already been used to identify proteins that are affected in tumors and hence lead to specific targets for drugs to treat different forms of cancer. In a similar approach, 2D electrophoresis is being carried out using postmortem central nervous system (CNS) from a large cohort of subjects with schizophrenia and tissue from the same CNS region of subjects with no history of psychiatric or neurological disease. We have modified the approach to 2D electrophoresis so that the analyses will measure the levels of over 10 000 proteins in each tissue sample. In collaboration with the Centre for Mathematics and Statistics of Complex Systems, we are now analyzing our 2D gels to identify grouping of differential protein expression patterns that might define different illnesses within the syndrome of schizophrenia. In this presentation, a proof of principal study to differentiating schizophrenia and bipolar disorder will be presented.

08-03

From biological marker to endophenotype: the role of animal models

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Our group has been exploring the concept that developmental vitamin D (DVD) deficiency may be the plausible neurobiological explanation for several important epidemiological correlates of schizophrenia, namely 1) the excess winter/spring birth rate, 2) increased incidence of the disease in second-generation Afro-Caribbean migrants and 3) increased urban birth rate. We have produced two pieces of direct support for this hypothesis in patients. DVD deficiency therefore is a plausible 'biological marker' for schizophrenia. We have recently resolved a major technological barrier that will now allow us to test this hypothesis in a major European developmental biobank. The genetic factors or heritability indicators that would endow DVD deficiency as a valid schizophrenia endophenotype are emerging. Our group has established a highly informative animal model to study the effects of DVD deficiency on brain development. This animal model reproduces the gross pathological features of the disease, that is, ventriculomegaly as well as sensitivity to amphetamine- and MK-801-induced hyperlocomotion and impairments in latent inhibition, behaviours analogous to the positive and negative symptoms of the disease in patients. We are now examining whether this model internally fulfils certain molecular endophenotypic criteria. Our initial data are encouraging as we find a 36 ± 11% decrease in the developmental expression of the candidate endophenotypic gene for schizophrenia, COMT. This animal model continues to provide good face and some construct validity with the disease in patients and illustrates how animal models can be used to progress plausible biological markers for schizophrenia into endophenotypes.

08-04

Endophenotypic biobehavioural markers for schizophrenia: how close are we to finding the Holy Grail?

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Research over several decades has showed that current operational diagnoses are unlikely to map directly onto the biological substrates of schizophrenia. This has led to increased interest in identifying endophenotypic markers that may provide an intermediate link to underlying genes. This talk will review some of the more promising biobehavioural markers currently being investigated, such as P50 sensory gating, reduced mismatch negativity amplitude and regionally specific gray matter volume loss, and highlight some of the challenges that still remain to be overcome. These include the potential impact of various potential confounds (eg treatment effects and comorbidity). Our current state of knowledge highlights the need for large-scale collaborative efforts that could provide convincing evidence for the utility of putative biobehavioural markers in furthering our understanding of the etiology of schizophrenia.

08-05

'Kraepelinian' and 'Bleulerian' schizophrenia: a genetic dissection of a cognitive endophenotype

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