Novel, large-scale EU collaborations…

…to identify causes and treatments for schizophrenia…

Schizophrenia and related psychotic disorders without doubt represent the most mysterious and costliest of mental disorders in terms of human suffering and societal expenditure. Psychotic disorders mostly affect young people: around 2-3% of adolescents and young adults will develop a psychotic disorder, often with a persistent course requiring life-long treatments that currently still cause many side effects.

Psychotic disorders represent a major challenge to scientists. First, there is a bewildering complexity of symptoms affecting the realm of emotions, thinking, perception and volition (Fig. 1) that vary substantially, not only between patients but also within patients over time. Second, patients often feel threatened – not viewing themselves as ill – and therefore are not always naturally inclined to work with the medical community and lobby for research funding and improved treatments. Third, psychotic disorders, representing madness, remain highly stigmatised and are therefore not natural candidates for health prioritisation, even though the young age of the patients and the long-term service dependence would justify such an approach from a public health point of view.

Until recently, researchers had relatively little to go on in trying to unravel the causes of psychotic disorders and identify better treatments with fewer side effects. The last decade, however, has seen significant progress, helping researchers in the EU for the first time to devise a rational strategy of large-scale collaboration.

With the help of significant funding in the Seventh Framework Programme of the European Commission (FP7), two unique, large-scale collaborative projects, together receiving support in excess of €24m, were started in May 2010, focusing on the causes and treatment of schizophrenia and related psychotic disorders.

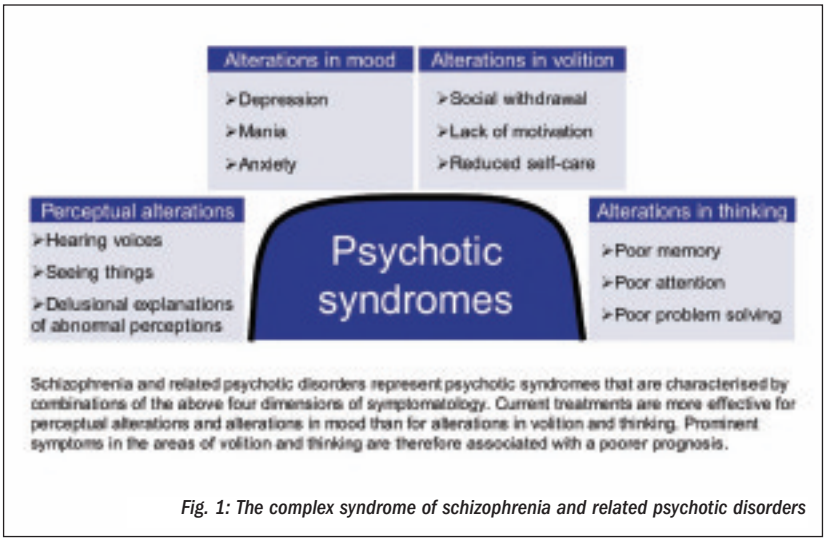

Fig. 1: The complex syndrome of schizophrenia and related psychotic disorders

Finding the causes of schizophrenia and related disorders

Environmental effects during childhood and adolescence

Epidemiological research has established that rates of schizophrenia and related psychotic disorders vary substantially under the influence of a number of non-genetic factors that point to powerful environmental effects impacting on, particularly, children and adolescents growing up in European societies.

Are Europe's big cities detrimental to mental health?

Children growing up in big cities have a more than twofold risk of developing schizophrenia or related disorders compared to children growing up in rural environments, independent of other factors. While the exact mechanism of this effect remains unknown, research has established that up to 25% of all schizophrenia can be explained by the effects of urbanicity. Given the increasing rate of urbanisation in European countries, and concern about the health effects of the built environment not only on mental health, but also on a range of somatic disorders, as well as crime and educational outcomes, this is clearly an area of prioritisation for scientific research.

