Chapter 3

Neuroscience and mental illness

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Overview

In this chapter we discuss recent advances in our understanding of the biology of mental illness. Alongside important social and psychological factors, the biology of psychiatric disorders plays an important role in their development and prognosis. The inclusion of this chapter in this report reflects the need to widen public awareness of the quality and breadth of scientific work currently under way to help those suffering from mental illness. There is a stark mismatch between the funding for such research and the considerable cost of these disorders to our society, exacerbated by the recent disengagement of many pharmaceutical companies from research related to brain disorders. Translating the promising findings presented here into improved clinical care requires this mismatch to be addressed urgently. One way of doing this is by building bridges between the diverse fields involved in the common pursuit of the promotion of public mental health, which is one of the aims of this chapter.

It would be impossible to summarise the entire field of biological psychiatry for such a chapter. Instead, we have adopted a 'horizon-scanning' approach to demonstrate the variety of techniques used in this area, and to highlight a few examples that are more likely to have a rapid impact on patients' care. The chapter is divided, by technique, into sections covering neuroimaging, neuropsychology, genetics, blood-based biomarkers and animal and cellular models of disease. Some of the work presented here is already available clinically, such as the genetic analysis in autism. Other work could have widespread clinical utility within the next 10 years, especially in the area of 'personalised' treatment – identifying *a priori* the best treatment for the individual patient. However, translating this neuroscience research into better patient care requires sustained support of experimental medicine and clinical trials.

It is our hope that this chapter demonstrates how biological research may aid diagnosis, risk stratification and the development of novel medications for the treatment of mental illnesses. Rather than distancing psychiatry from important psychological and social factors, much of modern biological research is aimed at understanding how these factors interact to produce disease states. Biological advances are likely to play a valuable part in the holistic management of patients.

We write this chapter to advocate that the biomedical and psychosocial models of mental illness are not antithetical, but are in fact increasingly conceptualised within a single unifying framework. While most of the important factors determining the risk and course of mental illnesses can be measured in a clinical interview, rather than in a laboratory, neuroscience research offers the exciting opportunity to understand the **mechanisms** by which these factors affect their clinical action. Unfortunately, at a public health level it appears that, while a biological model of mental illness enhances the acceptance of treatment, it does not seem to be associated with a reduction in stigma among the general population.

Our understanding of the biological correlates of mental health and illness is growing exponentially. As showcased in this chapter, we are beginning to see how this understanding could be developed to improve the medical care patients with mental illness receive, and to widen our understanding of mental illness as a truly bio-psycho-social construct.

Introduction

Many mental disorders are both chronic and disabling. It is estimated that they account for 14% of the global disease burden.[1] In 2011 the Department of Health estimated that mental health represented 23% of the UK national disease burden and was the single largest cause of disability.[2] The Centre for Mental Health found that in 2009/10 the total economic cost of mental illness in the UK was £105 billion, and it is estimated that treatment costs will double in the next 20 years.[2,3]

