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EDITORIAL

Neuroscience and the future for mental health?

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Psychiatry is in one of its regular crises. It is a crisis of its diagnostic systems despite – perhaps because – of the recurrent claims about the extent of diagnosable 'brain disorders'. It is a crisis of its explanatory systems despite – perhaps because – of its current wager on the brain as the ultimate locus for explanations of mental disorders. It is a crisis of its therapeutic capacities despite – perhaps because – more and more people are making use of its primary mode of intervention focussed on the brain – psychiatric drugs. In this editorial, I will suggest that this triple crisis of diagnosis, explanation and therapeutics arises from the dominant reductionist approaches to the role of neurobiology in psychiatry that priorities the analysis of brain mechanisms, at the expense of an understanding of the whole living organism in its milieu, and the processes which social experience shapes neurobiology from the moment of conception if not before. I shall suggest a different approach that starts from the experience of persons coping with adversity in their forms of life. This approach does not require giving up on our search for plausible explanations of mental health problems that engage neurobiological mechanisms, but it begins from a commitment to understanding, and hence intervening in, the ways in which social adversity shapes and blights the lives of so many of our fellow citizens.

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Introduction

Psychiatry is in one of its regular crises. This crisis particularly bears upon the relation that psychiatry should have with neuroscience. It is a threefold crisis: of its diagnostic systems; of its explanatory models; of its therapeutic capacities. Of its diagnostic systems despite – perhaps because – of the recurrent claims about the extent of diagnosable psychiatric disorder – 25 or 33% depending on which estimate is taken (Kessler *et al.* 2005; Wittchen *et al.* 2011). Of its explanatory systems despite – perhaps because – of its current wager on the brain as the ultimate locus for explanations of mental disorders – 'brain disorders' (Insel, 2014). Of its therapeutic capacities despite – perhaps because – more and more people are making use of its primary mode of intervention – psychiatric drugs (Medco, 2014; OECD/European Union, 2014) (see also the helpful overview, with data on China, at http://www.theguardian.com/news/2013/nov/20/mental-health-antidepressants-global-trends.). What I want to do – at the risk of great oversimplification – is, first of all, to point out the depth of this triple crisis of diagnosis, explanation and therapeutics and to suggest an alternative pathway out of it, which entails a rather different relation between clinical psychiatry and neurobiological research.

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Crisis of diagnosis

Perhaps the crisis of diagnosis is best illustrated by revision process of the Diagnostic and Statistical Manual (DSM). As is well known, the DSM was revised to its current approach in the Third Edition published in 1980: diagnoses were to be specified in terms of discrete categories each based on a set of observable symptoms. But despite this emphasis on the observable, and the wish to eschew commitment to any specific explanatory framework, the approach was based on belief that for each category, identifiable biological aetiology and diagnostic markers would eventually be found (Feighner *et al.* 1972; Kendler, 2009; Regier *et al.* 2009). This hope was expressed by many, including Steven Hyman, then Director of the National Institute for Mental Health (NIMH), as late as 2003 (Hyman, 2003). It underpinned a long and expensive search for such biomarkers: research costing many millions of dollars and many hundreds of thousands of person hours. When the revision process that led to the recent edition of DSM began about 15 years ago, there was great optimism that such biomarkers would be found for some psychiatric disorders, enabling clarity in diagnosis, targeting of therapy and perhaps early and presymptomatic identification and treatment of those at risk. But as we know, when DSM 5 was published in 2013, there was not a single clinically validated biomarker for any psychiatric disorder (American Psychiatric Association, 2013). Indeed, 5 years earlier, by 2008, Hyman and others

