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SPECIAL ARTICLE

# Report of the 3rd European Brain Policy Forum☆

## Informe del 3.er Foro sobre Políticas de Actuación del Consejo Europeo del Cerebro

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The 3rd European Brain Policy forum, entitled ''A Focus on Persons with Schizophrenia and the European Society'' was jointly organised by the Spanish Brain Council (SBC) and the European Brain Council (EBC) at the Instituto de Salud Carlos III in Madrid on February 23rd and 24th 2010.

In the opening session to set the scene and explain the purpose the meeting, José Navas (General Director, Instituto de Salud Carlos III) introduced Professor Julio Bobes (President of the SBC) who welcomed the participants to Madrid during the term of the Spanish Presidency of the European Union to discuss this serious and widely prevalent disease. He reported that the newly formed Spanish Brain Council was in good health and hoped that this first event of the organisation would lead to important recommendations about research and care needs in the field.

Professor Julien Mendlewicz (President of the EBC) introduced the EBC to the audience and supported the comments of Professor Bobes. He described the role of the EBC in increasing funding for brain research and summarised current EU grants in the area of schizophrenia. He expressed the wish that the conference would contribute ideas to the update of the EBC's Consensus Document on Brain Research in Europe.

Pablo Rivero, from the Spanish Ministry of Health and Social Policy, congratulated the SBC and EBC on their organisation of the meeting and for its focus on the need for integrated efforts to improve health and social policy. He spoke about the great challenges in health such as diabetes, cancer, rare chronic diseases, pain and mental health. In Spain, great progress has been made in the last twenty years in what he described as the three axes of mental health care and treatment—prevention and detection, treatment and clinical practice, and research. However, there was still a long way to go to integrate research with clinical guidelines

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in order to ensure that best practice was always followed. He mentioned two important meetings during the Spanish EU Presidency, the first on Digital Health in Barcelona in March and the second on Mental Health and Ageing in Madrid in April.

In concluding this session, José Navas acknowledged the important role that the EBC has played in coordinating efforts at the European level and highlighted the Joint Programming initiative on neurodegenerative diseases as the first example of efforts to align national programmes and budgets. He hoped and believed that more initiatives like this would follow.

Cyril Hoschl introduced the first Keynote Address by René Kahn (Professor of Psychiatry, University Medical Centre, Utrecht, The Netherlands), a leading expert on the changes in brain structure in schizophrenia. He described how modern magnetic resonance imaging can tell us about changes in brain volume and also about connections and networks. He explained that a decrease in brain volume is a normal feature or ageing and usually starts at age 35. However, this is accompanied by growth in some brain areas and the extent and pattern of change is linked to IQ, those with higher IQ encountering reduced loss of volume. People with schizophrenia start losing brain volume at an earlier age (e.g. as young as 20) and at a faster rate, and the greatest loss is in those patients with the poorest prognosis. The areas of the brain differentially affected in schizophrenia are the medial frontal lobe, temporal lobe and hippocampus.

Brain volume is highly heritable and studies of identical and non-identical twins, discordant for schizophrenia, suggest that the rate of white matter loss is inherited and therefore occurs in the affected and unaffected twin equally, but that grey matter loss is caused by the disease and is therefore greater in the affected twin.

In the future, more powerful brain imaging machines will enable these differences to be analysed at a much higher resolution perhaps helping us understand how networks differ according to IQ, and how genetic and environmental influences combine to affect the developing brain in health as well as in disease.

Theme 1 on the Patients' Journey was introduced by Francisco Artigas (Profesor de Investigación, Institut d'Investigacions Biomediques de Barcelona, CIBERSAM) who spoke of the need for translational research and greater efforts to ensure an effective dialogue between science and society. He mentioned the EBC's study showing that mental disorders account for two thirds of the cost of brain disorders and highlighted some of the Spanish and European efforts to bring together basic and applied research with clinical practice—the CIBERSAM network in Spain, and the NEWMEDS consortium of the Innovative Medicines Initiative. He gave an example from the latter of the work to develop a better animal model based on electrophysiological analysis of the effects of PCP on cortical oscillations and their reversal by antipsychotic drugs.