Despite the enormous health and economic burden that mental illness places on society, the funding for mental health research remains relatively limited. The Academy of Medical Sciences (2013)[4] found that mental health research spending was only 5.5% of total UK health research spending in 2009/10. This is significantly less than the proportion spent on cancer, infection, neurological disease or cardiovascular disease. The European College of Neuropsychopharmacology (ECNP)[5] highlights that, across the EU, neuroscience research receives just €465 million out of a total health research spend of €6,050 million – that is, less than 8%.
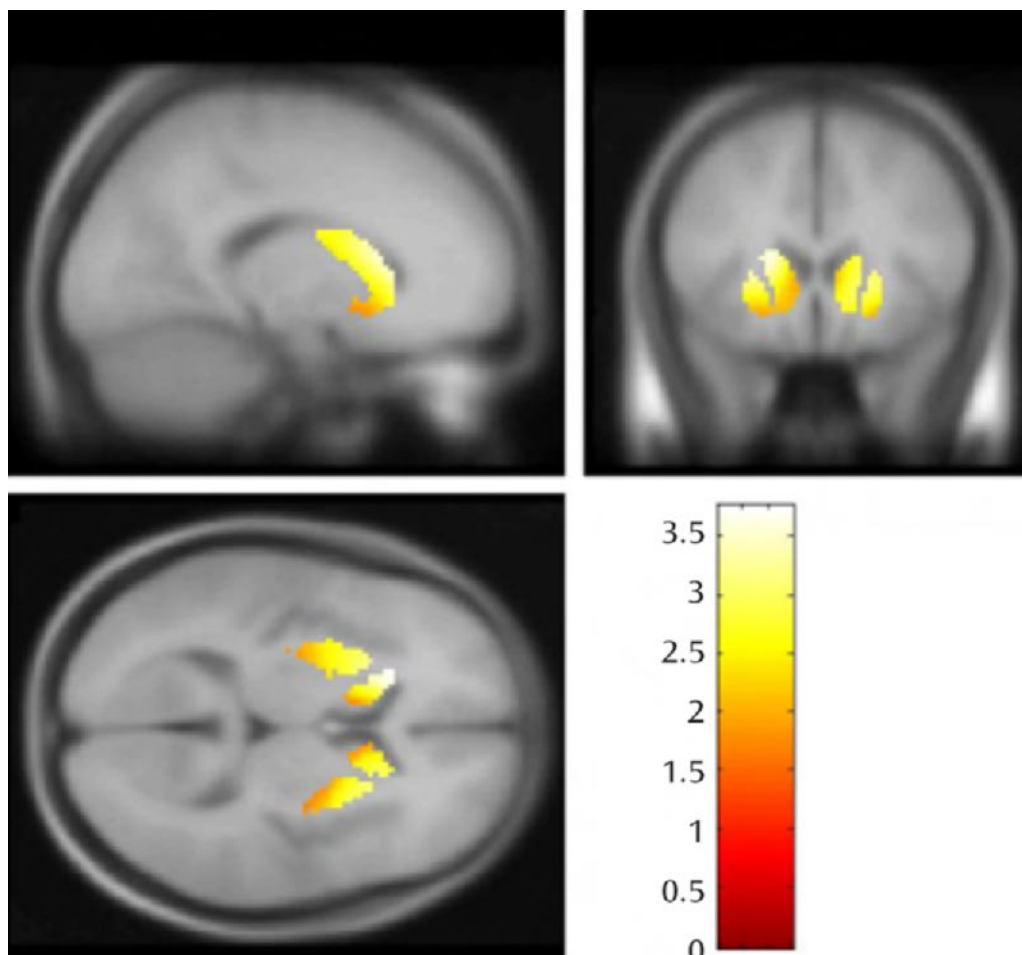
It is also interesting to note that both the report from the Academy of Medical Sciences (2013)[4] and the report from the ECNP[5] cite the recent withdrawal of pharmaceutical companies from brain research as a source of major concern.

This withdrawal is due, at least in part, to the challenge of translating research findings into clinical practice in psychiatry and psychopharmacology. For example, it takes on average 13 years to develop a drug for psychiatric conditions, significantly longer than for other medical specialities, and these drugs are also more likely to fail in the development process.[5] There is an urgent need to overcome these obstacles and to plug this 'translational gap'. In this chapter we will highlight research that aims to do just that, while emphasising that the translation of neuroscience research into better patient care requires sustained support of experimental medicine and clinical studies.

Cutting-edge methodology in neuroscience is being used to study psychiatric disorders, and findings from these studies may have the potential to change clinical practice and improve patient care. This chapter showcases a selection of established techniques. It is organised by methodology and highlights some of the advances in neuroimaging, neuropsychology, blood-based biomarkers, genetics and cellular neuroscience, all as applied to mental illness. Some of the work presented here is already available clinically, such as the genetic analysis in autism, whereas other work could have widespread clinical utility within the next 10 years, especially in the area of 'personalised' treatment – identifying *a priori* the best treatment for the individual patient.

Before we discuss the individual research areas, it is important to highlight that this chapter does not aim to present

Figure 3.1 PET imaging of dopamine synthesis in psychosis (from Howes et al 2011)

neuroscience research as antithetic to the psychosocial model of mental illness. Indeed, some of the most exciting research in this area is specifically focused on the understanding of how psychosocial factors affect brain mechanisms. Therefore, this chapter advocates a unified bio-psycho-social model, where clinical factors assessed in an interview and biological factors assessed in the laboratory can both contribute to the understanding of the individual patient's journey, and improve patient care by providing new treatment approaches or new personalised approaches to existing treatments.

