

SECTION I

Mental Health and Mental Disorder in Social Context





Editors' Introduction

The first chapter is written by a medical geneticist, Angus Clarke. As will be clearer in later chapters (see Thomas and Bentall in Section 2) bio-reductionism remains a recurring point of contention and grievance for social scientists studying mental health. It is useful then to begin with this topic but written by a professional biologist with a critical eye about, and commitment to, 'the social'. Clarke explains in some detail how geneticists think about behaviour, dismissing at the outset strong claims from either side of the 'nature–nurture' debate. He provides a useful and informed discussion for readers with no background in genetics about how that broad field considers mental disorders. Not only does this field entail empirical complexity, it also implies some pre-empirical questions about conceptual coherence in relation to distinctions between the normal and the abnormal.

In line with these more fundamental pre-empirical questions, if the empirical link between genetics and behaviour in its social context is complicated it is not a simple matter either to 'measure' mental disorder as the next chapter indicates. Jerome Wakefield and Mark Schmitz address this vexed question, in particular relation to community samples, which contain people who have had no professional contact and do not (necessarily) view themselves as being mentally disordered. The problems of both reliability and construct validity for psychiatric epidemiology also remain for social scientists, especially those reliant on nosological systems, such as DSM (from the American Psychiatric Association) or ICD (from the World Health Organization). Funding agencies like the NIMH in turn demand their use (whatever doubts might be harboured by individual researchers). The detailed methodological challenges addressed in this chapter are particularly pertinent to consider in the light of the DSM now going into a fifth edition, due to

appear in May 2013 (<http://www.dsm5.org/pages/default.aspx>). This further revision is being constructed at a time when hard and fast distinctions between particular disorders and between many disorders and normality are often still not easy to make.

In the next chapter, Benedikt Rogge offers a contribution from Germany (a special thanks to him, from us, for rising to the challenge, so admirably, of writing in a second language). He addresses the recent pre-occupation within social science and social policy about wellbeing and positive psychology and begins where the last chapter left off: mental health is a fuzzy concept. After the problems of defining mental health and mental disorder are addressed, Rogge then summarizes the shift towards 'positive psychology' and places it within a wider sociological context of debate about 'the self'. This draws our attention to the disciplinary separation (as well as potential common interest) between psychiatry, psychology and sociology. Positive psychology and the sociology of the self may now be complementary exercises to place alongside the clinical focus on defects, pathology and distress found in psychiatry and clinical psychology.

This prospect is also picked up in the next chapter by Gillian Bendelow, who begins as a sociologist with a focus on emotional health as a discourse to be considered separately from the concerns of clinical professionals. In particular she wants to start a discussion about mental health and the emotions with a re-consideration of the traditional psycho-somatic split, the legacy of Cartesian dualism. Her attention to medicalization and the limits of a focus on biomedical antecedents links to later chapters (particularly from Olafsdottir in this section and Thomas and Bentall in the next). However, Bendelow also cautions against the risks of new emphases on holism, which create the spectre of 'healthism' and invite new forms of surveillance and social control.

The next chapter returns us to social epidemiology, with a particular focus on ethnicity and race from a British viewpoint. James Nazroo and Karen Iley emphasize the role of social and economic inequalities in the production of both ethnic/racial differences in risk of severe mental illness. Those inequalities also construct the experience of ethnic/racial minorities, when their members experience mental health problems and have services contact. However, this chapter appears in this part of the book rather than the next because the process of service contact mirrors wider social processes about race and inequality. This and other chapters (see Chew-Graham, Hermann and Secker in the next section of the book) are a window into the established class gradient in mental health, which we simply take for granted now as social scientists (see our preface). The authors go on to examine methodological criticisms of studies in the field to date and round off their chapter with a consideration of the experience that ethnic/racial minorities have of their problems, which connect the experience of service contact with the shared wider racialised context which both patients and services are embedded in.

If race is one important dimension to the experience of mental health problems, so too is gender. This topic is discussed by Jane Ussher with a focus on the

experience of depression. She looks at the extensive empirical evidence on gender differences in the diagnosed incidence of depression and prevalence but then goes on to explore competing explanations. The latter include hormonal, as well as psychological and sociological accounts, especially in relation to material and role inequalities. She also introduces other variables, which are important but contested; domestic violence and lesbian relationships (discussed as well later, in the chapter by Pilgrim and Rogers). Gender inequality is thus posited as an important source of mediation between social stressors and personal distress. Ussher also summarizes some evidence on cultural differences, which is extended in the next contribution, also written from Australia.

Renata Kokanovic discusses depression, but this time in relation to the cross-cultural challenges of formulating the meaning of experienced and expressed distress. Her examination of depression raises some important conceptual points suggested in earlier chapters; Ussher's just noted, but also those from Bendelow, Rogge and most fundamentally from Wakefield and Schmitz. Can we readily distinguish depression from normality and is misery experienced and expressed in the same way in all cultural contexts? Given that the World Health Organization has been concerned about a 'pandemic' of depression, the other question implied is 'a pandemic of what?' Kokanovic's exploration allows us to reflect on these questions and like Ussher raises some challenges for social scientists about the tensions between realist and constructivist accounts of common distress.

Questions of stress and experienced distress are then considered more extensively by Susan Roxburgh, who focuses on the stress process model. This consists of three primary elements: stressors, intervening explanatory variables, and stress outcomes. Each of these elements is considered in turn by the author. The intervening variables include resources, such as social support, which are picked up for more consideration at the end of the book in the chapters by Secker and Pescosolido. Finally Roxburgh looks at the outcomes of stress, especially depression (sadness, demoralization and alienation) and anxiety (feelings of tension, restlessness and irritability). These are the main often mixed manifestations of 'common mental disorders' treated in primary care (see Chew-Graham in Section 2).

