

# A decade for psychiatric disorders

There are many ways in which the understanding and treatment of conditions such as schizophrenia are ripe for a revolution.

A media circus surrounded President Bill Clinton's visit to a New York medical centre in 2004 for a quadruple heart bypass. Yet barely a whisper was heard about other high-profile individuals' visits there for the treatment of psychiatric disorders.

In Britain, the public donates £500 million (US\$800 million) each year to charities for cancer research. For mental-health research, the figure is a few million, and most of that is for work on neurodegenerative diseases such as Alzheimer's, rather than for earlier-onset conditions that can undermine people's entire lives, such as depressive disorders.

It is time for such disparities to be addressed in a more coherent and aggressive way than in the past. The stigma of psychiatric disorders is misplaced, their burdens on society are significantly greater than more publicized diseases in developed and developing nations alike, and biomedical science is poised to make significant strides. The timescales are daunting and the challenges great — human neurons are less accessible than tumour cells, separating genetic and environmental influences is tough, and the diagnosis of the conditions is highly problematic. There is much to be done, and a decade is the timescale over which enhanced commitment is required.

The problem of stigma persists. In some countries, progress in this regard has been made with depression: a few high-profile and brave sufferers in some Western countries have stood up and identified themselves. By contrast, schizophrenia, when covered by the media at all, is mostly associated with murders carried out by a tiny minority of sufferers who have an acute form of the condition.

## Research challenges

Schizophrenia — a combination of delusions, reduced motivation and diminished cognitive functions — exemplifies many of the research challenges posed by psychiatric disorders as a whole. The extreme behaviours covered by the media are far from typical. Population studies indicate that the lifetime prevalence of all psychotic disorders (whose sufferers experience some sort of misperception of reality) is as much as 3%. Schizophrenia is controllable by medication and cognitive therapy, with a significant chance (a few tens of per cent) of beneficial positive outcomes.

Frustratingly, the effectiveness of medications has stalled. Nobody understands the links between the symptoms of schizophrenia and the crude physiological pathologies that have so far been documented: a decrease in white brain matter, for example, and altered function of the neurotransmitter dopamine. The medications, which are often aimed at the dopamine systems associated with delusions, have advanced over the decades not in their efficacy but in a reduction of their debilitating side effects.

Both diagnosis and drugs primarily address a late stage in the development of schizophrenia — the presentation of delusions. The earlier stages are much less well defined and are ambiguous in that, as currently

characterized, they could lead to a number of alternative conditions. Here, above all, is where progress is needed in the form of reliable biomarkers to identify those at risk and to allow biomedical or cognitive interventions to prevent or mitigate the development of the disorders. Early intervention would lead to better outcomes.

A deeper understanding of the underlying biology is essential to improve diagnoses and therapies. New techniques — genome-wide association studies, imaging and the optical manipulation of neural circuits — are ushering in an era in which the neural circuitry underlying cognitive dysfunctions, for example, will be delineated. tantalizingly, work in genetics is indicating how non-specific some genes are for schizophrenia, having associations in common with bipolar disorder and with autism. This suggests that the earlier stages of psychiatric disorders are multivalent, reinforcing the hope that early detection, coupled with a clearer understanding of the environmental factors, may allow prevention.

**“Early detection and a clearer understanding of environmental factors may allow prevention of psychiatric disorders.”**

## Environmental influence

Too little fundamental research is devoted to environmental factors. About 80% of the pattern of schizophrenia in populations seems to be determined by genetics, but part of that genetic influence lies in susceptibility to environmental influences. The remaining 20% of direct environmental influence is also ripe for more extensive investigation — epidemiological studies point to social stress (associated, for example, with migration or urbanization) as a significant influence, albeit in a minority of schizophrenia sufferers. As stated in a recent review of schizophrenia, a “worldwide challenge is to bring together the various disciplines that are needed to examine models of disease causation based on various aspects of gene–environment interplay” (J. van Os and S. Kapur *Lancet* **374**, 635–645; 2009).

Of course it won't be just the basic biology of molecules and their circuits that will be essential in understanding the mechanisms of schizophrenia. There is a higher level of explanation required to understand, for example, delusions and their persistence.

Whether for schizophrenia, depression, autism or any other psychiatric disorders, it is clear, as Tom Insel, head of the US National Institute of Mental Health has emphasized (T. R. Insel *J. Clin. Invest.* **119**, 700–705; 2009), that understanding of these conditions is entering a scientific phase more penetratingly insightful than has hitherto been possible. But Insel also highlights the disruptive impact of the science on the practices of clinical psychiatrists — as biological insights develop, the crudity of current psychiatric diagnoses will become all too clear. Yet the exposure of many psychiatrists to contemporary biology is shallow at best. That, too, will need to change over the next decade. ■