Finally, it is important to emphasise that the 'biological model' has brought both success and disappointment to the wider framework of social acceptance of mental illnesses. For example, while the wider understanding of the biology of mental illness seems to bring about better acceptability of professional help, it does not increase social acceptability, perhaps because it may increase a perception of 'otherness'.[6] Our position, therefore, is that neuroscience research should contribute to a balanced, integrated, bio-psycho-social model of these conditions.

Neuroimaging

Brain scans have played a role in psychiatry since the 1970s.[7] Using advanced neuroimaging techniques, researchers are able not only to see the structure of the brain in unprecedented detail but also to measure dynamic properties such as blood flow, metabolism, electrical activity and neurochemistry. The ability to combine both structural and 'functional' data is vital to understanding the nature of the complex relationship between brain abnormalities and mental illness.

While many studies over the years have used neuroimaging techniques to compare patients and controls in a cross-sectional manner, the most recent developments have focused on the use of neuroimaging as a tool to predict the **future** course of disorders.

For example, particular interest has been shown in the application of neuroimaging to detect patients at high risk of developing psychotic disorders.[8] Characterised by symptoms such as hallucinations, delusions and disordered thinking, psychotic disorders like schizophrenia are among the most disabling illnesses. Prior to the onset of illness it appears that patients display prodromal clinical features referred to as the 'at risk mental state'.[9,10] Subjects may not experience sufficient symptoms to warrant a diagnosis of a psychotic illness, but show warning signs. Approximately one-third of these patients go on to develop psychotic illnesses.[11] Reliably predicting this transition would allow patients to access treatment and support earlier, thus promoting recovery, reducing the need for emergency management and minimising the impact of illness on the patient's life. It is important to emphasise that these phenomena are not rare: for example, within the general population (where most people do not seek help from mental health services), 8–13% experience psychotic symptoms such as hallucinations or delusional ideas, with some experiencing both.[12]

Recent work shows that neuroimaging may be able to inform the risk stratification of these patients in the near future. Subtle changes in brain structure uncovered through magnetic resonance imaging (MRI), such as changes to the brain's grey matter volume, are detectable in patients before they develop psychotic illnesses and predictive of the change in clinical state.[13,14] Positron emission tomography (PET) has also shown that the capacity to synthesise the neurotransmitter dopamine in certain regions of the brain is elevated before the onset of psychosis in these 'at risk' patients.[15,16] Combining imaging modalities or adding other forms of data, such as genetic information, may improve the accuracy of these predictions and inform the clinical risk assessment.[17,18] Moreover, computational techniques like machine learning can also be used to evaluate MRI data and quantify the risk of transition to psychosis, as well as the individual course of illness in patients who have developed psychosis.[19,20]

Neuroimaging has also been used to investigate why some patients do not respond to treatments such as medication. Detailed structural imaging of gyrification (brain folding) and of white matter tracts has demonstrated baseline differences between patients with first episode psychosis who later respond to antipsychotic medications and those who do not.[21,22] PET imaging has found that a reduction in dopamine release predicts a lack of response to treatment and a worse clinical outcome in patients with cocaine and methamphetamine addiction.[23,24] A number of investigators have used neuroimaging to predict response to antidepressant treatment in patients with depression. The most consistent finding is that increased baseline activity in an area of the brain known as the 'anterior cingulate cortex' is predictive of a higher likelihood of positive response.[25] This evidence has also prompted the recent development of deep brain stimulation of the anterior cingulate area as a therapeutic strategy for patients with treatment-resistant major depression.[26]

One of the most exciting developments in neuroimaging is the analysis of the networks within the brain known as the 'connectome'. Using techniques such as diffusion tensor imaging (DTI) and functional MRI (f-MRI), it is now possible to map and measure connections within the brain.[27] It is believed that the many complex functions of the brain emerge from the co-ordinated activity of a number of regions, connected as specialised networks. Brain dysfunction can therefore be considered in terms of altered neural connectivity. A number of studies of schizophrenia have found evidence of altered connectivity between multiple brain regions,[28–30] including some highly specialised interconnected brain networks.[31] Bleuler, who coined the term 'schizophrenia' in 1911, believed that a central pathological process in this disease was the interruption of the 'thousands of associative threads which guide our thinking'.[32] Using modern imaging of brain networks, we may be closer to understanding whether there are robust and relevant biological underpinnings to his original clinical observations.