In the subsequent chapter by Scott Schieman, the stress process model is also used as a framework for understanding the relationship between faith and mental health. Despite a common assumption about secularization, belief in God as a causal agent remains important for many people (even if they have no agreed named religion or attend religious rituals regularly). For this reason, Schieman argues that it is important for students of mental health in society to look carefully at the interaction of faith, stressors and personal resources. This reminds us of the importance of 'intervening explanatory variables' in Roxburgh's earlier account. It is also an opportunity to rehearse competing arguments about whether religion is pathogenic or helpful in the lives of ordinary people.

In the next chapter Brea Perry joins one of us (BAP) to consider the emergence of stigma about mental disorder, especially in relation to that identified in early life. On the one hand, prevalence rates of recorded mental disorder are at their

highest in the very young (and the very old), on the other we know little about public attitudes towards childhood problems. This chapter provides an empirical account from the USA of how the general public comprehends health conditions in childhood (ADHD, depression and asthma). This makes a start at producing an evidence base about ordinary understandings of childhood problems that might be the basis for public education and other policies.

Stigma is addressed in a more general way by Graham Scambler in the next chapter, which starts with Goffman and Wittgenstein as early authoritative discussants about the separation of normal from non-normal conduct in society. Stigma has to be considered in the same sociological breath as norms: it cannot be understood as a free-standing topic. Scambler places specific consideration about mental illness within a wider context of the sociology of stigma and in relation to labelling theory, biographical disruption and narratives of personal tragedy. He extends this to challenges from disability theory, moving on to a discussion about the possibility of stigma reduction programmes. Once more, this discussion brings in some ontological and epistemological aspects of social science, in relation to the tension between materialist and constructivist accounts.

If stigma is one outcome of norm transgression, then the re-framing of the latter, from sin and crime to illness, is the starting point of Sigrun Olafsdottir's exploration of medicalization, with attention being paid to the interests of the medical profession, the drug companies and managed healthcare. As she notes, this confluence of interests is at its most obvious in the USA and hence the stronger interest in the medicalization thesis there than in other parts of the world. The author provides a critique of this US-bias in theorizing medicalization and introduces a comparative approach as a corrective. This does not undermine the basic model of medicalization but it does imply a needed sensitivity to cross-national/cultural differences.

In the final chapter in this section of the book two of us (DP and AR) start with a criticism of the taken-for-granted cultural assumption about mental disorder as the source of danger. We argue that a more valid account should understand it as a two way street. Danger is also a common source of mental disorder- in the home, on the streets, in the workplace and most dramatically in war zones. (The chapter by Roxburgh on stress is pertinent here, as is the part of Ussher's chapter that has already considered domestic violence.) The notion of danger is discussed in relation to both violence and risk and this permits us to note the tension, which exists in debates about mental health policy in relation to social control (serving the state and third party interests) and beneficent paternalism (the use of legal powers to ensure treatment of mental disorder). This policy emphasis starts to explore topics to appear in Section 2, especially in the chapters from Scull and Rose and Campbell.

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The Limits to Psychiatric and Behavioural Genetics

Angus Clarke

INTRODUCTION

My starting assumption, is that genes are ‘involved in’ behaviour; consequently, genetic variation contributes to variation in behaviour. To deny that would be not merely unreasonable but incoherent, although there is still some appetite for the old nature–nurture pseudo-controversy. The too-crude dismissal of the importance of genetic factors can still appeal to those who enjoy attacking the straw-man genetic determinist, who is thought to argue for the ‘primacy’ of genetics over the environment (Sonuga-Barke, 2010). If there is any sense in talk of the ‘primacy of genetics’, it is that an individual’s set of genes is given and fixed from conception and is from then on available for interaction with the (changing) environment. What does not make sense is to think of either an individual’s genes or their environment as being the principal determinant of future behaviours in isolation from their environment or their genes (respectively).

A full repertoire of genes is required for all behaviour (whether the latter is designated as normal or abnormal). All but a few of the smallest chromosomal deletions, that result in some genes being present in one copy per cell instead of the usual two, are associated with cognitive impairment and therefore with difficulties for the individual in organizing their behaviour. Even chromosomal duplications – resulting in three copies of the relevant genes – usually affect cognition and behaviour as well as other aspects of growth and development.

Such chromosomal anomalies become interesting – and challenge our understanding – when we find that a particular deletion or duplication is associated not merely with a diffuse cognitive impairment but with some more specific and unusual behaviours. The idea that a disruption to the set of chromosomes leads to a ‘spanner in the works’ and thereby a disruption to thought and communication can be accommodated within a very primitive model of ‘genes acting within the brain’; but how would a specific chromosomal anomaly lead to a specific behavioural anomaly?

The types of evidence we can draw upon to assess the effects of genetic variation on psychiatric disease and behaviour more generally include observations of people with disturbances of cognitive development and behaviour (including mental illness), where there is a good reason to accept a chromosomal or genetic basis for the disturbance. We might also observe the familial clustering of diagnosed mental illness or cognitive impairment, sometimes presented in terms of ‘heritability’. In addition, we might have an apparent association of genetic variants from across the genome with diagnosed mental illness or a variation in behavioural traits.

In this chapter, I examine the types of evidence and argument that have been used to relate genetic factors to behaviour, primarily that deemed to be abnormal. We consider what types of conclusion such evidence is able, in principle, to support in the light of a realistic model of gene–environment interaction.