The epidemic of schizophrenia in minority populations

It has now been established beyond doubt that immigrant populations moving to European countries develop much higher rates of schizophrenia and related psychotic disorders compared to the rate in both the host country and the rate in the country of origin. This is a matter of great concern, as it points to specific environmental effects associated with the interaction between migrants and host country majority populations. Thus, migrants living in areas with a high density of their own ethnic group have a much lower risk than migrants living in areas with low ethnic density, suggesting that psychologically 'toxic' interactions with the majority

population may play a role in bringing about the increased schizophrenia risk.

Schizophrenia as an outcome of cannabis use

Cannabis is the most widely used drug in Europe. Until recently, its effects were thought to be relatively harmless, but a large number of studies have now established that cannabis use, particularly heavy use during adolescence, increases the risk of later onset of psychotic disorders such as schizophrenia. Although the risk is not great, the impact of cannabis use on schizophrenia rates is not negligible as it is the most commonly used drug in Europe, so that small risks translate into large effects from a public health point of view.

Childhood victimisation and schizophrenia

A major shift in the way research has been approaching the study of schizophrenia is evidenced by recent work focusing on the link between childhood trauma and later psychotic disorders. At least 15% of populations in Europe have been the victim of significant abuse, neglect or bullying during childhood. Whilst significant adverse effects of childhood trauma have been described for a long time, epidemiological research pointing to a link between childhood trauma and schizophrenia and related disorders is much more recent. Nevertheless, the evidence is remarkably consistent in showing strong effects on the liability for schizophrenia and related disorders.

Gene-environment interaction

Twin and family studies have established that more than half of the vulnerability for schizophrenia is of genetic origin. However, despite enormous investments, it has proven extremely difficult to identify actual molecular genetic variants underlying schizophrenia liability. There are likely many reasons for this, but one important reason is the phenomenon of gene-environment interaction (GxE; Fig. 2).

Until recently, molecular genetic research in mental disorders focused on the model of genetic main effects (Fig. 2A). In EU-GEI, the alternative model that genes influence risk of disease by rendering individuals more sensitive to the effects of causal environmental risk factors (Fig. 2B) is considered as well.

Fig. 2: From gene-only to gene-environment interaction

Gene-environment interaction refers to the model that genes influencing risk for schizophrenia may not do so directly (Fig. 2A, the dominant model until recently), but indirectly by making individuals more sensitive to the effects of causal environmental risk factors, such as cannabis use, migration, urbanicity and childhood trauma (Fig. 2B).

If there is substantial gene-environment interaction underlying schizophrenia and related psychotic disorders, the most efficient way of elucidating the causes of schizophrenia is to focus on both genes and environments in the same research project. To date, however, it has proven extremely difficult to bring together the scientific disciplines that are necessary to undertake such a multidisciplinary endeavour, severely hampering progress in this area. Now, for the first time, such a focused collaboration has been organised in Europe, in the context of FP7.

The EU-GEI project

The EU-GEI project – coordinated by Professor Jim van Os and Dr Bart Rutten from Maastricht University Medical Centre, the Netherlands and King's College London – will bring together a multidisciplinary team of researchers from Turkey, the Netherlands, Ireland, Spain, the UK, Germany, France, Belgium, Greece, Austria, Switzerland, Italy, Australia, Brazil and Hong Kong, in the largest effort to date to find gene-environment interactions underlying schizophrenia risk.

More than 7,500 patients and their families will participate. The outline of the project is shown in Fig. 3. It will focus on the effects of gene-environment interactions on brain pathways and psychological vulnerability, and how these cerebral and psychological pathways mediate subtle, but measurable, behavioural expressions of vulnerability for psychotic disorder.

Follow-up research in the project will establish why, in some individuals, behavioural expression of vulnerability will never progress to overt illness, whilst in others, overt expression of schizophrenia will ensue.

Measuring vulnerability occasioned by GxE: PSYMATE technology

An important aspect of the project is the development of tools that allow for the actual measurement of the behavioural expression of vulnerability that is caused by gene-environment interactions. This will make it possible to monitor, and possibly modify, vulnerability at the behavioural level, thus preventing transition to overt illness.

