A desperate search for biomarkers in schizophrenia. What is going wrong?

PETER FALKAI

Department of Psychiatry, University of Göttingen, Germany

In their excellent review, Lawrie et al search for suitable biomarkers to establish the diagnosis of schizophrenia, and to predict the transition to psychosis and the response to treatment. They conclude that currently the diagnosis of schizophrenia by means of clinical criteria is reliable and that replacing this with another set of subjective criteria would be “comparable to rearranging deck chairs on the Titanic”. Despite their substantial effort to distil biomarkers out of the literature, the authors remain unsuccessful. What is the background and what can be done to change this lack?

Concerning biomarkers, we seem to envy the rest of medicine. In cardiology, for instance, we have a wealth of markers like ECG or blood parameters, helping to establish a firm diagnosis. Even when we look at neurology, a discipline obviously working on the same organ

we deal with, disease phenotypes like stroke, epilepsy or multiple sclerosis are easy to define. These disorders have a clear morphological substrate and often well identified etiological factors. Schizophrenia is a network disorder in which we find local abnormalities and a disconnection syndrome, but we are not able to discover a common neuropathological substrate or a set of established risk genes. The behavioural phenotype encompasses virtually all aspects of human behaviour. Therefore, we need to reduce the complexity of the phenotype under examination. Our task consists in designing simple experiments to answer a few questions or just one question. We need to focus on one “neurofunctional pathway” rather than leaving the interpretation of our data to “neuronal network hypotheses”.

We can rely on sophisticated research tools, namely molecular genetics and brain imaging, but the differences to be detected in schizophrenia are exiguous and heterogeneous. And we still look for

a static lesion explaining at least part of the psychopathology of schizophrenia. In a recent randomized trial, however, we could demonstrate that hippocampal volume reduction, one of the structural hallmarks of schizophrenia, is reversible with aerobic exercise over a period of three months (1). Therefore, our concept of a static neurodevelopmental lesion and/or degenerative brain process in schizophrenia might be wrong. We have to realize that any detrimental factor to the brain, such as obstetric complications, cannabis abuse or chronic psychotic symptoms, will lead to regenerative brain efforts. Therefore, it is vital to define the phase of illness of each patient under study.

Interestingly, there is consistent evidence for a heterogeneous outcome in schizophrenia. About 20 to 30% of patients with schizophrenia show a very favourable, around 20% a fair and the remaining 50% a more unfavourable outcome (2). Despite this evidence, there are no studies trying to define the

neurobiological basis of these different long-term outcomes. It would be a good start if neurobiological findings were interpreted on the background of the long-term outcome of the patients included in the study.

In summary, Lawrie et al's paper points to a wealth of neurobiological data from schizophrenia research, which currently are not helpful in identifying biomarkers for establishing the diagnosis, predicting the transition to psychosis or responding to treatment. This under-

scores the need to reduce the complexity of our observed phenotypes and to develop more focused study designs. Furthermore, in order to reach a better understanding of the neurobiological basis of schizophrenia, we need to focus on the different phases of illness, distinguishing prodromal, first- and multiple-episode cases. Finally, stratifying our findings on the background of the long-term outcome of the included patients could help us to develop a more sophisticated interpretation of our neu-

robiological data on schizophrenia.

References

1. Pajonk FG, Wobrock T, Gruber O et al. Hippocampal plasticity in response to exercise in schizophrenia. *Arch Gen Psychiatry* 2010;67:133-43.
2. Häfner H, an der Heiden W. Course and outcome of schizophrenia. In: Hirsch SR, Weinberger D (eds). *Schizophrenia*. Oxford: Blackwell 2003:101-39.