EVOLUTION AND ETHOLOGY

One context in which genes are related to behaviour is in discussions of our evolutionary past. It is clear that the behavioural patterns enabled by our genes have been compatible with our survival as a species. This has always entailed both cooperation and competition with our fellow humans; it is with whom one cooperates, with whom one competes that is important. Observations of primate behaviour can give insight into our remote past because our ancestors resembled contemporary primates (Cheney and Seyfarth, 2007). However, while such accounts may tell us something about the evolutionary success of different behavioural strategies, they do not allow us to draw inferences about how specific genes are related to particular behaviours. The genetic constitution of a species will impose constraints on the repertoire of behaviours available to an individual of that species but this gives us no access to understanding the way in which the genetic variation between individuals leads them to behave differently.

Armchair evolutionary reflection leads us to consider how the behaviour of an individual will let him or her contribute maximally to the next generation of the species. Such an approach focuses on competition within a species and forces us to acknowledge the importance of *sexual* selection, as well as the narrower type of natural selection for mere survival. While we must combat parasites and infectious diseases in order to survive, and be able to endure occasional injury

and famine, such qualities will not be transmitted to the next generation if we leave no offspring that is, if we cannot attract a mate and ensure that our children survive to maturity. A crude Darwinian approach starts from the position of 'selfishness' to identify the behavioural traits that will prove to be essential for individuals both to survive and to reproduce effectively. However, can we account through such reasoning for the range of human behaviours found in modern societies?

With such a question, as in science generally, one must search for the 'counter-examples' that could disprove a hypothesis. One obvious question has related to altruism. How can one make sense of apparently altruistic behaviour, such as issuing a warning cry about a predator or assisting members of the species in rearing their offspring, within a Darwinian framework? Risk-taking or burden-sharing by one individual on behalf of others can be accounted for through the conventional operation of natural selection, if those helped in this apparently 'altruistic' fashion are relatives. In such circumstances, the 'altruist' is promoting the survival of relatives and thereby the transmission of his/her own genes when they are passed on by a relative. Such considerations apply in particular to some of the social insects, as with sterile worker bees labouring to ensure the success of the hive, but also to birds and mammals with cooperative rearing of the young. More complex patterns of indirect reciprocity in human societies may have developed from such practices (Nowak and Sigmund, 2005) and looking for cooperation between non-kin does not provide clear counter-examples (Clutton-Brock, 2009).

Evolutionary psychology constitutes an attempt to account for a range of human behaviours and attributes – normal and abnormal – by postulating similarly 'natural' processes, explicable in terms of natural selection. Its weakness is that the processes it describes must have happened in the distant evolutionary past if they are to account for human behaviours, personality traits and psychopathology evident today. This field of enquiry is all too vulnerable to the criticism that it is essentially a series of Kiplingesque speculations in the tradition of the 'Just So Stories'. The descriptions of human gender roles and personality types may ring true, or may at least be amusing, but the causal accounts are largely speculative, neither adding firm knowledge nor yielding useful (testable) hypotheses.

However, despite this criticism, there are of course good reasons for expecting different patterns of social behaviour in male and female humans, as in many other animals, not only primates. One especially important factor in recent human evolution may have been the appearance of spoken language, which may have led to the rapid development of 'wit' – in both senses – through female choice of mate and the processes of sexual selection. However, one can only speculate about the details and the naturalistic fallacy – arguing from 'is' to 'ought' – is all too common in this domain. From the possibility that our hunter-gatherer forebears may (at certain times, in certain places) have had a particular pattern of social organization, we can draw no conclusions about how we *should* organize our collective lives today.

Claims about 'intelligence' are related to the speculations of evolutionary psychology. Thus, the idea that the human X chromosome is especially involved in 'intelligence' receives a limited degree of support from some evidence. There does appear to be an excess of X chromosome genes among those in which mutation causes serious cognitive impairment (Turner, 1996), although that does not allow one to conclude that variation in genes on the X chromosome accounts for more than that chromosome's rightful share of the genetic contribution to variation in intelligence (however, this is measured). Such reasoning is entirely invalid. Furthermore, these claims ignore the greater chance of a gene on the X chromosome coming to attention through mutation and the greater chance of the mode of inheritance being apparent.

In summary, an evolutionary (Darwinian) approach to the study of animal (and human) behaviour is necessary – "nothing in biology makes sense except in the light of evolution" – *but* such an approach is limited in what it can establish as fact about the past or, as desirable, about the present. There are altogether too many examples of popular science writing that seek for solutions to today's social and political problems through the application of crude ideas about our collective past.

'IT'S A KNOCK-OUT': STRUCTURE AND FUNCTION IN THE BRAIN

Other approaches in addition to genetics have been taken in the search for understanding of the central nervous system (CNS). These approaches all have in common a commitment to the reductionist project. This is not intended as a criticism because a reductionist approach has to be the starting point for any scientific study of the central nervous system. Only in this way can one recognize the limits of reductionist explanation – by coming up against them. Assigning functional roles to specific regions of the brain through the analysis of the effects of damage from tumour, infarction, haemorrhage or experimental lesions is a long-established approach that was essential in the early stages of neuroscience and remains so today. The central difficulty of this approach has been to understand the rules of inference from the observations made, which are remarkably similar between the different contexts of neuroscience and genetics. In neuroscience, what can one conclude about the function of part X of the brain if behaviour Y occurs when a lesion is produced there? In genetics, what can one conclude from the emergence of behaviour Q when gene P is inactivated or altered (mutated) in some other way?