Guadalupe Morales of the SBC and the Fundación Mundo Bipolar, kindly delivered the presentation of Dolores Gauci (President, GAMIAN Europe) who was unable to attend the meeting at the last minute. She spoke of how important the voice of the patient is at national and EU level. Patients must be at the centre of healthcare provision and for that they need information for themselves, and professionals must receive appropriate education and training. Together they can increase awareness and understanding, help to remove stigma and fight for the rights of patients. It is important that the different perspective of patients is recognised. Physicians focus on efficacy, safety and tolerability of interventions. Patients want quality of life, simple compliance and convenience. They also want respect and a focus on what they CAN do, not on what they cannot. Their issues therefore encompass housing, jobs, social interactions and family. What therefore can the psychiatrist do better? They should listen as well as talk, and provide information and support. They must also offer integrated treatment that includes attention not only to the mental health of the patient but also to their physical wellbeing, an important consideration for people with schizophrenia who live not only with the disease but the side effects of antipsychotic drugs. The comorbid conditions of diabetes, obesity and cardiovascular illness pose not only great health risks but cause social and psychosocial problems leading to poor compliance and a deteriorating quality of life. The extent of this problem is insufficiently recognised by physicians and therefore undertreated.

The dialogue between patient and physician is critical since both have expertise that is relevant to the patient's condition. Effective communication should lead to better management of the patient's needs, a result that is good for both patient and physician.

Joy Ladurner from the European Federation of Associations of Families of People with Mental Illness (EUFAMI) described the organisation and its goals of reducing stigma, promoting good practice, lobbying for legislative equality of patients, promoting research and campaigning for better resourcing of health and social care. EUFAMI supports families, and Joy described the impact of child mental illness on parents and family members—the phases of shock, coping, despair but eventual action. Her own mother had severe mental illness and Joy described honestly and movingly how the family learned to cope, not always asking questions and demanding answers, but accepting certain traits of her mother and coming to an understanding. This needs an informed perspective of carers and professionals as well as hope, faith and respect for the needs of the individual affected. The problems for those coping are formidable though—stigma, limited access to services, insecurity, lack of information, disruption to normal life and social and economic difficulties. In the particular case of schizophrenia, carers may have to manage a disease with an early onset but that may take a long time to receive a correct diagnosis. They will encounter crisis situations of patients who may have a poor insight into their own condition, and they have to deal with the side effects of medication, and the continual fear of relapse.

In the ensuing debate, Joy was congratulated on sharing her personal experiences and was asked to comment on how these challenges for families should be tackled in the future. She stressed the need for integrated care that takes account of physical as well as mental health. Greater awareness is needed to counteract stigma. The side effects of antipsychotic medication are severe and lead to poor socialisation. Treatment needs to be optimised for those so affected. And finally, the efforts of all those involved in care need to be

better coordinated, including those in policy making and education.

In Theme 2 on Understanding Schizophrenia and the Health System, Nicholas Tarrier (Professor of Clinical Psychology School, University of Manchester, UK) described the uses of psychosocial intervention in the management of schizophrenia. He explained the four levels of intervention. The first is about treating patients as people, showing respect, establishing communication and helping them deal with environmental stresses such as hospitalisation. The second level of non-specific psychosocial intervention provides counselling and emotional support. The third level of low intensity specific psychosocial support requires training of the specialist, and interventions guided by specific protocols and under supervision. The fourth level of high intensity specific psychosocial support involves complex intervention, high levels of training for practitioners and individualised, not protocol-guided, procedures. He reviewed the efficacy of various interventions and stressed the need for a better evidence base. While the evidence that cognitive behavioural therapy is effective in reducing hospitalisation rates and alleviating both positive and negative symptoms, most other treatments lack evidence to support their use: counselling, psycho-education, social skills training, cognitive remediation, psychodynamic and psychoanalytic interventions. Family interventions seem to be effective but access is very limited.