Early work shows that the behavioural expression of vulnerability, occasioned by gene-environment interactions, is best captured as subtle alterations in mood, perception, volition and thought in response to small stressors in the flow of daily life. To date, no tools exist to adequately monitor these subtle alterations in mood, thinking, perception and volition in response to small daily life stressors. Therefore, European enterprises and start-ups in EU-GEI will develop new technology

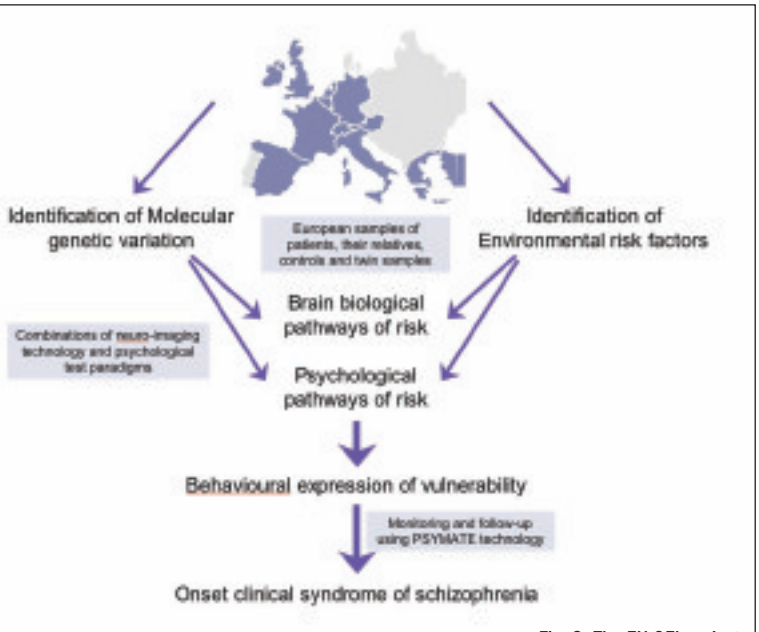

Fig. 3: The EU-GEI project

allowing for momentary assessment of subtle alterations in mood, thinking, perception and volition in response to small stressors in the flow of daily life.

A prototype has been developed, the PSYMATE (Fig. 4), a device that individuals can carry with them during the day for easy data input on mental state, context and activities at random moments in the flow of daily life. It is hoped that this technology will also be used in clinical practice, as it usefully captures the 'film' rather than a 'snapshot' of daily life reality of patients, fuelling new research into the gene–environment–experience interplay underlying psychopathology and its treatment.

The Optimise project: better treatment for schizophrenia and related disorders

The aim of the Optimise trial is to improve treatment for patients with schizophrenia. This goal will be reached in two ways:

- By optimising currently existing treatment;
- By identifying new treatment strategies.

The first path: Optimising existing treatment

The first drug with specific anti-psychotic action was produced in 1950. Since then, numerous new anti-psychotic drugs have been introduced. Most of these drugs are largely equal in efficacy and differ mainly in profile of side effects. Up until now, it has remained unclear which anti-psychotic drug should be the first choice for schizophrenia patients with a first psychotic episode.

Furthermore, if the first drug fails to induce remission of psychosis after several weeks of treatment, it is unclear if another anti-psychotic drug should be tried or if treatment should be continued with the first drug. For patients who fail to reach remission after two anti-psychotic agents, general consensus is that clozapine, the most potent anti-psychotic drug, should be started. However, despite this general agreement, clozapine treatment is frequently delayed for years or not commenced at all.

Fig. 4

This large-scale European study, coordinated by Professor René Kahn from the Utrecht Medical University Centre, and Professor Shitij Kapur from King's College London, aims to improve current treatment of schizophrenia by finding treatment guidelines for drug therapy of first episode psychosis.

To achieve this, a consortium of 18 European psychiatric institutes has been formed from which 350 medication naïve patients with first episode psychosis and a diagnosis of schizophrenia or schizophreniform disorder will be enrolled. All patients that participate in the study will start a four week period of treatment with amisulpride. This drug showed high efficacy in the 'EUFEST study', another European study that included 500 first episode schizophrenia patients. In addition to high efficacy, amisulpride had a favourable side effect profile, with few motor problems and no general weight gain.