In relation to neuroanatomy, there has been a progressive development of our ability to make such inferences as the working model of the brain has increased in sophistication through the accumulation of our knowledge of previous observations and experimental interventions. The *normal* function of one of the basal ganglia, for example, might not be most helpfully understood as the suppression of involuntary contra-lateral writhing movements, although that might be the most prominent feature of a lesion there, whether pathological or experimental.

There has been a similar process of sophistication in our understanding of the function of genes. The naming of genes is now more formalized but used to be based upon the phenotype that arose when a mutation occurred in the gene. The ‘white-eye’ gene of *Drosophila* usually produces eye pigment, which is not produced when the gene is mutated so that the eyes are then white. In one sense, this leads to a paradoxical naming of a normal gene or the corresponding protein by its opposite (as with the dystrophin protein, a lack of which results in Duchenne muscular dystrophy) or the naming of a gene by a disease-related feature irrelevant to the function of the normal gene (as with the archetypal example of the polyglutamine repeat diseases, Huntington’s Disease, and the huntingtin protein, whose normal function is related to the disease after which it has been named by coincidence only).

More recently, the role of particular neural circuits and pathways has been defined in animal models in increasing detail using these approaches of inferring function from the effects of the ablation of brain structures. Two recent illustrations, drawn almost at random from many, include the switching on or off of fear in mice (Herry et al., 2008) and the pursuit of rewards in rats (Burke et al., 2008).

Another productive, reductionist approach to structure–function relationships in the brain is that of imaging, including functional imaging, which is able to identify neural circuits active during specific tasks and sensory processing. As David Hume indicated long ago, the temporal association of two events does not establish causation. Such experiments may therefore not be able to distinguish the causal driver of a neural process from those associated circuits involved in its modulation, if indeed there is usually something corresponding to a ‘causal driver’ so that the distinction has a meaning (Logothetis, 2008).

With this approach, it may even be difficult to distinguish actual neural activity from anticipated but aborted activity, as blood flow in the cortex can be directed in anticipation of an imminent task that then fails to be carried through to performance (Sirotin and Das, 2009). Whether the findings of such studies are regarded as explanations or, more properly, as increasingly detailed descriptions of the phenomena to be explained, will depend upon the investigator’s point of view.

This rather abstract argument is relevant to the topic of this chapter when considering the question of a behavioural phenotype and what shape an explanation of such a phenotype might take, if an explanation can be discerned at all. Let us look at the parallels in a closely related field. The recognition of an unusual pattern of physical features is the core activity in dysmorphology – the clinical study and delineation of patients with congenitally abnormal physical features, often also accompanied by abnormalities of the CNS and of cognitive development.

The early development of this discipline centred on the recognition of recurrent patterns of malformation or unusual physical features and whether these were usually sporadic events in a family or had a tendency to recur. Once cytogenetics had developed to the point of diagnostic applications, some conditions but not others were found to be associated with chromosomal anomalies, initially with

an abnormal chromosome number (as in Down syndrome or Turner syndrome) and then with more subtle anomalies, such as chromosomal deletions or duplications. The extent to which trisomy 21 is not only associated with but can be said to 'explain' Down syndrome is an interesting question at many levels, with obvious parallels in the neurosciences. While trisomy 21 may explain why one child rather than another is affected by Down syndrome, it only permits a detailed mechanistic explanation of some of the physical and behavioural features of the condition. Even where it can account for the incidence of dementia at an early age in those with Down syndrome, *it is unable to account for why an individual has a specific lapse of memory on one occasion but not another.*

The interplay between clinical and laboratory genetics has been enormously productive in developing a taxonomy of dysmorphology. The recognition of an association between cases of a clinical disorder and particular cytogenetic or molecular genetic findings leads to the recognition of a subgroup of the clinical disorder where this association is not apparent. Such atypical cases will often have a different cause and may, in time, be recognized as an altogether different entity in their own right. One could mention the emergence of Noonan syndrome from Turner syndrome as an example, or the recognition of CDKL5-related disease from among the 'early onset of seizures' variant of Rett syndrome. To what extent can we expect similar progress in our understanding of the genetic basis of the disorders affecting behaviour?

SYNDROMES AND BEHAVIOUR

Many of the dysmorphic syndromes affecting embryogenesis and then physical and cognitive growth and development are associated with abnormal patterns of behaviour. These abnormal behaviours are most often the result of substantial cognitive impairments that restrict the assimilation of sensory input, its cognitive processing and then the behavioural responses. Some of these syndromes show very characteristic patterns of behaviour, such as the 'cocktail party' chatter of a child with Williams syndrome, the social awkwardness of some males with fragile X syndrome or the social interest but slow responses of someone with Rett syndrome. Such behaviours can sometimes be recognized as a part of the overall 'gestalt' of the condition or they may be more apparent when behaviour is studied with objective systems of description and measurement. In relation to the physical features of some dysmorphic syndromes, it is becoming possible to sketch out a plausible sequence of events from the underlying genetic cause of the condition through the consequences of that in the embryo and foetus to the physical features of the affected child or adult, as with the structural proteins disrupted in Williams syndrome (including a deletion of the elastin gene) or Marfan syndrome (a fibrillin gene mutation).

Are we then beginning to be able to give a coherent account of the pathway from the genetic alteration underlying a syndrome to the specific behavioural

features found in that condition? The short answer – all we have space for here – is ‘No!’. Such explanatory pathways for these and other dysmorphic syndromes have not yet been constructed in a plausible fashion, except to state the obvious, that an abnormality in a gene required for normal brain development and function will have cognitive and behavioural consequences.