He concluded that these interventions serve to optimise the efficacy of drug treatments, and where they are shown to work they should be widely available, which is not currently the case. It is important that they are used by practitioners who have undertaken a long-term training programme.

Celso Arango (Hospital General Universitario Gregorio Marañón, Universidad Complutense de Madrid, CIBERSAM) discussed the particular issues around schizophrenia in children and adolescents. Typically the first symptoms of the disease appear in the 12–22 year age range. Below 13 years of age patients are defined as very early onset schizophrenia (VEOS) and above 13, but adolescent, as early onset (EOS). For these young people there is a high comorbidity with compulsive disorder, oppositional defiant disorder and depression. Their schizophrenia is associated with a high incidence of negative symptoms, hallucinations, motor disturbance, phobic and obsessive behaviour. Misdiagnosis is frequent because the condition is rare, confused by the comorbidities, and there is a reluctance to label such young patients with such a potentially devastating disease. Compared with adult schizophrenia, EOS is associated with more genetic differences and is more treatment-resistant.

He recommended a treatment strategy to address both the positive and negative symptoms, and the social, educational and cultural implications of the illness. The treatment should involve pharmacotherapy and psychotherapy and include family as well as patient support.

The third speaker in this session, Wolfgang Fleischhacker (Professor of Psychiatry, Medical University of Innsbruck, Austria) described the goals of treatment which are, in the acute phase, to develop the ''therapeutic alliance'' between patient and physician and establish the basis for subsequent maintenance and prevention of relapse. Early intervention is necessary to treat acute psychotic symptoms, to manage behaviour, to reduce subsequent neuronal damage and to alleviatie social issues. Intervention at the prodromal stage might be more beneficial, but since only 10–40% of patients exhibiting prodromal signs progress to schizophrenia, there is inherent risk associated with treating the other 60%, as well as the issue of stigmatising these patients unnecessarily. On issues of safety and tolerability of antipsychotic medication, Professor Fleischhacker commented that extrapyramidal side effects are not longer considered the most significant, and weight gain, metabolic effects, prolactin increase and cardiovascular effects are now the important issues. Responsibility for the physical health of patients is very variable across Europe. Psychiatrists and mental health practitioners need to take this more seriously, and communication between primary care physicians and specialists must improve. Professional education must integrate the mental and physical aspects of the illness.

In the ensuing debate, Professor Fleischhacker commented that the gap between the first episode of psychosis and treatment was not only due to time to diagnosis but also that patients do not present themselves even when treatment is available.

The first day of the meeting was concluded by the European Brain Council Lecture, delivered by Oscar Marín (Profesor de Investigación, Instituto de Neurociencias de Alicante) who asked what brain development can tell us about schizophrenia. He predicted that in 10 years we would be able to link causes to the syndrome and that this would be essential for the development of better drug treatments. Currently, we know that schizophrenia is associated with abnormalities in cortical GABA interneurones that control pyramidal cell excitability and synchronicity. Children who are later diagnosed with schizophrenia have cognitive and behavioural impairments indicating an early brain lesion which then progresses as shown by the accelerated loss of grey matter. The susceptibility gene, neuregulin-1 (Nrg-1), is known to control embryonic migration of GABAergic interneurones by mediating chemoattraction. He proposed that the decrease of brain volume is likely to result from loss of connections not necessarily loss of neurones, and therefore posed the question whether Nrg-1 is involved in synapse formation since it is known to be strongly associated with glutamatergic (pyramidal cell) synapses. The other susceptibility gene, ErbB4 (receptor for Nrg-1) is expressed on the axon terminals of the interneurones and on the dendrites where synapses occur between the pyramidal cells and the interneurones. Overexpression of Nrg-1 leads to increased synapse formation while Nrg-1 knockout has the opposite effect. Reducing expression of ErbB4 also leads to fewer synapses.