already recognised the problems: there was no clear boundary of ill and well, there were no simple genetic disorders, similar symptomology could arise from different biology, similar biology could lead to different symptomatology (Hyman, 2008, 2010). But what were the lessons learned? To abandon DSM and go straight to the brain. Now, so it was thought, diagnosis based on observable symptoms was fundamentally misleading when it came to underlying causes and hence when it came to clinical decisions. Clarity – about causation, aetiology and treatment had to be found elsewhere. And the wager was that it was to be found in the brain – that the brain will, at some point in the future, provide an objective basis for diagnostic classification based on causal pathways which would provide effective targets for therapeutic intervention. Before the ink was dry on the proofs of DSM 5, Thomas Insel, the current Director of the NIMH announced that it would be redirecting its research efforts away from DSM – which had framed all its research funding for almost three decades – towards the development of its the Research Domain Criteria – RDoC (see Insel's 'Director's Blog' of 29 April 2013: http://www.nimh.nih.gov/about/ director/2013/transforming-diagnosis.shtml); – and that the RDoC approach would now underpin the research it funds onto the bases of psychiatric disorders (Insel & Wang, 2010; Insel *et al.* 2010; Insel, 2014) (this is also the approach of the Human Brain Project, whose Medical Informatics Platform is federating large quantities of clinical data from patients who have undergone treatment for mental or neurological problems, and mining it in the search for brain signatures of disorders Rose (2014)). The belief that the brain holds the key seems unshakeable. But this belief in the neural foundation of such disorders is an unproven hypothesis. Yet more and more of our fellow citizens, internationally, are being diagnosed with what are now often termed 'brain disorders' – where this category includes conditions from addiction to Alzheimer's, from obesity to obsessive compulsive disorder (OCD) – underpinned by a hypothesis that these all share common mechanisms (Wittchen *et al.* 2005, 2011). Perhaps it is time to question that hypothesis, except in the most general sense that there are common mechanisms underpinning most if not all human mental activity.

Crisis of explanations

'Brain disorders' has been the wager – or in the case of the NIMH and RDoC, disordered brain circuits (Cuthbert & Insel, 2013). But it has proved very hard to make this hypothesis come true – that is to say, to identify the disordered brain circuits that are hypothesised to underpin or subserve the specific anomalies in cognition, affect or volition that characterise the experience of mental health problems (of course, this problem is not unique to psychiatric neuroscience: even research in such a 'simple' condition as osteoporosis has achieved limited progress in linking genes, molecules, cells, systems, symptoms and the experience of individual patients. But if that is so, how much more 'complex' will the task be in the case of mental health problems.). One example has been the relative failure of search for genomic bases of psychiatric disorders using the genome wide association studies (GWAS) methodology – while GWAS in psychiatry have identified some variants of small effect, and detected the significance of copy number variations in some cases, few if any of these variations are either necessary for or sufficient for the development of any particular psychiatric disorder. Of course, not all agree. Some argue that, over a relatively short period, GWAS studies of common complex non-psychiatric disorders have shown that single nucleotide polymorphism (SNP) variation, taken together across multiple sites, can explain a significant proportion of the known variation in susceptibility for such disorders, and has already begun to identify biologically and clinically relevant pathways (Visscher *et al.* 2012). Others argue, as we have seen, that the failure to find genomic biomarkers in GWAS research in psychiatry arises from the heterogeneity of the DSM categories used to structure such research, but that even so, for severe disorders such as schizophrenia, biologically and clinically meaningful results have been obtained which offer novel insights into the aetiology of the condition (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

But even if such genomic associations can be found by such methods, the percentage of the variance explained by genetic sequences – even by algorithms of multiple sequences – remains small. Many of the sequence variations identified in the schizophrenia study are not in coding regions of the genome – that is to say they are not in – or even close to – 'genes'. And where the genetic variants can be linked to particular biological pathways, the disruption identified seems to refer to very basic neuronal pathways involved in multiple normal and abnormal functions and to be present in a range of different phenotypic conditions: none of the variants alone is necessary – let alone sufficient – to indicate the clinical or experiential presence of a disorder in any particular individual. The dispute between those who believed that there were common variants for complex psychiatric disorders and those who argued that it was more likely that multiple rare variants specific to families or

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lineages led to similar symptomatology, perhaps via some final common pathways seems to have been settled – common disorders are a complex mixture of both! Further, at present, we have no idea how such multiple genetic variations are linked to the pathways or circuits that underpin higher cognitive functions. Indeed while neuroscientific research has made great progress in understanding basic neural elements – membranes, ion channels, receptors, etc – it is currently impossible to move up the levels from genes, to cells, to circuits to cognitive functions. This is the challenge that is being addressed by the many 'big brain projects – such as the Human Brain Project and the US BRAIN project – but despite the hype, serious researchers involved recognise that it will, at the least, take decades to begin to unravel the complexities in the formation of 'brain circuits' let alone to understand how these give rise to higher cognitive properties. Since we cannot understand how these 'levels' – if that is the right term – are related in 'normal' brain functioning, we are a long way from identifying neural bases of mental disorders. But one thing that we do now know: it is not all in the neurotransmitters!