Finally, neuroimaging is contributing to our understanding of the impact of psychosocial factors on brain function. For example, recent research has shown that patients at their first episode of psychosis show a smaller volume of the brain structure known as the 'hippocampus' if they experienced traumatic experiences in their childhood, and that this effect is due to an increase in peripheral blood hormones related to stress (see also 'Blood-based biomarkers').[12]

Neuropsychology

The cognitive theory of depression highlights the importance of thinking errors in this condition.[33] A person suffering from depression is more likely to interpret a neutral stimulus as being negative, and focus on (and remember) negative stimuli more than positive ones.[34] For example, when recognising emotional facial expressions patients with depression are more likely to demonstrate a reduced perception of happy facial expressions and an increased perception of negative facial expressions.[35–37] These 'negative biases in information processing' are believed to feed a cycle that results in worsening mood, and helping to correct them is a fundamental part of cognitive behavioural therapy (CBT) for depression, a form of talking therapy.

It has now been demonstrated that antidepressants may also help to address these biases, and appear to do so much earlier than they affect mood.[38] Using modern neuropsychological techniques,[35] it is possible to measure these changes in biases in a standardised way and correlate them with changes in brain activity. For example, seven days of antidepressant treatment in healthy volunteers results in measurable increases in positive biases, such as reduced recognition of negative facial expressions.[39,40] These findings have also been correlated with reduced brain activity in regions associated with threat, such as the amygdala.[41] Similar changes have even been reported after single doses of the antidepressant citalopram, given both intravenously and orally.[42,43] A similar effect has been demonstrated in patients suffering from depression.[44,45] For example, in one randomised double-blind placebo-controlled trial, patients with depression and controls were given either a single dose of the antidepressant reboxetine or an inactive placebo.[44] In the patients who were given reboxetine, the negative biases in information processing recorded before treatment were reversed three hours after dosing. Despite the changes in bias, in none of these studies was there a resultant subjective change in mood, suggesting that altering emotional processing may be an early effect of antidepressant treatment. Building on this work, studies have shown that measurable early changes in emotional processing may be a predictor of later clinical response[46] and can be used to determine whether novel drugs can act as antidepressants.[47,48]

Neuropsychology is one area of research that has specifically focused on the bridging of biology and psychology. The work presented here demonstrates that it is possible to develop robust and standardised ways of measuring certain psychological aspects of mental illnesses within a biological framework, and to use these findings to develop biomarkers of disease and treatment response.

Genetics

In the past decade our knowledge of psychiatric genetics has expanded greatly. Alongside rapid advances in genetic technology, recent successes are largely attributed to large-scale international collaborations in the field.[49,50] The Psychiatric Genomics Consortium (PGC), for example, represents a collaboration of hundreds of scientists working in 19 different countries and over 60 different academic institutions.[51] Such collaborations allow groups to share methodology and data from genome-wide association studies (GWAS) and studies of genomic structural variation, to improve the power and accuracy of their analyses. This approach is called 'genome wide' because it assesses all the genes of a single individual at the same time.

GWAS are designed in a similar way to classical case control studies. Their aim is to detect small changes to the genetic code, called single nucleotide polymorphisms (SNPs), and see whether they are associated with disease cases. To date the PGC has reported the findings of large GWAS analyses in four major disorders: major depression,[52] bipolar affective disorder (BPAD),[53] schizophrenia[54] and attention deficit hyperactivity disorder (ADHD).[51,55] In the analysis of BPAD, over 11,000 patients were compared with over 51,000 controls.[53] This analysis found a significant association between BPAD and SNPs in a number of genes, including CACNA1C, which is associated with calcium channel function, and ODZ4, a gene implicated in cell signalling and neuronal path finding. Similarly, seven SNPs, including in the miR-137 gene, a regulator of neural development, were found to be significantly associated with schizophrenia.[54] In a 'cross-disorder' analysis, the PGC also demonstrated that certain genes, including CACNA1C, might actually be associated with more than one disorder.[56] Surprisingly, in the study of major depression, despite the inclusion of over 18,000 patients, PGC researchers were unable to find any statistically significant findings. Similarly, analyses of GWAS data by other large international collaborations found no reliable SNPs that predict treatment response to antidepressants.[57,58] The authors of the PGC study cite a number of potential reasons for the lack of findings in depression.[52] First, compared with the prevalence of depression in the community, the sample size may still be too small to detect results. Second, depression may be particularly heterogeneous, both clinically and aetiologically. Finally, the authors raise the possibility that an interaction between risk genes and environment stressors may be particularly important in the manifestation of depression, and as such the GWAS approach may not appropriately capture this form of 'genetic architecture'.