Putting these facts together, he argued that in schizophrenia the reduced GABAergic control of glutamatergic pyramidal cell leads to hyperexcitability and asynchrony causing loss of gamma rhythm and impaired cognition. He proposed targeting inhibition of glutamatergic transmission or increasing GABAergic inhibition as approaches to the treatment of the cognitive aspects of schizophrenia. His talk illustrated how a neurotransmitter-based understanding of brain circuitry can rationalise genetic information leading to plausible hypotheses about the causation of aspects of schizophrenia and rational proposals for drug interventions.

To kick off the second day, Professor Bobes welcomed everyone back and reminded them of the importance of agreeing some policy statements at the end of the meeting. He introduced the second keynote address by Hans-Ulrich Wittchen (Professor of Clinical Psychology and Epidemiology, Technische Universitaet, Dresden, Germany) who spoke of the burden and impact of schizophrenia. The concept of burden is a complex notion especially for a disease such as schizophrenia. It has to encompass the burden to the patient, to the care-giver, to the treatment system and to society, all of which vary from one European country to the next. Why is schizophrenia so difficult in this context? According to Professor Wittchen, the first challenge is that the impact and burden are different at different stages of the disease. The second is that schizophrenia at any stage is enormously variable. And the third is the difficulty of measuring burden in a disease whose care process is long and complicated, going through steps of recognition and treatment through to stabilisation and rehabilitation.

The general principles of treatment should follow the stages of fast reduction of florid symptoms to reduce the length and severity of the acute episode, reduction of the risk of relapse, ensuring compliance with treatment, and rehabilitation and continuity. The means of doing this, as emphasised by other speakers, are medication and psychosocial interventions, which can interact to optimise therapy, and then post-acute psychological interventions as add-ons to medication. The challenge is the choice of medication to establish compliance and continuity.

The current pattern of the disease course and outcomes is the following: 22% experience only one episode of psychosis; 35% have several episodes, but with no progressive impairment; 28% have several episodes with increasing levels of impairment; and 15% have a persistent non-remitting illness with increasing impairment. This is probably a better picture than 10 years ago.

Schizophrenia is not a very common disease but the treatment needs, and therefore burden, are high. It has the highest cost per case after dementia even though the indirect costs are probably underestimated, and it accounts for 30% of the direct healthcare costs of mental disorders. These costs are mainly due to hospitalisation, absenteeism and sick leave. Medication costs are surprisingly only 5% of the total and the cost of psychosocial interventions is negligible even though they are helpful in the post-acute phase in adherence, improving social skills, reducing relapse rates and improving cognition. As Nicholas Tarrier had pointed out earlier, some of these interventions are not useful but CBT, social skills training; integrated neuropsychiatric training and family education have value. However, in most countries psychotherapy is rarely provided.

In summary, Hans-Ulrich Wittchen stated that the burden of schizophrenia is underestimated, especially caregiver burden and indirect costs, and that treatment is suboptimal. It has been estimated that current treatment reduces only 13% of the burden of disease but optimised use of what is currently available could increase this to 22–35%. In the future, what is needed is continuity of care, early recognition of the disease, new preventative treatments, evidence-based evaluation of psychological interventions and data collection on service provision.

In the ensuing discussion, Tarrier asked why psychosocial interventions are not more widely available. Wittchen thought that it has been difficult to provide these outside the hospital setting and outreach services have not been well developed, particularly in Germany. Hans-Jürgen Müller commented that in the outcome analysis reported above, the term ''remission'' may still include a considerable level of symptomology. It is not by any means the complete absence of the disease. Wittchen agreed, but pointed out that many patients in remission manage well without relapse particularly in low stress environments such as developing and rural areas with a simpler life style and better social networks. Ladurner asked what families can do to provide the best outcomes for patients. Wittchen replied that it was very hard to generalise and commented that an over-stimulated emotional environment can be damaging, and that families must work with the physician and the patient to balance risks. It is not always the case that close family support is the best option.