We must indeed be very cautious in attributing behaviours common in those with a specific condition directly to the primary genetic basis of the condition, rather than to some indirect habits of social interaction that develop because of the physical appearance of the young child, the pattern of their cognitive abilities or particular difficulties they have with the senses or with organizing motor activities. However, the observation of an association between a genetic anomaly, its particular physical features and a particular pattern of behaviour is not fundamentally in doubt, even if the mechanisms through which the genetic change leads to the pattern of behaviour often remain obscure.

SINGLE GENE EFFECTS

Are we any further forward with understanding the effects of single genes on behaviour in the absence of developmental problems and severe cognitive impairment? As with development of the brain, so with conditions which lead to its degeneration: single gene disorders that lead to the loss of neurons and neuronal connectivity lead to the loss of capacity and so to dementia – as in Huntington Disease and the familial forms of early-onset Alzheimer’ dementia. But what about the effects of single genes on more specific items or patterns of behaviour, other than simply causing severe cognitive impairment?

There are distinct single-gene (Mendelian) disorders and chromosomal deletion syndromes associated with patterns of behaviour more usually seen in the absence of a clear genetic anomaly. The behavioural pattern of autism, for example, is often found in children with tuberous sclerosis (TS) (caused by mutation in the TSC1 or TSC2 genes) and sometimes in children with constitutional PTEN gene mutations (Butler et al., 2005). The diagnosis of ‘schizophrenia’ occurs at a high frequency (more than 25 per cent) in adults with the 22q11 deletion typical of people affected by the di George and Shprintzen (velo-cardio-facial) syndromes. Children with TS usually develop benign intra-cerebral tumours (tubers) and those with mutations in PTEN – another tumour suppressor gene affecting growth in early life – often show macrocephaly and so the effect in both cases may be mediated by abnormal growth of the brain.

Other Mendelian loci in which mutation is associated with autism are those encoding the neuroligin proteins NLGN3 and NLGN4 (Jamain et al., 2003). These cell adhesion molecules are positioned on the postsynaptic side of synapses and are believed to interact specifically with neurexin 1 on the presynaptic side; it is of great interest – although perhaps tantalizing – that deletions and other disruptions of the neurexin 1 gene NRXN1 are implicated as contributing

to 'schizophrenia' (Kirov et al., 2009). Such single gene effects, however, have been found in few cases of psychiatric disease and in no cases of behavioural variation 'within the normal range'. Given the high frequency of psychiatric disease, with 'schizophrenia' having a life-time incidence of ~1 per cent, and given the long history of investment in research into these conditions, what can we say about the contribution of genetic factors to these important disorders? Recent studies of genetic variation across the genome suggest an overlap between the factors contributing to 'autism' and to 'schizophrenia', raising the possibility that these conditions may not be distinct diagnostic entities.

PSYCHIATRIC DISORDERS AND MULTI-FACTORIAL INHERITANCE

Genetic research into psychotic disorders, such as 'schizophrenia' (SZ) and 'bipolar disease' (BPD) has long been justified by its proponents indicating studies of heritability, especially twin studies comparing identical twins with fraternal twins or siblings. These studies often show a high value of heritability (up to 80 per cent in many studies). As molecular genetic studies became feasible in the 1980s, researchers set out to identify familial cases of SZ and BPD in order to conduct linkage analyses and map the important loci.

Although there were a few positive results, it became clear that single genes of major effect segregating in families (that is Mendelian loci) are not contributing substantially to the incidence of these disorders. As molecular methods developed along with the statistical and bioinformatic methods required to interpret their findings, it became possible to search for loci of lower penetrance – less likely to cause disease – until with current methods it has become clear that even powerful genome-wide association studies (GWAS), with (cumulatively) many thousands of cases and controls, have been unable to identify genetic variation accounting for more than a small fraction of the supposed genetic contribution to the risk of these diseases.

However, it is important to note that a few loci, implicated through segregation of disease in those rare families where a gene of major effect does seem probable, have now also been implicated in these more recent GWAS studies as perhaps contributing weaker disease predispositions in a much greater number of cases (O'Donovan et al., 2009). Of particular interest is the finding that two of the loci at which variation is associated with SZ are also associated with the risk of BPD. This raises the possibility that the genetic predisposition to both disorders is at least partly shared, so that they may not be two distinct conditions but instead somewhat different manifestations of a single category of major psychosis. And these factors also overlap with those implicated in autism.

The research community now needs to learn from these findings what they can tell us about the mechanisms underlying these disorders: what cellular mechanisms and/or neural pathways become dysfunctional in the presence of the predisposing variants, and how does this increase the risk that an individual will

become psychotic? Understanding these functional mechanisms – the basic neurophysiology – may give insight into new therapeutic possibilities for these common and immensely distressing and burdensome conditions. (For other accounts of psychosis see Bentall and Thomas, this handbook.)

LIMITATIONS OF THE COMPLEX DISEASE MODEL OF THE PSYCHOSES

Although the overview of current research into the genetic basis of SZ and BPD outlined above is fair, there are some complexities that need to be considered if we are to place the recent research findings in context. We need to question the evidence on which SZ has been considered so highly heritable and we need to think about what the term ‘heritability’ includes.

At this point, I should make explicit my ‘ideological’ position as both a paid-up realist (Bhaskar, 1975) and social constructionist (Berger and Luckmann, 1966). The world and our observations of it are real; the ideas we have about the world, however, are constructed and communicated in language and through processes of social interaction and negotiation. Diagnostic categories are social constructions that may correspond in more or less helpful and appropriate ways to observable reality; the construction of diagnoses in psychiatry has been and inevitably remains a more complex and contested area than in trauma surgery but the suffering associated with ‘psychiatric disease’ is real – incontestable – whatever labels we choose to employ.

