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this issue:

Closing in on biomarkers

The PRISM project (Psychiatric Ratings using Intermediate Stratified Markers), is a joint Industry-Academia project to relate biological characteristics to clinical diagnosis in mental health. The first part of the project, PRISM1, was initiated in 2016. PRISM2 was recently funded by the EU's Innovative Medicines Initiative to build on the findings from the original PRISM project.

PRISM aims to build on the RDoC (Research Domain Criteria) concept, put forward by Tom Insel and Bruce Cuthbert at the NIMH in the USA, to correlate clinical diagnosis with measurable biomarkers, and so to move on from the traditional diagnosis of mental health problems based only on an analysis of symptoms. Of course, reliable biomarkers are seen as something of a 'Holy Grail' for mental health medicine, and while several labs are working on this, the international PRISM collaboration is probably the most ambitious.

Here, Professor Martien Kas is interviewed by Tom Parkhill. Professor Kas is the PRISM academic project coordinator and Professor of Behavioural Neuroscience at the University of Groningen. He is also the President-elect of the ECNP.

TP: Tell me about the history of PRISM – what does it aim to do and how did it come about?
MK: Firstly, PRISM is funded through the EU's Innovative Medicines Initiative (IMI). It was funded to address a call for studies on quantitative biology for neuropsychiatry, to provide us with quantitative parameters for symptoms which are seen across neurological and psychiatric disorders. The PRISM consortium wrote a project proposal to assess 4 different domains across these disorders, ranging from social functioning, sensory processing, working memory, and attention. We chose these because they were 4 domains the consortium felt were highly affected across disorders.

The main focus has been on the social domain, because we know, from input from the EUFAMI patient family organisation, among others, that social withdrawal and isolation is one of the major burdens which patients experience. As part of the project, EUFAMI surveyed patients and families. Social isolation has an effect on the lives of patients, but also on the lives of their close relatives who may be taking care of them. And really, there isn't much in the way of treatment for this particular symptom.

PRISM is a joint Industry-academia initiative; how did this come about, and what's the history?
The general concept of an IMI project is that they are funded partly through the EU's Horizon 2020 initiative, with an equivalent cash contribution coming from industry. The European Federation of Pharmaceutical Industries and Associations (EFPIA), which represents the biopharmaceutical industry operating in Europe, coordinates the industry input. PRISM1, which ran from 2016, received €16.5m funding in total, and had 22 participants, including 7 from the pharmaceutical industry. PRISM2 will receive €7.9m funding, and will have 14 participants. The ECNP is a participant in both stages.

We kicked off in 2016 with a clinical study where we did a lot of deep phenotyping in schizophrenia and Alzheimer's disease patients, who were characterised for high and low social withdrawal. These patients, and a control group, were assessed for all kinds of quantitative biological parameters in the 4 domains I have mentioned. These assessments ranged from neuroimaging assessments (both structural and functional), EEG and scan data, but also social measurements using for example questionnaires and smartphones. Many other measurements were included. Based on this dataset we obtained more than 4000 biological endpoints, and used advanced statistical analysis we tried to see if we could group these patients on the basis of biology, rather than on the original clinical diagnosis.

And how did that go?
We found a relationship, at different levels, between the default mode network and social functioning, irrespective of the traditional diagnosis. This seems to mean that the variations in the default mode network relate to certain variations in social functioning, irrespective of diagnosis. This is what we want to confirm and investigate in PRISM2. In PRISM 1 we found evidence for this in resting state connectivity measures, as well as structural and EEG measures – also at the level of questionnaires and the digital measures of social functioning. In a genetic part of the study we were able to identify 19 loci for sociability, and that many of these genes are expressed in circuits related to the default mode network.

So PRISM has started to build a neurobiological framework, where there could be a potential relationship between the level of social dysfunction in these different disorders and the functional and structural integrity of a specific brain network.

In parallel, PRISM 1 has developed a preclinical test-battery to assess phenotypes corresponding to those assessed in the human clinical study, This platform will be used in PRISM2 to back translate the human findings and to provide causality between the identified neural network and social functioning in rodents.

On top of that, PRISM started a dialog with the EMA Innovation Task Force, on the digital measures of social functioning.

What's the plan for PRISM2?
Read the complete interview (pdf).

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