The third theme on Schizophrenia—Future research and Health Policy, was chaired by Patrice Boyer who introduced the first speaker, Jim van Os (Professor of Psychiatry, Maastricht University Medical Centre, Maastricht, The Netherlands). Professor Van Os spoke about the genetics of schizophrenia and where it was taking us. He discussed the large scale genome-wide association studies and the reasons why these have only accounted for a small amount of the heritability of the illness. There are many possible explanations: it may be that each genetic variation is rare and causes a different form of schizophrenia; copy number variants (CNVs) or gene-gene interactions may be more important than SNP variants; the analysis may be confused by the imprecision of diagnosis; and epigenetic and gene-environment interactions may play a role. In summary, it is very difficult to identify rare variants of small effect and research on candidate genes and pathways is more profitable.

CNVs are a new area of research in schizophrenia and there is evidence that deletions are involved. Gene–environment interactions are also likely to be important and these can take the form of genetic susceptibility to environmental factors or a direct involvement of the environment on gene expression through epigenetic modification. He called for more EU-wide collaboration and multidisciplinary efforts to improve our understanding of gene–environment interactions.

Hans-Jürgen Müller addressed the issue of why treatments work and why they fail. He reminded us that the term ''remission'' may still involve a considerable level of residual symptomology and furthermore that one third of patients are refractory to treatment. Predictors of poor outcome include: the duration of untreated psychosis; multiple psychotic episodes (i.e. relapse); poor social adaption; and drug-related issues (non-compliance, or poor choice of drug or dose).

Refractoriness does not seem to be related to lower D2 receptor occupancy, and increased occupancy is not helpful. However, pharmacokinetic issues, such as high first pass metabolism, can underlie poor treatment response and should be checked. Atypical antipsychotics seem more effective in refractory patients, especially clozapine. They may also exert some neuroprotective effect due to increased

nerve growth factor production and the reduced brain volume loss noted above. Genetic prediction of drug efficacy would be very useful, but although some SNP's have been found associated with efficacy, the effect size is small, maximally 10%. Lastly he spoke of interventions with immunological drugs to improve the efficacy of antipsychotics, citing the example of risperidone and the NSAID, celecoxib.

Antonio Fernández (Government Affairs, Janssen-Cilag, Madrid) was the Voice of Industry. He mentioned that there is huge interest in the development of new drugs for schizophrenia with 45 currently in development in 102 clinical trials at the end of 2009. Ominously though, only one of these was in phase 3, suggesting that the demonstration of clinical efficacy is difficult. The preclinical drivers of innovation continue to be based on monoamine neurotransmitters, accounting for 50% of the development pipeline. However, newer targets include other neurotransmitter systems (glutamate, neurokinins and acetylcholine) but these are all in phase 2 and no marketed products yet exploit these possibilities. In the clinic, the regulatory guidelines still focus on psychometric scales (BPRS, PANSS) and safety issues. The former suffer from their lack of resolving power to distinguish between different drugs in terms of efficacy. In the future Dr Fernandez urged that preclinical R&D should pursue high risk strategies in the search for innovative therapies. He proposed that we should move from psychometric scales to outcome-based measures and that these should be incorporated into regulatory criteria. Regulators and payers must also recognise the value of incremental innovation. To achieve success, he stressed the necessity of collaborative R&D initiatives bringing academic and industrial researchers together.

In a more philosophical and reflective final Keynote Address, Carlos Belmonte (President, International Brain Research Organization) asked the question whether brain research can help our society. It is not a surprise that his answer was yes. He explained how our brains have evolved for exploration and movement and how our social behaviour is fundamental to our nature. Brain research is important because our brains are structures of enormous complexity and highly vulnerable to disease. But brain research can help us understand and deal rationally with the issues that human society faces, as well perhaps as posing challenges for the future. The problems of violence or drug abuse for example have remained unsolved by current policies because there is a fundamental lack of knowledge of what causes such behaviours. We do not know how society should react to the idea of emotional modification through pharmacological means. We struggle with allocating legal responsibility for acts against society. We worry about the use of imaging methods for preference detection – the creation of the so-called neuroeconomy. But we are gaining more knowledge about the external modulation of brain activity through trans-cranial magnetic stimulation and perhaps techniques such as this will lead us to new learning techniques.