Crisis of treatment

More and more people worldwide are taking psychiatric drugs. In the USA in 2010 about 15% of men, 26% of women, 7% of boys, and 5% of girls are regularly prescribed such medication (Medco, 2014). The most widely prescribed psychiatric drugs are those usually termed 'antidepressants' – although they are now prescribed for many conditions other than depression (OECD/European Union, 2014). In 2013 in England alone over 53 million prescriptions were issued for antidepressants, a 6% increase on the previous year and a 92% increase since 2003 (Health and Social Care Information Centre, 2014) (this report is available at http://www.hscic.gov.uk/catalogue/PUB14414/pres-disp-com-eng-2003-13-rep.pdf). The generation of drugs that came onto the market from the 1980s onwards were all based on a 'neurotransmitter' theory of mental disorders – the theory that most if not all such disorders arose from anomalies in the neurotransmitter system, and could be alleviated by drugs that acted on that system – on the synthesis, activity, reuptake, metabolism of neurotransmitters (Schildkraut, 1965; Rose & Abi-Rached, 2013). Further, it was believed that specific disorders arose from a specific pattern of such anomalies and hence effective drugs for each disorder would act on that specific pattern (Healy, 1996). Yet few now believe in the basic explanatory form of neurotransmitter hypothesis of mental disorder, let alone the dream of specificity – that each psychiatric disorder could be linked to a specific anomaly related to one – or a small number – of dopamine, serotonin, glutamate or any of the many dozens of neurotransmitters that have now been identified. If the drugs work – and that remains an open question for many persons and many conditions, especially those forms of mild to moderate distress that are the conditions most treated by such drugs – they almost certainly do not work in this way. Further, the new generation of specifically designed and targeted drugs have proven to be no more effective than those discovered by serendipity from the 1950s and 1960s, although some have a lower 'side effect' profile. Despite the lure of huge markets, to the frustration of the pharmaceutical companies – and the psychiatrists and patients hoping for effective treatments – the pipeline of central nervous system (CNS) drugs lacks new chemical entities. Such are the difficulties and costs of bringing new drugs to the clinic, that most big drug companies are withdrawing from this sector of the market. As Thomas Insel remarked 'The biggest problem is not the announcements by Glaxo SmithKline (GSK) and AstraZeneca, it is when you look at the pipeline and see what companies are actually doing in psychiatric drug development… There are very few new molecular entities, very few novel ideas, and almost nothing that gives any hope for a transformation in the treatment of mental illness' (see also de Leon, 2014, quoted in Miller, 2010; O'Brien *et al.* 2014) (for recent discussions, see the article in the *New York Times* by Richard Friedman: http://www.nytimes.com/2013/08/20/health/a-dry-pipeline-for-psychiatric-drugs.html?src=twr&_r=1 and http://psychnews.psychiatryonline.org/doi/10.1176/appi.pn.2014.11a2 reporting the O'Brien study referenced here.). As Steven Hyman puts it – in a paper entitled 'revolution stalled' – this is largely because of an inability to demonstrate efficacy (Hyman, 2012). Hence the paradox – more and more people are taking the drugs, especially for relatively minor problems of mental health – while the hypothesis on which they are based is no longer viable. And we are now seeing a search for new modes of intervention – Deep Brain Stimulation, Transcranial Magnetic Stimulation – but still focussed on the brain (Hyman, 2014).

A better way forward?

It is time to go back to some basics. First, a disorder – even a 'mental disorder' – is a disorder of a whole person (not just a brain) – a living organism shaped by time and development from conception, and always in transaction with a social and environmental setting – a form of life (Goldstein, 1995 [1939]). Second,

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'brain' and 'body' are inseparable, not just biologically and neurobiologically, but also clinically – consider, for example, the level of comorbidity of 'mental' and 'physical' disorders . Third, an organism is not merely a sum of parts that can be isolated and experimented on in the purified space of the laboratory, then simply extrapolated to the whole as it lives in the wild world of real existence (Canguilhem, [1965] 2008: 113). Fourth, multiple sociological and epidemiological studies have shown very clear correlations between diagnoses of mental disorder and a whole range of undesirable social conditions – this is what Nature magazine recently referred to as 'sociology's vindicated research' in an editorial focussing specifically on what we know about the relation between life stresses and patterns of disorder (Nature, 2012). Fifth, what counts as a disorder is inseparable from the form of life in which it can be judged to be abnormal – hence – as can be seen in the descriptions in our diagnostic manuals – many of our current ailments can only be understood when placed in the context of our contemporary norms of personhood that stress autonomy, self-control and choice (Rose, 1999). To point this out is not just 'hand waving' but demonstrated by over a century of clinical, epidemiological and sociological studies.

