Invited Paper

Trajectories of psychosis: towards a new social biology of schizophrenia*

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SUMMARY. Over the last 2 decades, discourse on the causes of schizophrenia was conducted almost entirely in terms of biological risk factors. This was probably the result of social trends in the research community, and in popular culture, as a wave of techno-optimism promised answers to big human questions in terms of small pixels and even smaller molecules. The human genome project inflated expectations further, and the pharmaceutical industry conspired with the desire of psychiatrists for scientific respectability. ‘Social factors’, whether at macro-societal or locality/family level, came to be seen as ‘fall-out’ from biological mechanisms, a kind of padding to our understanding of human disease. But changes are in the wind. New understandings of the influence of social factors on the long-term outcome trajectories of psychosis, their potential role in risks associated with migration, and recent findings from genetic high risk studies, are raising fresh questions about social factors and causation. This paper does not argue that the evidence (yet) is strong. But after 2 decades of often crudely articulated dualism, it is time once again for social experience to be integrated with more sophisticated theory development and hypothesis testing in the search for the causes of schizophrenia.

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In the closing years of the last century discourse surrounding the aetiology of schizophrenia became focused almost entirely within a biological framework. As the new sciences of brain imaging excited our imagination we could actually see hallucinations as they lit up the brains of our patients- and the new genetics held out the prospect of a ‘gene for schizophrenia’, we discovered that schizophrenia was a ‘brain disease’. Over the same period, the search for non-genetic risk factors also flourished. But the risk factors placed under the microscope were also nearly all biological insults to the developing brain: infection, nutrition, trauma and so on. ‘Social factors’ were relegated to the margins, a kind of ‘padding’ around the biological or, at best, a product of reverse causality. Thus, a biological hegemony was established in the world of schizophrenia research, controlling the visibility given to different conceptual models and, importantly, the allocation of research funds. For many, social psychiatry had had its day. The future was bright. The future was biological.

How did the aetiology of schizophrenia come to be framed in terms of such biological reductionism? Why did researchers become ensnared by such simplistic dualism that the biological character of a disease became synonymous with its biological causation? The answer probably lies in the convergence of 4 ‘social’ trends in the research community, and in popular culture, in the early to mid-1980’s. First, there was a legitimate and timely reaction to the quality of family studies of schizophrenia conducted in the 1960’s and 1970’s. Their flawed
research designs and poor methodological quality provided ample case material for journal clubs and trainers in research methods. A generation of young psychiatrists were trained in these studies as exemplars of the scientific folly of social psychiatry. And we rightly recoiled from the stigma that accrued to patients and families as a result of loosely based talk of ‘schizophrenogenic’ mothers and ‘refrigerator’ parents.

But then, secondly, we became enthralled by the techno-optimism of ‘big science’. The potential of the human genome project seemed limitless. Newly immersed in this popular scientific culture we, too, were seduced by the idea that the answers to big human questions would be found in small pixels and even smaller molecules. As new brain scanning techniques provided a kind of phrenology of the late 20th century, the size and shape of our grey matter promised to become the vehicle of our understanding.

Thirdly, ‘real’ science not only promised new and better results, but for those psychiatrists confused about their identity and uncomfortable with their public stigma, it held out the promise of respectability. Taking our seats among the neuroscientists, we could find respect, peer approval, research funding and, in countries where other professions edged ever further into psychotherapy, a more secure financial future. And lastly, there was the growing role of the pharmaceutical companies. Industry was only too ready to conspire with our newfound ambitions to be proper doctors and scientists. Experts in managing behavioural change among clinicians, they happily assisted in re-focusing our conceptual world toward their biological horizons.

But changes are in the wind. In this paper, I argue that we stand at the threshold of a new paradigm in schizophrenia research. I detect a renewed interest in the role of psychosocial as well as biological risk factors. More importantly, there is a hunger for conceptual models that transcend the simplistic reductionism of the recent past to offer integration and interaction. Dissatisfied with the old polarities, we are searching for a new social biology of the disorder.

The case for a new social biology of schizophrenia is built on three strands of evidence. The first comes from ‘big science’ itself. I shall briefly review developments in genetics and gene to environment interactions, together with emerging evidence about the role of social factors in brain plasticity and connectivity. Then I shall argue that a re-examination of the possible role of social factors is required because of the re-conceptualisation of schizophrenia as a ‘life course phenotype’ in which both social and biological risk factors shape the developing phenotype in foetal life and infancy, through adult life and then on to old age. The third and final strand of evidence comes from epidemiologists working on other complex biological diseases. For coronary heart disease and other chronic disorders, their biological character has not prevented researchers from investigating their social origins. And psychiatrists, too, are re-awakening to the fact that biological in character need not mean biological in causation.