In the final Panel Discussion, chaired by Ian Ragan (EBC) and Carmen Cavada (SBC), the participants debated and discussed what we had learned over the two days in order to agree on some action points to be used in policy discussions and to form the basis of the revision of the Consensus Document on Brain Research in Europe. The debate was excellent and rather than reiterate all the arguments, the final and agreed policy statements are listed below. These were incorporated into a post-meeting press release to the European media and to the co-ordinators of the Consensus Document revision.

In the closing addresses from Felipe Pétriz (Secretary of State for Research, Spanish Ministry of Science and Innovation) and Professors Bobes and Mendlewicz, there was total agreement that the meeting had been an outstanding success in achieving everything that had been hoped of it. They thanked all those who had contributed to the organisation of the meeting and of course, the speakers for their excellent presentations and insight, and finally, the participants in the debates and discussions which were central to the success of the meeting.

## Agreed policy statements

1. Schizophrenia is not only a neurodevelopmental disorder but also affects the developing brain and is associated with progressive changes in brain structure. Further multidisciplinary research is needed to advance basic understanding of brain function and neural development, to uncover the role of genetic and environmental factors and their interaction in the disease, and to explore the role of immunological and neuroendocrinological factors.
2. Schizophrenia is primarily diagnosed on the basis of clinical symptoms and its functional consequences. Research on specific biomarkers is needed to increase reliability and validity of diagnosis, as well as to improve prognosis. Further research and advances in neuroimaging and other diagnostic approaches are needed. Progress in understanding schizophrenia will require large collaborative projects through the further development of pan-European networks.
3. Early detection of patients is much needed because early intervention reduces burden on the patients, families/carers and all others involved, and improves prognosis. Research is needed to identify effective therapies in early onset schizophrenia, to assess the value of early intervention, and work is required to raise awareness of the importance of early diagnosis and improve accessibility to treatment. More research is needed on childhood/adolescent onset schizophrenia to understand its characteristic features and its relative refractoriness to treatment.
4. Treatment should be holistic, including appropriate pharmacotherapy, integral physical health care, evidence-based psychosocial therapies and active patient and family involvement. This requires specific training of health professionals, as well as cooperation and coordination of all involved: policy makers, health insurance companies, physicians, nurses and other health professionals.
5. Specific attention should be paid to the side effects of pharmacotherapy. This is a matter of particular concern not only for patients, but also professionals, because side effects interfere with socialisation, with medication compliance and with physical health. Further research is needed to find drugs minimising side effects.

6. Considering that schizophrenia is one of the most costly of all mental disorders in the EU and that treatment appears suboptimal at present, further effort is needed to: a) collect data on service provision and its impact, disease burden by country and region, and the role of cultural factors contributing to social stress (e.g. immigration, migration, urbanisation), b) to evaluate the efficacy and effectiveness of various therapeutic approaches in different settings, and c) to evaluate new approaches.
7. Novel drugs are needed. This demands new approaches to development, including public and private support of high-risk collaborative pan-European projects engaging academia, industry, patients, families and other institutions, as well as regulatory revision (e.g. expansion from symptom focus to multidimensional outcome measurement). Novel drugs focusing on specific aspects of the disease (e.g. cognitive impairment, negative symptoms) are also needed.
8. There is a need to integrate existing data and efforts on schizophrenia research at the European level by promoting the development and/ or merging of European research networks of national networks or centres of excellence.

## Conflicts of interest

The authors have no conflicts of interest to declare.