–509
DOI 10.1007/s00406-009-0025-1

LETTER TO THE EDITORS

Review of the 6th symposium for the search for the causes of schizophrenia, Sao Paulo, Brazil, 3–6 February 2009

James Bowes Kirkbride · Linda Scoriels

Received: 12 May 2009 / Accepted: 3 June 2009 / Published online: 16 June 2009

Abstract In this review, we present the main findings of the 6th Symposium for the Search for the Causes of Schizophrenia, which took place between 3 and 6 February 2009, in Sao Paulo, Brazil. In a few short years, the landscape of the causes of schizophrenia has changed dramatically. The flat and featureless epidemiological horizon has developed undulating contours, which promise new avenues for research, particularly if we are able to integrate such findings with tantalising new findings from genetics as novel methods for identifying genuine sites of genetic risk emerge. The Search highlighted and fostered the emerging acknowledgement that we will need to integrate knowledge across traditionally disparate disciplines in psychiatry in order to develop complex, testable hypotheses in the search for the causes of schizophrenia. Such challenges are beginning to be addressed. From epidemiology, gene–environment studies are becoming more sophisticated, while neuroscience is increasingly concerned about social organisation and how social factors impinge upon biological pathways to potentially lead to psychosis. Tantalising new insights from genome-wide association studies offer new clues about rare genetic mutations, which have large effect sizes for schizophrenia, including copy number variants and de novo mutations. It is only through forums such as the 6th Symposium for the Search for the Causes of Schizophrenia that the seeds of integrated collaborations across disciplines can be sown to address the complex polyfactorial basis of schizophrenia.

J. B. Kirkbride (✉) · L. Scoriels
Department of Psychiatry, University of Cambridge, Addenbrooke's Hospital, Box 189, Hills Road, Cambridge CB2 0AH, UK
e-mail: jbk25@cam.ac.uk

L. Scoriels
e-mail: ls387@cam.ac.uk

Report

The *Search for the Causes of Schizophrenia* is now well into their third decade. Originally established by Professors Heinz Hafner and Wagner Gattaz to bring together schizophrenia researchers from around the world, these periodic, timely symposia offer an intimate, convivial forum for academic discussion and debate of the latest advances in schizophrenia research. The 6th Symposium was no different. Dedicated to recognise the achievements of Professor Hafner, the organisers Professor Wagner Gattaz and Doctor Geraldo Busatto invited 36 speakers from over 10 countries to the Institute of Psychiatry, Sao Paulo, to discuss new findings from epidemiology, psychopathology, pathophysiology genetics and treatment since the fifth Symposium in 2003. Six years ago, there was great hope and expectation that advances in genetic research would lead to the identification of one or more candidate genes for psychosis, if not schizophrenia [14]. In the intervening years, the weight of expectation has only been, disappointingly, matched by the absence of any clear consensus on candidate genes for schizophrenia. Where the failure to find consistent evidence for a mono- or polygenetic basis for schizophrenia might have otherwise led to implosion [10], in Sao Paulo, the mood was not of failure, but of optimism as to how we might capitalise on novel, integrative approaches from traditionally disparate disciplines—including genetics, pharmacology, physiology, neuroscience and epidemiology—in order to identify the pathways that lead to schizophrenia. The absence of

parallel sessions ensured each specific topic session was well-attended, fostering many synergistic, interdisciplinary debates as to how we might best conceptualise this rather complex disease.