First, it has become clear that some cases of diagnosed SZ are associated with the *de novo* occurrence (in the proband) of a small chromosomal deletion or, less often, a duplication. These are known collectively as copy number variants (CNVs) and are detected on DNA microarrays (gene chips), which can compare the relative dosage of gene sequences from across the genome. The same technology is proving very useful in identifying the genetic basis of previously unexplained cases of dysmorphic syndromes and other disorders of physical and/or cognitive development.

What does this mean? Well, comparisons of identical and fraternal twins have been the mainstay of heritability studies in SZ and, if a condition has been caused by a new genetic change of major effect (such as a CNV) then it is likely to affect both of a pair of identical twins but only one of a pair of fraternal twins. A CNV arising as a new mutational event will therefore lead to a high estimate of heritability for the disorder simply because it is a new mutation of high penetrance affecting identical but not fraternal twins. This will lend unwarranted support to the ideas of the ‘complex disease’ origin of SZ, because the causal model underlying the estimate of heritability will have been misconceived. CNVs known to be associated with SZ are being recognized in 2–3 per cent of cases, and *de novo* CNVs in as many as 10 per cent of cases of SZ (Xu et al., 2008) although that figure is higher than other published figures (reviewed in O’Donovan et al., 2009).

What remains uncertain is whether the de novo CNVs found in SZ represent a small subgroup of SZ. In contrast, they could be the tip of the iceberg, with many other cases arising as de novo events undetected by microarray technology because they are much smaller, perhaps point mutations or other intragenic mutations within loci included in the CNV sites. It may take a few years for uncertainty to be clarified, especially if de novo events contribute to some classes of disease and not to others. If the CNVs constitute only the tip of an iceberg of new or recent mutations occurring in the last few generations, then this could account for both the high estimates of heritability and the lack of success of GWAS studies in accounting for more than a small fraction of the heritability. The new generation sequencing technologies will help to resolve the issue in the long term, as much greater volumes of sequence data become available from patients with different patterns of disease. In the short to medium term, however, such data will doubtless generate more information than can be interpreted with confidence, as more sequence variants of uncertain significance will be encountered.

The second complexity we need to address is the nature of the 'heritability' estimated in twin studies and other experimental designs. This is the proportion of the variance in a quantitative trait that can be attributed to variation in the relevant genetic factors as a fraction of the total phenotypic variance. So the term applies only to quantitative traits and not to categorical traits, and it includes all the relevant genetic factors and not only the straightforward (independent) components of these factors. If all the relevant genetic factors interacted by modifying the risk of disease in a simple, multiplicative fashion, as would be the case for combining independent risk factors, then there would be less reason to query the interpretation of heritability estimates (although the point made in the paragraphs above would still remain valid). From what we know of other (lower) organisms, however, it seems most unlikely that GxG and GxE effects can be ignored. The problem is that, for many reasons, humans are poor organisms for estimating interactions between (that is among) genes and between genes and the environment.

Specific gene–gene (GxG) interactions are difficult to identify unless one has access to information about the phenotypes associated with each genotype from among the range of those possible. Because of the vast range of genetic variation within the human species, the nonrandom pattern of mating among humans, the long time-course from birth to maturity and the quantity of phenotypic information required, it is doubtful if enough data could ever be captured to permit such analyses. Indeed, there may not be enough people alive for the range of relevant genotypes to be represented. And this puts to one side the question of analysis and of interactions with the environment.

Our environments, of course, are also highly complex and variable; we live for decades and early experience may well shape our later mental health; we do not often marry or mate 'at random' and our family sizes are small and becoming smaller. The possibility of gathering enough information about the mental health outcomes of a large enough set of individuals of known genotype to assess the

risks of disease for a range of specific genotypes at numerous interacting loci and in the face of a range of different early and adult environments is therefore small unless one makes vastly simplifying assumptions as to what factors can be ignored. If the GWAS studies had shown (or come to show) that specified genetic factors do account for a large proportion of the (estimated) heritability, then that would have supported the simplifying assumptions underlying that work.

However, none of this has happened (yet). Given this complexity and uncertainty the methodological assumptions about psychosis and heritability in psychiatric genetics in the first part of the twentieth century were clearly flawed and driven by eugenic pre-suppositions. Indeed many of assumptions embedded in the legacy of that period in biological psychiatry remain highly speculative (Kingdon and Young, 2007). Put simply, the eugenic assumption of degeneracy pre-figured the desire to find confirmatory empirical evidence and weak methodologies of inquiry were deployed to find the latter (Marshall, 1990; Pilgrim, 2008).

GENE INTERACTIONS IN QUANTITATIVE TRAITS

In model organisms, where experimental designs are possible and mating can be controlled, such as with the fruitfly *Drosophila melanogaster* in particular, data can be collected that give us good insight into gene–gene (GxG) and gene–environment (GxE) interactions influencing a wide range of traits including important behaviours. Especially helpful has been a long series of studies by Trudy Mackay and her colleagues, often using recombinant inbred strains of flies kept in a small number of distinct environments and studied with the help of breeding programmes. Of course, none of these facilities exist in human populations but the difficulty of demonstrating or measuring in humans the effects that have been identified in fruit flies does not mean that they are absent from our species.

Trudy Mackay's work in *Drosophila* on both life-span (longevity) (Leips and Mackay, 2000; Vieira et al., 2000) and sensory bristle number (Dilda and Mackay, 2002) shows that there are strong interactions between genes, between genes and sex and between genes and the environment, especially temperature (as I have outlined in more detail elsewhere – Clarke, 2004). This work has been integrated with microarray studies of gene expression to identify genes likely to be important influences on lifespan (Geiger-Thornsberry and Mackay, 2004; Lai et al., 2007). The methods required for the quantitative genetic analysis of behavioural traits have been established some years ago (Anholt and Mackay, 2004) and have begun to yield important insights (Ayroles et al., 2009), although it is interesting that research focused on mutagenic screens to identify single gene loci influencing such traits is still yielding the most important findings (Vosshall, 2007).