After four weeks on amisulpride, those patients who have not obtained remission of psychosis will be randomised over two treatment conditions: continue on amisulpride or switch to olanzapine. Olanzapine is another anti-psychotic drug that has a mechanism of action slightly different from amisulpride that showed favourable efficacy in the EUFEST study.

However, olanzapine induced weight gain and drowsiness in many patients. This part of the study will be blind, which means that both patients and their doctors will not know who is taking olanzapine and who continues to use amisulpride. A small part of the initial 350 patients, approximately 25-30%, will still have many psychotic symptoms even after this blind treatment phase. These patients will be treated with clozapine in an open label fashion.

Although psychotic symptoms are frequently a first sign of schizophrenia, they can also be the result of neurological abnormalities, such as a brain tumour. It is essential to identify

these patients, as they may need urgent neurosurgical interventions. It is currently unknown which percentage of patients with a first psychosis has such a brain abnormality; because the exact percentage is unclear, it also remains uncertain if general screening of all psychotic patients for neurological abnormalities is useful.

In the Optimise trial, 200 patients with a first episode psychosis will have an MRI scan of the brain. If a relatively large percentage of these patients show neurological abnormalities that necessitate an intervention, it will be recommended to screen, in the future, all psychotic patients with an MRI scan of the brain.

Most patients will obtain remission of psychosis with a first, second, or third anti-psychotic agent. Once in remission, many patients wish to discontinue their anti-psychotic treatment because of side effects, or they experience loss of autonomy or fear stigmatisation by taking psychiatric drugs.

However, anti-psychotic drug therapy is not only necessary to obtain remission, it is also of pivotal importance to stay on these drugs in order to remain in remission. The main reason why patients relapse into psychosis is because they discontinue drug therapy.

In the Optimise trial, psycho-social interventions such as family psychoeducation, motivational interviewing and mobile phone text message reminders for drug intake will be used in an attempt to increase treatment adherence. If treatment adherence could indeed be increased, this would reduce the number of relapses and improve long-term outcome for patients with schizophrenia.

The second path: finding new treatment strategies

Current pharmacological treatment for schizophrenia is largely based on the blockade of the dopamine D2 receptors in the midbrain. For most patients, this is an effective strategy to combat psychotic symptoms, although not without side effects. However, a significant minority of patients do not respond to current anti-psychotic treatment. In addition, the negative symptoms of schizophrenia show almost no improvement with this type of medication. It is therefore necessary to expand current therapeutic options.

One candidate drug that may have anti-psychotic potentials and could also ameliorate negative symptoms is cannabidiol, a non-psychoactive constituent of the cannabis plant. Cannabidiol does not block the dopamine D2 receptor, but rather affects the internal cannabinoid system. The first studies in schizophrenia with this new compound are promising, but they need to be replicated in a large group.

As part of the Optimise trial, 150 patients with a first psychosis will be treated with either cannabidiol, the anti-psychotic drug olanzapine or placebo. The type of treatment will not be known to patients or their doctors. If cannabidiol is indeed an effective agent for schizophrenia, the group treated with cannabidiol will do better than the group on placebo and similar to, or perhaps even better than the group on olanzapine.

Apart from cannabidiol, other strategies to improve drug therapy will be studied. This will be done by means of blood analysis. All 350 patients who participate in the medication trial will be asked to provide a small quantity of blood at several stages of the treatment. The expression of several compounds, such as proteins, fatty acids and inflammation parameters, as well as the genetic code of the DNA will be measured in the blood, as these could provide new directions for treatment. We aim to use these genetic and neurochemical markers to predict response to treatment.

In addition, a special type of MRI scan will be performed in a subgroup of patients. This MRI scan is called magnetic resonance spectroscopy (MRS) and is sensitive for a specific chemical compound in the brain. In the Optimise trial we will apply MRS to investigate glutamate in the brain of patients with psychosis.

The Optimise trial will last six years. At the end of this study, we will be able to provide treatment guidelines for drug therapy of patients with a first episode psychosis. We will also be able to recommend if MRI screening for neurological abnormalities is necessary. Further, we will know the efficacy of psycho-social interventions to improve drug adherence. And finally, we hope to have new treatment strategies for those patients who respond poorly to current anti-psychotic treatment.

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