The meeting opened with a review of the major recent findings from the epidemiology of schizophrenia by Paulo Menezes. He himself has conducted robust epidemiological research in Sao Paulo [35], curiously observing lower incidence rates of schizophrenia in this urban setting compared with other large cities. This finding, dubbed "Sao Paulo Syndrome", raises the possibility that the socio-environmental processes involved in the aetiology of schizophrenia may be different across cities, and more complex than simple linear associations with urbanicity. Professor Menezes went on to highlight other notable research from the last decade, which has helped to dispel the dogmatic paradigm that the incidence of schizophrenia occurs equally worldwide [7, 23, 31]. It is now clear that variation in the incidence of schizophrenia exists at a variety of geographical levels—globally, nationally and locally—paving the way for an environmental component in the aetiology of disorder [27]. Much of this variation appears to be contextually dependent [1, 3, 22, 50, 51], such that the risk of schizophrenia for individuals is dependent on the type of environment they are exposed to, and, in part, their own individual level of social disadvantage [36]. Jim van Os went on to consider how variation in environment risk factors might provide an explanation of the absence of clearly elucidated genetic effects on schizophrenia risk, proposing that gene–environment interactions may hold the key to revealing aetiological pathways, and that genetic variance may confound the relationship, as well as lie on the causal pathway between social disadvantage and schizophrenia. Judith Allardyce reminded us that epidemiology has utility beyond the identification of risk factors important in the aetiology of schizophrenia, demonstrating evidence from systematic reviews that the outcome of schizophrenia is characterised by largely unexplained variance rather than universally poor outcome [34, 49]. This challenges the prevailing assumption that schizophrenia is associated with universal deficit and deterioration.

Of particular note was the reception which the epidemiological session received. At other meetings, epidemiology has often been on the periphery of the research agenda, at best attended by a self-selecting group of devout researchers, and at worst abhorred by non-believers. It has not been uncommon for psychiatric epidemiologists to find themselves—as the saying goes—preaching to the choir. In Sao Paulo, the absence of parallel sessions focused attention onto each session, and Ezra Susser's ebullient summary of the state-of-play in psychiatric epidemiology, and the need to incorporate epidemiology with epigenetics and genetics, was well received, stimulating lively discussion as to how genetic and epidemiological research might move together to elucidate the likely complex polygenetic, poly-environmental aetiology of schizophrenia. The absence of dissenting voices may present a notable shift in the paradigm of psychiatric research and foster collaboration between previously distal fields including genetics, pathophysiology, neuroscience and epidemiology.

There was no evidence that this new epidemiological congregation were mere passive consenters. In the session dedicated to genetics, both Antony Grace and Andreas Meyer-Lindenberg presented data from animal models compatible with how environmental stressors might lead to psychosis. Antony Grace presented new findings on genetic and developmental animal models of schizophrenia, demonstrating how the firing of mesolimbic dopamine neurons in rats could be sensitised following the repeated administration of psychostimulants or via restraint stress paradigms [26]. Andreas Meyer-Lindenberg presented evidence showing how social hierarchies, and our position within them, may affect neural networks, thus mediating the impact of social status on human health and behaviour [54]. He also presented some preliminary research, which will test whether unstable social hierarchies in an animal paradigm leads to increased stress response in the striatum, potentially implicating a pathway through which social hierarchies affect schizophrenia risk. This work marks a significant step forward in linking findings from social epidemiology regarding social isolation and fragmentation with understanding how these effects impinge directly on biological alterations in brain behaviour. As argued by John McGrath [33], incorporating a more complete, holistic understanding of how seemingly distal environmental factors link to biological alterations in pathophysiology, via genetic and epigenetic processes, will be critical in unravelling the multifactorial basis of schizophrenia.

The overall theme to emerge from the genetics session was the emphasis on the importance of identifying pathways, which may lead to a better understanding of genetic phenomena, such as epigenetic modulation, gene–environment interactions and sites of high mutation, including copy number variations and de novo mutations. Emmanuel Dias-Neto focused on genetic and proteomic studies in schizophrenia and presented the work conducted at the host institution, in the laboratory directed by Prof. Gattaz. One of the focuses of the team was to investigate DNA polymorphisms in neurogenesis-related genes mapped to genomic regions relevant to schizophrenia. After identifying and validating 41 DNA alterations in 39 different genes the group found polymorphisms with positive associations with schizophrenia. Examples given included a poly-glutamine repeat in NUMBL (a gene in the NOTCH-pathway) and a WNT-receptor. Most importantly, the reported

associations were confirmed in an independent and larger sample set of patients and controls from Denmark [41]. Dias-Neto also presented the results of an analysis of these neurogenesis-related genes and brain morphometric alterations seen in schizophrenia patients, with potential markers for alterations in the gyrification index and in brain ventricular measures [15]. Techniques are improving in the field and candidate genes are emerging. Of particular interest, the Serial Analysis of Gene Expression technique has enabled researchers investigate the expression levels of >20,000 genes that lead to up to 20 genes that might be specific to schizophrenia. To conclude proteomic studies done by shot-gun and 2D-gel analyses were presented, reinforcing the link of schizophrenia and of pathways such as calcium homeostasis, oligodendrocyte and energy metabolism [28–30].