Such work demonstrates that the genetic architecture of complex traits involves many loci interacting in a truly complex fashion and suggests that the studies that

could feasibly be conducted in humans will fail to identify many such effects, at least into the medium term. In addition, it seems that there are single genes of great importance for specific behaviours – and in which mutation will disrupt one or more such behaviours – but that many loci influence patterns of behaviour in a complex web of GxG and GxE interactions, even if they cannot all be identified in our own species. For this to be true, there must be a high level of genetic polymorphism that is of functional importance and that is maintained not merely by mutation and drift (the random consequences of breeding patterns and not the effects of selection).

Is that likely? The answer has to be ‘yes’ in *Drosophila* and there is no reason why it would not also be true for our own species. Phenomena such as frequency-dependent selection, density-dependent selection, sexually antagonistic selection and other types of disruptive selection are well known (Rice et al., 1992; Sokolowski et al., 1997) so that there is no need to expect heterozygote advantage and drift as the only mechanisms to account for high levels of polymorphism. The evidence in favour of recent natural selection in humans is limited but this relates principally to shifts in allele frequency leaving evidence in the pattern of linkage disequilibrium; such findings tell us nothing about the maintenance of polymorphism as discussed here.

GENE–ENVIRONMENT INTERACTIONS IN MENTAL DISORDERS

Thoughtful reviews of the genetics of complex disorders in humans have indicated such difficulties as those identified above in looking at such traits and disorders in humans (Kendler and Greenspan, 2006; Lewis and Brunner, 2004; Weiss, 2008). It would clearly be immensely difficult to obtain data about GxG interactions across a range of standardized environments in our species, without assuming that other genes are not involved in the trait under investigation. Despite this, some information has been collected about the overall effect of specific single alleles in at least two different environments (that is the GxE interactions) for several psychiatric disorders.

Highly dramatic and largely unsupported claims have been made about the contribution of genetic variation at the MAO locus to violent behaviour but more modest claims about the interaction of a functional polymorphism at this locus with a personal history of physical abuse as a child do have some supporting data, indicating that those subject to abuse in childhood and who have lower levels of MAOA activity are more likely to display antisocial behaviour as adults (Caspi et al., 2002).

Another example of GxE interactions evident in humans is of the association between a genetic variant in another enzyme influencing levels of amine neurotransmitters and antisocial behaviour. Among those given a label of ADHD, the frequency of antisocial behaviour differed with the alleles of a polymorphism at the COMT locus (Caspi et al., 2008) and similar findings have been made

elsewhere (Fowler et al., 2009; Maestu et al., 2008). The interpretation of such findings, however, is not straightforward and needs great care to avoid erroneous over-generalizations (Thapar et al., 2007a). In particular, the intrauterine environment may modify the effects of genotype and postnatal environment as influences on subsequent psychopathology (Langley et al., 2007) and there are methods that could begin to disentangle such effects (Thapar et al., 2007b).

Turning to autism, the findings of an association with CNVs (deletions and duplications) as discussed above is of great interest, especially because of the implication of specific genomic regions containing plausibly 'relevant' gene loci (Glessner et al., 2009; Wang et al., 2009). While autism is clearly not a single disorder, and can be strongly associated with mutations at some specific genes (for example Butler et al., 2005), most cases are not associated with a clear Mendelian disease. Therefore, extent to which the CNVs identified in these two 2009 studies have arisen *de novo* (or have been transmitted from an affected parent) is also of great interest because of the distorting (inflating) effects of such events on measures of heritability, as discussed above.

The degree to which common variants in the population modify the phenotype of autism while individually rare but cumulatively common major mutations (such as CNVs or the presence of rare Mendelian diseases) trigger the development of such problems remains to be determined; at least it is clear that these issues are now being addressed by the molecular researchers, who are not content to adopt a 'traditionally' deterministic stance (Happé et al., 2006; Stephan, 2008; Weiss et al., 2009).

In the area of 'depression', too, evidence is emerging that people of certain genetic constitutions are more liable than others to respond to stressful life events by becoming sad and distressed (Caspi et al., 2003; Risch et al., 2009). Such findings bring psychiatric genetics much closer to the lay perspective on causation of such illness as being in part triggered by circumstance, in part the result of personality.

In the case of SZ, some of the predisposing genetic factors appear to be the same as in autism and BPD (Lichtenstein et al., 2009 and references cited above). If these findings are upheld by further evidence, then these diagnostic categories will clearly require reassessment. The finding of post mortem epigenetic differences within specific regions of the brain between patients affected by SZ and controls lends some credibility to the idea that early life experience may contribute to disease through such a mechanism (Mill et al., 2008). While some familial mutations are known that can act as strong triggers of SZ (Blackwood et al., 2001), it is perhaps intrinsically unlikely that such inherited variants of major effect would be common as the fertility of those with disease is likely to have been impaired both by reduced survival (especially in the past, before effective treatments) and impaired social skills.

The frequent finding of novel CNVs affecting genes in neurodevelopmental pathways in cases of SZ (Walsh et al., 2008) suggests that many cases of such disorders arise *de novo* and that other such new mutation events undetectable by

array CGH will account for further cases. The most plausible conclusion at present seems to be that major (and often new) events trigger disease and that common functional variants will modify the nature and course of disease and perhaps thereby influence the particular diagnosis made according to today's taxonomy; polymorphisms at the loci of major effect (for example Stefansson et al., 2003) may also act as such modifiers when the trigger is a major event elsewhere in the genome (Carroll and Owen, 2009).