POST GENOME AND THE NEW SOCIAL BIOLOGY

The human genome project continues to have far reaching effects that will revolutionise the way human beings think about themselves. But in a sense, in terms of popular expectations at least, it has failed. This is because hopes of simplicity have been forced to give way to the reality of yet more complexity. The sheer quantity of the information being generated embraces orders of magnitude that exceed our statistical (and conceptual?) capacity. The issue of how genes and environments interact remains complex and mysterious. The field is further complicated by new knowledge on ‘epigenetics’ – the study of heritable changes in gene expression that occur without changes in the DNA sequence (Wolfe & Matzke, 1999). In addition, there is the phenomenon of pleiotropy – the same genes producing different phenotypic outcomes – and the unknown role that experience and environment may play in the way proteins are folded into their 3 dimensional structures.

Then there is the problem of how to define the phenotype in the genetics of psychotic illness. The ‘phenotype’ of schizophrenia is almost certainly a conflation of overlapping more ‘deeply rooted’ traits associated with the disease, each with several gene loci contributing to their development. Searching for multiple genes of small effect will inevitably prove a slow and long drawn out task. The challenge will be to disentangle multiple associations between many genes, many environmental factors, among many phenotypes. Because of these and other factors, the genetics of complex psychotic disease (with non-Mendelian transmission) remains largely obscure.

But a potent argument for a new social biology of schizophrenia comes from the finding that genes respond to experience. We have tended to think of our genes as constructing a static ‘blueprint’ that codes for proteins that simply ‘unfold’ into the environment. But genes are not molecular military personnel barking orders but tak-
ing none. Through foetal life into old age, genes recon-
struct, remodel, and sculpt the brain- in response to expe-
rience. The development of vision provides a helpful
illustration of this interplay between genes and experi-
ence. Experiments in mice, for example, show that the
capacity for normal vision requires exposure to light dur-
ing a critical period following birth (e.g. Huang et al.,
1999). When mice are reared in darkness during this peri-
od they remain blind as adults no matter how much light
they later experience. It appears that exposure during the
critical early period ‘switches on’ the gene that codes for
a protein called brain derived neurotrophic factor
(BDNF). It seems that the development of circuitry in the
visual cortex required for vision is critically dependent on
experience.

Further evidence for the role of social experience in
neural function comes from primate studies. Experi-
mental designs involving the administration of neurotropic
substances such as amphetamines show that the develop-
ment and ‘tightening’ of synaptic connections, and their
responsiveness to exogenous neuro-modulators, is asso-
ciated with different dimensions of social experience.
For example, Knobbout et al. (1996), showed that pat-
terns of socially avoidant behaviour in Java monkeys
reared with amphetamines were strongly associated with
the monkey’s position within the existing hierarchical
social structure. In other words, prior social experience
had a direct and measurable influence on the biologically
mediated response to amphetamine treatment.

Maguire et al. (2000) reported one of the most com-
pelling pieces of work in this field, and certainly the most
intriguing. Using imaging techniques to measure the area
of the hippocampus associated with mapping ability, a
sample of London taxi drivers was compared with con-
trols. In the taxi-drivers the area was found to be larger,
although total brain volume remained the same. The
explanation that this simply reflected a selection bias of
individuals predisposed to work involving visual-spatial
mapping was countered by the finding of a linear rela-
tionship between the size of difference and the length of
taxi driving experience. In other words the longer a dri-
ver had been navigating the streets of London, the larger
the area of the brain that looks after mapping. It seems
that, in terms of synaptic connectivity, we ‘use it or lose
it’. Against a background of gene to environment inter-
action, the experiences we encounter, the choices we make,
the lifestyles we pursue continue to sculpt and refine our
brain structure throughout our lives. We absorb our ex-
perience. It is therefore highly likely that social experience
contributes in some way to the genesis of complex bio-
logical disorders such as schizophrenia.