Alongside small genetic changes like SNPs, research has also demonstrated that much larger structural variation in the genome may be important in psychiatry.[59,60] So-called copy number variations (CNVs) result in cells having an abnormal number of copies of large sections of DNA. These regions vary in size, from over 1,000 DNA base pairs to millions, and

are thought to account for 13% of the human genome.[61] In autism, assessments of CNVs have found abnormalities in a number of genes, such as NRXN1,[62] which is associated with cell adhesion in the nervous system. It is now estimated that there may be over 200 CNVs associated with autistic spectrum disorders.[62] Notably this area is one example of work that has already begun to be translated into the clinical field, where chromosomal 'microarrays' (tools capable of detecting clinically relevant CNVs) are now recommended in the clinical assessment of some patients with autism.[63] Similarly a variety of CNVs, such as the deletions at 22q11.2 and duplications at 16p11.2, have been discovered to be associated with schizophrenia.[64,65] It has been argued that, given the prevalence of CNVs in patients with schizophrenia,[66] the use of clinical microarray testing should also find a role in the assessment of these patients in the near future.[64,66] In keeping with the cross-disorder GWAS data, analyses show that some CNVs, such as deletions in NRXN1, are associated with more than one form of mental illness.[64]

Alongside these changes to the DNA code, it is now recognised that the external environment can also have an impact on gene regulation, and that these changes can be inherited.[67] These effects can happen without altering the underlying DNA sequence and so are referred to as 'epigenetic'.[68] Molecular mechanisms of epigenetic changes include the methylation of DNA and histone modification – that is, the addition of small chemical groups to the DNA and the associated proteins. Again, this research area has been instrumental in encompassing the biological, psychological and social aspects of a patient's difficulties by bridging genes and the environment.[69] For example, one study found differences in DNA methylation in genes such as ALS2 in the hippocampal tissue of people with a history of severe childhood trauma when compared with controls. ALS2 controls a broad spectrum of cellular and molecular processes, including signalling cascades, neuronal morphogenesis, axonal growth and neuroprotective processes.[70] Moreover, recent papers have implicated epigenetic changes in the 'glucocorticoid receptor' as a key mechanism in regulating the stress response, a fundamental means by which early exposure to life stressors permanently changes stress reactivity.[71,72] There is also some evidence that epigenetic mechanisms may be important in determining treatment response to antidepressants.[73]

As mentioned earlier in this section, the lack of consistent genetic findings in the GWAS of depressed patients has been partly explained by the fact that 'gene–environment interactions' (GxEs) might be more important than genetic effects alone. Indeed, the concept of GxEs is one more methodological approach that allows the integration of biological and psychosocial factors in a single model. Within this framework, perhaps the most important finding is the notion that life stress induces psychopathology only in a sub-group of patients, whose vulnerability is in part due to their genetic make-up. Moreover, while we have known for many years that specific genetic variables only increase the risk of psychopathology when challenged by specific environments (that is, life stressors),[74] recent studies have examined the molecular mechanisms underlying these GxEs. For example, a recent paper has shown that a functional polymorphism in the FK506 binding protein 5 (FKBP5) gene, an important regulator of the stress hormone system, increases the risk of developing stress-related psychiatric disorders by regulating DNA demethylation in response to stress.[75] These kinds of studies may help to explain why genetic findings, to date, do not fully explain the estimated heritability of most mental illnesses.[76,77] Taken together with the 'epigenetic' studies described above, this area of research has potentially profound public health implications, as it clearly highlights the primacy of individual vulnerability or resilience (determined by a combination of genetic make-up and early life experience) in the trajectory to the development of mental illness(es).

