Editorial

Biological psychiatry: time for new paradigms

David Linden

Summary

Biological psychiatry has not yet produced clinically viable biomarkers for any of the major psychiatric diseases, and the past 25 years have not brought any fundamentally new biological treatment principles. I discuss reasons for this slow progress and suggest avenues for the development of biomarkers and the discovery of new treatment targets.

Declaration of interest

None.

David Linden is an academic psychiatrist in Cardiff. He uses cognitive neuroscience methods to understand the mechanisms of mental disorders and to develop new treatments.

Although the methods available to biological psychiatry, for example functional neuroimaging, molecular genetics and epigenetics and transgenic animal models, have become substantially more sophisticated in the past 20 years, the field is still waiting for the translation of biological models of psychiatric disorders to impact on clinical practice. I would like to highlight the following three main shortcomings.

(a) Diagnosis and classification of mental disorders are still based on reported symptoms and observed behaviour but not on biomarkers and aetiology, and there is no indication that this will or could change in the forthcoming new classification systems.

(b) We still know relatively little about the mechanisms behind the many effective biological treatments, for example psychotropic drugs or brain stimulation.

(c) The past 25 years of research in biological psychiatry have not yielded major new clinical treatments, and few new biological treatment principles are in sight.

What are the reasons? The main psychiatric disease entities comprise considerable phenotypic heterogeneity, and even the same clinical phenotype can involve different biological processes. The number of psychopathological or neuropsychological changes that can be recognised in humans is much smaller than the number of potential biological changes, which makes it likely that different neurobiological mechanisms can lead to the same symptoms. Furthermore, much of psychopathology is dimensional and thus categorical phenotyping alone may not be optimal.

Without clear biological phenotypes to target, the discovery of drugs and other biological treatments for mental disorders has had to be serendipitous. Although the mechanisms of psychotropic drugs are well understood at the synaptic and sometimes also at the postsynaptic level and animal models have been successfully used to study their effects on neural networks and behaviour, this knowledge only rarely allows us to explain or even predict clinical effects. This would require behavioural phenotypes in animals that reliably model features of human psychopathology (have good face validity) and show similar drug effects (have good predictive validity), and only few such animal models are available,[1] making rational drug screening very difficult.

Strategies for stratification

One way to tackle the biomarker problem would be through reduction of heterogeneity of study groups. However, attempts to produce more homogeneous clinical phenotypes through subtyping (e.g. into 'positive' and 'negative schizophrenia') have not produced any more stable biological associations. Breaking clinical phenotypes down further into constituent behavioural, cognitive or personality traits that can be investigated in a dimensional and quantitative fashion may be more promising. For example, recent functional and structural imaging studies have revealed the changes in brain networks that may underlie impulsivity in drug addiction.[2] However, the genetics of personality traits seems to be at least as complex as that of any full clinical syndrome.[3] Another promising approach to biomarker development may be through genetic stratification. This would entail subgrouping patients from a diagnostic group or spectrum, for example psychotic disorders, according to specific genetic variants or genetic pathways. In this way it could be investigated whether patients with rare variants affecting a particular biological system, for example the protein complex of the postsynaptic density,[4] show similar downstream changes as patients with several common variants of small effect affecting the same system. Patient groups defined by such measures of genetic similarity may be more homogeneous biologically than unselected clinical groups and thus have a higher chance of yielding intermediate phenotypes that inform about the mechanisms by which the genes influence biology and function and can be used as biomarkers for stratification and treatment monitoring. The translational scope would be to explore whether these biologically defined subgroups of patients will respond better to specific existing or novel treatments.

A 'functional systems' approach

The search for biomarkers on the basis of better phenotypic and genotypic stratification relies on the assumption that homogeneous biological deficits underlie particular clinical phenotypes, or groups of related phenotypes that can be identified through biomarkers and become specific targets for new treatments. I shall call this the 'dysfunctional systems' approach. This model has been immensely successful in most fields of medicine but, as argued above, has so far failed to advance clinical psychiatry. Several clinical and epidemiological observations suggest that it does not capture the full complexity of psychiatric illness:

(a) most psychiatric disorders are relapsing/remitting and may even occur only in one episode and improve without treatment;

(b) patients vary greatly in their ability to cope with the illness and consequently in function and well-being;

(c) gene × environment interactions seem particularly important, compared, for example, with the inheritance of many neurological diseases.

Any biological study of psychiatric diseases will therefore have to distinguish carefully between correlates of symptomatic states and persistent traits or vulnerability markers that can also be picked up in pre-symptomatic and remitted phases. The markers of disease states may very well change over time and vary with every new environmental challenge. Such 'dynamic' lesions may prove to be moving targets, making the search for biomarkers an almost impossible task. Conversely, the biological correlates of the mechanisms that help to overcome mental illness such as emotion regulation or fear extinction[5] may be more consistent – across patients, situations and disorders – and more easily observable. I therefore propose supplementing the currently reigning dysfunction model of biological psychiatry with a 'functional systems' approach that investigates the biological processes supporting prevention, coping and recovery. The ultimate aim would be to use this knowledge for the development of new treatment biomarkers and treatments, in analogy to the dysfunctional systems approach, but without predicating this on a primary dysfunction which we may be never able to prove.

Markers of resilience and recovery

The same techniques as used in the investigation of dysfunctional systems can also be used to elucidate the biological basis of preserved or protective functions. The past 20 years of cognitive neuroscience have yielded detailed insight into the neural systems supporting the regulation of affect, thought and social interaction in healthy individuals. In more specific psychiatric applications we can study the neural substrates of successful task performance or coping by comparing high- and low-functioning patients. One particularly promising approach seems to be to probe large existing cohort studies for psychological or biological markers of resilience. This can be achieved by comparing people at high environmental[6] or genetic risk who do and who do not develop a mental disorder. Much of this work so far has been conducted on victims of early traumatic experiences, but comparing prodromal patients who go on to develop schizophrenia with those who recover completely might be another worthwhile example. Because modulation of one and the same neurotransmitter system can improve very different psychiatric syndromes with very different antecedents, we may assume that the biology of resilience or recovery will be less variable than that of common mental disorders. For example, serotonergic drugs are effective for both anxiety and depression, and for patients who develop these symptoms after a stroke or other brain lesion as well as for those without demonstrable organic causes.

New treatment targets

We can test this hypothesis by investigating the biological correlates of treatment effects (or inversely of symptom induction) and those of spontaneous remission (or recurrence).[7] Even if we do not assume that (or simply do not know whether) the treatment in question is correcting an underlying biological dysfunction, studying its biological effects may point us to biological processes that can be targeted with new treatments. One limitation of the extant work on neural mechanisms of coping and remission has been its general lack of molecular resolution. It has thus not yet yielded new pharmacological targets. However, work on changes in dopamine receptors after cognitive training[8] suggests that human molecular imaging studies of such protective or neuroplastic mechanisms are in principle possible.

A better understanding of the genetics, pharmacology and neurophysiology of resilience, coping and remission might create targets for new treatments that promote these mechanisms. These can then be modulated in experimental studies of new interventions that operate at many different levels. This may lead to the development of new drugs, but also new biologically motivated psychological interventions,[9] brain stimulation or neurofeedback[10] protocols targeting the relevant functional systems. Mental disorders are creating an increasing burden on the health and well-being of the population and already account for a quarter of all disease-related disability worldwide. There is now a considerable body of neuroscience work on cognitive and affective processes whose enhancement might be beneficial in psychiatric disorders. Any approaches for speedy translation of these recent advances in basic and cognitive neuroscience into new treatments should be welcome.

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