THE LIFE COURSE PHENOTYPE
OF SCHIZOPHRENIA

Although the literature on the relationship between
social experience and the causation of schizophrenia is
relatively thin, there is some measure of agreement that
social experience is related to the longer-term outcome of
the disorder. For example, there is evidence that treat-
ments that attempt to manipulate social experience at
micro-social level (e.g. altering levels of expressed emo-
tion among family members) can shape the course and
outcome after the appearance of positive symptoms. In
addition, psychological approaches utilising cognitive
techniques may also modify the course of the disorder in
some cases (Cormac et al., 2003). The strongest evidence
comes from observational studies carried out in different
social and cultural settings. The largest such study was
co-ordinated by the World Health Organisation (Harrison
et al., 2001). Drawing on first episode samples identified
in earlier WHO studies, and supplemented by compara-
ble samples elsewhere, the authors followed up 14 cul-
turally diverse cohorts over a 15 year period. There was
remarkable heterogeneity of outcome across the study
population and between the study centres. The strongest
predictors of long-term outcome were early (2 year) pat-
tern of course and, independently, the social context
(‘centre’) in which the cases had been originally identi-
ified.

The earlier two year follow-up of WHO cohorts
reported by Jablensky et al., 1992 showed more
favourable outcomes in developing countries: a signifi-
cantly higher percentage of subjects (56%) in developing
countries achieving ‘mild’ patterns of course, compared
to their counterparts in developed countries (39%).
Conversely, 40% of cases in so-called ‘developed’ coun-
tries had ‘severe’ patterns of course compared with only
24% in developing countries. The same held true over the
longer period of follow-up reported by Harrison et al.
(2001). Analysis of the 15 year course and outcome data
(Hopper & Wanderling, 2000) showed that early
favourable ‘centre’ effects in developing countries held
over the longer term with comparable effect sizes. This
effect held whether a narrow (ICD-10) or broad spectrum
classification of schizophrenia was used and could be
sustained after careful re-analysis taking into account
diagnostic differences, potential sampling biases and dif-
fferences in attrition and follow up. The difference could
not be explained by the higher incidence of ‘acute-remit-
ting’ psychoses and even those with ‘poor’ early out-
comes did better over the longer term if they lived in
developing centres.

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The reason for this variation between developed and developing centres remains a mystery. Various authors have attempted to explain them in terms of a disparate list of anthropological variables such as flexible and more accommodating work patterns in the local setting, alternative or ‘self-exempting’ attributions of illness and more socially integrated subjectivities. But none of these speculations have been subject to rigorous enquiry and the issues remain unresolved.

However, whatever the specific factors involved, the social patterning of long-term outcomes provides further evidence of a general role for social factors in shaping the trajectory of the disorder. We have argued elsewhere (Harrison & Eaton, 2002) that a cleavage between ‘onset’, influenced solely by biological determinants and ‘outcome’, influenced by social factors is conceptually inadequate. It is now clear that schizophrenia is a life course phenotype, with antecedent ‘outcomes’ manifest throughout infant development and early childhood. Both risk and protective factors interact across the life span. This far-reaching, longitudinal view of disease causation is radically altering our understanding of several chronic physical disorders (see below), and the same is happening in schizophrenia. The schizophrenia phenotype does not ‘start’ at the appearance of the first positive psychotic symptom. Multiple exposures modify a pattern of outcomes that appear in early childhood, develop through early and intermediary phenotypes, prodromal symptoms, positive psychotic symptoms and negative ‘deficit’ syndromes. There is no reason why psychosocial factors should not play a role in earlier, as well as later, phases of this trajectory. We should at least be ready to take a look.

The mechanisms by which social risk factors may contribute to the risk of adult onset psychosis are unclear. Their absence from scientific thinking has inhibited theory development and more work is needed. But it is likely that gene to environment interactions result in ‘reciprocal escalation’ (Rosenthal, 1963) in which early ‘outcomes’ such as dissociative behaviour during childhood or sporadic hallucinations are intensified. This process is likely to involve abnormalities of developmental psychology such as the effects of aberrant source monitoring and mis-attribution, accentuated by such factors as social isolation or family experience of boundary diffusion and/or emotional restriction (Wahlberg et al., 1997). The Finnish adoptive family study (Ternary et al., 2004) and the Copenhagen high risk study (Carter & Fairburn, 2002) produce evidence of either genetic control of sensitivity to environmental factors, or environmental control of gene expression. A recent meta-analysis of twin studies in schizophrenia (Sullivan et al., 2003) confirmed a small but significant effect of shared environment over and above that of the genetic contribution. These data herald a new era of theory development integrating biological risk factors, developmental psychology and different levels of social exposures.