Let me take a brief example from the work of my group on 'the urban brain' which is exploring characteristic patterns of mental disorders across urban space (Fitzgerald *et al.* 2015). These patterns – of concentration of particular types of disorder in particular parts of towns and cities – have long been recognised, and are often relatively stable over many years (Faris & Dunham, 1939; Hollingshead & Redlich, 1958; Srole *et al.* 1962; Boydell *et al.* 2001; March *et al.* 2008; Hatch *et al.* 2011). Initially understood as arising from the exigencies of metropolitan life itself, in the second half of the 20th century, the high levels of particular psychiatric diagnoses in certain areas of cities came to be understood in terms of 'urban drift' – those with propensities to mental illness found their way into the less salubrious urban areas. However these disorders are now widely recognised as at least in part arising from the ways in which different types of stresses within particular urban forms of life are experienced and perceived by individuals in relation to their own biographies, biologies, capacities and resiliencies (Abbott, 2012; Lederbogen *et al.* 2013; Söderström, 2013; Morgan *et al.* 2014). Hence such mental disorders are probably best understood, not in terms of a diagnosis that seeks to individuate an underlying brain state, but in terms of an older idea of the formulation (Engel, 1977; Bolton, 2014; Lewis, 2014; Smith, 2014). That is to say, a collaboratively produced account (such a collaborative account arises from conversations between physicians, patients, carers and other professionals) that seeks to make sense of a person's difficulties and ailments in the context of their personal and social relationships, the realities of their lives and their ways of understanding these – for example, it is the perception of being isolated, not the fact of solitude that is pathogenic (Cacioppo *et al.* 2014). While neurochemical intervention may play a part, the most effective and long-lasting forms of intervention are often those that prioritise both the adverse social conditions under which those diagnosed with disorder live their lives, and the resources, including sense making resources, that shape the ways that individuals live their lives under such conditions.

How does adversity 'get under the skin'?

How might one begin to create an account of the mechanisms involved here. Perhaps one way to begin is by asking 'how does adversity get under the skin? There are a number of suggestive candidates for mechanisms within contemporary neuroscience. Perhaps via the work of Michael Meaney's group on epigenetic changes arising from early upbringing (Champagne & Meaney, 2006; Szyf *et al.* 2008; Meaney & Ferguson-Smith, 2010). Perhaps via Sandro Galea's work in Detroit on epigenetic markers correlated on the one hand with experience of violence and abuse, and on the other, with diagnoses of post traumatic stress disorder (PTSD) and depression (Galea *et al.* 2011; Goldmann *et al.* 2011). Or perhaps via Meyer Lindenberg's work that shows how individuals brought up in different kinds of environments process stress in different ways (Meyer-Lindenberg & Tost, 2012; Lederbogen *et al.* 2013; Haddad *et al.* 2014). Or perhaps via Elizabeth Gould's suggestions that adversity gets under the skin via its effects on neurogenesis (Stranahan *et al.* 2006; Leuner *et al.* 2010). Or perhaps via a better understanding of neuroplasticity in relation to different kinds of environmental inputs (Pittenger & Duman, 2008; Davidson & McEwen, 2012). This is not just a challenge for intervention but also a challenge for research – not to start from the neural, but to proceed in precisely the reverse direction: to ask 'what kinds of adversity' through what mechanisms, in relation to what kinds of life course and what modes of making sense of the world, leads to what kinds of mental disorders.

There is conceptual work to be done here. We need to think of gene sequences, not as an inherited programme that merely reveals itself, but as they activate and de-activate, methylate and demethylate over the course of development, and always in relation to

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their milieu. We need to recognise that neurotransmitter hypotheses of psychopathology are partial at best, and fail to grasp the complex and distributed nature of the brain circuits that subserve cognitive functions by many orders of magnitude. We need to reject a conception of brain functions that is based on the idea of localisations – these may be given support by the technological and methodological routines of functional magnetic resonance imaging (fMRI), but the tools of visualisation should not shape our theories. We have to realise that, when it comes to mental distress, we are dealing with living organisms and that there is a real limit to what we can learn from animal studies in laboratories where a living organism is deprived of the very basic capacities that life requires – the capacity to shape and reshape ones milieu. We need to start our investigation of mental ailments from the human being in his or her form of life and to recognise that a form of life is not a brute fact, but a mode of experience And perhaps, historians of our psychiatric age will conclude that the most revolutionary development did not come from our current wager on the brain, but from the ending of that centuries long monologue of reason about madness, the recognition that the voices of those who are the subjects of psychiatry must have a crucial role in shaping the ways in which their ailments are understood and treated.

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Conflict of Interest

None.

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