In summary, the emerging picture is that many psychiatric disorders have complex genetic underpinnings. It appears that genetic risk factors do not follow conventional diagnostic boundaries and there are few genes that are either necessary or sufficient to cause disease on their own. In many cases, multiple genetic risk factors, combined with important social and psychological stressors, place people at risk of developing mental illness. Identifying and understanding genetic contributions to mental illness is likely to have a role in developing our understanding of diagnoses in psychiatry, identifying those at risk of developing illness and potentially helping to guide treatment.

Blood-based biomarkers

Developing reliable blood tests for mental illnesses would represent one of the most significant advances in psychiatric practice. Ideally such tests would aid in diagnosis and in the prediction and monitoring of treatment response. A major focus for the development of blood-based markers, especially in depression, has been the interplay between the stress response and the immune system.

Meta-analyses have shown that depression is associated with measurable increased activity in the hormonal stress response systems, also called the hypothalamic-pituitary-adrenal axis,[78] and with measures of inflammation, such as C-reactive protein (CRP),[79] interleukin-6 (IL-6) and tumour necrosis factor.[80] In recent studies, psychosocial risk factors for the future development of mental illnesses, such as an experience of early life trauma or of socio-economic disadvantages, have been found to be associated with increased inflammatory biomarkers in adulthood. Elevated blood levels of CRP in otherwise healthy and euthymic individuals have also been found to be associated with the subsequent development of depressive symptoms,[81] supporting the notion that increased inflammation may be on the causal pathway to depression. Importantly, this notion is also supported by recent clinical trials showing that anti-inflammatories may have an antidepressant action.[82] Furthermore, in a recent clinical trial of the anti-inflammatory drug infliximab in treatment-resistant depression, only the subset of patients with raised inflammatory markers showed some response to this treatment.[83]

The mechanism by which both the stress response and inflammation could contribute to the development of depression may be related to the inhibition of neural growth factors like brain derived neurotrophic factor (BDNF) affecting neuroplasticity in the brain.[84] For example, a recent study examining the effects of early life trauma on structural changes in the brain showed that a smaller hippocampus was linked with higher levels of IL-6 and lower levels of BDNF.[85] This emphasises the importance of blood-based biomarkers in our search for the potential mechanisms by which psychosocial factors affect brain function and lead to mental illnesses.
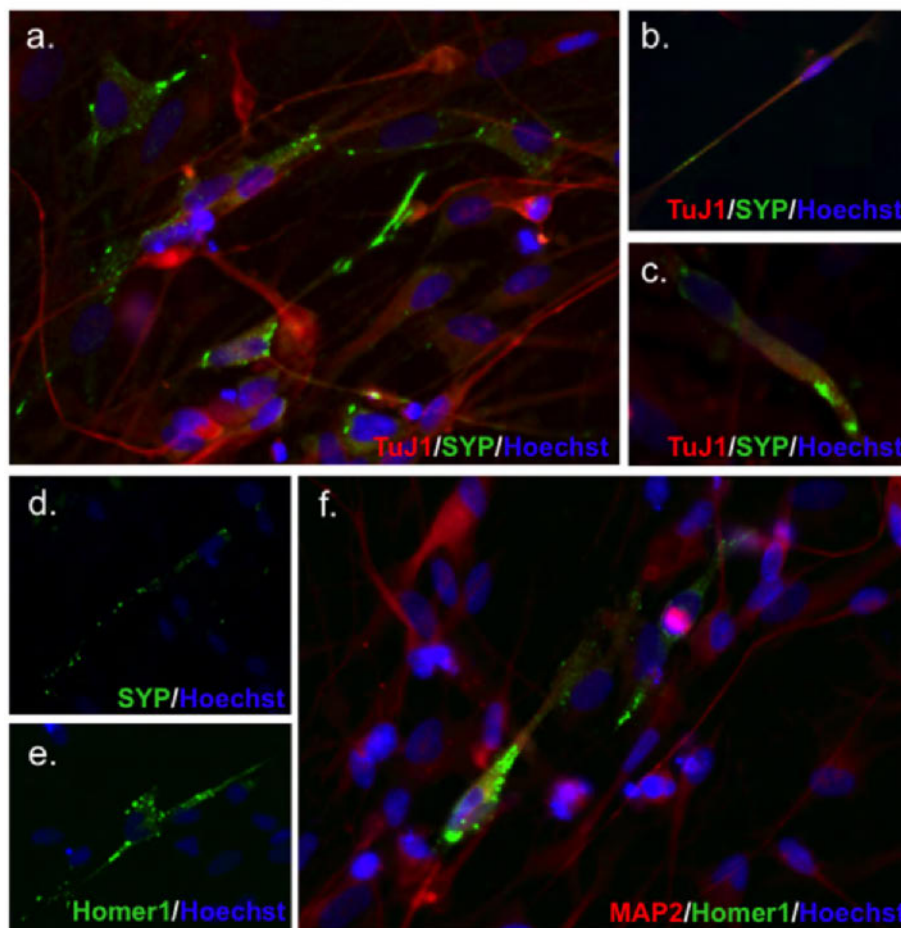
One biomarker technique recently used in psychiatric research is the measurement of gene expression in the blood. By measuring the levels of messenger RNA (mRNA) in blood cells, it is possible to establish which genes are being expressed and to what extent. This appears to be particularly promising in the development of blood-based biomarkers for depression.[86] For example, one group measured the gene expression of 15 different genes associated with stress, inflammation and neuroplasticity in patients with depression, before and after they had treatment with antidepressants.[87] They found that, of the 15 genes, high baseline levels of mRNA in three genes associated with inflammation (IL-1β, MIF and TNF-α) predicted a poor response to treatment. Symptom reduction, however, was associated with changes in the level of expression of other genes, such as a reduction