THE SOCIAL BIOLOGY OF OTHER COMPLEX CHRONIC DISEASES

This far-reaching longitudinal view of disease causation has already transformed our understanding of several other chronic physical diseases. The epidemiology of coronary heart disease is a case in point (Barker, 1992; Barker et al., 2001). Here, findings of an association between low birth weight and adult-onset disease led to the ‘foetal programming’ theory in which physiological insult during a ‘critical’ developmental period was held to ‘programme’ the organism for adult onset disease. There are obvious parallels with the neurodevelopmental theory of schizophrenia (Weinberger et al., 1992). However, other epidemiologists were researching associations between coronary heart disease and risk factors operating during adult life. The socio-economic gradient in the incidence of coronary heart disease was of particular interest. The Whitehall 2 series of studies (Marmot et al., 1991) found that low socio-economic position, and particularly subjective reports of low control over work environment, made the largest contribution to the risk of heart disease. This group of researchers suggested that the socio-economic gradient in ill health and mortality widened during the 1990’s as a result of the rise in job insecurity associated with more part-time and temporary work, and self-employment. But which was it, programming of the foetus in utero or social experience in adult life? In a signal piece of work, Barker et al. (2001) utilised a longitudinal cohort design to marry these two perspectives to study the relationship between birth weight (or ‘thinness’) and adult social class. The most important finding was not the independence of childhood and adult conditions, but their interaction: low adult social class was related to coronary heart disease more strongly for men who had been thin at birth (adjusted for parental social class). Commenting upon their finding Marmot (2001) wrote ‘It is a common tendency in science to argue that in order for my pet hypothesis to be correct yours must be wrong. Indeed it is somewhat unsatisfactory for both yours and mine to be right at the same time’.

A new social biology of schizophrenia will allow us to move beyond the ‘pet hypotheses’ of the past to
explore the role of social as well as biological risk factors across its life course trajectory.

**EARLY POINTERS**

The highly replicated finding of a strong association between risk of schizophrenia and migration family background points to the potential importance of ecological context and social setting. (Harrison et al., 1988; Harrison et al., 1997). In the UK, Britains of African-Caribbean decent have a 6-fold greater risk of developing schizophrenia and related psychotic illnesses. (Eaton & Harrison, 2001). So far, investigations of biological risk factors such as genetics and obstetric complications have proved unfruitful (e.g. Hutchinson et al., 1997) and answers may lie in studies of social experience and social position. British born African Caribbeans achieve less academically compared with the population as a whole and more are unemployed in adult life. It is conceivable that chronic exposure to social adversity and discrimination may provoke a paranoid attributional style (Sharpley & Peters, 1999) placing individuals at risk of developing psychotic illness (Gilvarry, 1999). This conjecture finds some support in work carries out by Boydell et al. (2001) that showed an association between higher rates of psychosis in African-Caribbeans and residents in low-density ethnic populations. In other words, those individuals living in areas with fewer people from similar ethnic backgrounds, were at greatest risk. Such conclusions are inferential of course, but these data provide fertile ground for theory development to enable future hypothesis testing strategies.

As we noted above, a promising recent finding has come from a long-term follow-up study of Finnish adoptees (Tienari et al., 2004). Adoptees at high genetic risk for schizophrenia were much more sensitive to problems in the rearing adoptive family, such as ‘critical/conflictual’, ‘constricted’ and ‘boundary problems’ family interactional styles. If these findings can be replicated, it does indeed appear that ‘genes set the boundaries of the possible; environments parse out the actual’ (Eisenberg, 2004).

So we find ourselves in a new and exciting era for schizophrenia research. A renewed interest in social experience is happening not in spite of the human genome project, and the other achievements of ‘big science’, but because of them. Inevitably progress will be slow and frustrating as we attempt to unravel interactive chains of risk in a low prevalence disorder comprised of overlapping narrow phenotypes of uncertain specification. Perhaps we need a ‘human phenome project’ to allow the disaggregation of homogenous phenotypes from chaotic, clinical syndromes such as schizophrenia. There remains much confusion, too, over the classification and conceptualisation of ‘social factors’. There are micro-social levels such as the family; ‘mezzo-social’ levels embracing local area networks and locality culture; and macro-social factors embracing shared cultural norms and political policy making. The biology of the human condition is played out across hierarchies of social organisation in a constantly evolving interactive system.

If only life were simpler. But to quote Einstein, ‘our view of the Universe should be as simple as possible…. but not more simple than that’.

**REFERENCES**


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