Due attention was devoted to pathophysiology and biological systems in the onset of psychotic symptoms and schizophrenia. Co-organiser Geraldo Busatto reviewed the evidence for schizophrenia as a neurodevelopmental or neurodegenerative disorder [44], finding more evidence in favour of the former. A former proponent of the neurodevelopmental hypothesis, Professor Robin Murray, argued that all risk factors for psychosis, currently identified, made their impact through dopaminergic pathways [11], pointing to evidence from recent studies with regard to variation in dopamine expression in the ventral striatum by age and sex [37]. Further, Professor Murray highlighted the overlap in striatal pre-synaptic dopamine synthesis in families as consistent with the familial congregation of schizophrenia [19], while there is also evidence that social defeat and social isolation in animal models may sensitise the dopamine system over time [16, 45]. In particular, there was new evidence to support Kapur's hypothesis [21] that risk factors for psychosis impacted on the dopamine system through aberrant salience—erroneous interpretation—of otherwise neutral stimuli; Graham Murray and colleagues in Cambridge have recently shown an excessive striatal dopamine response in people with schizophrenia to neutral stimuli [39]. It is salient to note, however, that the dopamine hypothesis is only one potential pathway through which psychosis may operate and Bita Moghaddam provided a sober reminder that other systems such as glutamate and glutamate–dopamine interactions [18] or the central role of the hippocampus [12] in regulating the emotional context of our position in space and time may provide equally illuminating avenues for research. Professor Moghaddam presented work that studied the targeting of glutamate receptors as an alternative way of treatment for schizophrenia [43]. Patients showed significant improvements in their positive and negative symptoms and did not seem to suffer from side effects commonly found in classical anti-psychotics. She presented further data showing that the use of NMDA receptors antagonist-induced cognitive impairments similar to those found in schizophrenia [46].

The current arguments for and against schizophrenia as part of the continuum of psychotic experience in the general population received due attention during the Symposium, with Richard Linscott reminding us that there is little point searching for causes of a disorder, if we do not have a good idea of what the disorder itself is. Using data from a systematic review of studies which considered the taxometric properties of schizophrenia [25], he suggested that most research appears to support a categorical classification of disorders. However, given heterogeneity of methodological approaches, violation of modelling assumptions and other threats to the validity of many of these studies, he concluded that there was insufficient evidence to reject the possibility that psychotic symptoms are continuously distributed in the general population, supporting current calls for both dimensional and categorical classifications to be included in forthcoming revisions to the Diagnostic and Statistical Manual of Mental Disorders [DSM-V] and the International Classification of Diseases [ICD-11] [2].

The session on psychopathology, cognition and outcome focused mainly on the prodromal stage of schizophrenia and the importance to recognise early symptoms. Tyrone Cannon demonstrated that it is possible to predict the onset of the disease relatively reliably and stressed the importance of biomarkers in that field [6]. Alison Yung emphasised on cognitive dysfunctions present at the prodromal stage of the disease and its links with later onset [4]. Keith Nuechterlein reminded us that cognitive deficits are one of the best predictors of schizophrenia, highlighting their centrality in symptomatology. He demonstrated that cognitive deficits were most deleterious between the prodromal stage and the first onset, making it critical to target such deficits as early as possible [5]. Daniel Freeman added a further contribution to this session, focusing on one specific symptom of schizophrenia; paranoia. He showed that people with high levels of paranoia were more likely to suffer from anxiety, depression and perceptual anomalies, as found in patients with schizophrenia [13]. Environmental risk factors were also similar to those found for schizophrenia and urban regions were shown to have a detrimental impact on symptomatology.