in IL-6 (also associated with inflammation) and an increase in neural growth factors, including BDNF.[87] These findings are too preliminary to implement into current clinical practice. However, it is possible to envisage a future where blood-based biomarkers, such as peripheral gene expression, guide clinical decision-making regarding antidepressants and help us identify patients early on who may not respond to first-line treatments.

Pre-clinical models

Using pre-clinical models (i.e. animal or cellular models) is an important approach in neuroscience research relevant to mental illness. The ultimate goal of such research is to uncover the fundamental biological processes that lead to states of illness, changes in behaviour or responses to medications. Examples include studies where rodents are exposed to stressors that are mild but unpredictable, thus resembling human life experience, or where *in vitro* brain cells are exposed to stress hormones or to antidepressants in their culture medium. These techniques are vital for developing our understanding of these conditions and for drawing up new targets for medications. Obviously the findings and predictions of these 'pre-clinical' models have to be tested and validated in humans before they can be presumed to apply to patients suffering from mental illnesses. As an example of this validation process, the epigenetic changes mentioned above to the FKBP5 gene in patients exposed to

Figure 3.2 Multipotent, hippocampal progenitor cell line HPC03A/07, stained with synaptic markers and hippocampal granule cell markers.

early life stressors resemble findings from models of rodents exposed to environmental stress and nerve cells exposed to stress hormones.[75] Similarly, a recent study found an increase in the stress-related protein SGK1 in the blood of patients with depression. The same protein has been found to be increased in the brains of animals exposed to stress and in nerve cells exposed to stress hormones.[88]

Understanding how medications work at a cellular and molecular level would not be possible without the use of pre-clinical models. Equally, these approaches are vital for identifying new molecular targets in the disease process for the development of novel medications. For example, it has recently been demonstrated that ketamine, an anaesthetic, has rapid antidepressant effects in patients with treatment-resistant depression.[89] Unfortunately, due to concerns over its safety, the potential for abuse and its ability to induce psychotic symptoms, ketamine is of limited use clinically. Researchers are therefore trying to understand how ketamine causes its antidepressant effects, in order to develop novel and safe antidepressants for clinical use that lack the dangerous side-effects of ketamine. Using animal models of depression, it has been shown that ketamine activates a signalling pathway within cells known as the mammalian target of rapamycin (mTOR) pathway.[90] Blocking the mTOR pathway results in the loss of the antidepressant effect of ketamine, demonstrating that it is crucial for this effect.[90] Moreover, it has been shown that the production of the neural growth factor BDNF is also crucial for this antidepressant action,[91] as mice genetically unable to produce BDNF do not respond as well to ketamine. Finally, and as an example of the translational pathways mentioned above, a recent study has shown that patients with depression who have the same BDNF genetic mutation as the mice models were also poorer responders to ketamine.[92] Aside from BDNF, other animal models have shown that the inhibition of an enzyme called GSK-3β is also important in the antidepressant response to ketamine.[93,94] This enzyme is believed to be involved in a process that leads to a reduction in the number of connections between neurons, called 'synaptic pruning'. These studies demonstrate that using pre-clinical models to elucidate some of the mechanisms of action of ketamine have yielded a number of molecular targets on which novel antidepressants could be based.