GENETICS OF NORMAL TRAITS AND INTELLIGENCE

There is a long tradition of studies of 'intelligence', as measured by the Intelligence Quotient, and its heritability. These have usually used twin and adoption studies and have indicated a high heritability (often of 0.6 – 0.8). These findings have then often been misused by those with a prior political commitment to support some particular social policy such as – typically – the uselessness of investing in the early education of those belonging to lower social classes or specific ethnic groups.

Such misapplications of research findings make the elementary error of treating heritability, as if it were a fixed biological constant instead of being a variable that depends upon *the particular social environment* operating at the time. Moreover, this error is compounded when we consider that the environments to which different research groups were exposed were systematically different, as is the case in societies with wide socioeconomic differentials (Fischer et al., 1996; Lewontin, 1991). There is no need for us to recite these analyses here (Gould, 1981). Instead, let us simply recall that the prospect of misapplication of research findings in this area – looking at IQ differences between social and ethnic groups – is so great and the chance of 'useful' results contributing to the educational success of future generations so slim that the case for undertaking or supporting such research hardly exists (Clarke, 1997a; Harper, 1997). Some did believe in good faith that elucidating the genetic basis of variation in IQ within the normal range would help to understand the causes of severe cognitive impairment but these studies have failed to deliver that promise and were never likely to do so as the methodologies involved were intrinsically flawed.

It is clear that many measures of the heritability of IQ in contemporary society have been systematically inflated by the techniques employed (Devlin et al., 1997) and that IQ as measured is heavily dependent on socio-economic status (Turkheimer et al., 2003). Furthermore, the idea that there are 'genes for intelligence' seems implausible. *Rather, there will be specific patterns of alleles at multiple loci that interact with each other and the environment to modify a number of cognitive abilities.*

The suggestion that one particular allele at a locus will be consistently associated with superior 'wit' is most implausible. In that case, one would expect there to be strong selection – both conventional natural selection and, especially, sexual

selection – in favour of that allele and it would then not remain polymorphic. Rather, it is much more likely that variation at loci important for cognition and communication is maintained by the advantages brought by each allele in different GxG and GxE circumstances – as discussed above for *Drosophila* longevity, for example. The whole sorry saga of the genetics of IQ appears to be a tale of misunderstandings by researchers who have either been politically motivated or who have simply placed too much value on a narrow, scholastic intellect that happens to have brought them a degree of academic success.

APPLICABILITY OF GENE-WIDE ASSOCIATION STUDIES (GWAS) TO CLINICAL RISK ASSESSMENT

The research into the association between common genetic variation and the risk of the common, complex diseases has been struggling to explain its lack of success in accounting for more than a small fraction of the heritability of disorders, from cancer and diabetes to ‘schizophrenia’ (Maniolo et al., 2009). The reader who has reached this point will be familiar with much of the explanation. We have seen inflated estimates of heritability, as well as the difficulty in assessing GxG and GxE interactions in our species. However, there are some additional factors to consider: epigenetic variation acquired in early life as a ‘predictive adaptive response’ (Moore and Williams, 2009); the often underestimated contribution of rare variants to common diseases (Bodmer and Bonilla, 2008); and the impossibility of pangenome panels of SNPs (Conrad et al., 2009; Estivill and Armengol, 2007) to capture CNVs that have relocated to other sites around the genome (Schridder et al., 2010).

Even in the case of disorders, where the nosology is relatively straightforward – and certainly much less contested than in psychiatric disease – the use of genetic association studies using the SNP-based GWAS approach is of little, if any, value. It is poor at assigning healthy individuals to risk categories and so generally of little, or no, value. If it could be justified as at least accurate, there would remain many reasons as to why it may not be helpful, such as the sometimes paradoxical (medically unhelpful) behavioural and psychological responses to high or low risk information (Clarke, 1995, 1997b). However, its power to account for the heritable fraction of disease risk is so limited, not even that inadequate justification is available to those who offer such ‘services’ on the open market (Edelman and Eng, 2009; Janssens et al., 2008). Such irresponsibility must surely be motivated by desire for a quick return on investment rather than any professional sense of good healthcare (Clarke, 1995, 1997b). The scientific value of the underlying research is not in doubt – it is only the *application* of the research findings to assign healthy individuals to risk categories that is unwarranted (Jakobsdottir et al., 2009).

The suggestion that such tests should be made available to assess the risk that an individual might suffer from psychiatric disease is still less justified for at

least two important reasons (Braff and Freedman, 2008; Couzin, 2008). First, those likely to seek such testing will probably have a close family history of psychiatric disease. Accordingly, the SNP-based GWAS results will be irrelevant if the disease in the person's family is at least in part caused by an important *de novo* genetic event or at least one that has occurred within the last few generations. Second, such results could add to the stress known to precipitate at least some types of psychiatric morbidity.

CONCLUSION

Genetic variation contributes substantially to the occurrence of psychiatric disease and research into this is not only worthwhile but has recently begun to yield important results. However, from what we know of the genetic factors involved, the claims made about the genetic contribution to psychiatric disease in the past – especially some of the assessments of ‘heritability’ – appear to have been inflated and to have minimized the contribution to disease of the combined effects of many rare genetic variants and of Gene \times Environment and Gene \times Gene interactions. It is likely that our understanding of mental disorder and its classification may well require a radical revision, when and if our understanding of the genetic factors involved has been consolidated; this reassessment may also prove to be very helpful in developing new therapeutic approaches.

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