The Symposium also devoted sufficient time to advances in treatment and drug discovery. Rajiv Tandon initiated a vibrant debate on the use of first- versus second-generation anti-psychotics, presenting findings from the CATIE and CUtLASS trials [20, 24]. Atypical anti-psychotics did not seem to differ from typical anti-psychotics, but Rajiv Tandon suggested that we should be cautious when interpreting these results, since there were notable differences in extra-pyramidal side-effect

profiles. He also presented data which demonstrated that treatment was more effective when patients did not switch medication, prompting Professor Tandon to call for a greater need for clinicians to offer individualised drug regimes on a case-by-case basis [40, 48]. Anthony David demonstrated the evidence supporting the use of long-acting anti-psychotics on improved outcomes of schizophrenia, arguing that use of depot medication alone was not sufficient to enhance relapse prevention, but should be used in conjunction with understanding the patients' beliefs and attitudes towards adherence and associated benefits [42]. Advocacy for greater patient–clinician dialogue, together with Wulf Rossler's commentary on stigma and treatment impairment, triggered some of the most heated debate of *The Symposium* regarding the role psychiatrists play in perpetuating stigmatised beliefs within the field, and the degree to which patients themselves are empowered during the treatment, course and outcome of disorder. The jury was hung.

In a few short years, the landscape of the causes of schizophrenia has changed dramatically [32]. The flat and featureless epidemiological horizon has developed undulating contours which promise new avenues for research, particularly if we are able to integrate such findings with important new discoveries from genetics. Some of the promising peaks of the genetic landscape, glimpsed from afar over the last decade have turned out, in part, to be cloudy mirages. Nevertheless, new tantalising findings from genetics are emerging as novel methods for identifying genuine sites of genetic risk emerge. More than anything, the Search highlighted and fostered the emerging acknowledgement that we will need to integrate knowledge across traditionally disparate disciplines in psychiatry in order to develop complex, testable hypotheses in the search for the causes of schizophrenia. Such challenges are beginning to be addressed. From epidemiology, gene–environment studies are becoming more sophisticated, while neuroscience is increasingly concerned about social organisation and how social factors impinge upon biological pathways to potentially lead to psychosis. Tantalising new insights from genome-wide association studies offer new clues about rare genetic mutations which have large effect sizes for schizophrenia, including copy number variants and de novo mutations [8, 38, 47, 52, 53]. The importance of epigenetic processes in understanding the relationship between genes, environment and schizophrenia is also beginning to gain traction in schizophrenia research [9, 17]. It is only through forums such as *the 6th Symposium for the Search for the Causes of Schizophrenia* that the seeds of integrated collaborations across disciplines can be sown to address the complex polyfactorial basis of schizophrenia.