Developing models that take into account the complex genetic architecture of psychiatric conditions is also crucial in understanding pathophysiology and developing novel treatment targets. Human neurons obtained from embryonic tissue can be used to identify molecular mechanisms activated by 'depressogenic' stimuli and antidepressant drugs.[95,96] The two studies mentioned above that exposed neurones to stress hormones used this approach.[75,88] However, this field will truly be revolutionised by the development of induced pluripotent stem cells (iPSCs), which represents a major advance in our ability to develop cellular models. Yamanaka and colleagues (2006) demonstrated that it was possible to reprogramme a specialised cell taken from an adult organism into a stem cell – that is, a cell that

can then be reprogrammed into any type of cell in the body, including neurons.[97] By making these cells express specific 'transcription factors' that regulate protein synthesis, they were able to demonstrate that both mouse[97] and human skin cells called fibroblasts[98] could be converted into stem cells. Using this technique, it is possible to take cells from the skin of a patient and produce stem cells that retain the patient's genetic make-up. These iPSCs derived from patients can then be stimulated to become functional nerve cells. Since this discovery, iPSCs have been used to model a number of different conditions, such as spinal muscular atrophy[99] and Rett's syndrome.[100] In psychiatry, iPSCs have so far successfully been derived from patients with schizophrenia. In one study they were derived from two siblings with schizophrenia who shared a rare associated mutation in the DISC-1 gene.[101] It has also been shown that it is possible to convert iPSCs derived from patients with sporadic schizophrenia into functional neurons,[102] including dopaminergic neurons.[103] These early studies have found evidence of abnormal neuronal function, as shown by decreased neurite numbers (that is, less cellular ramification) and decreased connectivity in neurons derived from patients. The use of this technology to model disease is in its infancy, but it remains one of the most exciting areas for medical research.

It is undoubtedly difficult to truly replicate mental illnesses using pre-clinical models, and this may be one of the reasons why drug discovery in psychiatric disorders is slower than in other fields of medicine. However, it is impossible to understand the molecular and cellular mechanisms underlying psychiatric conditions such as autism and schizophrenia without these approaches. Equally, identifying new targets for treatment and testing their safety prior to their use in patients would not be possible without this type of scientific research.

Conclusion

The classical psychiatric approach to helping a patient is one that encompasses the biological, psychological and social aspects of their distress. Neuroscience research does not refute this holistic approach to care, but rather seeks to understand how crucial psychological and social events lead to the development of illness. This approach has yielded important results in recent years and it has only been possible to describe a handful of these findings in this chapter. There is now an urgent need to translate this work into improved care for patients suffering from psychiatric conditions. This is likely, however, to be a challenging process and not all discoveries will impact on patient care. Further, successful translation requires more academic training in neuroscience-based psychiatric research and increased research funding to levels matching the disease burden. In particular, neuroscience research will not deliver improvements to patient care unless there is institutional support for the whole process by which promising early findings are tested in humans, first through proof-of-concept studies and then through larger clinical trials. Finally, we need to be aware that the 'biological model' on its own does not seem to have delivered an improved public perception of mental illnesses. Therefore, combating the stigma that dogs mental illness may require a balanced and integrated bio-psycho-social model – one that both explains how psychological and social factors affect brain function and defends the importance of the individual's choices and freedom.

Authors' suggestions for policy

- When compared with other health problems, there is a mismatch between the societal costs of mental illnesses and the funding going into research and development for new therapeutic approaches. This has recently been further exacerbated by disinvestment by pharmaceutical companies.

- Neuroscience research is not antithetic to the psychosocial model of mental illness, and some of the most exciting research in this area is specifically focused on the understanding of how psychosocial factors affect brain mechanisms.

- Some of the approaches described in this chapter will deliver clinical benefits, especially in refining 'personalised treatment' for individual patients. However, translating neuroscience research into patient benefits requires sustained support of clinical studies testing these new approaches.

- Integrating neuroscience research within a bio-psycho-social model of mental illness could not only foster better acceptance of treatment but also reduce stigma, something neuroscience research alone seems unable to do.

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