References

1. Allardyce J, Gilmour H, Atkinson J et al (2005) Social fragmentation, deprivation and urbanicity: relation to first-admission rates for psychoses. Br J Psychiatry 187(5):401–406
2. Allardyce J, McCreadie R, Morrison G et al (2007) Do symptom dimensions or categorical diagnoses best discriminate between known risk factors for psychosis? Soc Psychiatry Psychiatr Epidemiol 42(6):429–437
3. Boydell J, van Os J, McKenzie K et al (2001) Incidence of schizophrenia in ethnic minorities in London: ecological study into interactions with environment. Br Med J 323(7325):1336–1338
4. Brewer WJ, Wood SJ, Phillips LJ et al (2006) Generalized and specific cognitive performance in clinical high-risk cohorts: a review highlighting potential vulnerability markers for psychosis. Schizophr Bull 32(3):538–555
5. Cameron SC, Deanna MB, Robert WB et al (2008) Identifying cognitive mechanisms targeted for treatment development in schizophrenia: an overview of the first meeting of the cognitive neuroscience treatment research to improve cognition in schizophrenia initiative. Biol Psychiatry 64(1):4–10
6. Cannon TD, Cadenhead K, Cornblatt B et al (2008) Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch Gen Psychiatry 65(1):28–37
7. Cantor-Graae E, Selten J-P (2005) Schizophrenia and migration: a meta-analysis and review. Am J Psychiatry 162(1):12–24
8. Consortium IS (2008) Rare chromosomal deletions and duplications increase risk of schizophrenia. Nature 455(7210):237–241
9. Crow TJ (2008) Craddock & Owen vs Kraepelin: 85 years late, mesmerised by "polygenes". Schizophr Res 103(1–3):156–160
10. Crow TJ (2008) The emperors of the schizophrenia polygene have no clothes. Psychol Med 38(12):1681–1685
11. Di Forti M, Lappin JM, Murray RM (2007) Risk factors for schizophrenia—all roads lead to dopamine. Eur Neuropsychopharmacol 17(Suppl 2):S101–S107
12. Ebner F, Tepest R, Dani I et al (2008) The hippocampus in families with schizophrenia in relation to obstetric complications. Schizophr Res 104(1–3):71–78
13. Freeman D, Gittins M, Pugh K et al (2008) What makes one person paranoid and another person anxious? The differential prediction of social anxiety and persecutory ideation in an experimental situation. Psychol Med 38(8):1121–1132
14. Gattaz WF, Hafner H (eds) (2004) Search for the cause of schizophrenia. Steikopff-verlag, Darmstadt
15. Gregório SP, Sallet PC, Do K-A et al (2009) Polymorphisms in genes involved in neurodevelopment may be associated with altered brain morphology in schizophrenia: preliminary evidence. Psychiatry Res 165(1–2):1–9
16. Hall FS, Wilkinson LS, Humby T et al (1999) Maternal deprivation of neonatal rats produces enduring changes in dopamine function. Synapse 32(1):37–43
17. Heijmans BT, Tobi EW, Stein AD et al (2008) Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci 105(44):17046–17049
18. Homayoun H, Moghaddam B (2008) Orbitofrontal cortex neurons as a common target for classic and glutamatergic antipsychotic drugs. Proc Natl Acad Sci 105(46):18041–18046
19. Huttunen J, Heinimaa M, Svirskis T et al (2008) Striatal dopamine synthesis in first-degree relatives of patients with schizophrenia. Biol Psychiatry 63(1):114–117
20. Jones PB, Barnes TRE, Davies L et al (2006) Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: cost utility of the latest antipsychotic drugs in schizophrenia study (CUtLASS 1). Arch Gen Psychiatry 63(10):1079–1087

21. Kapur S (2003) Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 160(1):13–23
22. Kirkbride J, Boydell J, Ploubidis G et al (2008) Testing the association between the incidence of schizophrenia and social capital in an urban area. Psychol Med 38(8):1083–1094
23. Kirkbride JB, Fearon P, Morgan C et al (2006) Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-Center ÆSOP study. Arch Gen Psychiatry 63(3):250–258
24. Lieberman JA, Stroup TS, McEvoy JP et al (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353(12):1209–1223
25. Linscott RJ, Allardyce J, van Os J (2009) Seeking verisimilitude in a class: a systematic review of evidence that the criterial clinical symptoms of schizophrenia are taxonic. Schizophr Bull (in press)
26. Lodge DJ, Grace AA (2008) Amphetamine activation of hippocampal drive of mesolimbic dopamine neurons: a mechanism of behavioral sensitization. J Neurosci 28(31):7876–7882
27. March D, Hatch SL, Morgan C et al (2008) Psychosis and place. Epidemiol Rev 30:84–100
28. Martins-de-Souza D, Gattaz W, Schmitt A et al (2009a) Prefrontal cortex shotgun proteome analysis reveals altered calcium homeostasis and immune system imbalance in schizophrenia. Eur Arch Psychiatry Clin Neurosci 259(3):151–163
29. Martins-de-Souza D, Gattaz W, Schmitt A et al (2009) Alterations in oligodendrocyte proteins, calcium homeostasis and new potential markers in schizophrenia anterior temporal lobe are revealed by shotgun proteome analysis. J Neural Transm 116(3):275–289
30. Martins-de-Souza D, Gattaz WF, Schmitt A et al (2008) Proteomic analysis of dorsolateral prefrontal cortex indicates the involvement of cytoskeleton, oligodendrocyte, energy metabolism and new potential markers in schizophrenia. J Psychiatr Res (Epub ahead of print)
31. McGrath J, Saha S, Welham J et al (2004) A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med 2:13
32. McGrath JJ (2007) The surprisingly rich contours of schizophrenia epidemiology. Arch Gen Psychiatry 64(1):14–16
33. McGrath JJ, Susser ES (2009) New directions in the epidemiology of schizophrenia. Med J Aust 190(4):S7–S9
34. Menezes NM, Arenovich T, Zipursky RB (2006) A systematic review of longitudinal outcome studies of first-episode psychosis. Psychol Med 36(10):1349–1362
35. Menezes PR, Scazufca M, Busatto G et al (2007) Incidence of first-contact psychosis in Sao Paulo, Brazil. Br J Psychiatry 191:S102–S106
36. Morgan C, Kirkbride J, Hutchinson G et al (2008) Cumulative social disadvantage, ethnicity and first-episode psychosis: a case-control study. Psychol Med 38:1701–1715
37. Munro CA, McCaul ME, Wong DF et al (2006) Sex differences in striatal dopamine release in healthy adults. Biol Psychiatry 59(10):966–974
38. Murphy KC (2002) Schizophrenia and velo-cardio-facial syndrome. Lancet 359(9304):426–430
39. Murray G, Clark L, Corlett P et al (2008) Incentive motivation in first-episode psychosis: a behavioural study. BMC Psychiatry 8(1):34
40. Parks J, Radke A, Parker G et al (2008) Principles of antipsychotic prescribing for policy makers, Circa 2008. Translating knowledge to promote individualized treatment. Schizophr Bull, sbn019
41. Passos Gregorio S, Gattaz WF, Tavares H et al (2006) Analysis of coding-polymorphisms in NOTCH-related genes reveals NUMBL poly-glutamine repeat to be associated with schizophrenia in Brazilian and Danish subjects. Schizophr Res 88(1–3):275–282
42. Patel MX, de Zoysa N, Bernadt M et al (2008) A cross-sectional study of patients' perspectives on adherence to antipsychotic medication: depot versus oral. J Clin Psychiatry 69(10):1548–1556
43. Patil ST, Zhang L, Martenyi F et al (2007) Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. Nat Med 13(9):1102–1107
44. Sallet PC, Elkis H, Alves TM et al (2003) Reduced cortical folding in schizophrenia: an MRI morphometric study. Am J Psychiatry 160(9):1606–1613
45. Selten JP, Cantor-Graae E (2005) Social defeat: risk factor for schizophrenia? Br J Psychiatry 187(2):101–102
46. Stefani MR, Moghaddam B (2005) Systemic and prefrontal cortical NMDA receptor blockade differentially affect discrimination learning and set-shift ability in rats. Behav Neurosci 119(2):420–428
47. Stefansson H, Rujescu D, Cichon S et al (2008) Large recurrent microdeletions associated with schizophrenia. Nature 455(7210):232–236
48. Tandon R, Belmaker RH, Gattaz WF et al (2008) World psychiatric association pharmacopsychiatry section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophr Res 100(1–3):20–38
49. van Os J, Allardyce J (2009) The clinical epidemiology of schizophrenia. In: Kaplan B, Saddock J, Saddock V (eds) Comprehensive textbook of psychiatry. Williams and Wilkins, London
50. Veling W, Selten J-P, Susser E et al (2007) Discrimination and the incidence of psychotic disorders among ethnic minorities in The Netherlands. Int J Epidemiol 36(4):761–768
51. Veling W, Susser E, van Os J et al (2008) Ethnic density of neighborhoods and incidence of psychotic disorders among immigrants. Am J Psychiatry 165(1):66–73
52. Walsh T, McClellan JM, McCarthy SE et al (2008) Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science 320(5875):539–543
53. Xu B, Roos JL, Levy S et al (2008) Strong association of de novo copy number mutations with sporadic schizophrenia. Nat Genet 40(7):880–885
54. Zink CF, Tong Y, Chen Q et al (2008) Know your place: neural processing of social hierarchy in humans. Neuron 58(2):273–283